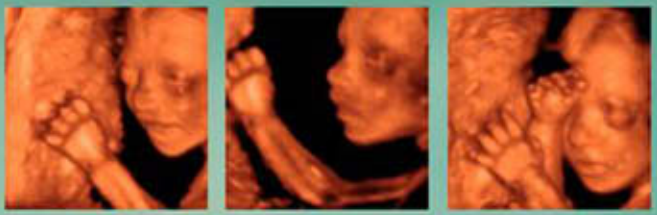
# Controversies in Obstetric Anesthesia and Analgesia



Edited by **Ian McConachie**

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Edited by

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# Foreword

Obstetric anesthesia and analgesia has been a mainstay of our anesthesia practice and profession since its beginning, dating back to the nineteenth century. It can be one of the most challenging anesthesia practices in our profession impacting on two patients (mother and baby). The current practice of obstetric anesthesia has been characterized by advanced age and increased comorbidity in these patients to be managed in the perinatal period. There has been better understanding and advancement in obstetric anesthesia in perinatal and fetal physiology, pharmacology, analgesia techniques and procedures, though controversies in obstetric anesthesia and analgesia continue to exist with new research evidence being generated for best practice in these patients.

This practical book edited by Dr Ian McConachie, who is an experienced academic clinician, highlights the controversies in current obstetric anesthesia management in the perinatal period. This book provides a concise, problem-oriented source of practical information by very experienced clinicians. The outstanding contributors selected by Dr McConachie from both sides of the Atlantic have covered a spectrum of controversial topics on pathophysiology, medication, technique, procedure, emergency care, and critical care of the obstetric patient. I am sure you will learn or refresh the principles and approaches presented in these chapters and improve the obstetric anesthesia care in your practice.

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# Preface

- This text is aimed primarily at trainees in anesthesia, though more experienced practitioners may find it useful as a refresher in recent concepts and advances.
- It may also be of interest to obstetric nurses and midwives.
- A basic knowledge and experience of obstetric physiology, pharmacology, and anesthesia is assumed.
- It may be a useful "aide memoire" for postgraduate examinations in anesthesia.
- It is not a substitute for the major obstetric anesthetic texts but concentrates on areas of current and recent controversy.
- In addition, principles of management of some of the most challenging obstetric anesthesia cases are highlighted.
- The text aims to provide guidance to help manage these patients in the perioperative and perinatal periods in line with modern concepts of anesthesia and critical care, and the potential role of the anesthesiologist as perioperative physician.
- The choice of topics is selective but should appeal and be useful to the majority of practitioners of obstetric anesthesia. Important information not readily available in general anesthesia texts is also included.
- The format is designed to provide easy access to information presented in a concise manner. We have tried to eliminate superfluous material.
- Selected important or controversial references are presented as well as suggestions for further reading.
- The style of the chapters varies. This is deliberate. Some relate more to basic principles, physiology, pharmacology, etc. – bookwork. Others are more practical in nature, discussing the principles of anesthetic techniques for certain obstetric situations, or discussing the management of certain obstetric complications.
- Some chapters discuss topics which are more controversial than others. Often these are longer chapters as there is more to debate! Others are included as "controversial" where evidence from the literature has yet to be translated into changes in practice and patient care.
- The authors are all practitioners working with and caring for high-risk obstetric patients. Many are actively involved in research. The authors are committed to providing a high level of perioperative and perinatal care of patients undergoing obstetric anesthesia and analgesia.
- The editor has enlisted contributors active in both practice and training from institutions on both sides of the Atlantic. The aim has therefore been to produce a text of international relevance.
- By way of disclosure, many drugs discussed in this text and many trials reported and discussed involve use of drugs in "off label" situations. Use of drugs in such situations is at the discretion of individual physicians after full evaluation of the circumstances at the time. Similarly, dosages presented in this text represent dosages commonly found in the literature, but physicians should always seek guidance from appropriate pharmaceutical literature.

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Chapter 1

# Substance abuse in pregnancy

Dr A Schwartz and Dr N Imasogie

## Introduction

- The last three decades have seen a substantial rise in recreational drug use in the Western world.
- In a survey carried out in the US, 90 % of the women who abused drugs were of child-bearing age [1].
- Between 2007 and 2008 an estimated 5.1% of pregnant women used illicit drugs, a conservative estimate as most parturients deny drug use on direct questioning.
- The most commonly abused drugs include opioids, amphetamines, marijuana, ketamine and other hallucinogens, caffeine, solvents, tobacco, alcohol, and cocaine [1]. Abuse of multiple drugs concurrently is common.
- Maternal drug use can lead to significant morbidity and potential mortality in both mother and fetus.
- Maternal drug abuse also can have significant economic implications and also implications for being involved in criminal activities.
- Mothers who abuse drugs are 80% more likely to require the involvement of the anesthesiologist for analgesia and anesthesia in labor [2].

## The controversies

The controversies are not as to whether substance abuse occurs, but more around the following.

- The exact prevalences of abuse for different substances – which are often poorly identified and almost certainly underestimated. Surveys are often suspect as self-reporting is almost certainly low.
- The significance of this abuse for the mother and fetus – especially regarding newer agents of abuse.
- Detection, recognition, and maternal screening.

## Recognition

Recognition of substance abuse is important due to the potential consequences for fetal death, premature labor and "withdrawal" symptoms in both the mother and baby. A high

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index of suspicion among healthcare workers is important. The American College of Obstetricians recommends direct questioning of all parturients. Some authorities recommend screening in pregnancy for illicit drug use.

## General comments

In many instances substance abuse will be associated with poor general health, malnourishment, chronic and acute infections, and poor dentition. However, this is possibly a stereotype and substance abuse is also seen in parturients from stable, affluent backgrounds. Substance abuse does, however, often seem to be associated with lack of antenatal care during pregnancy.

There may be implications for healthcare providers – especially where the drugs are injected intravenously. Venous access may be notoriously difficult and there are high prevalences of transmittable viral diseases, such as hepatitis viruses and human immunodeficiency virus (HIV), in populations who self-inject drugs of abuse.

Detailed accounts of the effects of these drugs of abuse on mother and fetus can be found elsewhere, but brief summaries of the implications of the commoner substances of abuse, and the management of acute complications arising from them, will be presented in this chapter.

## Alcohol

- 5.8% of parturients in Canada in a survey from 2007 to 2008 admitted alcohol consumption [3].
- In another survey, from 2002 to 2007, 19% of parturients consumed alcohol in their first trimester, 7.8% in their second trimester, and 6.2% in their third trimester; 8% admitted to binge drinking in the first trimester, 1.8% in the second, and 1% in the third [4].
- Among pregnant teenagers, 20.3% admitted to alcohol consumption [5].

Chronic alcohol ingestion, acute intoxication, and withdrawal can all pose a challenge to the anesthesiologist.

### Maternal and fetal considerations

- Alcohol withdrawal symptoms can occur 6 to 48 hours after abstinence and include autonomic instability, tachycardia, hypertension, cardiac failure, and seizures.
- Autonomic instability can be life threatening and if treated with beta blockade, may reduce the fetus's ability to cope with the stress of labor. Small doses of diazepam or midazolam can be used and will not cause neonatal depression. Alpha-2 adrenergic agonists such as clonidine may also be useful [1].
- Alcohol crosses the placenta and the primary metabolite is directly toxic to the fetus and placenta. This leads to the teratogenic effects of fetal alcohol syndrome (FAS): craniofacial dysmorphology, growth retardation, microcephaly, mental retardation, and cardiac malformations.
- Alcohol ingestion during pregnancy is the leading cause of mental retardation in developed countries, the leading cause of preventable birth defects in the USA, and a major factor in neonatal mortality.

## Anesthetic considerations

- Acute intoxication is a relative contraindication for general anesthesia (GA) as the risk of maternal aspiration and fetal distress is increased. However, if GA cannot be avoided, aspiration prophylaxis and rapid sequence induction (RSI) should be done. Induction doses should be reduced [1].
- Parturients who chronically ingest alcohol may require increased anesthetic induction doses due to cross-tolerance and increased plasma volume. However, patients presenting with hepatic dysfunction, cardiac failure, and hypoalbuminemia may require smaller doses. Succinylcholine use is not affected by the reported reduction in pseudocholinesterase levels, and non-depolarizing muscle relaxants can have a variable effect due to altered potassium and magnesium levels.
- Regional anesthesia is safe in this group of parturients, provided liver dysfunction and coagulation disorders are ruled out.

# Cocaine

- The prevalence of cocaine use in Canada in women of 15 years and older in 2009 was reported to be 1.2% [6].
- In the USA, cocaine is the most commonly used recreational drug in pregnancy – 6.8% of pregnant teenagers surveyed used cocaine in 2007 [5].
- Cocaine is often co-abused with other drugs, most commonly alcohol.
- The cocaine-abusing parturient does not fit into any particular ethnic, socioeconomic, or cultural profile.
- Some characteristics associated with cocaine abuse are: multiparity, lack of prenatal care, use of other illicit drugs, ethanol abuse, cigarette use, and a positive syphilis serology [7]. The single most important predictor is absence of prenatal care.

## Maternal and fetal considerations

- Pregnancy increases the cardiovascular sensitivity to cocaine secondary to increased catecholamine release and α-adrenoceptor sensitivity. Cocaine increases oxygen demand of the myocardium by increasing heart rate, systemic vascular resistance, and left-ventricular contractility. This increase in demand and α-adrenoceptor-mediated coronary vasoconstriction predisposes the parturient to myocardial ischemia, infarction, and arrhythmia [8].
- Cocaine also causes hypertension, tachycardia, seizures, hyper-reflexia, fever, proteinuria, and edema, and may be misdiagnosed as eclampsia or pregnancy-induced hypertension [9]. Liver function tests, renal function tests, and urine latex tests can aid in the differentiation from acute cocaine ingestion.
- Maternal complications such as placental abruption, uterine rupture, preterm labor, hepatic rupture, cerebral infarction, and death have all been reported.
- Fetal effects may result from cocaine crossing the placenta, and from maternal vasoconstriction and subsequent diminished uteroplacental blood flow. Compromised oxygenation has been reported to lead to spontaneous abortions, a four-fold increase

in placental abruptions, preterm delivery, and fetal distress leading to ceasarean section [2].

- General effects on the fetus include intrauterine growth restriction (IUGR), low birth weight, depressed fat stores, and low birth length and head circumference.
- Cocaine may have teratogenic effects on almost every system in the body with genitourinary malformations among the most common.

## Anesthetic considerations

- Regional anesthesia – considered to be the ideal method of anesthesia and analgesia – may be contraindicated by cocaine-induced thrombocytopenia. Hypotension may be resistant to ephedrine, but phenylephrine is an alternative.
- Alterations in pain perception may occur, such that an adequately functioning epidural or subarachnoid block may not provide adequate analgesia. Intrathecal opioids have a shorter duration in these parturients [2, 7].
- General anesthesia can be given with some caveats. Halothane should be avoided as it sensitizes the myocardium to catecholamines. Ketamine should also be avoided because of its sympathomimetic actions. The effect of succinylcholine may be prolonged because cocaine metabolism has depleted pseudocholinesterase. Propofol and thiopentone are safe for induction.
- Prophylactic management of the hypertensive response to laryngoscopy is recommended. β-blockers are contraindicated as they would lead to unopposed α-receptor stimulation with subsequent coronary vasoconstriction. Labetalol, a combined α- and β-blocker is preferable. Hydralazine can be used but may cause a reflex tachycardia. Glyceryl trinitrate and sodium nitroprusside have been used successfully. The use of calcium channel blockers is controversial [7]. Combinations of intravenous magnesium sulfate and opioids such as remifentanil or alfentanil have been used [2].
- Cocaine-induced myocardial ischemia and chest pain should be treated with oxygen, glyceryl trinitrate, and benzodiazepines. Thrombolytic therapy should only be considered if angiographic evidence of vessel occlusion and if angioplasty are not available [8].
- There is a cocaine-binding vaccine under investigation in phase I and II trials. This vaccine may prevent cocaine entry into the central nervous system (CNS) through antibody-mediated binding and reduce cravings. It may also help pregnant patients who take cocaine by blocking the toxic effects [10].

# Amphetamines

Amphetamines are sympathomimetic drugs, which include methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA), also known as ecstasy.

- Between 1992 and 2007 methamphetamine abuse among parturients increased from 4.3 to 18.8% [5].
- Methamphetamine is the most commonly abused drug in this class [2].
- In Canada, in a survey in 2009, 0.9% of pregnant women admitted to using ecstacy, and 0.4% admitted to using amphetamine sulfate (also known as speed) [5].

## Maternal and fetal considerations

- Amphetamine intoxication leads to the release of catecholamines, which produce hypertension, tachycardia, cardiac dysrrythmias, seizure, stroke, hallucinations, and cortical alertness. Other effects include dilated pupils, shallow respirations, hyperthermia, hyperactive reflexes, dry mouth, appetite suppression, weight loss, and postpartum hemorrhage [11].
- Acute intoxication may be mistaken for pregnancy-induced hypertension or eclampsia [1]. Cardiac effects of amphetamines resemble those of cocaine (hemodynamic instability, arrhythmias, myocardial infarction, and aortic dissection) but with two important differences: amphetamines and their derivatives lack local anesthetic properties, and can inhibit monoamine oxidase activity leading to decreased catecholamine degredation [1].
- In the fetus, vasoconstriction decreases uteroplacental blood flow leading to IUGR, cerebral hemorrhage, placental abruption, and preterm birth. Fetal and infant death have been associated with amphetamine abuse.

## Anesthetic considerations

- Liver and renal function tests may distinguish amphetamine use from eclampsia [12].
- Regional anesthesia may be complicated by refractory hypotension, due to the downregulation of β-receptors and the sympathetic activity of amphetamines. Hypotension can often be successfully treated with phenylephrine.
- Recommendations for general anesthesia are similar to those for cocaine abuse. Intoxicated patients have increased requirements for induction agents and volatile anesthetics. Chronic use may decrease anesthetic requirements and the minimum alveolar concentration (MAC) for volatile agents. Temperature monitoring is advisable, as amphetamines can alter thermoregulation, causing heat stroke [2].

# Opioids

It is estimated that 1.6 to 2.7% of parturients abuse opioids in the USA. In 2007, 3.1% of pregnant American teenagers used heroin [5].

## Maternal and fetal considerations

- Opioid abuse in pregnancy can be complicated by cellulitis, abscesses, sepsis, HIV, and acquired immune deficiency syndrome (AIDS). Viral hepatitis, endocarditis, and malnutrition can also occur.
- These patients may present with overdose or withdrawal. Overdose may present with respiratory depression, gastric aspiration, and respiratory arrest progressing to death. Opioid withdrawal syndrome manifests with signs of increased sympathetic activity such as tachycardia, sweating, diarrhoea, restlessness, hypertension, and insomnia but is not life threatening [2].
- In the fetus, opioid abuse may cause spontaneous abortions, IUGR, low birth weight, preterm labor, placental abruption, chorioamnionitis, and fetal distress. Withdrawal in the fetus may cause meconium staining, perinatal asphyxia, and neonatal death [1].

- Neonates may also exhibit hypertension, respiratory distress, seizures, hyperthermia, mottling, increased tone, abnormal sleep, poor feeding, diarrhoea, and sudden infant death syndrome (SIDS).
- Methadone maintenance is associated with decreased withdrawal symptoms in the fetus and reduced opioid use in the mother.

## Anesthetic considerations

- Opioid withdrawal should be treated with supportive management. Clonidine, an $\alpha_2$-agonist, and doxepin, a tricyclic antidepressant can be used. Re-introduction of opioids may also be done in selected cases.
- Although opioid antagonism should be avoided during labor and delivery, to prevent withdrawal, it should be considered if the parturient is acutely intoxicated and unresponsive. Mixed agonist/antagonists such as nalbuphine, which is commonly used for labor analgesia in some institutions or in the treatment of neuraxial opioid-induced pruritus, should be avoided due to the risk of inducing withdrawal.
- Regional anesthesia is safe, provided cellulitis, coagulopathy, sepsis, endocarditis, and septic arthritis are ruled out [1]. There are reports in the literature of an increased incidence of spinal, epidural, and disk-space infection in intravenous drug abusers but this is independent of the type of anesthesia used.
- Regional anesthesia is preferred, whenever possible, as adequate systemic opioid doses are difficult to predict. Opioid-addicted patients may experience failed neuraxial analgesia similar to the non-addicted parturient, and inadequate pain relief should be investigated and not immediately blamed on their addiction An increased tendency for hypotension should be anticipated [1].
- Methadone is the recommended maintenance therapy for opioid-addicted parturients [1]. When patients are on methadone, it should be continued throughout labor and delivery, and additional (but alternative) mu-agonists should be used for acute pain control. Postoperative pain may be exaggerated and difficult to control; regional, and local anesthetics within a multimodal regimen should be the goal. Withholding analgesia for fear of cravings or relapse in previously addicted patients is not acceptable as studies have shown that anxiety and pain can precipitate a relapse.
- General anesthetic induction requirements are increased with chronic opioid use but decreased with acute ingestion. Other CNS depressants are affected similarly. Intravenous access may prove a challenge in these patients and central venous access may be necessary [2].
- Naltrexone implants have been used in opioid-addicted parturients with no associated withdrawal in the newborn. This method, however, makes adequate postoperative analgesia difficult [13].
- Babies born to opioid-addicted parturients require special neonatal care. Neonatal abstinence syndrome is usually delayed until the second or third day of life, occurring in 70 to 80% of babies born to women on heroin or methadone. It also occurs in babies born to women on buprenorphine, but less frequently [2].

# Tobacco

Tobacco is one of the most commonly used drugs in pregnancy.

- In a 2000 to 2001 Canadian survey, 17% of parturients smoked and another 17% of non-smokers were regularly exposed to smoke during their pregnancy [14].
- In the USA between 2002 and 2007, 21.8% parturients smoked during the first trimester, 14.4% during the second trimester, and 13.9% during their third trimester [4]. Another estimate puts the percentage of parturients who smoked between 2006 and 2007 at 59% [15].
- Of smokers who learn of their pregnancy, 20 to 40% are able to quit smoking, but 60 to 80% return to smoking within six months post partum.
- Cessation should be encouraged. Nicotine replacement therapy has not been sufficiently evaluated in pregnancy but is recommended when non-pharmacologic mechanisms have failed.
- Cigarette smoke contains up to 4,000 compounds including nicotine, carbon monoxide, and cyanide. Nicotine and carbon monoxide are most researched, and little is known about the toxic effects of the other chemicals on the developing fetus.

## Maternal and fetal considerations

- Nicotine releases catecholamines by stimulating peripheral and central nicotinic receptors, leading to increased sympathetic tone, raised heart rate, systolic and diastolic pressure, increased myocardial work, and peripheral vasoconstriction. Alpha-adrenergic stimulation can cause coronary vasoconstriction, coronary heart disease, as well as peripheral vascular disease.
- Respiratory complications include diffusion capacity abnormalities, decreased pulmonary immune function, increased bronchitis, chronic obstructive pulmonary disease, airway irritability and increased risk of lung cancer. A combination of increased mucous production, and reduced ciliary transport, lead to small airway closure and diminished gas exchange.
- At carbon monoxide levels of 3 to 15%, maternal and fetal oxygen carrying capacity is reduced. Carbon monoxide affinity for hemoglobin is much greater than that of oxygen, leading to reduced oxygen delivery in both mother and baby.
- The consequences of maternal smoking for the fetus include ectopic pregnancy, spontaneous abortion, IUGR, low birth weight, placenta previa, placental abruption, fetal hypoxia, prematurity, and impaired neonatal respiratory function [11].
- The chemical composition of cigarettes affects fetal growth more closely than the actual number of cigarettes smoked, and second-hand smoking can have the same effect.
- Maternal smoking cessation would reduce morbidity markers such as low Apgar scores, resuscitation, and neonatal intensive care unit stays by 10 to 15% [16].

## Anesthetic considerations

- Respiratory morbidity is increased by mucous hypersecretion, impaired tracheobronchial clearance, and acute bronchospasm, therefore avoiding airway manipulation is preferable.

- Neuraxial anesthesia is the recommended modality to avoid airway manipulation and respiratory complications that may follow general anesthesia [17].
- General anesthesia has increased perioperative respiratory complications and can also be complicated by increased gastric volume and aspiration risk, and hepatic microsomal enzyme alteration of function, which may alter the metabolism of induction agents. Tobacco use is not thought to affect the MAC.

# Benzodiazepines

There is little information on the prevalence of benzodiazepine (BDZ) use in parturients, but it is thought to be uncommon.

## Maternal and fetal considerations

- Benzodiazepine abuse is associated with sedation, lethargy, respiratory depression, impaired psychomotor skills, impaired judgement, ataxia, hypotonia, decreased reflexes, slurred speech, nystagmus, cardiovascular instability, and death [11]. Maternal withdrawal may present with tremulousness, insomnia, seizures, anxiety, agitation, muscle cramps, hypertension, anorexia, and fever [11].
- Benzodiazepines cross the placenta readily. The risks to the baby include increased risk of prematurity, low Apgar scores, neonatal intensive care unit (ICU) admissions, and respiratory distress syndrome [18].
- Neonates may experience withdrawal (irritability, hypertonicity, and vomiting), floppy baby syndrome, sucking difficulties, and altered thermogenesis.

## Anesthetic considerations

- Anesthesia requirements for induction and maintenance may be increased [2].
- The MAC in diazepam use is decreased.

# Barbiturates

Little is known about barbiturate abuse in pregnancy. Fetal exposure to barbiturates is more commonly as a result of maternal treatment of epilepsy than abuse.

## Maternal and fetal considerations

- Barbiturates depress the CNS. Overdose in the mother may cause slurred speech, ataxia, irritability, loss of pharyngeal and deep tendon reflexes, respiratory depression, and coma. Cardiac complications include vasomotor depression resulting in hypotension, and myocardial depression. Acute renal failure may also occur as a result of rhabdomyolysis [2, 11].
- Withdrawal may cause seizures, cardiovascular collapse, hypertension, agitation, tremulousness, sleep disturbances, and hyperthermia [2, 11].
- Barbiturates freely cross the placenta. Effects may include reduced head circumference, neural tube defects, congenital heart disease, urinary tract defects, and cleft lip [19]. Many papers focus on barbiturate use for treatment of epilepsy rather than abuse, and the teratogenic effect seen may be related to underlying epilepsy. In non-epileptic mothers,

there does not seem to be a significant risk of structural defects, but neurodevelopmental problems, fetal intelligence, hemorrhage (due to vitamin K depletion), and withdrawal in the infant are concerns.

- Withdrawal in the neonate is noted by irritability, constant crying, sleeplessness, tremors, hiccups, and mouth motions [20].

### Anesthetic considerations

Hypotension should be treated with fluids. Withdrawal symptoms can be treated with phenobarbital titrated to effect. Increased doses of induction agents may be required.

## Marijuana

After tobacco and alcohol, marijuana is arguably the most commonly abused drug in pregnancy [1].

Estimates of prevalence of marijuana use in pregnancy range from 2.9 to 27%. Among pregnant teenagers in the USA in 2007, 45.9% used marijuana [5].

### Maternal and fetal considerations

- Marijuana has been used for recreational and medicinal purposes for thousands of years being a naturally occurring substance. It is obtained from the plant *Cannabis sativa*. It is smoked for its hallucinogenic effects and although 61 cannabinoids have been identified from the plant, the most potent psychoactive chemical is Δ9-tetrahydrocannabinol (THC).
- It is thought that about 50% of the smoked drug enters the blood stream. Cannabinoids are metabolized by the liver, resulting in about 20 psychoactive metabolites [1].
- Marijuana use increases sympathetic nervous system activity and decreases parasympathetic activity. Effects include increased heart rate, orthostatic hypotension, irritability, anxiety, paranoia, insomnia, diaphoresis, nausea and vomiting, appetite stimulation, diarrhea, euphoria, and conjunctival vasodilation and reddening.
- At high doses parasympathetic tone is increased and the patient may become bradycardic and hypotensive.
- Acute intoxication can affect cognitive and motor performance and effect ST and T changes on electrocardiogram (EKG) tracing, although life-threatening arrhythmias are rare in patients without pre-existing cardiac disease.
- Chronic use can decrease attention and memory, and decrease the ability to process complex information.
- Overdoses are not usually fatal, and withdrawal is characterized by sleep latency, negative mood, and behavioral symptoms.
- Smoking marijuana also releases carbon monoxide and other toxins, which reduce the oxygen-carrying capacity of hemoglobin and have similar effects as tobacco. Smoking marijuana may increase rare forms of oropharyngeal cancer, lead to bronchitis, squamous metaplasia, emphysema, and a decrease in hormonal and cell-mediated immune response.
- Marijuana readily crosses the placenta and accumulates in fatty tissue with a slow elimination, leading to fetal exposure for as long as 30 days [1]. Marijuana is not known to

cause congenital anomalies, but may cause IUGR, decreased birth weight, prematurity, and alterations in the pituitary–adrenal axis and hormone production.

### Anesthetic considerations

- Respiratory complications are increased, and oropharyngeal and uvular edema have been reported.
- Marijuana may potentiate anesthetic agents affecting heart rate and blood pressure. Adverse interactions with propranolol and physostigmine have been reported. Drugs that increase the heart rate, such as ketamine, pancuronium, atropine, and adrenaline (epinephrine), should be avoided.
- The sedative effects of alcohol, barbiturates, opioids, benzodiazepines, and phenothiazines may be potentiated by marijuana.
- Marijuana inhibits cholinesterase activity and may prolong the effect of succinylcholine.
- Pain scores may show a biphasic effect – low doses not affecting pain, moderate doses reducing pain scores, while high doses increase pain scores [1].

For all these reasons, regional anesthesia is the preferred method of management.

## Caffeine

Caffeine is present in coffee, tea, cola, and chocolate, so the vast majority of parturients consume caffeine daily.

### Maternal and fetal considerations

- Caffeine acting on the dopaminergic system can cause diuresis and a mild increase in blood pressure, or tachycardia.
- Cessation after chronic use can cause headache, fatigue, anxiety, and bladder dysfunction.
- Moderate doses (<400 mg/day) do not appear to affect the cardiovascular system adversely in most healthy people.
- Caffeine crosses the placenta and has a long half life. The fetus is unable to metabolize caffeine. However, there is no evidence that it is teratogenic.

### Anesthetic considerations

- Withdrawal from caffeine can cause a headache, which can be mistaken for a postdural puncture headache (PDPH). The use of caffeine for preventing or treating PDPH is covered in another chapter.
- Caffeine may enhance β-adrenergic agonists, such as epinephrine and salbutamol, and increases the risk of hypertensive crises in patients taking monoamine oxidase inhibitors.

## Ketamine and other hallucinogens

Hallucinogens include ketamine, lysergic acid diethylamide (LSD), phencyclidine (PCP), psilocybin (magic mushrooms), and mescaline. The prevalence of hallucinogen use in pregnancy is unknown.

- Hallucinogens can cause auditory, visual, and tactile hallucinations, anxiety and panic attacks.
- Activation of the sympathetic system by these drugs can cause tachycardia, hypertension, hyperthermia, and dilated pupils.

### Maternal and fetal considerations

- An overdose of hallucinogens can lead to respiratory depression, seizures, and coma – but death rarely occurs [2, 21].
- PCP crosses the placenta, and may cause seizures, irritability, poor feeding, lethargy, and tachycardia in the newborn. Hyperthermia may increase maternal and fetal oxygen consumption and heat-induced neurologic injury may occur.
- Ketamine readily crosses the placenta but is not known to have any adverse effects on the fetus. When used for induction of general anesthesia, ketamine may lead to lower Apgar scores and an increased requirement for resuscitation of the fetus.

### Anesthetic considerations

- Patients on hallucinogens require avoidance of stress, which may induce panic attacks. Benzodiazepines have been used successfully to limit anxiety and panic attacks but major tranquilizers are relatively contraindicated, as they may aggravate the toxic effects of these drugs.
- Regional anesthesia is preferred if the patient is cooperative. General anesthetic effects may be prolonged by hallucinogens enhancing the respiratory effects of opioids [2].
- PCP and LSD can inhibit plasma cholinesterase and theoretically prolong the effect of succinylcholine, but there is little clinical evidence of this.
- Ketamine use may decrease the MAC.

## Solvents

Solvents of abuse include toluene, ethylene glycol, and volatile agents such as gasoline, propane, and butane from lighter fluid.

- It is estimated that in 2006, 783,000 people in the USA abused solvents for the first time [21].
- Usage has been increasing in the UK and the majority of abusers are young adults.
- Prevalence in parturients is difficult to estimate.

### Maternal and fetal considerations

- Solvents have variable mechanisms of action, are absorbed through the lungs, and metabolized in the liver.
- Cardiac effects of solvent use include potentially fatal arrhythmias, hypertension, tachycardia, myocardial infarction, and congestive cardiac failure [2, 21].
- Patients may experience acute respiratory distress, increased airway resistance, bronchospasm, pulmonary hypertension, and hypoxemia as a result of carboxyhemoglobin and methhemoglobinemia. Choking and aspiration may also occur. Deaths from suffocation, aspiration, or sudden arrhythmias have been reported.

- No specific withdrawal symptoms have been noted.
- Liver toxicity and renal failure have also been reported [22].
- Solvent abuse may lead to IUGR, preterm delivery, and perinatal mortality.Withdrawal is noted in the neonate by a high-pitched cry, sleep disorders, CNS irritability, and poor feeding. Phenobarbitol may be of use in neonatal withdrawal syndrome.

## Anesthetic considerations

- A patent airway is a priority, as well as breathing and circulation.
- Electrolyte abnormalities must be corrected if present.
- Neuraxial anesthesia is acceptable if the patient is cooperative. Because chronic solvent abuse can cause significant CNS and peripheral neurological deficits, a full neurological examination to document any deficits should be carried out. Epinephrine-containing solutions should be avoided as they may precipitate arrhythmias.
- General anesthesia is an option if the patient is not cooperative; RSI is advised. Hypotension should be treated with fluid replacement, and phenylephrine, ephedrine, and atropine should be available.
- Sustained tachyarrhythmias may be treated with β-blockade, to decrease the effect of myocardial sensitization by catecholamines.
- End-tidal volatile agent measurement may be unreliable with solvent abuse. A case report showed a falsely higher end tidal agent in a parturient [23]. The MAC itself is not thought to be altered by solvents.
- The goal of the anesthetic is to minimize the stress response to surgery and avoid catecholamine release.

# Gamma-hydroxybutyrate

Gamma-hydroxybutyrate (GHB) is also known as liquid ecstasy. It is a naturally occurring short-chain fatty acid found in mammalian brain tissue. It has a short half life and the absence of toxic metabolites reduces its detectability.

Little is known about the use of GHB in pregnancy.

## Maternal and fetal considerations

- GHB is a CNS depressant, but has mixed sedative–stimulant effects. GHB intoxication may induce myoclonic seizures, confusion, aggression, enhanced tactile sensation, urinary incontinence, increased gag reflex, nausea and vomiting, and impaired memory.
- 20 to 30 mg/kg induces sleep and drowsiness, and 50 to 60mg/kg induces anesthesia and is associated with hypotonia, nystagmus, bradycardia, hypotension, mild hypothermia, bradypnea, Cheyne–Stokes respiration, severe cardiorespiratory depression, seizures, and coma [24].
- Withdrawal is characterized by tremor, sweating, tachycardia, agitation, insomnia, hypertension, nausea and vomiting, and auditory and visual hallucinations.
- There are no reports of GHB use in pregnancy in the literature.

## Anesthetic considerations

Acute use of GHB may cause respiratory depression requiring respiratory support. There are no known antidotes and management is supportive.

# Summary

Table 1.1 summarizes the important implications of agents of abuse discussed in this chapter.

**Table 1.1** Summary of implications of agents of abuse.

| Substance | Overdose potential | Withdrawal | Teratogen | Induction dose for general anesthesia | Minimum alveolar concentration (MAC) |
|---|---|---|---|---|---|
| Alcohol | Yes | Yes, delirium tremens can be fatal | Yes, fetal alcohol syndrome | Decrease | – Increased in chronic use<br>– Decreased in acute use |
| Amphetamines | Yes, may be fatal | Yes | Likely | – Increase in acute use<br>– Decrease in chronic use | – Increased in acute use<br>– Decreased in chronic use |
| Barbiturates | Yes | Yes | Possibly | Increase | Decreased |
| Benzodiazepines | Yes | Yes | Possibly | Increase | Decreased (diazepam) |
| Caffeine | No | Yes, non-fatal | Unlikely | No change | No change |
| Cocaine | Yes | Yes, usually non-fatal | Yes, genitourinary most common | Possibly no change or same as amphetamines | – Increased in acute use<br>– Decreased in chronic use |
| GHB | Yes | Yes | No | Decrease | Possibly decreased |
| Ketamine and hallucinogens | Yes, low-mortality | No | No | No change | Decreased |
| Marijuana | Unlikely to be fatal | Non-fatal | No | Decrease | Decreased |
| Opioids | Fatal | Non-fatal | No | – Increase in chronic use<br>– Decrease in acute use | Decreased |
| Tobacco | No | Non-fatal | No | No change | No change |
| Solvents | Yes, may be fatal | No | Possible fetal solvent syndrome | Possible decrease | – Possibly increased with chronic use<br>– Possibly decreased with acute use<br>– Accurate measures of end-tidal agent difficult. |

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Chapter 2

# Cardiac disease in pregnancy

Dr S Singh, Dr A Dhir and Dr R Lavi

## Introduction

Maternal cardiac disease complicates up to 4% of pregnancies and is a major cause of maternal death.

- Rheumatic heart disease, specifically mitral stenosis, used to be the most common cardiac disorder in pregnancy.
- Pregnancy is becoming more common in women with congenital heart disease.
- Ischemic heart disease is also increasing due to the increasing proportion of mothers with advanced age.

The anesthetic management of affected obstetric patients can be challenging and requires a thorough understanding of the cardiac pathophysiology and the physiological effects of pregnancy.

## Cardiovascular changes of pregnancy

The normal physiological changes of pregnancy result in a hyperdynamic cardiovascular system:

- There is a 50% increase in intravascular volume that peaks by the middle of the third trimester.
- There is a decrease in systemic vascular resistance throughout pregnancy so that systolic pressure decreases but mean arterial pressure is maintained at normal values because of a 30% increase in cardiac output.
- Significant increases in cardiac output, up to 50%, are observed during labor due to pain-related catecholamine releases. Each uterine contraction increases central blood volume, resulting in an increase in cardiac output of up to 25%. Post partum there is further increase in central blood volume by relief of the vena caval obstruction.
- There is increased hypercoagulability and the need for anticoagulation should be considered.

These changes may significantly compromise the parturient with cardiac disease and affect anesthetic management for labor and delivery.

*Controversies in Obstetric Anesthesia and Analgesia*, ed. Ian McConachie. Published by Cambridge University Press. 

## General considerations during pregnancy

Obstetric patients with cardiac disease require an early anesthesia consultation to allow appropriate anesthetic management to be determined.

- The functional capacity of the parturient and the severity of the disease should be established and the effects of the physiologic changes of pregnancy, labor, and delivery anticipated.
- Treatment plans to optimize cardiac status must be considered.
- Cardiac medications, serial echocardiograms, and electrocardiograms should be reviewed.
- The risk for peripartum hemorrhage and the effect of uterotonic drugs should be considered.
- Antibiotics for bacterial endocarditis should be considered.

## Considerations for vaginal delivery

Delivery should be planned in advance with the input of a multidisciplinary team in a tertiary center.

- Vaginal delivery with a shortened second stage is usually preferred although there are some important exceptions (aortic dilation, Marfan syndrome with aortic root involvement, severe aortic stenosis, recent myocardial infarction, and acute congestive heart failure).
- A short and pain-free labor and delivery minimizes hemodynamic instability. During the first stage of labor, analgesia is important to decrease pain-related increases in catecholamine levels, which increase heart rate, blood pressure, and cardiac output and may be poorly tolerated by the obstetric patient with cardiac disease.
- Carefully titrated epidural analgesia with limited dermatomal block from T10 to L2 using low-dose local anesthetic and opioids is usually optimal. Local anesthetic infusions containing epinephrine are best avoided.
- It is important to minimize the hemodynamic effects of sympathetic blockade and invasive hemodynamic monitoring is often helpful.
- Hypotension is usually better treated with phenylephrine rather than ephedrine.
- For the second stage of labor, anesthesia of the perineum is also required. A pre-existing epidural block may be carefully extended or if not already in place then a low spinal block or pudendal nerve block may be used.
- It is preferable to minimize pushing to avoid the deleterious decreases in preload associated with Vasalva's maneuvre. The delivery may be assisted with the use of forceps or a vacuum extractor. The lithotomy. position may need to be avoided to prevent an acute increase in central blood volume.

## General considerations for cesarean delivery

Cesarean delivery may be indicated in some patients with cardiac disease.

- It is crucial to avoid abrupt changes in cardiovascular parameters. Regional anesthesia may produce extensive sympathetic blockade.

- A single-shot spinal anesthetic is generally poorly tolerated by parturients with cardiac disease.
- Carefully titrated epidural anesthesia using small incremental doses of slow-onset local anesthesia guided by invasive monitoring has been well described in the literature in parturients with a variety of cardiac diseases.
- There have also been many reports of successful management of affected obstetric patients using carefully administered general anesthesia (GA). Opioid-based techniques are frequently described as they minimize increases in systemic and pulmonary pressures during laryngoscopy and avoid the myocardial depressant effects of volatile agents.
- The anesthetic technique must be tailored to the individual patient.

## General considerations for postpartum management

- Post partum, the effects of uterotonic agents must be considered. The use of oxytocin in cardiac patients is discussed elsewhere.
- In the postdelivery period, patients with severe cardiac disease should be observed in the high dependency unit/intensive care unit for careful monitoring of fluid therapy and hemodynamics.
- During the first 24 to 72 hours, significant fluid shifts occur, which may cause arrhythmias and congestive heart failure.
- Adequate analgesia minimizes pain-induced catecholamine surges resulting in hypertension and tachycardia.
- Early ambulation decreases the risk of deep vein thrombosis and embolization.

## Pregnancy and congenital heart disease

- Congenital heart disease (CHD) affects about 7 or 8 newborns per 1,000 live births, and with improved management 85% of patients survive into adulthood [1].
- Women with CHD are now presenting to maternity services with increasing frequency. Congenital heart disease leads the cardiac causes of maternal morbidity and mortality.
- Physiological changes associated with pregnancy and labor place these patients at increased risk of pulmonary edema and heart failure, aortic dissection, paradoxical embolism, arrhythmia, and worsening of cyanosis.
- A detailed knowledge of different lesions and hemodynamic implications is necessary.
- Types of lesions likely to cause problems are the lesions with pulmonary hypertension or Eisenmenger syndrome, severe left ventricular outflow tract obstruction, and cyanotic heart disease.
- Fetal prognosis is generally poor if the maternal arterial saturation is below 80%, hematocrit is above 60%, or there is recurrent syncope [2].
- The offspring of a parent suffering from CHD also has an increased risk of having CHD (2 to 16%) – a higher risk when the mother, rather than the father, is affected [3].

## Fetal cardiac development

Cardiac formation is almost complete by 55 to 60 days after conception. The most active period is between 25 and 40 days. At first, the heart is just a tube. As it grows, it needs more space, so it bends and twists back. Critical events are as follows.

1. Formation of the heart tube: from the heart-forming regions of the mesoderm.
2. Primitive heart-tube dilatations. Five dilatations appear along the length of the tube:
   - sinus venosus
   - primitive atrium
   - primitive ventricle
   - bulbus cordis
   - truncus arteriosus.

   The following structures arise from these dilatations:
   - the smooth part of the right atrium and coronary sinus (sinus venosus)
   - trabeculated parts of both the right and the left atria (primitive atrium)
   - trabeculated parts of both ventricles (primitive ventricle)
   - smooth parts of both ventricles (bulbus cordis)
   - the aorta and pulmonary trunk (truncus arteriosus)
   - the atrioventricular (AV) canal develops between the primitive atrium and primitive ventricle while the conoventricular (CV) canal develops between the primitive ventricle and the bulbus cordis.
3. Dextral looping. Venous blood flows first to the left ventricle before entering the right ventricle (RV). This is corrected by the key event of dextral looping where the AV canal and the CV canal are properly aligned and nestled.
4. Aortico-pulmonary (AP) septum. In this phase, there is formation of truncal and bulbus ridges, which grow and twist around each other in a spiral fashion. The ridges eventually fuse to form the AP septum, dividing the truncus arteriosus and bulbus cordis into the aorta and pulmonary trunk. Abnormalities in the formation of the AP septum lead to congenital heart defects such as:
   - persistent truncus arteriosus (failure to form)
   - transposition of great arteries (failure to rotate)
   - Fallot's tetralogy (failure to align).
5. Atrial septation. The sequence of events is as follows.
   - The septum primum forms in the roof of the primitive atrium and grows toward the AV cushions in the AV canal.
   - The space between the free edge of the septum primum and the AV cushions is called the foramen primum.
   - The septum primum fuses with the AV cushions thereby closing the foramen primum.

- The foramen secundum forms in the center of the septum primum to allow blood flow from the right atrium (RA) to the left atrium (LA) during embryonic life.
- The septum secundum forms to the right of the septum primum.
- The space between the upper and lower limbs of the septum secundum is the foramen ovale.
- The foramen secundum enlarges as the upper portion of the septum primum degenerates.
- Later, the upper limb of the septum secundum fuses with the remaining portion of the septum primum.
- The foramen ovale may be closed completely or remain open.

6. Atrioventricular septum. The dorsal and ventral AV cushions approach each other and fuse to form the AV septum, which partitions the AV canal into right and left. Abnormalities in the development of the AV septum cause:
   - primum atrial septal defect (ASD)
   - persistent AV septal defect
   - Ebstein's anomaly
   - tricuspid atresia.
7. Interventricular septum. The muscular interventricular septum develops in the midline on the floor of the primitive ventricle and grows towards the fused AV cushions. The interventricular foramen is located between the free edge of the muscular interventricular septum and the fused AV cushions. The foramen is closed by the membranous interventricular septum (formed by the AP septum) meeting and fusing with the muscular interventricular septum.

## Types of lesions and hemodynamic consequences

Congenital heart lesions may be classified as intracardiac shunts (left-to-right or right-to-left) or obstructive lesions.

- In lesions with shunts, the volume of shunted blood depends upon the size of the orifice, pressure gradient across the orifice, and the ratio of the systemic vascular resistance (SVR) to the pulmonary vascular resistance (PVR).
- The increased plasma volume, cardiac output, and heart rate associated with pregnancy, labor, and delivery may increase left-to-right shunt flow and increase pulmonary pressures.
- A pre-existing left-to-right shunt can be reversed because of increases in PVR or decreases in SVR. The decrease in SVR that occurs in pregnancy can worsen a right-to-left shunt and worsen hypoxemia.
- There is always a risk of paradoxical air embolism with cardiac shunts and, as pregnancy is a hypercoaguable state, anticoagulation is often required and must be considered when deciding on anesthetic technique for delivery. Vascular lines must be carefully de-aired to avoid air embolism, and loss of resistance to saline may be preferred to air when placing epidural catheters.

# Left-to-right shunts (acyanotic heart disease)

Blood returning from the lungs is recirculated back to the lungs without going to the body.

- Heart failure may develop depending upon the volume load and duration of the disease.
- Usually small left-to-right shunts are well tolerated in pregnancy and delivery.
- However, pregnancy-related increases in plasma volume and cardiac output increase flow through the left-to-right shunt and pulmonary blood flow, which may lead to development of pulmonary hypertension, and right ventricle (RV) hypertrophy.
- Once right-sided pressures are more than those on the left side, the shunt reverses (becoming right-to-left).
- Later, the increased PVR becomes irreversible leading to permanent hypoxia (Eisenmenger syndrome).
- The major problems occurring in parturients with CHD occur in the presence of pulmonary hypertension.

Anesthetic considerations for the parturient with left-to-right shunt include avoiding changes that increase flow through the shunt, such as avoidance of increases in SVR and heart rate.

- For labor and vaginal delivery, epidural analgesia blunts the increase in SVR and heart rate associated with painful contractions.
- For cesarean delivery, epidural or spinal anesthesia can be used. If general anesthesia is necessary then the traditional RSI must be modified so that increases in SVR associated with intubation are avoided. It is also important to avoid increases in SVR during emergence and extubation.

## Lesions

**Atrial septal defects (ASD)**. Right ventricular volume overload. Ostium secundum (labeled A in Figure 2.1) is the commonest; ostium primum defect (labeled B in Figure 2.1) is often

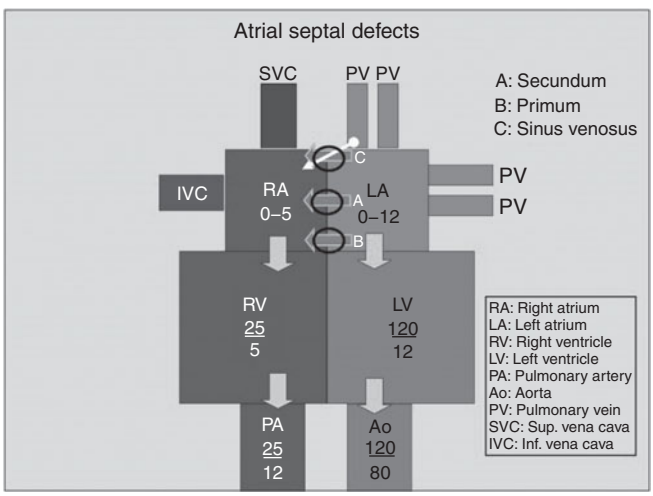


**Figure 2.1** Atrial septal defects. (See plate section for color version.)

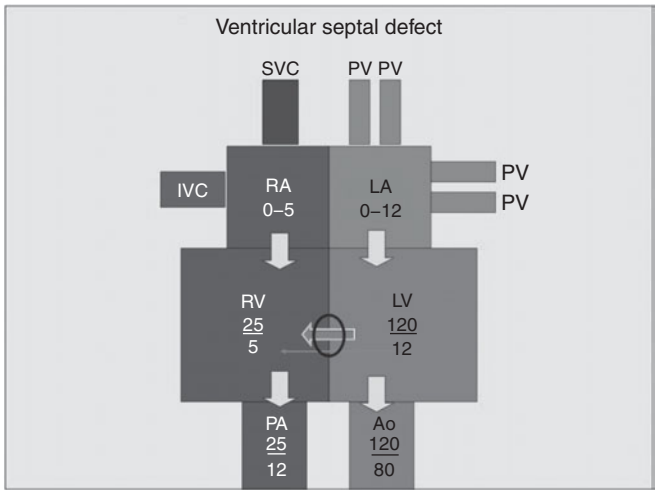


**Figure 2.2** Ventricular septal defect. (See plate section for color version.)

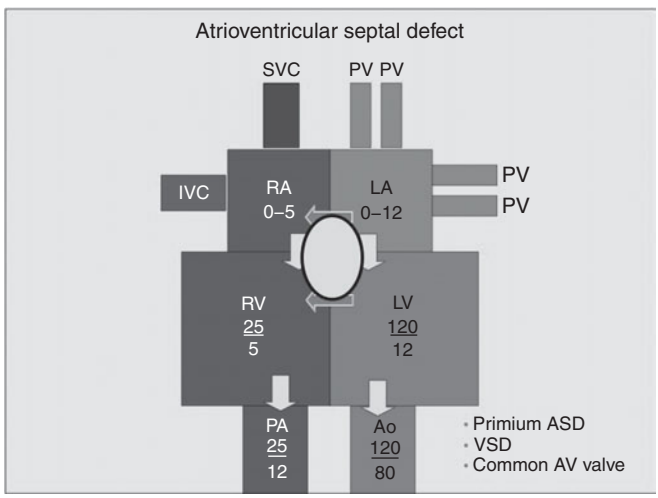


**Figure 2.3** Atrioventricular septal defect. (See plate section for color version.)

associated with cleft mitral valve. Sinus venosus defect (labeled C in Figure 2.1 is invariably associated with partial abnormal pulmonary venous drainage of the right upper pulmonary vein.

**Ventricular septal defect (VSD)** (Figure 2.2). The most common of all CHD lesions with two thirds closing spontaneously. Causes biventricular volume overload. Membranous VSD is the commonest.

**Atrioventricular septal defect (AVSD)** (Figure 2.3). Complete AVSD consists of primum ASD, inlet VSD, and a common AV valve, which straddles both ventricles. Left-to-right shunt is large and pulmonary hypertension develops early.

**Patent ductus arteriosus (PDA).** Causes increased left ventricle (LV) volume overload (Figure 2.4). Pregnancy is well tolerated in women with silent and small PDA or in patients with functional class 1 or 2 prior to pregnancy.

**Pulmonary hypertension (PHT) and Eisenmenger syndrome (ES)** (Figure 2.5). Pulmonary hypertension in pregnancy irrespective of the etiology is associated with high

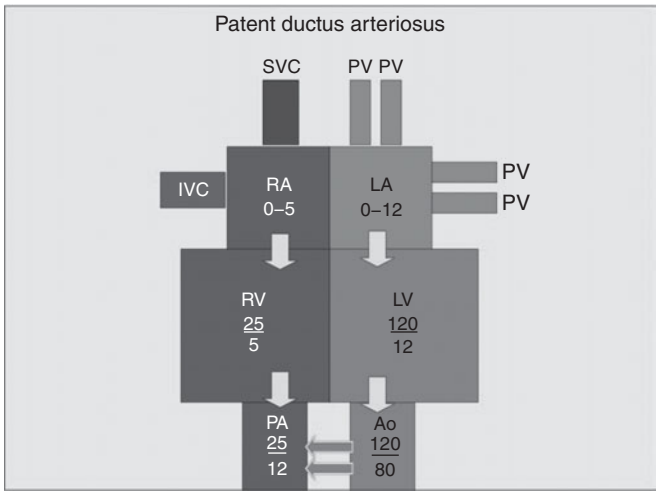


**Figure 2.4** Patent ductus arteriosus. (See plate section for color version.)

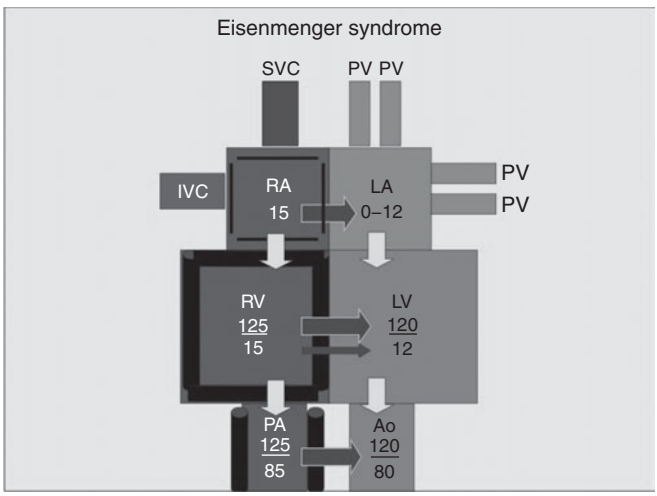


**Figure 2.5** Eisenmenger syndrome. (See plate section for color version.)

mortality (especially when the pulmonary artery (PA) pressure exceeds 70% of systemic pressure). Maternal mortality was 17%, 28%, and 33% in PHT due to idiopathic, CHD, or other causes, respectively [4].

- A pregnancy-induced drop in SVR increases right-to-left shunting and hypoxia, thereby further increasing pulmonary vasoconstriction.
- The increase in blood volume during pregnancy precipitates right heart failure.
- Hospitalization and bed rest are advisable from mid-gestation.
- Supplemental oxygen helps to reduce pulmonary vascular resistance and shunt flow.
- Delivery must be planned in advance with a multidisciplinary team and carried out usually before term gestation in a tertiary care center with close hemodynamic monitoring and the ability to provide pulmonary vasodilators.

- These women must be followed closely after delivery. A recent review of pregnancies in women with ES showed that all deaths in this group occurred after delivery, with a median time to death of six days postpartum [4].

Anesthetic goals for delivery include avoidance of any decrease in SVR or increase in PVR, both of which would increase shunt flow and worsen hypoxemia. Anesthetic management of cesarean delivery has been reported in the literature:

- Low-dose combined spinal–epidural (CSE) (hyperbaric bupivacaine 5 mg, sufentanil 2.5 μg, and preservative-free morphine 100 μg), continuous spinal anesthesia (slowly titrated hyperbaric bupivacaine 12 mg through a spinal catheter), and carefully titrated epidural anesthesia, have been successfully used [5, 6, 7].
- Recently, general anesthesia with ketamine, etomidate, and remifentanil has been described for the anesthetic management of a patient with ES having cesarean section (CS) [8]. The patient remained hemodynamically stable and had a good outcome.

## Right-to-left shunts: cyanotic heart disease

Blood returning from the body is recirculated back to the body without going to the lungs to be oxygenated. Pregnancy in patients without prior surgical correction constitutes a considerable risk to both the mother and baby. The fall in SVR during pregnancy and hypotension during labor may increase the right-to-left shunt and aggravate pre-existing cyanosis. Fetal outcome depends upon maternal saturation and there is a high incidence of premature and low birth weight infants.

The primary anesthetic goal during labor and delivery is avoidance of any decrease in SVR.

- For labor, carefully titrated CSE or epidural analgesia using low-dose local anesthetic with opioid and invasive arterial blood pressure monitoring should maintain hemodynamic stability. Vasopressors should be readily available to treat any hypotension.
- For cesarean delivery, general anesthesia may be preferable to avoid extensive sympathetic blockade associated with regional anesthesia. However, there are some reports of the successful use of carefully titrated epidural and spinal anesthesia with the aid of close hemodynamic monitoring.

### Lesions

Right-to-left shunt with reduced pulmonary blood flow:

- tetralogy of Fallot (TOF) (Figure 2.6)
- tricuspid atresia (Figure 2.7)
- pulmonary atresia.

Right-to-left shunt with variable pulmonary blood flow:

- transposition of the great arteries (TGA) (Figures 2.8 and 2.9)
- total anomalous pulmonary venous connection (TAPVC) (Figure 2.10)
- truncus arteriosus (Figure 2.11)

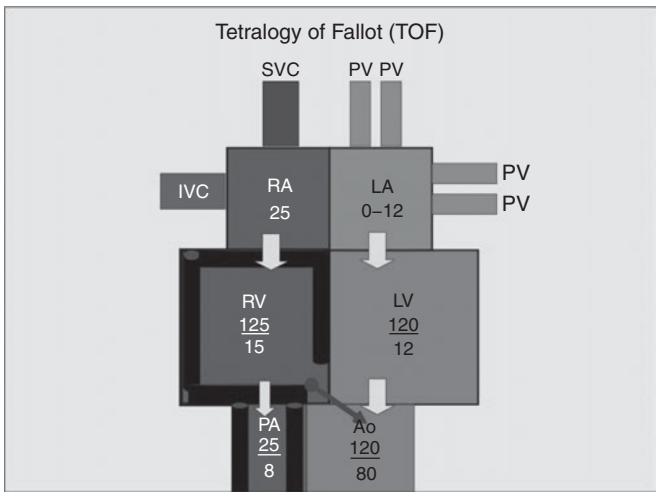


**Figure 2.6** Tetralogy of Fallot (TOF). (See plate section for color version.)

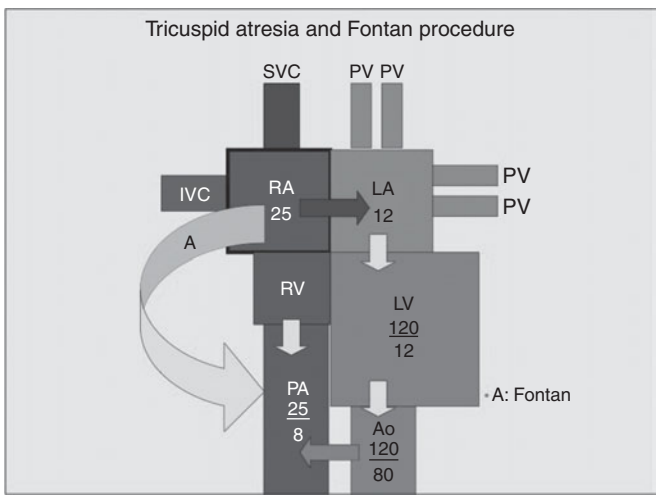


**Figure 2.7** Tricuspid atresia and Fontan procedure. (See plate section for color version.)

**Tetralogy of Fallot**. The AP septum fails to align and moves towards the pulmonary artery side, causing:

- pulmonary stenosis: sub-valvular (infundibular) and valvular
- aorta overrides both ventricles
- sub-arterial VSD
- right ventricular hypertrophy.

In patients with significant residual lesions (right ventricular outflow tract obstruction, severe pulmonary or tricuspid regurgitation, RV dysfunction), pregnancy precipitates right heart failure and arrhythmias in about 7%. [9].

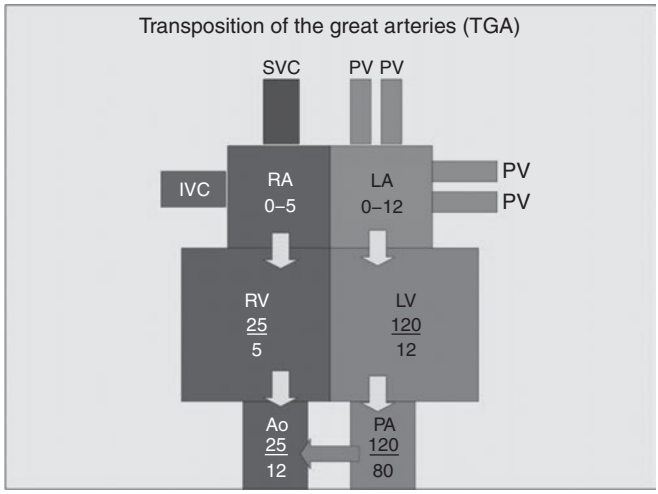


**Figure 2.8** Transposition of the great arteries (TGA). (See plate section for color version.)

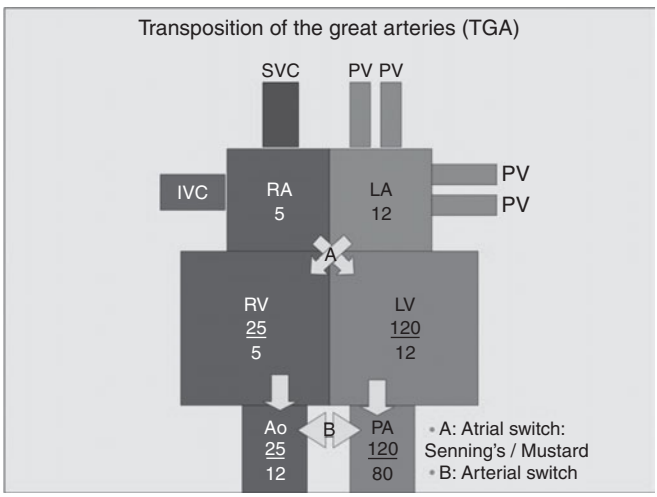


**Figure 2.9** Transposition of the great arteries (TGA). (See plate section for color version.)

**Transposition of the great arteries (TGA).** The AP septum fails to rotate so that the aorta arises from the RV and the pulmonary artery arises from the LV.

- An "arterial switch" operation (labeled B in Figure 2.9) is the operation of choice where the great arteries are anastomosed with appropriate morphological ventricles. Subsequent pregnancy, in theory, should be well tolerated.
- Atrial switch operations (Mustard and Senning's, labeled A in Figure 2.9), performed in the past, predispose to atrial arrhythmias. The morphologically right ventricle (systemic ventricle) fails in the third or fourth decade. The ability to tolerate pregnancy depends on the function of this systemic ventricle and its AV valve. Worsening of systemic ventricular function during pregnancy is reported in about 10% of patients.

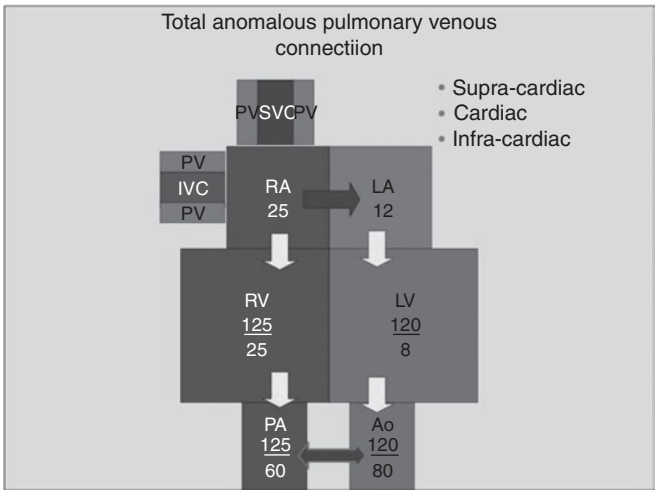


**Figure 2.10** Total anomalous pulmonary venous connectiion. (See plate section for color version.)

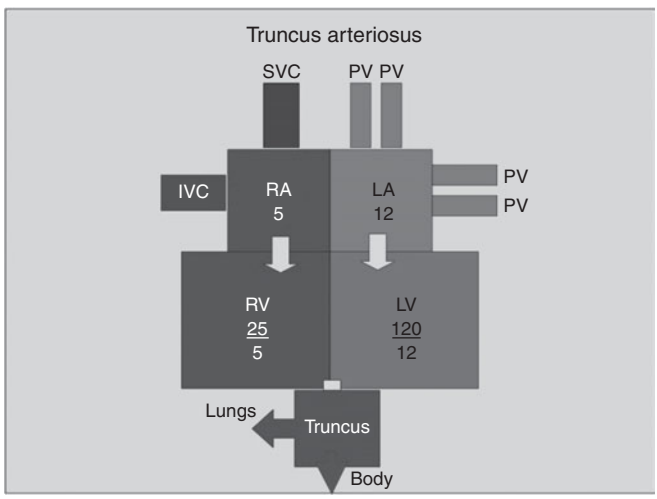


**Figure 2.11** Truncus arteriosus. (See plate section for color version.)

**Congenitally corrected TGA**. This results in atrioventricular and ventriculo-arterial discordance – that is, there is transposition of both, the ventricles as well as the great arteries. The blood flows from the LA→RV→aorta and from the RA→ LV → PA. The outcome depends on systemic ventricular function (which starts failing in the third or fourth decade). Pregnancy may be associated with a marked deterioration in systemic right-ventricular function. Substantial maternal morbidity with fetal loss has been observed and close supervision is recommended. There is a recent case report of the successful use of low-dose spinal anesthesia for cesarean section in a patient with TGA who had invasive arterial and central blood pressure monitoring and careful fluid loading [10].

**Tricuspid atresia**. The RV is hypoplastic and the only surgical option is a univentricular repair. Main repairs performed are the classic Fontan (RA → PA anastomosis), or the modified Fontan with cavopulmonary connection (SVC and IVC → PA anastomosis).

- Modified Fontan procedures have improved the long-term survival of patients with single ventricle physiology.
- Patients have low cardiac output, which is preload dependent.
- The venous return to the single ventricle depends upon venous pressure, PVR, and AV valve competence.
- Pregnancy is possible; however, there is increased risk of ventricular failure, atrial arrhythmia, worsening of systemic AV valve regurgitation, systemic venous congestion, thromboemboli and paradoxical emboli (if the Fontan is fenestrated).
- Very careful patient selection, and meticulous cardiac and obstetric supervision is essential.
- Maternal outcome again depends on functional capacity and ventricular function.
- First trimester fetal loss occurs in 30% of pregnancies [11] with a high incidence of premature delivery and postpartum hemorrhage.

The primary anesthetic goal for the parturient with Fontan circulation is to maintain pulmonary blood flow and cardiac output with close attention to preload.

- For labor and vaginal delivery, epidural analgesia using low-dose local anesthetic and opioid with arterial blood pressure monitoring has been described [12].
- For cesarean delivery, epidural anesthesia and general anesthesia with arterial blood pressure monitoring have been described [13]. However, positive pressure ventilation associated with general anesthesia may decrease pulmonary blood flow and cardiac output.

## Obstructive lesions

**Coarctation of the aorta**. Should be repaired prior to pregnancy; after a successful repair, pregnancy is low risk. There is a higher incidence of hypertension in unrepaired or residual coarctation. Management of upper-limb hypertension may cause unacceptably low pressure below the coarctation leading to loss of the fetus. Aortic aneurysm at the repair site should be ruled out. The risk of aortic dissection or aneurysm rupture increases during pregnancy and labor and either may be fatal.

The anesthetic goals involve avoiding increases in SVR and maintaining heart rate and preload.

- There is a recent case report of a parturient with complete coarctation of the aorta who underwent induction of labor and vaginal delivery with epidural analgesia and invasive radial and femoral arterial blood pressure montoring [14]. An IV esmolol infusion was used to keep the right radial systolic blood pressure between 140 and 160 mmHg and the left femoral systolic blood pressure greater than 90 mmHg with a heart rate of 75 bpm. The patient remained hemodynamically stable.

**Aortic stenosis and left ventricular outflow tract obstruction (LVOTO)**. Discussed below.

**Right ventricular outflow tract obstruction (RVOTO)**. With significant RVOTO pregnancy may precipitate right heart failure or atrial arrhythmias, and the obstruction should be relieved prior to conception.

# Valvular heart disease

- In general, stenotic lesions are poorly tolerated during pregnancy due to the inability to increase cardiac output relative to the increased intravascular volume.
- However, regurgitant lesions are usually well tolerated in pregnancy because the increased intravascular volume and lowered systemic vascular resistance lead to increased cardiac output.

## Mitral stenosis

Mitral stenosis (MS) from rheumatic fever is the most common valvular disease in pregnant women worldwide. It is considered severe when the valve area is 1 $cm^2$ or less. The incidence of maternal and fetal complications correlates with the severity of MS. Maternal mortality may approach 15% if MS is associated with symptomatic pulmonary hypertension.

The decreased mitral valve area prevents adequate left atrium emptying and left ventricular filling and leads to decreased cardiac output, left atrium dilatation, and increased pulmonary pressures. Atrial fibrillation and thrombi may develop so that anticoagulation may be necessary. Pulmonary hypertension may lead to right ventricular hypertrophy and right heart failure.

Women with severe MS often do not tolerate pregnancy because the increased volume load and decreased filling time due to tachycardia may cause increased left atrial pressures, atrial fibrillation, and pulmonary edema. After delivery, the sudden increase in the preload due to autotransfusion from the uterus, may cause severe pulmonary edema. In addition, there continues to be autotransfusion of blood for 24 to 72 hours after delivery.

The goals of anesthetic management are to:

- avoid tachycardia
- maintain sinus rhythm
- avoid sudden increase in venous return
- avoid sudden decrease in SVR
- prevent increase in pulmonary vascular resistance
- avoid pain, hypoxia, hypercarbia, hypothermia, and acidosis.

For vaginal delivery:

- Adequate analgesia prevents tachycardia and increased pulmonary vascular resistance associated with painful contractions.
- Carefully titrated segmental epidural analgesia with attention to preload, afterload, heart rate, and rhythm should be well tolerated.
- There are reports of the use of CSE with spinal fentanyl (15 to 25 μg) followed by dilute epidural bupivacaine and fentanyl infusion with stable hemodynamics [15].
- Hypotension should be treated with phenylephrine rather than ephedrine to avoid tachycardia.
- Second stage delivery should be assisted with forceps to avoid the deleterious effects of the Valsalva maneuver.

For cesarean delivery:

- Single-shot spinal anesthesia should be avoided because the sudden decrease in SVR could precipitate poorly tolerated reflex tachycardia and pulmonary edema.
- Carefully titrated epidural anesthesia has been shown to provide stable hemodynamics in women with moderate to severe MS [16].
- Kocum *et al.* describe the successful use of epidural anesthesia with invasive monitoring for cesarean delivery in a patient with MS and pulmonary hypertension. They used the epidural catheter postpartum as well to provide analgesia with low-dose bupivacaine and fentanyl via patient-controlled epidural anesthesia (PCEA) [16].
- If regional anesthesia is contraindicated, GA may be safely given.
- It is important to avoid increases in heart rate and PVR associated with intubation and emergence.
- Pan and D'Angelo have reported the use of a modified RSI (with sufentanil, esmolol, etomidate, and succinylcholine) with invasive monitoring (PA catheter and arterial line) in a patient with severe mitral stenosis [17]. This patient developed rapid atrial fibrillation after delivery and responded well to digoxin and furosemide.
- The use of remifentanil for general anesthesia for cesarean delivery in a parturient with severe mitral stenosis and pulmonary edema has been described [18].
- With either regional or general anesthesia techniques, invasive monitoring should be used in patients with severe disease to help guide fluid and drug therapy.

## Aortic stenosis

A congenital bicuspid valve is the most frequent cause for aortic stenosis (AS) in parturients. The severely stenotic valve (area <1 $cm^2$; mean gradient ≥50 mmHg) results in a markedly increased afterload and subsequent left ventricle hypertrophy. Severe AS carries a high risk of maternal morbidity and mortality. Patients with severe AS cannot meet the metabolic demands of pregnancy because of fixed left ventricular outflow tract obstruction. The inability to respond by increasing cardiac output may lead to cardiac decompensation and possibly maternal death. Anesthetic management of parturients with aortic stenosis is controversial. Regional anesthesia has traditionally been thought to be contraindicated in patients with AS because it can cause a sudden decrease in SVR resulting in decreased blood pressure and coronary flow, and tachycardia.

The goals of anesthetic management are to:

- avoid tachycardia
- maintain sinus rhythm
- avoid sudden decrease in venous return
- avoid sudden decrease in SVR.

Ioscovich *et al.* reviewed the anesthetic management of parturients with moderate or severe aortic stenosis in two institutions as well as published cases [19]:

- They found that carefully titrated regional analgesia (epidural and CSE) was usually well tolerated in parturients having vaginal or cesarean delivery.

- When GA was necessary, a combination of etomidate or propofol with opioids, including remifentanil, was effective in preventing the sympathetic response to intubation and maintaining hemodynamic stability.
- All patients with severe AS had invasive monitoring. Postpartum observation in a high dependency unit for 24 to 48 hours was often used.

## Mitral regurgitation

Mitral regurgitation (MR) is the second most common valvular lesion in pregnancy and is often due to mitral valve prolapse. Moderate and severe MR may result in chronic left atrial and ventricular volume overload and left atrial and ventricular dilatation. Mitral regurgitation is usually well tolerated in pregnancy. The increase in heart rate during pregnancy decreases the regurgitant flow and the increased blood volume should promote forward flow. However, increased blood volume can also lead to atrial fibrillation and pulmonary edema The decrease in SVR during pregnancy promotes forward flow across the aortic valve. However, during the peripartum period, labor pain and uterine contractions can cause an increase in SVR and regurgitant flow leading to acute left ventricular failure.

The goals of anesthetic management are to:

- avoid bradycardia
- maintain sinus rhythm
- avoid sudden decrease in venous return
- avoid sudden increase in SVR
- prevent increase in pulmonary vascular resistance
- avoid pain, hypoxia, hypercarbia, hypothermia, and acidosis.

For delivery:

- Adequate analgesia prevents an increase in SVR and PVR associated with painful contractions.
- Epidural anesthesia should decrease SVR and promote forward blood flow but it may also cause decreased venous return.
- Therefore it is important to maintain preload and left ventricular filling by left uterine displacement and careful fluid administration.
- Hypotension is best treated with ephedrine rather than phenylephrine.
- When GA is necessary, drugs associated with an increased heart rate (ketamine and ephedrine) are useful.
- Symptomatic patients may benefit from careful monitoring of invasive arterial blood pressure and central pressures.

## Aortic regurgitation

Aortic regurgitation (AR) may be acquired or congenital. If it is acquired it is often due to rheumatic heart disease, endocarditis, or aortic root dilatation. If congenital, it is usually associated with other lesions. Chronic AR results in left ventricular volume overload and dilatation. The diastolic filling pressure is reduced, and end diastolic pressure is increased.

Aortic regurgitation is usually well tolerated in pregnancy because the normal physiological changes favor forward blood flow. The increase in heart rate that normally occurs decreases the time for regurgitant flow during diastole. The increased blood volume and decreased SVR promote forward flow of blood. However, during labor, pain and uterine contractions can cause an increase in SVR and regurgitant flow leading to acute left ventricular failure.

The goals of anesthetic management are to:

- avoid bradycardia
- maintain sinus rhythm
- avoid sudden decrease in venous return
- avoid sudden increase in SVR.

The anesthetic considerations for delivery are similar to those for patients with MR:

- Epidural anesthesia is desirable to prevent pain-related increases in SVR, but bradycardia must be avoided.
- Patients with symptomatic congestive heart failure should have invasive monitoring.
- Sheikh *et al.* have reported the use of carefully titrated epidural analgesia for labor and forceps delivery in a parturient with severe AR [20]. The patient was hemodynamically stable during delivery but required emergency aortic valve repair on postpartum day 2. It was felt that the rapid increase in central blood volume as well as increase in SVR postdelivery precipitated acute pulmonary edema.
- Zangrillo *et al.* have described the successful use of epidural anesthesia in a pregnant patient with severe AR having cesarean delivery [21]. Epidural anesthesia was slowly titrated to a T4 sensory level using 2% lidocaine with the aid of invasive monitoring (arterial and central lines). However, the use of epidural anesthesia has been associated with maternal death in an earlier report in a patient with severe AR and pre-eclampsia having cesarean section [22].

## Post valve replacement

- Parturients who have had valves replaced are at increased risk for maternal and fetal complications.
- Maternal complications include thromboembolism, valve dysfunction, and endocarditis.
- Anticoagulation is usually necessary and increases the risk of neuraxial hematoma with regional anesthesia.
- Heparin is usually used instead of warfarin, which is teratogenic.
- If low molecular weight heparin (LMWH) has been used then regional anesthesia should not be performed unless the drug has been stopped for at least 12 to 24 hours.
- If unfractionated heparin is used, it can be discontinued at the start of labor, the coagulation parameters normalized, and then regional anesthesia may be used.

## Coronary artery disease

Coronary artery disease (CAD) and acute myocardial infarction (AMI) during pregnancy are rare, occurring in 1 in 35,000 pregnancies [23]. Independent predictors of AMI during pregnancy include chronic hypertension, advanced maternal age, diabetes, and

pre-eclampsia. Most AMIs occur during the third trimester in women older than 33 years who have had multiple prior pregnancies. Coronary spasm, intra coronary artery thrombosis, and coronary dissection occur more frequently than classic obstructive atherosclerosis. Maternal mortality is highest in the antepartum and intrapartum periods. Recent studies have found a 5 to 7% case-fatality rate in women with pregnancy-associated AMI.

- The increased heart rate and blood volume that occur in pregnancy increase the myocardial oxygen demand.
- However, hemodilution and the decrease in SVR decrease diastolic blood pressure and the oxygen supply so that there is an increased risk of ischemic events during pregnancy.

The goals of anesthetic management are to:

- avoid tachycardia
- avoid decrease in SVR.

Slowly titrated regional anesthesia for delivery has been well described in parturients with CAD.

- Smith *et al*. described their anesthetic management of six parturients with CAD [24]. Three women had elective cesarean deliveries with carefully titrated combined spinal–epidural anesthesia. Two women had vaginal deliveries, one with gradually induced epidural analgesia. The sixth woman had unstable angina requiring percutaneous coronary intervention during pregnancy and then went on to have a cesarean delivery under carefully induced general anesthesia. Regional anesthesia was avoided because of antiplatelet medication. Invasive arterial blood pressure monitoring was used in all women having cesarean deliveries. In this series, the preferred method of anesthesia was a carefully titrated regional technique.

# Cardiomyopathies

## Hypertrophic obstructive cardiomyopathy

Hypertrophic obstructive cardiomyopathy (HOCM) is an autosomal dominant disorder with variable degree of penetrance. The disorder, which occurs in 0.05 to 0.2% of the general population, is a primary myocardial disease characterized by left ventricular hypertrophy and blockade of the left ventricular outflow tract due to marked thickening of the myocardial muscle.

- The left ventricular diastolic dysfunction caused by the thickened myocardium decreases inflow duration and can cause a dynamic obstruction of the left ventricle.
- Furthermore, the elevated end diastolic blood pressure in the left ventricle may affect myocardial perfusion, with the consequences of ischemia of the thickened heart and various types of arrhythmia.
- Maternal decompensation during pregnancy and delivery has led to an increase in operative delivery rates in parturients with HOCM.

The goals of anesthetic management are to:

- maintain high preload
- maintain high SVR
- decrease myocardial contractility.

Slowly titrated epidural and CSE anesthesia with invasive blood pressure monitoring has been described for labor and delivery in parturients with HOCM [25].

## Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is defined as the development of idiopathic left ventricular systolic dysfunction (demonstrated by echocardiography) in the interval from the last month of pregnancy up to the first five postpartum months in women without pre-existing cardiac dysfunction. The incidence of PPCM in the USA is estimated to be 1 in 3,000 to 4,000 live births. The exact cause of PPCM is unknown, although viral myocarditis, autoimmune and specific genetic mutations that ultimately affect the formation of prolactin have been proposed as possible causes. Symptoms can appear during the second and third trimester.

- Treatment includes bed rest, salt restriction, diuresis, digoxin, vasodilators, β-blockers, and anticoagulants.
- More than half of women with PPCM completely recover within six months of delivery.
- Complete recovery is more likely in women with a left ventricular ejection fraction of more than 30% at diagnosis.
- The remainder experience persistent stable left ventricular dysfunction or continue to experience clinical deterioration.
- Maternal mortality is approximately 9%. Women with PPCM and persistent left ventricular dysfunction who attempt subsequent pregnancy face a high risk of maternal morbidity and mortality.
- These women should be counseled against subsequent pregnancies.
- Anesthesia management should rely on echocardiography finding and left ventricular reserve.

The goals of anesthetic management are to:

- maintain normal heart rate and rhythm
- avoid sudden increase in preload
- avoid sudden increase in afterload
- avoid myocardial depression.

For vaginal delivery, it is important to blunt the stress response and subsequent tachycardia and hypertension associated with labor.

- Gradually titrated epidural, CSE, and continuous spinal analgesia with invasive monitoring have been described for labor analgesia in parturients with PPCM.
- A shortened second stage with forceps or vacuum delivery decreases the hemodynamic changes.

Cesarean delivery is reserved for obstetric reasons.

- Gradually titrated regional anesthesia has been described [26]. Opioid-based general anesthesia techniques have been recommended to blunt the hyperdynamic responses associated with intubation and emergence [27].
- Invasive monitoring is recommended to guide fluid and drug therapy.

## Heart transplantation

Assessment should include the cause for heart transplant. For patients who underwent cardiac transplantation due to PPCM there is a theoretical risk of recurrent PPCM. When there is a clinical suspicion of rejection a biopsy should be performed during the pregnancy. However, the rejection rate was not found to be increased in this group of patients. Hypertension and pre-eclampsia are more common in this group of patients, as well as infections. These pregnancies might be complicated by increased fetal morbidity and mortality due to the use of immune suppression, early pregnancy loss, congenital malformations, stillbirth, infection, prematurity, and low birth rate. Previous cardiac transplant is not an indication in itself for cesarean section, but cesarean sections are common in this population.

- Epidural anesthesia is recommended to control pain and pain-induced sympathetic stimulation, although it has an increased risk of infection due to maternal immune suppression state.
- Continuous ECG monitoring to detect arrhythmia should be individualized and may be required in patients with underlying pulmonary hypertension, graft dysfunction, and rejection status.
- In a case series of pregnancies in 16 heart-transplanted women, regional anesthesia (epidural and spinal) was used in five cesarean deliveries and four vaginal deliveries with good maternal and neonatal outcomes [28].

## Summary

- Management of obstetric patients with cardiac disease should be undertaken by multidisciplinary teams in tertiary care centers.
- The physiological effects of pregnancy on the cardiac disease must be considered when planning for pregnancy, labor, and delivery.
- Planned elective delivery is preferable.
- Vaginal delivery with carefully titrated regional anesthesia is usually appropriate for most women with cardiac disease.
- Postpartum monitoring should occur in a high dependency unit.

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Chapter 3

# Hemodynamic management of pre-eclampsia and eclampsia

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## Introduction

Pre-eclampsia is a multisystem disorder unique to human pregnancy [1]. Over the years, advances in the understanding of the pathophysiology and hemodynamics of the disease have greatly impacted its obstetrical and medical management.

## Epidemiology

Pre-eclampsia/eclampsia is one of the leading causes of maternal and neonatal morbidity worldwide, especially among developing countries, accounting for 63,000 maternal deaths in the year 2000 [2]. About 12% of pregnancies worldwide are affected by pre-eclampsia and 3 to 5% in the Western world [2, 3].

Many maternal, paternal, and pregnancy-related risk factors have been proposed in the development of pre-eclampsia. These are listed below:

| Maternal | Paternal | Pregnancy-related |
|---|---|---|
| Primiparity | Family history | Multiple pregnancy |
| Previous history | Paternal history | Fertilization with donor sperm |
| Family history | Primipaternity | |
| Obesity | | |
| Diabetes | | |
| Renal disease | | |
| Chronic hypertension | | |
| Maternal infection | | |
| Non-smoker | | |
| Androgen excess | | |
| Insulin resistance | | |
| Dyslipidemia | | |
| Thrombophilias | | |
| African–American race | | |

*Controversies in Obstetric Anesthesia and Analgesia*, ed. Ian McConachie. Published by Cambridge University Press. 

# Definitions

The term "pre-eclampsia" refers to the hypertensive disorders of pregnancy and has been re-introduced instead of "pregnancy-induced hypertension" for its brevity and its international use [4].

- **Hypertension in pregnancy** is defined as diastolic blood pressure (DBP) ≥90 mmHg, as an average of two measurements taken in the same arm. Systolic blood pressure (SBP) is still used in the definition of **severe hypertension in pregnancy** (SBP ≥160 mmHg or DBP ≥110 mmHg), as there is an increased risk of stroke in pregnancy at this level.
- In women with **pre-existing hypertension** (pre-dating pregnancy or occurring before 20 weeks gestation), **pre-eclampsia** is defined as resistant hypertension, new or worsening proteinuria, or one or more adverse conditions.
- For women with **gestational hypertension** (occurring at or beyond 20 weeks gestation), **pre-eclampsia** is new proteinuria, or one or more adverse conditions.
- These adverse conditions consist of maternal symptoms, abnormal maternal laboratory testing, or fetal morbidity.
- **Severe pre-eclampsia** is defined as SBP ≥160 mmHg or DBP ≥110 mmHg, with onset before 34 weeks gestation, heavy proteinuria (3–5 g/24 hours) or with one or more adverse conditions.
- Edema and weight gain are not included in the definition since they are neither sensitive nor specific for pre-eclampsia.
- **HELLP syndrome** is a variant of severe pre-eclampsia characterized by the development of hemolysis, elevated liver enzymes and low platelets.

# Pathophysiology

Considerable research into the pathophysiology of pre-eclampsia is ongoing and many areas are still debated. The current and most widely accepted ideas are discussed here.

- Pre-eclampsia results from the presence of a placenta and, in particular, the trophoblast cells that are found only in this tissue and form either the epithelial layer of the villi or a tissue interface in the decidua.
- The clinical syndrome can be ascribed to generalized maternal endothelial dysfunction.
- There are two broad categories of pre-eclampsia: placental and maternal, although mixed presentations are common [5].

## Placental pre-eclampsia

This may also be referred to as early onset pre-eclampsia (<34 weeks gestation) and is associated with abnormal uterine artery Doppler, fetal growth restriction, and adverse maternal and fetal outcomes [6, 7].

- A two-stage model is generally used to explain the pathophysiology of the condition [8–10].
- Stage 1 may be defined as "pre-clinical" or occurring at <20 weeks gestation.
- Stage 2 refers to the onset of the clinical syndrome and is seen at >20 weeks gestation.

### Stage 1

Inadequate invasion by extravillous cytotrophoblasts into the decidual and myometrial segments of the spiral arteries leads to absent or incomplete remodeling needed for adequate placental perfusion [5].

- **Normal pregnancy**. The luminal diameter of the spiral arteries increases fourfold and the elasticity of the wall smooth muscle and intima falls, resulting in flaccid tubes with a low resistance circuit to intervillous spread, and poor responsiveness to vasoactive stimuli [8].
- **Pre-eclampsia**. These changes are either not present or are limited to the superficial portion of the vessels in the decidua. The vessels in the myometrial portion remain small, constricted, and hyper-responsive to vasoactive stimuli. The reason for this inadequate remodeling may be insufficient activation of uterine natural-killer cells, which prematurely halts the process of placental development and maternal decidual spiral artery remodeling [8].
- As a result there is:
  1. Decreased placental perfusion resulting in hypoxia and ischemia.
  2. A subsequent oxidative stress response and the release of cytokines, inflammatory mediators, and debris.
  3. The release of a number of placentally produced anti-angiogenic peptides, which have been implicated in pre-eclampsia, including soluble FMS-like tyrosine kinase (sFLT-1) and soluble endoglin, along with imbalances in angiogenic growth factors, e.g. vascular endothelin-derived growth factor (VEGF) and placental growth factor (PlGF) [3, 5, 10].
- The overall result is a generalized, systemic inflammatory response in the mother, with global vascular endothelial dysfunction: vasoconstriction and vasospasm, leukocyte adherence, activation of the clotting cascade and occlusive microthrombi, mitogenesis, pro-oxidation and vascular inflammation with loss of fluid from the intravascular space.
- Endothelial dysfunction is a central pathophysiological feature of the disorder and the one responsible for the clinical manifestations of pre-eclampsia [11].

### Stage 2

This refers to the clinical syndrome, e.g. hypertension and renal dysfunction. Not all women with decreased placental perfusion develop pre-eclampsia. There has to be an interaction with genetic, behavioral, and environmental factors, all of which are themselves modified by the physiological changes of pregnancy or may be involved with maternal pre-eclampsia. Studies on genetic variables have many limitations but it has been suggested that a major dominant gene with variable penetrance or multifactorial inheritance may be responsible. The maternal genome is mainly responsible but with some paternal contribution [8].

## Maternal pre-eclampsia

This may also be referred to as late pre-eclampsia and typically occurs at >34 weeks gestation. It is associated with normal or slightly increased uterine resistance index, a low rate of fetal involvement, and more favorable perinatal outcome.

It is considered to be more of an abnormal maternal response than an abnormal pregnancy, and arises from an interaction between a normal placenta and a maternal

constitution that is susceptible to, or suffers from, microvascular disease, e.g. hypertension, diabetes, and obesity [5].

## Hemodynamics of pre-eclampsia

The following are the physiological characteristics of a normal pregnancy:

- Increased heart rate, cardiac output, stroke volume, and left ventricular end-diastolic volume to accommodate the growing metabolic needs of the pregnancy.
- Decreased total peripheral vascular resistance as a consequence of the presence of the low-resistance placental circulation.

Pre-eclampsia has been classically described as being associated with high total vascular resistance and low cardiac output, and while this area is still subject to considerable research, it appears that the hemodynamics between the two groups discussed above (i.e. placental/early vs. maternal/late pre-eclampsia) may be different [12].

- At 24 weeks gestation, in patients who go on to develop pre-eclampsia, a hypodynamic state with high peripheral resistance and low cardiac output has been seen in those who developed early-onset, severe disease.
- A hyperdynamic state with low total resistance and high cardiac output has been seen in the group that developed late-onset disease (>80% of cases). Other changes are summarized in Table 3.1 [12].

This more up-to-date view on the types of pre-eclampsia is likely to have a bearing on treatment, which will be discussed in more detail later. For example, it seems counter-intuitive to treat hypertension with a β-blocker in a patient with early-onset disease and the hemodynamic profile detailed above; a vasodilator may be a more appropriate choice.

Numerous different methods have been used to assess the hemodynamics in both normal pregnancy and pre-eclampsia:

- The "gold standard" remains invasive pulmonary artery catheter monitoring, although this is rarely used nowadays.
- Invasive measurements of central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) have been found to agree poorly in pre-eclampsia. Pulmonary edema can occur in the presence of a "normal" CVP due to left ventricular dysfunction

**Table 3.1** Hemodynamic differences between pre-eclampsia subsets.

| Early-onset | Late-onset |
|---|---|
| Low cardiac output | High cardiac output |
| High total vascular resistance | Low total vascular resistance |
| Failure of atrial contribution to diastole | Increased atrial contribution to diastole |
| Increased relative LV wall thickness | Intermediate relative LV wall thickness |
| Small LV diameter | Larger LV diameter |

LV = left ventricle

[13]. Central venous pressure is therefore a poor measure of left ventricular preload in this patient group.

- Non-invasive (or less invasive) monitoring techniques, e.g. bioimpedance, bioreactance, pulse wave analysis, and echocardiography have also been used [14–16].
- These techniques may be increasingly used in sicker pre-eclamptic patients to aid management decisions, as they allow management of patients to be tailored to maintenance of cardiac output rather than previously used surrogates such as heart rate or non-invasive blood pressure.
- However, while data comparisons between non-pregnant, healthy pregnant, and pre-eclamptic patients have been made, validation against the gold standard in the latter patient subgroup has not been performed.

## Predictors of pre-eclampsia

There is a long history of studies searching for a test to predict pre-eclampsia, with the usual practical approach having been an evaluation of risk based on maternal history. In 2004, a large systematic review concluded that no single test met the clinical standards for a predictive test [17].

Current general consensus suggests a combined approach using clinical measurements and serum markers of placental abnormality appropriate for gestational age. Of note, while this is valid for many developed countries, these facilities are not available in the developing world where the maternal/fetal risk is all the more great.

### Clinical screening

- Assessment of maternal history to ascertain risk level.
- Uteroplacental Doppler ultrasound looking at flow-waveform ratios and diastolic uterine arcuate vessel notching as assessments of impedance to flow in the uterine arteries.
- In the future, non-invasive hemodynamic assessment as outlined above may be useful, particularly in the prediction of early, severe pre-eclampsia, e.g. using bioimpedance to assess hemodynamic variables at 24 weeks gestation.

### Biochemical markers

Angiogenesis from existing endothelium is essential for normal placental development, and it has been proposed that placental ischemia developing as a result of abnormal cytotrophoblastic invasion leads to the release of placental factors and an imbalance of angiogenic factors [3].

Angiogenic growth factor levels, factors that antagonize them, and their relative ratios have been studied in comparisons of pre-eclampsia to normal pregnancy. It has been shown that in cases of pre-eclampsia:

- Vascular endothelial growth factor levels (VEGF) are decreased.
- Placental growth factor (PlGF) is decreased.
- Soluble FMS-like tyrosine kinase (sFLT-1) levels are increased.
- Soluble endoglin levels are increased.
- Placental protein 13 levels are decreased.

### Genomics

A number of gene polymorphisms have been associated with the development of pre-eclampsia. However, a well powered study in 2005 [18] did not confirm significant associations between single nucleotide polymorphisms in candidate genes and pre-eclampsia.

### Proteomics and metabolomics

- **Proteomics** refers to the comparison of protein patterns between healthy patients and those with disease, and may be useful for early detection of disease, setting targets for treatment, and assessing response to that treatment.
- **Metabolomics** refers to the study of the unique chemical fingerprints and metabolites that specific cellular processes leave behind.
- Studies in both these areas are developing and can be performed on routine samples of urine, plasma, or serum.

## Prevention of pre-eclampsia

### Aspirin

Aspirin has been the most widely studied drug therapy in the prevention of pre-eclampsia. However, opinions regarding its use have changed frequently over time.

- A Cochrane review [19] concluded that "antiplatelet agents, largely low-dose aspirin, have moderate benefits when used for the prevention of pre-eclampsia and its consequences. Further information is required to assess which women are most likely to benefit, when treatment is best started and at what dose."
- A recent meta-analysis [20] concentrating on giving low-dose aspirin before 16 weeks gestational age found a significant decrease in pre-eclampsia and severe pre-eclampsia in women identified to be at moderate or high risk of pre-eclampsia. There was no benefit seen when aspirin was started after 16 weeks.

### Vitamin supplementation

Despite the role of oxidative stress in pre-eclampsia, vitamins C and E have not been shown to reduce the risk of developing the disorder. While calcium supplementation is currently recommended by the Society of Obstetricians and Gynaecologists of Canada [4] for women who have low dietary intake, supplementation with magnesium, zinc, or fish oils has not been shown to have any benefit in the prevention of pre-eclampsia.

### Antihypertensives

- Antihypertensive treatment does not prevent pre-eclampsia or associated perinatal outcomes.
- It does decrease by half the incidence of development of severe hypertension among women with mild hypertension.

# Medical management of pre-eclampsia

Obstetric management, in short, is expectant only when the fetus is immature and there are no adverse conditions. Delivery remains the definitive treatment and is instigated when the patient is at or near term, or there are progressively worsening adverse maternal and fetal conditions.

## Antihypertensives

- A goal-directed antihypertensive therapy is recommended [4]:
  - it should be directed to a SBP ≤160 mmHg and a DBP ≤110 mmHg for women with severe pre-eclampsia to decrease maternal morbidity and mortality [21]
  - for non-severe pre-eclampsia: SBP 130–155 mmHg and DBP 80–105 mmHg
  - for women with co-morbid conditions: SBP 130–139 mmHg and DBP 80–89 mmHg.
- Current recommendations [4] suggest treatment with labetalol, nifedipine, or hydralazine. Magnesium sulfate should not be used as an antihypertensive agent. Anesthesiologists are generally familiar with these drugs; however, some area-specific points of note are:
  - **Hydralazine** is a less effective antihypertensive than nifedipine or labetalol and may be associated with more adverse outcomes, including maternal hypotension, placental abruption, abnormal fetal heart rate patterns, cesarean section, low Apgar score at 1 minute, and maternal oliguria [22]. The dose is 5 mg IV, then 5 to 10 mg IV every 30 minutes to a maximum of 20 mg.
  - **Labetalol** may be associated with an increased incidence of neonatal bradycardia requiring intervention [22]. The dose is 20 mg IV, then 20 to 80 mg IV every 30 minutes to a maximum of 300 mg.
  - **Nifedipine** is now considered safe to use with magnesium sulfate; the risk of neuromuscular blockade with this combination is <1% and can be reversed with IV calcium gluconate [23]. The dose is a 5 to 10 mg capsule to be bitten and/or swallowed every 30 minutes or a 10 mg PA (intermediate-release) tablet every 45 minutes to a maximum of 80 mg/day.
  - **Nitroglycerine** and **sodium nitroprusside** have instantaneous onset of action and can be used to manage hypertensive emergencies. There is, however, a risk of excessive hypotension and reduced uteroplacental blood flow, and hence direct arterial pressure monitoring is recommended when these drugs are used.
- In comparative trials, β-blockers (including the mixed-action labetalol) may be better antihypertensives than methyldopa, but no other differences in maternal or fetal outcomes have been demonstrated [24–26].
- A Cochrane review summarizes that "there is no evidence to justify a strong preference for any one of the various drugs that are available for treating severe hypertension in pregnancy" [27]. However, as noted earlier, if the use of non-invasive monitoring increases, it may be possible to tailor treatment more appropriately depending on each patient's hemodynamic status. Previous studies looking at the beneficial and side effects of specific drugs have not investigated patient groups on the basis of these more contemporary study findings.

# Eclampsia

Eclampsia is defined as the new onset of seizures or unexplained coma during pregnancy or the postpartum period in a woman with signs and symptoms of pre-eclampsia and without a pre-existing neurologic disorder.

- The onset of convulsions can occur before (38 to 53%), during (18 to 36%) or after delivery (11 to 44%) and although most occur within 48 hours, there are case reports as late as 23 days postpartum. In up to 16% of cases, hypertension may be absent [28].
- The cerebral pathogenesis is unclear: there may be loss of the normal cerebral autoregulatory mechanism resulting in hyperperfusion and interstitial or vasogenic cerebral edema and decreased cerebral blood flow.
- As, radiologically, there are similarities with hypertensive encephalopathy, this may result from forced dilatation of the myogenic vasoconstriction of cerebral arteries and arterioles and increased blood–brain barrier permeability.
- The level of DBP, the presence of proteinuria, and the presence of clonus may prompt anticonvulsive treatment. Prophylaxis is not recommended in the absence of proteinuria.

## Prevention of eclampsia

Magnesium sulfate is well established as the drug of choice for treatment of eclampsia but what about prevention? A previous Cochrane review was recently updated to include several more trials and includes the MAGPIE trial data [29].

- In women with pre-eclampsia, when compared with placebo, administration of magnesium sulfate more than halved the incidence of seizures.
- In severe pre-eclampsia, the number needed to treat (NNT) to prevent one seizure was 50 (95% CI 34, 100).
- Magnesium sulfate reduces the incidence of eclampsia compared to phenytoin: risk ratio 0.08 (95% CI 0.01, 0.6).
- No clear difference in serious maternal and neonatal morbidity and mortality was established in patients with severe pre-eclampsia.
- A role for magnesium in patients with mild pre-eclampsia has never been proven and is not currently recommended.
- Antihypertensive therapy alone does not reduce the risk of seizures.

## Treatment of eclampsia

- Magnesium sulfate remains the drug of choice for treatment of eclamptic seizures. It has been established as superior to either diazepam [30] or phenytoin [31] for prevention of recurrent seizures. Several modes of action of magnesium in the treatment of pre-eclampsia/eclampsia have been proposed but are still debated [32].
  - **Vasodilation**. It is a well known vasodilator through its calcium-antagonistic actions, but this role is not clear in a clinical context. Some studies have shown no significant change in cerebral blood flow, large cerebral artery diameter, or middle cerebral artery velocity with magnesium treatment, prompting the suggestion that its efficacy is more likely related to an effect on peripheral vascular resistance and lowering of systemic blood pressure.

  - **Effect on cerebral edema and the blood–brain barrier**. The calcium antagonistic actions result in inhibition of endothelial contraction and opening of tight junctions, with improved paracellular transport of vascular contents, ions, and proteins, which may decrease vasogenic edema and seizures. Magnesium may also reduce transcellular transport by limiting pinocytosis, which is known to occur rapidly during acute hypertension. Finally, it may downregulate aquaporin 4, which is associated with cerebral edema formation.
  - **Central anticonvulsant activity**. It has been postulated that this may be related to its role as an NMDA receptor antagonist, with seizures thought to be mediated at least in part by stimulation of glutamate receptors such as the NMDA receptor.
- Magnesium is administered as a loading dose of 4 g iv over 20 to 30 minutes, followed by an infusion of 1 to 2 g/hr. Due to the continued risk of eclampsia, the infusion should be continued for at least 24 hours postpartum.
- However, if its use precedes seizure onset, another bolus of 2 to 4 g is indicated, depending on maternal weight (higher dose if patient >70 kg).
- Routine monitoring of blood levels is not supported by evidence, but hourly clinical evaluation for loss of reflexes, muscular weakness, and respiratory depression is essential.
- Of note, the vast majority of initial seizures are self-limiting and standard control measures must include an airway, breathing, and circulation approach, including high-flow oxygen and the left lateral position.
- If seizures persist despite the above measures, intubation with appropriate drug dosing and choice to blunt the pressor response to laryngoscopy will be indicated, as discussed in the anesthetic management section of this chapter.

## HELLP syndrome

- HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) complicates 10 to 20% of cases of severe pre-eclampsia and develops mostly preterm (50%). About 20% of affected women do not have hypertension or proteinuria [33].
- The clinical diagnosis of HELLP syndrome is based on the following laboratory findings:
  - reduced platelet counts (<100,000/$mm^3$)
  - elevated liver enzymes (aspartate transaminase [AST] >70 IU/L)
  - evidence of microangiopathic hemolytic anemia – lactate dehydrogenase (LDH) >600 IU/L; bilirubin >1.2 mg/dL; decreased haptoglobin; and schizocytes on peripheral smear.
- Patients with HELLP syndrome are at greater risk of abruptio placentae, disseminated intravascular coagulation, acute renal failure, eclampsia, pulmonary edema, and subcapsular liver haematoma, with a significantly high overall maternal and perinatal mortality [33].
- Prophylactic platelet transfusion is not recommended when the platelet count is >50,000/$mm^3$ and there is no excessive bleeding or platelet dysfunction. Platelet transfusion is indicated prior to cesarean and vaginal delivery when the platelet count is <20,000/$mm^3$ [4].
- Corticosteroids, particularly dexamethasone, may have a role in improving maternal hematological and biochemical indices (including platelet counts) and possibly the rate of

regional anesthesia in women with HELLP syndrome. However, no benefit has been demonstrated on primary maternal and perinatal outcomes [34, 35].

- Definitive therapy is delivery of the placenta. Medical management is directed toward stabilization of the affected organ systems.

## Anesthetic management and implications

The severity of pre-eclampsia can have profound implications on the outcome of pregnancy as well as the feasible anesthetic options for labor and/or delivery. The anesthesiologist should be prepared for immediate cesarean delivery at all times due to the unpredictable nature of the disease.

### Preoperative assessment

In view of the extensive pathophysiology and multisystem involvement of pre-eclampsia as discussed earlier, these patients need critical assessment to evaluate their perioperative risk. The anesthetic considerations with respect to individual system involvement are outlined in Table 3.2.

### Perioperative monitoring

- Invasive arterial blood pressure monitoring may be indicated in severely pre-eclamptic patients to: (a) guide hemodynamic management if the blood pressure is poorly controlled; (b) assess the response to antihypertensive drugs; (c) control the pressor response during laryngoscopy; and (d) allow repeated blood sampling for hematological parameters.
- Evidence suggests that there is a limited role for central hemodynamic monitoring for pre-eclampsia itself unless indicated by the severity or the complications, such as pulmonary edema, severe cardiac disease, severe renal disease, or if difficult fluid management is anticipated in the peripartum period.
- As discussed earlier, the role of CVP vs. PCWP monitoring is still debated due to lack of correlation with each other and little evidence of the effectiveness of PCWP monitoring in the perioperative period.
- Measurement of cardiac output using non-invasive monitors, as mentioned earlier, may have some promise in the perioperative hemodynamic monitoring of severely pre-eclamptic patients.
- Using whole-body impedance cardiography during cesarean delivery under spinal anesthesia, it has been demonstrated that pre-eclamptic women show an increase in their cardiac output due to an increase in heart rate but may be unable to increase stroke index at delivery. This is speculated to be due either to the existence of a lower preload after delivery than in healthy patients, or to diastolic dysfunction resulting in an inadequate adaptation to volume load at delivery, potentially predisposing these patients to life-threatening pulmonary edema in the early puerperium [36].

## Regional anesthesia for labor and delivery

Over the years, the practice guidelines for the administration of regional anesthesia in severely pre-eclamptic patients have improved significantly.

**Table 3.2** Anesthetic considerations in patients with pre-eclampsia.

| System involvement | Anesthetic implications |
|---|---|
| *Airway:*<br>Pharyngolaryngeal edema<br>Subglottic edema<br>Capillary engorgement and tissue friability | Potentially difficult intubation<br>Airway obstruction<br>Bleeding during intubation<br>Need for smaller size endotracheal tube |
| *Respiratory system:*<br>Increased pulmonary vascular permeability due to endothelial dysfunction | Risk of pulmonary edema |
| *Cardiovascular system:*<br>Increased vascular tone and high blood pressure<br>Variable cardiac output, decreased in severe forms<br>Hyperdynamic ventricular function, depressed in severe forms<br>Volume depletion | Increased sensitivity to vasopressors<br>Exaggerated hypertensive response to intubation<br>Risk of cardiovascular complications |
| *Hematological system:*<br>Thrombocytopenia<br>Hemolytic anemia<br>Hypercoagulability<br>Activation of fibrinolytic system leading to DIC | Implications for regional anesthesia<br>Need for transfusion of blood products |
| *Hepatic system:*<br>HELLP syndrome<br>Increased serum transaminases<br>Hepatocellular necrosis, periportal, or subcapsular hemorrhage<br>Hepatic rupture | Considered an obstetric emergency<br>Potential for bleeding<br>Altered drug metabolism |
| *Central nervous system:*<br>Headache, visual disturbances, hyperexcitability<br>Hyperreflexia, coma<br>Eclampsia (seizures) | Need for emergency airway management<br>Measures to prevent and treat convulsions |
| *Renal system:*<br>Decreased glomerular filtration rate, proteinuria<br>Hyperuricemia, oliguria | Maintenance of fluid balance and intravascular hydration<br>Monitoring urine output |

DIC = disseminated intravascular coagulation
HELLP = hemolysis, elevated liver enzymes, and low platelets

- Patients with pre-eclampsia may exhibit an exaggerated hemodynamic response to labor pain. Epidural and combined spinal–epidural (CSE) anesthesia have been shown to have beneficial effects in preventing the catecholamine-induced surges in blood pressure during labor contractions [37].
- The revised obstetric practice guidelines by the American Society of Anesthesiologists (ASA) suggest prophylactic insertion of a spinal or epidural catheter to reduce the need for general anesthesia in pre-eclamptic parturients [38].

- Women with severe pre-eclampsia (particularly with HELLP syndrome) may have thrombocytopenia and coagulation abnormalities, which increase the risk of bleeding into the epidural or intrathecal space during a neuraxial procedure.
- Mildly pre-eclamptic women with a platelet count exceeding 100,000/$mm^3$ rarely develop coagulopathy, while those with counts less than 100,000/$mm^3$ may show abnormal coagulation parameters [39].
- A platelet count of 75,000/$mm^3$ is considered adequate for the administration of neuraxial anesthesia, unless there is a coagulopathy, falling platelet concentration, or co-administration of an antiplatelet agent [4].
- Currently, the lowest platelet count to perform neuraxial blockade safely has not been identified. However, there is a consensus that platelet count lower than 50,000/$mm^3$ precludes the administration of neuraxial anesthesia.
- For women with a platelet count between 50,000/$mm^3$ and 75,000/$mm^3$, the risks and benefits of neuraxial anesthesia must be weighed against the risks of general anesthesia for the individual patient if emergency cesarean delivery is required.
- The trend in the platelet count is important in addition to the absolute platelet numbers; a rapidly falling platelet count is a cause for concern and indicates the severity of the condition. In women with HELLP syndrome, the platelet count usually reaches a nadir on the second or third postpartum day and then gradually returns to the patient's normal baseline [40].
- Platelet count and coagulation parameters should be serially monitored before administration of regional anesthesia and removal of epidural catheter. The role of platelet function tests such as platelet function analyzer (PFA-100) and thromboelastography (TEG) is not clear, as there is no evidence that an abnormal result increases bleeding risk [4].
- Measurements should be obtained every six hours when the platelet count is relatively stable; however, more frequent measurements, for example, within the last one to three hours, may be required before the neuraxial procedure when the platelet count shows evidence of a significant fall.
- In patients with thrombocytopenia and coagulopathy, epidural vein trauma at the time of catheter removal can result in bleeding, increasing the possibility of epidural hematoma. The platelet count should be checked for evidence of a return toward normal levels and coagulation deficits should be corrected before removal of the indwelling epidural catheter.

# Anesthesia for cesarean delivery

## Regional anesthesia

The trend in anesthetic management of patients with severe pre-eclampsia has changed dramatically in the last decade based on several studies that favor regional over general anesthesia for cesarean delivery in patients without coagulopathies.

- In the past, epidural anesthesia was the preferred choice and the use of spinal anesthesia was considered controversial in patients with severe pre-eclampsia due to the potential for exaggerated hypotension and reduced uteroplacental perfusion. However, a number

of studies have shown that spinal anesthesia can be safely administered without increasing maternal or fetal risk.

- The advantages of spinal over epidural needle placement include ease of technique, faster onset, and less traumatic insertion due to its smaller size.
- There is a potential for accidental dural puncture and trauma to the epidural venous plexus during epidural placement. If a coagulopathy develops after catheter placement, removal of the catheter may increase the risk of epidural hematoma and delayed removal may increase the risk of infection.
- The incidence of hypotension in severely pre-eclamptic patients receiving spinal anesthesia may be higher than [41] or the same [42, 43] as that after epidural anesthesia. However, the hypotension is usually transient and easily treatable.
- Studies have found no clinical differences in fetal or maternal outcomes between the two techniques [41–43].
- Clinical studies have demonstrated a lower incidence of hypotension, a smaller decrease in blood pressure, and a need for lower doses of ephedrine and phenylephrine to restore maternal blood pressure during spinal anesthesia in pre-eclamptic women compared to healthy pregnant women [16, 44]. This could be because pre-eclampsia is characterized by increased sympathetic activity, increased production of circulating factors with potent pressor effect, and increased sensitivity to vasoconstrictors [45].
- Dyer *et al.*, using lithium dilution cardiac output monitoring in severe pre-eclampsia, showed that neither spinal anesthesia nor treatment of hypotension with modest doses of phenylephrine reduced maternal cardiac output during cesarean section, further supporting the safety of spinal anesthesia in this patient population [16].
- The use of epinephrine in local anesthetic solutions in severely pre-eclamptic women is still debated due to lack of randomized controlled trials. Arguments against its use include the potential for decreased umbilical blood flow velocity and decreased uteroplacental perfusion, and possibly exaggerated cardiovascular effects due to a greater sensitivity to vasopressors from systemic absorption of epinephrine [45–47].

## General anesthesia

- General anesthesia may be preferred in severely pre-eclamptic patients with suspected placental abruption, severe coagulopathy or thrombocytopenia, severe pulmonary edema, eclampsia, and severe fetal distress.
- When compared with regional anesthesia, general anesthesia carries concerns about:
  - difficult intubation due to airway edema
  - risk of aspiration
  - risk of severe hypertension with intubation leading to increased risk of cerebral events
  - reduction in uterine blood flow during laryngoscopy due to the release of catecholamines
  - exacerbated hypertensive response to anxiety, pain, and noxious stimuli, and more hemodynamic instability
  - transient neonatal depression due to anesthetic agents.

- As compared to spinal and epidural anesthesia, general anesthesia in severely pre-eclamptic patients is associated with higher blood pressure during both induction and the emergence period [43]. The National Report on the Confidential Enquiry into Maternal and Child Health (CEMACH) 2003–2005 highlighted the deaths of two women from intracranial hemorrhage due to high systolic blood pressure during induction of anesthesia [48].
- General anesthesia for cesarean delivery has also been shown to be an independent risk factor for postpartum stroke within six years of delivery when compared with neuraxial anesthesia. This has been related to variable effects of the two techniques on the neuroendocrine stress response, incidence of thromboembolism, and magnitude of endothelial dysfunction [49].
- Continuous invasive blood pressure monitoring and concomitant administration of drugs such as lidocaine, short acting opioids (remifentanil, alfentanil), magnesium sulfate, nitroglycerine, labetalol, or hydralazine are advocated for obtunding the pressor response.
- Magnesium sulfate therapy may interact with anesthetic management in several ways:
  - potentiates the actions of muscle relaxants
  - augments sedation and analgesia
  - causes direct vasodilation leading to decrease in blood pressure
  - obtunds the pressor response during intubation
  - decreases the requirement of volatile agents
  - decreases uterine tone but the risk of postpartum hemorrhage has not been shown to be higher
  - toxicity may produce respiratory and circulatory collapse.

### Uterotonic therapy

- Oxytocin should be given slowly in the form of an infusion as its hemodynamic effects may be less predictable in women with severe pre-eclampsia compared to healthy pregnant women. A lower plasma volume and diastolic dysfunction in some women with severe pre-eclampsia could explain their inability to increase stroke volume as a response to the vasodilatory effects of oxytocin [50].
- Ergot alkaloids are relatively contraindicated in pre-eclamptic patients due to their potential for producing severe hypertension and cerebral hemorrhage. They should not be administered if the blood pressure is high or is not checked [48].
- Carboprost (methyl prostaglandin F2α) should be considered if oxytocin fails to achieve appropriate uterine contractility.

## Complications

Severe morbidities associated with pre-eclampsia and eclampsia include stroke, pulmonary edema, renal failure, cardiac arrest, adult respiratory distress syndrome, coagulopathy, and liver failure. The details of two important complications are highlighted below.

## Stroke

- Cerebral hemorrhage is the single most common cause of maternal death in pre-eclampsia.
- In the past, DBP was considered a predictor of stroke. However, it is now recognized that SBP may play a greater role. The present recommendations of the CEMACH Report 2003–2005 advocate treatment of SBP above 160 mmHg to avoid intracranial bleeding [48].
- Patients with pre-eclampsia have high cerebral perfusion pressures and disturbed dynamic cerebral autoregulation, which predisposes them to overdistention of cerebral vasculature and hypertensive encephalopathy [51].
- HELLP syndrome and the hypertensive response during general anesthesia for cesarean delivery in patients with severe pre-eclampsia could potentially increase the risk of stroke.

## Pulmonary edema

- Pulmonary edema is a rare but serious complication of pre-eclampsia, seen in 3% of cases [52].
- The incidence is higher in older women, multigravidas and in those with pre-existing chronic hypertension [52].
- Endothelial dysfunction and increased vascular permeability, reduction in the colloid osmotic pressure, and increased hydrostatic pressure in pulmonary capillaries as a result of left ventricular dysfunction or iatrogenic fluid administration may lead to a loss of intravascular fluid and protein into the interstitium, predisposing these patients to pulmonary edema [53].
- About 70 to 80% of cases occur in the postoperative period in association with excessive fluid administration, as the resolution of pre-eclampsia is heralded by marked diuresis and mobilization of extracellular fluid increasing intravascular volume [52, 54].
- Intravascular volume depletion correlates with the severity of pre-eclampsia. However, plasma volume expansion prior to regional or general anesthesia has been shown to be of no benefit and is not recommended [4].
- Both maternal and perinatal mortality are high in the presence of pulmonary edema; 4/37 maternal deaths and 530/1,000 perinatal deaths have been reported in one study [52].

# Summary and recommendations

- Pre-eclampsia is a pregnancy-specific disease characterized by the development of concurrent hypertension and proteinuria, which may eventually progress into a multisystem disorder. It is associated with significantly high maternal and neonatal mortality and morbidity.
- Recent investigations on the pathophysiology of this disorder have prompted modifications in the definitions and management options of pre-eclampsia.
- Early onset pre-eclampsia may have poor hemodynamics and long-term cardiovascular consequences as compared to late onset pre-eclampsia.
- The cure is "delivery," but the decision is based on severity, maternal status, and fetal well-being.

- Among antihypertensive agents, there is no evidence of superiority of one drug over the other. Magnesium sulfate is the drug of choice for prophylaxis and treatment of eclampsia.
- Systolic blood pressure above 160 mmHg is the risk factor for cerebral haemorrhage, which is also the major cause of maternal mortality in pre-eclampsia.
- Neuraxial anesthesia is the technique of choice for labor analgesia in severe pre-eclamptic women if there is no evidence of coagulopathy.
- Hypertensive response to direct laryngoscopy and intubation can cause intracranial hemorrhage in women with severe pre-eclampsia.
- Spinal anesthesia is an acceptable option for women with severe pre-eclampsia, especially as an alternative to general anesthesia in emergency cesarean section.
- Adequate control of blood pressure and judicious fluid administration is recommended in the perioperative period.
- Prompt recognition of the severity and complications of the disorder, stabilization of the mother and the fetus, and a multidisciplinary approach toward management is recommended.

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Chapter 4

# Management of major obstetric hemorrhage

Dr A Wise and Dr V Clark

## Introduction and definition

Despite being the most common cause of maternal mortality worldwide, there is no universally accepted definition of major obstetric hemorrhage:

- The World Health Organization (WHO) refers to postpartum hemorrhage (PPH) as blood loss ≥500 ml within 24 hours of birth and severe PPH as blood loss ≥1,000 ml within the same period [1].
- The Royal College of Obstetricians and Gynaecologists (RCOG) categorizes PPH as minor (500 to 1,000 ml), moderate (1,000 to 2,000 ml), or severe (>2,000 ml) [2].
- The Scottish Confidential Audit of Severe Maternal Morbidity (SCASMM) defines major hemorrhage as blood loss ≥2,500 ml, or transfusion of ≥5 units of blood, or treatment for coagulopathy [3].

Different definitions of hemorrhage can make meaningful comparisons between studies difficult. Further, obstetric blood loss is notoriously difficult to quantify and is often significantly underestimated. Additional resources should be mobilized once estimated blood loss >1500 ml.

## Incidence

The number of maternal deaths in 2008 has been estimated at 358,000, equating to a global maternal mortality ratio (MMR) of 260 maternal deaths per 100,000 live births. Disparities between countries are great: Afghanistan has the highest MMR at 1,400 in comparison to the MMR for the UK, which is 12 [4].

In the UK, the Royal College of Obstetricians and Gynaecologists (RCOG) takes the view that "maternal deaths due to hemorrhage must be considered preventable" [2]. The most recent Confidential Enquiry into Maternal Deaths in the United Kingdom, Saving Mothers' Lives 2006–2008 details:

- hemorrhage being the sixth direct cause of maternal death. The downward trend in mortality rate is gratifying, although not statistically significant
- nine deaths (0.39 per 100,000 maternities) directly attributable to hemorrhage, including one due to uterine rupture

*Controversies in Obstetric Anesthesia and Analgesia*, ed. Ian McConachie. Published by Cambridge University Press. 

- substandard clinical care in two-thirds of cases (lack of senior multidisciplinary staff involvement, poor postoperative monitoring and failure to act on signs and symptoms of hemorrhage [5].

Fortunately maternal mortality is now too infrequent in developed countries like Scotland to be a useful indicator of quality of care. The Scottish Confidential Audit of Severe Maternal Morbidity was therefore established in 2003 to examine the causes of severe maternal morbidity, i.e. "near misses." The most recent figures for 2008 [5] indicate that hemorrhage was the cause in approximately 75% of the cases reported to SCASMM. Of the 60,000 deliveries in Scotland that year:

- Case assessments were received for 251 women who suffered major obstetric hemorrhage.
- 127 of the 251 women were delivered by cesarean section (CS) – 103 emergency and 24 elective.
- 23 of the 103 emergency cesareans were performed at full dilatation, which was identified as an independent risk factor for hemorrhage.
- The most common causes of bleeding were uterine atony, retained placenta/membranes, vaginal laceration/haematoma, extension to uterine incision and placenta previa.
- The standard of care was judged to have been appropriate in 64% of cases [3].

The International Postpartum Hemorrhage Collaborative Group has observed an increasing trend in PPH and its severity in a number of high-resource countries including the UK (based in part on the SCASMM data), Australia, Canada, and the United States [6].

## Risk factors

Postpartum hemorrhage is unpredictable. The RCOG categorizes the following risk factors as:

- **Substantial** (delivery in a consultant-led maternity unit is advised): placental abruption, placenta previa, multiple pregnancy, pre-eclampsia, and gestational hypertension.
- **Significant** (falling short of substantial, but should be taken into account when discussing the setting for delivery): previous PPH, Asian ethnicity, obesity, and anemia.
- **Labor or delivery related**: delivery by CS, induction of labor, retained placenta, mediolateral episiotomy, operative vaginal delivery, prolonged labor, large baby, pyrexia in labor, and age >40 years (not multiparous) [2].

## General considerations

Antenatal optimization of hematinic status may avoid the need for transfusion should a hemorrhage occur. This is particularly important for women with identified risk factors or who refuse blood.

Active management of the third stage of labor is recommended for all women involving:

- the use of uterotonics
- early clamping of the umbilical cord
- controlled cord traction for delivery of the placenta.

## Diagnosis

Early recognition of physiological derangement is vital and modified obstetric early warning systems, tracking changes in maternal physiology, have been introduced. However, there is no evidence that these reduce the morbidity or mortality in critically ill women.

The physiological changes of pregnancy initially buffer the effects of hemorrhage so early signs such as:

- tachycardia
- decreased urine output
- and, (most sensitive of all) tachypnoea

should be sought. Hypotension is a late and ominous sign.

## Management

The aim is to resuscitate the patient by stopping the bleeding and restoring a circulating blood volume with oxygen-carrying potential.

- The first step is to call for additional help: experienced midwives, obstetricians, and anesthesiologists should be present.
- A major obstetric hemorrhage protocol should be in place and followed, where appropriate, to alert obstetric consultants, the Blood Transfusion Service and other staff (e.g. porters).

Management should proceed as follows, as far as possible simultaneously:

- Assess the patient: quantify blood loss and ascertain the cause of the bleeding.
- Give oxygen at 15 L/minute.
- Monitor the patient: EKG, non-invasive blood pressure, oxygen saturation, and hourly urine output are all mandatory. One of the team should document events throughout. Consider invasive monitoring via an arterial or central line.
- Establish intravenous (iv) access with two large bore cannulae. Take blood for full blood count, urea and electrolytes, and coagulation screen. Cross-match six units of blood. Consider near patient testing if available (HemoCue, thromboelastography). If IV access proves difficult, intraosseous access can be achieved quickly and easily (EZ-IO® powered drill device).
- Give fluids: crystalloid then colloids, followed by blood. Ensure that no more than 3.5 litres of clear fluid is given prior to blood. O rhesus-negative blood should be immediately available.
- Avoid hypothermia by using forced warm-air heaters and warm all fluids with rapid delivery devices (Level 1®/Belmont® Rapid Infuser).
- Ensure calcium levels are kept within the normal physiological range. Aim for >0.9 mmol/L with calcium chloride.
- Consider a transfusion strategy. Platelets should be given through a clean giving set, otherwise they may stick to red blood cells and reduce the effective platelet dose. [7].

## Transfusion strategy

The recommendations of "Management of bleeding following major trauma: an updated European guideline" published in 2010 have been adopted by many in the obstetric field and suggest the following levels be maintained [8]:

- hemoglobin of 7 to 9 g/dL
- APTT/PT ratios <1.5 times control (in cases of massive bleeding, an early initial dose of 10 to 15 ml/kg of fresh frozen plasma (FFP))
- platelets >50 × $10^9$/L
- fibrinogen >1.5 to 2 g/L.

When dealing with actively bleeding patients, some studies have suggested there may be benefits in maintaining a slightly higher hemoglobin level of around 10 g/dL [9].

The RCOG's existing guidance on transfusion in obstetrics refers to maintaining fibrinogen >1 g/L [10].

- However, normal fibrinogen levels are between 2 and 4 g/L and increase by up to 50% during pregnancy so a concentration of 1 g/L would be very low.
- One study found that a fibrinogen level ≤2 g/L had a positive predictive value of 100% for severe PPH – the only marker among those investigated to do so [11].

Experience of treating battlefield casualties in Iraq and Afghanistan has encouraged the early and aggressive use of coagulation products, with an equal 1:1:1 ratio (packed red blood cells:FFP: platelets), and early damage control surgery to try and prevent the "lethal triad" of metabolic acidosis, hypothermia, and coagulopathy [12]. However, the Association of Anaesthetists of Great Britain and Ireland (AAGBI) currently advises that "1:1:1 regimen, as used by the military, are reserved for the most severely traumatised patient and are not routinely recommended" [7].

## Stopping the bleeding

If uterine atony (the most common cause of bleeding) is suspected, perform bimanual compression by "rubbing up the fundus" to stimulate a uterine contraction.

Other causes of bleeding should be excluded, e.g. ensure the bladder has been emptied and check for genital tract lacerations/retained placenta.

## Uterotonics (pharmacological agents)

### Oxytocics

- Oxytocin is the established drug of choice for both prophylaxis and treatment of hemorrhage. Five units are given by slow IV bolus at delivery unless the woman has cardiac disease, in which case she should be given 5 units as an infusion over 20 minutes. This is usually followed by an infusion, e.g. 40 units of oxytocin over 4 hours. Care must be taken when the patient is haemodynamically unstable or otherwise compromised because oxytocin can cause vasodilatation and subsequent hypotension. Oxytocin is further discussed in its own chapter.
- Carbetocin, a long-acting oxytocin analogue, is an alternative. A single 100 μg dose is given, either intravenously or intramuscularly, at delivery. A review of three studies

found that there was limited evidence to determine if carbetocin is as effective as oxytocin, although it was found to be associated with reduced need for additional uterotonics and uterine massage [13].

- A subsequent trial compared the effectiveness of carbetocin and oxytocin administered after CS and found that significantly more women in the oxytocin group required additional oxytocics [14]. Other trials are under way (e.g. "Carbetocin versus Oxytocin and Hemodynamic Effects" in Oslo University Hospital, in Norway http://clinicaltrials.gov/ct2/show/NCT00977769).
- The RCOG currently recommends against the routine use of carbetocin because of the lack of data and its expense relative to oxytocin.

### Ergot alkaloids

Ergometrine is as effective as oxytocin at reducing blood loss. It is associated with side effects such as nausea and vomiting but this should not discourage its use. A dose of 500 μg is given either intravenously or intramuscularly [15]. It is contraindicated in hypertensive patients because it elevates blood pressure.

### Prostaglandins

- Carboprost is given as a 250-μg intramuscular injection. Further doses can be given at 15-minute intervals, up to a maximum of 2 g in total. It must not be given intravenously as it can cause severe bronchospasm and pulmonary shunting. It is not licensed for intramyometrial use.
- Misoprostol can be given orally, sublingually or rectally. A dose of 600 μg is normally given – higher doses increase the chance of pyrexia and shivering. Although less effective than oxytocin, a large review concluded that 600 μg given orally or sublingually showed "promising results when compared to placebo in reducing blood loss after delivery" [16]. It is inexpensive, and easy to administer and store (it is stable at temperatures >30°C). The WHO recommends the use of misoprostol to prevent and treat PPH in low- and middle-income countries where oxytocin and other injectable uterotonics are not available [17]. The RCOG also recognizes that misoprostol may be useful in the home-birth setting [2].

## Surgical management

If uterotonics fail to stem the bleeding, or surgical intervention is otherwise indicated, the following procedures may be considered.

### Balloon tamponade

A specialized balloon – Rusch or Bakri – is inserted within the uterine cavity and inflated with fluid to exert tamponade on the internal wall of the uterus. The Bakri balloon is preferred because it has an orifice that sits at the fundus, allowing drainage of blood and detection of further bleeding. Although anesthesia is not required for insertion or removal of the balloon, it is often necessary to permit a full examination to rule out other causes of bleeding. Typically, the balloon is left in situ for 24 hours then gradually deflated. Continuous monitoring is required together with antibiotics and an oxytocin infusion.

## Compression (or brace) sutures

Compression sutures are a useful technique in cases of uterine atony where the patient has responded to bimanual compression. They provide external pressure that opposes the posterior and anterior walls of the uterus. A variety of methods have been described including B-Lynch, Hayman's horizontal brace, and Cho's multiple square sutures. Although subsequent successful pregnancies have been reported, intrauterine bands have been observed at cesarean section and other complications include pyometria, uterine necrosis, and intra-abdominal adhesions.

## Arterial ligation

Arterial ligation used to be a first-line surgical intervention. However, recently its use in the UK has been limited [3] and it is more commonly used in developing countries where the newer, more expensive techniques described above are not generally available [18].

Arterial ligation is technically more difficult to perform than either balloon tamponade or compression suturing and requires the involvement of senior surgical staff. The uterine artery should be ligated, failing which the anterior division of the internal iliac artery. Reported complications include damage to neighboring veins, arteries, and ureters. Inadvertent ligation of the external iliac artery can cause leg and buttock ischemia.

## Comparison of conservative surgical procedures

The RCOG notes that a lack of comparative studies makes it impossible to assess which of these three procedures is the most effective [2]. The SCASMM nevertheless estimated the "success rate" of each procedure (the criterion for success was avoiding hysterectomy) [3]:

- 46 of 53 women (87%) who had balloon tamponade avoided hysterectomy
- 17 of 21 women (81%) who had compression sutures avoided hysterectomy
- 3 of 4 women (75%) who had iliac artery ligation avoided hysterectomy
- but, neither of the two women who had uterine artery ligation avoided hysterectomy.

A meta-analysis by Doumouchtsis found no evidence that one procedure was significantly better than the others. The success rates were:

- balloon tamponade 84%
- compression sutures 91.7%
- arterial ligation 84.6%.

It was suggested that balloon tamponade be performed first as it is the "least invasive and most rapid approach" [19, 2].

If surgical hemostasis cannot be achieved, cross-clamping the aorta may buy valuable time to resuscitate and stabilize the patient before performing a hysterectomy.

The SCASMM has noted a "significant change in the surgical management" of major obstetric hemorrhage since 2003, with an increase in conservative surgical management (balloon tamponade and compression suturing) and a corresponding decrease in peripartum hysterectomy (from 14% in 2003 to 8% in 2008) [3].

## Peripartum hysterectomy

Peripartum hysterectomy should be considered sooner rather than later if other interventions fail to stem the bleeding, or the cause of bleeding is likely to necessitate it (e.g. placenta accreta, uterine rupture).

- Subtotal hysterectomy is quicker and easier to perform and "is the operation of choice in many instances of PPH." The RCOG recommends that the decision to perform a hysterectomy should be made by an experienced consultant clinician who should, if possible, discuss the decision with a peer [2].
- Previous UK Confidential Enquiries into Maternal Deaths (Saving Mothers' Lives 2003–2005) noted that some obstetric consultants may lack the necessary expertise to carry out an emergency hysterectomy and advised in such circumstances "to call straight away for the aid of colleagues with greater gynaecological surgical experience." Consultant anesthesiologists should also be involved [5].

The UK Obstetric Surveillance System (UKOSS) previously studied women undergoing peripartum hysterectomy across the UK.

- 53% had uterine atony, 39% had a morbidly adherent placenta, and 10% had both.
- The case fatality rate was 0.6% and there were some common complications: 21% suffered damage to other structures (bladder damage was more likely with placenta accreta than uterine atony), 20% required further surgery, and 19% experienced additional severe morbidity [20].

Further work estimated the national incidence of peripartum hysterectomy at 4.1 per 10,000 births and identified that it was "strongly associated" with previous cesarean delivery. The risk increased with a number of factors including [21]:

- increasing number of previous cesarean deliveries
- maternal age >35 years
- parity >3.

Studies carried out by Wright in the USA have shown that:

- peripartum hysterectomy was associated with a significantly higher rate of mortality (×25) than gynecological hysterectomy [22]
- women undergoing peripartum hysterectomy at hospitals where the procedure was performed in high volumes had 71% lower perioperative mortality than women undergoing the procedure at hospitals where it was performed in low volumes [23].

# Adjuncts

## Interventional radiology

Interventional radiology (IR) is now recognized as a safe, effective, and minimally invasive treatment for PPH [24]. Catheters are inserted into the femoral artery and angiography is performed:

- if this identifies a bleeding point, the appropriate artery and any collateral vessels are embolized

- if no bleeding point is identified, the uterine artery is embolized
- if neither is possible due to anatomy, time, or hemodynamic instability, the anterior division of the internal iliac artery is embolized instead.

Arterial occlusion is used for prophylaxis in cases of abnormal placentation: catheters are inserted into the femoral artery allowing balloons to be placed in either the uterine or internal iliac arteries and, following delivery, the balloons are inflated to reduce bleeding (the ovarian arteries contribute approximately 10% of blood supply to the uterine fundus so bleeding may still be considerable).

- Embolization may be performed if necessary; however, PPH caused by abnormal placentation "seems particularly resistant" to it.
- Recent case reports demonstrate that previous arterial ligation does not rule out subsequent successful arterial embolization [25].
- Doumouchtsis demonstrated a success rate of 90.7% for arterial embolization [19]. Only four women were reported to SCASMM as having undergone arterial embolization in 2008, but three of them avoided hysterectomy [3].

Complication rates for embolization have been put at 6 to 9%.

- Most are minor and relate to arterial puncture or the contrast used.
- "Post-embolization syndrome" (nausea, abdominal pain, fever, and a mild leukocytosis) has been recognized.
- More significant complications are rare, and result from impaired blood supply to the pelvis: buttock ischemia and uterine/vaginal/cervical/bladder necrosis have all been reported [25].

Most women resume their normal menstrual cycle after embolization. Follow-up studies have recorded subsequent successful pregnancies but also recurrent PPH [26].

In cases where elective IR is contemplated, some advocate that delivery should take place in the IR suite (with its superior imaging equipment) [27], while others prefer the obstetric operating theater (where all surgical and anesthetic equipment is to hand, and IR can be performed using a C-arm image intensifier) [28]. Whichever is the correct view, the transfer of a sick and bleeding woman should not be undertaken lightly.

A survey of maternity units throughout the UK in 2007 found that:

- none had IR equipment on the labor ward
- 58% had an IR service but only 29% had 24-hour access to it
- 11% had transferred patients to other hospitals for IR [29].

## Intraoperative cell salvage

Over the past decade, there has been growing acceptance of cell salvage as a safe way of conserving blood and avoiding the risks of allogeneic transfusion. In 2005, the National Institute for Health and Clinical Excellence (NICE) published guidance about its use in conjunction with a leukodepletion filter (Pall LeukoGuard® RS Leukocyte Reduction Filter) [30] and the RCOG recommends it where intraoperative blood loss >1,500 ml is anticipated [31].

Adoption of cell salvage in obstetrics has lagged behind other specialities because of concern that it might precipitate amniotic fluid embolus (AFE).

- AFE is rare but accounts for a significant proportion of maternal deaths – 13 deaths in the most recent Confidential Enquiry [5].
- It is now believed to be an anaphylactoid reaction rather than embolic in nature.
- The role of fetal squames in AFE is still unclear as they have been found in otherwise healthy parturients.

The washing process has been found to reduce levels of alpha-fetoprotein to normal levels and the use of the leukodepletion filter prior to re-infusion significantly reduces leukocytes, lipid globules, and microaggregates.

Opinion is divided on whether cell salvage should begin:

- at the start of CS (using one suction device to collect all blood and amniotic fluid)
- or, postdelivery (using one suction device to aspirate as much amniotic fluid as possible then another to collect blood).

The latter approach is more common and intuitively seems safer, but the opportunity to salvage substantial volumes of blood is lost if the placenta is anterior. In fact, a study comparing the two approaches found:

- the combination of the washing process and the use of a leukodepletion filter meant there was no significant difference in contamination
- the filter significantly reduced fetal squames in most, but not all, cases (however, it is not validated for this use by the manufacturer)
- for maximum washing efficiency, only complete bowls in automatic mode should be processed [32].

Three cases of sudden, severe hypotension associated with the re-infusion of salvaged blood through a leukodepletion filter have recently been reported in the UK [33]. None of the patients suffered long-term harm – in each case the re-infusion was stopped and vasopressors given. In one case salvaged blood was then re-infused without the filter. The Serious Hazards of Transfusion (SHOT) Report 2009 includes similar incidents (www.shotuk.org/wp-content/uploads/2010/07/SHOT2009.pdf).

In an open letter, representatives of the UK Cell Salvage Action Group and the AAGBI advocate the routine use of a leukodepletion filter, but would "not hesitate" to remove it if necessary, "particularly when salvaged blood is required to be re-infused under pressure or if there is unexplained hypotension shortly following re-infusion of salvaged blood" [34].

Lack of training was pinpointed as the single biggest barrier to the use of cell salvage in a survey of UK maternity units. Other issues were the 24-hour availability of staff and equipment [35].

# Haemostatic agents

## Tranexamic acid

Tranexamic acid is the treatment of choice if there is evidence from thromboelastography of fibrinolysis but there are conflicting recommendations about its pre-emptive use:

- On the one hand, current RCOG guidelines state "there is a consensus view that fibrinolytic inhibitors (such as tranexamic acid) seldom, if ever, have a place in the management of obstetric hemorrhage" [2].
- On the other, the WHO's guidelines for PPH suggest that tranexamic acid may be used to treat PPH caused by uterine atony, lower genital tract trauma, or uterine rupture after other options have been tried [1], and the newly issued Guidelines for Resuscitation 2010 advise that tranexamic acid should be considered for the correction of life-threatening obstetric hemorrhage [36].

The WHO recommends a dose of one gram over one minute, with a further one gram after 30 minutes if bleeding continues, and has called for clarification of the role of tranexamic acid in treating obstetric hemorrhage as a priority. The evidence to date is sparse but promising:

- Following an earlier review of the role of antifibrinolytics in reducing transfusions in general surgery, a Cochrane review examined the role of tranexamic acid in preventing PPH and concluded that it appeared to decrease blood loss following vaginal delivery or CS, albeit based on two trials of "unclear quality" [37].
- The Clinical Randomisation of Anti-fibrinolytics in Significant Hemorrhage (CRASH-2) trial has since reported on the early administration of tranexamic acid to trauma patients, finding that it significantly reduced both all-cause mortality and risk of death due to bleeding without any apparent increase in vascular occlusive events [38].
- The most recent data supports its use in reducing blood loss after vaginal delivery [39] and CS [40].

The international WOrld Maternal ANtifibrinolytic trial (WOMAN) has been set up to assess the effects of the early administration of tranexamic acid on PPH after vaginal delivery or CS. It will run until 2015 and hopefully provide much needed answers.

## Recombinant activated factor VIIa

Recombinant activated factor VIIa (rFVIIa) may be used to treat intractable obstetric hemorrhage on an off-label basis. The RCOG advises that it may be given in cases of "life-threatening PPH" after consulting a hematologist.

There is broad consensus on dosage and conditions for use [41]. If conventional methods fail to stop the bleeding:

- give 90 μg/kg as IV bolus over three to five minutes. If no response after 20 minutes administer a second dose
- ensure patient has adequate clotting products on board including platelets and fibrinogen
- minimize acidosis, hypothermia, and hypocalcaemia.

Questions have recently been raised about the safety of using rFVIIa off-label:

- In May 2009, the European Medicines Agency requested the product characteristics for NovoSeven® (rFVIIa) be updated to mention the higher risk of arterial thromboembolism observed in off-label use and to state that it should not be used outside approved indications.
- A review assessing the safety of rFVIIa on an off-label basis found higher rates of arterial (but not venous) embolism with rFVIIa than placebo, particularly with age ≥65 years [42].

- The WHO has acknowledged that rFVIIa can be life saving but that it is also associated with "life-threatening side effects," is costly, and can be difficult to administer. It has therefore recommended that rFVIIa should only be used to treat PPH where the woman has "specific haematological indications" [1].

### Fibrinogen concentrate

Cryoprecipitate has been used to treat hypofibrinogenemia for years but fibrinogen concentrate, also derived from human plasma, has emerged as the most rapid and effective treatment. It quickly increases fibrinogen concentration and:

- does not need to be thawed
- can be given as a small volume bolus
- improves global coagulation results
- reduces the requirements for red blood cells, FFP, and platelets [43].

As fibrinogen concentrate is not yet licensed in the UK, it must be given on a named-patient basis [7]. Its use in obstetrics is limited, but a recent case series, involving six patients, suggests that it can quickly correct hypofibrinogenemia during obstetric hemorrhage [44].

### Topical hemostatic agents

These are widely used in other surgical specialties to promote local tissue coagulation and their successful use has been reported in obstetric hemorrhage. [45].

## Placenta previa, accreta and percreta

The placental site should be localized by grey Doppler at the 18- to 20-week fetal anomaly scan. If there is a low-lying placenta, further imaging should be carried out at 32 weeks [46]. Placenta accreta is most commonly associated with a combination of a low-lying placenta and uterine trauma from an earlier CS. However, the placenta need not be low lying, and the trauma may be as the result of other surgery (e.g. myomectomy, surgical termination of pregnancy, evacuation of retained products of conception or retained placenta) or an infection. Specialized imaging in terms of color Doppler and magnetic resonance imaging (MRI) may be necessary to estimate the degree of placenta invasion into the myometrium. In extreme cases of placenta percreta, the placenta invades through the myometrium into the peritoneal cavity (Figure 4.1).

As placenta previa and accreta both represent substantial risk factors for obstetric hemorrhage, the National Patient Safety Agency, the Royal College of Midwives, and RCOG have put together a care bundle advising on the delivery of such patients [47]. The key elements are:

- Delivery by planned elective CS at 38 to 39 weeks in cases of placenta previa (40% of women will have an emergency CS before 38 weeks). The RCOG recommends delivery of suspected placenta accreta cases at 36 to 37 weeks [46].
- Multidisciplinary involvement in pre-operative planning: delivery should be planned and directly supervised by a consultant obstetrician; blood, blood products, and a level-2 critical care bed should be available on site; cell salvage and IR should be considered, or if neither is available, a transfer should be considered to a unit that can offer one or, ideally, both.

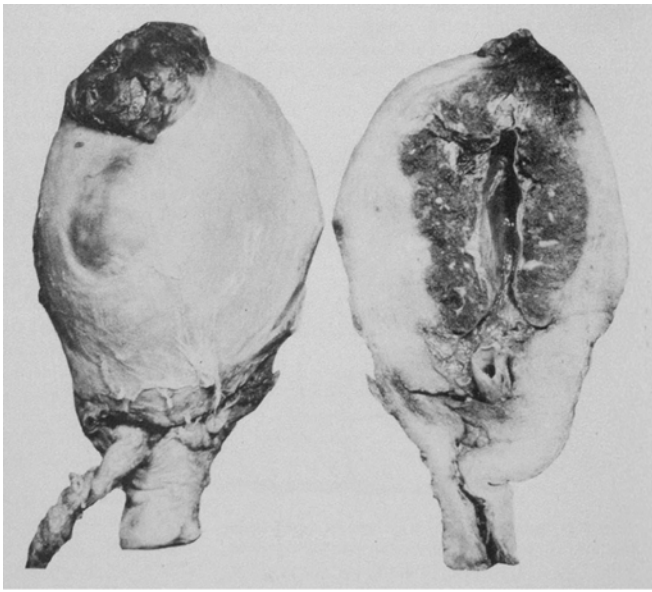

**Figure 4.1** Placenta percreta.

- Discussion of interventions and possible outcomes with the patient to ascertain any preferences she may have.
- Direct involvement of a consultant obstetric anesthesiologist during antenatal planning and surgery.
- The surgical approach should take into account the location of the placenta in accreta cases.
- Recommendations for care when the placenta is left in place.

There is a body of opinion that if the placenta fails to separate, it should not be actively removed at delivery as this may significantly increase early maternal morbidity and is associated with greater blood loss than either leaving the placenta in place or proceeding to hysterectomy [48].

The placenta should only be left in situ if there is minimal bleeding, hemodynamic stability, and a desire for future fertility as there is risk of significant bleeding and infection for several months following delivery:

- Placental re-absorption should be monitored with serial serum beta-human chorionic gonadotropin (ßHCG) and imaging.
- Possibility of infection should be monitored with serial full blood count and C-reactive protein (FBC/CRP). Antibiotics may reduce the risk of infection [49].
- The use of methotrexate to aid placental re-absorption is not routinely recommended [2].

If the placenta separates and bleeding ensues, conventional surgical methods must be used and hysterectomy is likely. Anecdotal evidence from the USA suggests that preoperative ureteric stents may reduce early morbidity [48].

The UKOSS is currently gathering data on placenta accreta in order to estimate national incidence, management (including anesthetic), and outcomes of the condition.

## Women who refuse blood

There is an increased risk of death from hemorrhage in these women. There must be full and frank discussion antenatally as to what an individual patient will accept as this varies between patients. The fatal consequences of the refusal of blood must be stressed. A signed advance directive should be in the patient's notes [31].

Key issues for management are:

- optimize hematinics
- active management of third stage, and prophylactic oxytocin infusion postdelivery
- early recourse to surgery with all adjuncts being considered (cell salvage, rFVIIa, tranexamic acid).

## Anesthesia

The anesthetic used for such cases is at the discretion of the anesthesiologist but very much depends on individual circumstances [46].

- Elective placenta previa cases can be managed with a regional technique as this allows the woman to remain awake and is associated with less blood loss.
- Consideration should be given to a combined spinal–epidural (CSE) technique to allow prolonged surgery.
- An anterior placenta previa in the presence of a previous cesarean section scar, or a known placenta accreta, may well be better managed with general anesthesia (GA) [50].
- Regional anesthesia is an option but the patient and the anesthesiologist should be prepared for conversion to GA if there is hemodynamic instability.

The UKOSS is currently gathering data on the type of anesthetic used in placenta accreta cases.

In emergency cases, massive blood loss or hemodynamic instability dictate that general anesthesia is used. Senior staff should be involved in all cases of major hemorrhage. Most patients should be managed postpartum in a high dependency setting or critical care unit.

## "Fire drills"

Drills should be run regularly to raise awareness, ensure guidelines are understood and followed, and that hospital systems (portering, laboratory communication) are in working order. They have been endorsed by the RCOG, CEMACH, and the Obstetric Anaesthesiologists' Association (OAA). The Bristol, UK PROMPT (PRactical Obstetric Multi-Professional Training) course has demonstrated that incorporating drills into base hospitals can improve obstetric and perinatal outcome (www.prompt-course.org).

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Chapter 5

# Anesthetic drugs and the developing fetal brain

Dr A Gauthier and Dr C Bradbury

## Introduction

- Over the last decade there has been an explosion of literature published on the neuroapoptosis induced by anesthetic drugs in animals and the potential impact this may have on fetuses, neonates, and infants.
- Millions of pregnant women, neonates, and infants receive anesthetic drugs every year.
- General anesthesia during pregnancy may be required for cervical cerclage, incidental or emergency surgery, in utero fetal surgery, or for cesarean section.
- Inhalational nitrous oxide is commonly administered for labor analgesia.
- Neonates and infants may themselves require general anesthesia.
- The sequelae of neurotoxicity include adverse health effects, impaired cognitive function including psychomotor, memory and attention deficits, affective disorders, and degenerative disorders, although the impact of anesthetic drugs on these outcomes is unknown.

## Fetal brain development

The first two weeks of development following fertilization, involve rapid cell division and the formation of an embryo. During this period, the embryo is typically not susceptible to teratogens, but rather exposure to substances either damages enough cells to cause embryonic death or such few cells such that there is no effect on the further development of the embryo [1].

- The period of organogenesis occurs between weeks 5 and 10 of gestation (or three to eight weeks by embryonic age). This is the period during which is the embryo is most susceptible to exposure, and the result is more likely to be major structural and morphologic abnormalities [1].
- The fetal period begins by the end of the tenth week by gestional age (or eighth week by embryonic age) and exposure during this period results in functional defects and minor morphological abnormalities. The central nervous system has the longest period of susceptibility, and because neuronal development continues even after birth, exposure during the postnatal period may also result in functional defects.

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- The period of brain growth when synaptic differentiation occurs, also called synaptogenesis, occurs from the sixth month of gestation to 24 months after birth in humans. This is in contrast to rodents and primates, where it occurs mainly during the postnatal period [2]. Apoptosis, or programmed cell death, is an important component of synaptogenesis, and occurs over years in humans. In fact, apoptotic neurodegeneration occurs naturally in up to 70% of neurons and progenitor cells [3].

## Teratogenicity

The teratogenicity of a substance is multifactorial and includes species susceptibility, dose, duration and timing of exposure, and genetic predisposition.

- Manifestations of teratogenicity include death, structural abnormality, growth restriction, and functional deficiency.
- The stage of gestation at which exposure occurs determines the target organs or tissues, the types of defects, and the severity of damage [1]. Shepard's *Catalog of Teratogenic Agents* [4] discusses the above characteristics of teratogens, and lists all known human teratogens.
- Anesthetics are listed as unlikely teratogens by this source. Although anesthetic agents have not been found to be teratogenic, they have been shown to influence neuronal apoptosis and fetal/perinatal brain development.

## Mechanism of anesthesia-induced neurotoxicity

Anesthetics have been shown to cause apoptosis in numerous cell types as well as cause neurotoxicity in a concentration- and time-dependent manner in in-vitro and in-vivo models, and mechanisms have been proposed based on the receptor activity of the anesthetic agents (reviewed in [2]).

Anesthetics fall under three categories:

- N-methyl-D-aspartate (NMDA) receptor antagonists (inhibitory), e.g. ketamine, nitrous oxide, xenon
- λ-aminobutyric acid ($GABA_A$) receptor agonists (excitatory), e.g. benzodiazepines, barbiturates, propofol, and etomidate
- inhalational anesthetic agents likely exert their effects on both receptor pathways in addition to other poorly understood mechanisms.

The first report of anesthetic-induced neuronal damage was by Ikonomidou *et al.* in 1999, where they published that NMDA receptor antagonists induced extensive neuroapoptosis in the developing rat brain [5]. These findings have been repeated numerous times and expanded to include $GABA_A$ receptor agonists and it has also been reported that exposure to a combination of anesthetic agents worsens the neurotoxic effects, particularly with a combination of the two classes [6–9]. These effects have been extensively reviewed [3, 10–15].

- Further evidence points to the time of exposure as being critical in determing the outcome, meaning that exposure during periods of peak synaptogenesis results in increased neurotoxicity [9, 16].

- It is hard to extrapolate this animal data to humans since the critical periods of synaptogenesis vary widely between humans, non-human primates, and rodents, as discussed above.

It has been suggested that exposure to anesthetics leads to abnormal neuronal inhibition, triggering apopotosis of susceptible neurons [8, 17].

- Apoptosis is an energy-consuming process that ensures the safe elimination of cells, such that their toxic contents are not released to damage surrounding cells.
- This is in contrast to necrosis, in which cellular contents are released and an inflammatory state is generated. Neurodegeneration, or apoptosis, is observed by exposure to both NMDA receptor antagonists and $GABA_A$ receptor agonists and occurs by both intrinsic (receptor mediated) and extrinsic (mitochondrial mediated) apoptotic pathways, although the exact mechanisms remain unclear.

There are numerous cellular signaling molecules involved in the apoptotic pathway that are conserved among mammals including caspases, FAS, Bax, ERK and Bcl-2, but studies have shown that the absence of these pathways in knockout animal models does not lead to significant morphological or functional defects [18], suggesting that non-apoptotic mechanisms of synaptogenesis and fetal development exist. There are also other reports of neuronal cell death being regulated by an excitatory mechanism independent of apoptotic pathways [19], suggesting that exposure to neuroexcitatory substances might cause functional defects in the developing fetus, such as exposure to $GABA_A$ receptor agonists.

Animal studies have also demonstrated that anesthetic exposure is associated with inhibition of neurogenesis or synaptogenesis.

- Firstly, anesthetics have been shown to decrease brain-derived neurotrophic factor (BDNF) [20], a protein supporting neuronal survival, growth, and differentiation. Isoflurane appears to inhibit the conversion of pro-BDNF into BDNF via inhibition of the conversion protein tissue plasminogen activator, resulting in enhanced apoptosis [21].
- Secondly, inhalational anesthetics have been shown to increase dendritic density in fetal rat brains, thus impairing the development of normal dendritic spine architecture [22].

The majority of the histological data demonstrating a link between anesthetic agents and neuroapoptosis comes from experiments in rats and mice. Similar findings have also been shown in guinea pigs [23]. Although it would clearly be unethical to reproduce such studies in humans, similar results have been demonstrated in primate studies, both with fetal and neonatal exposure [9, 24]. The applicability of these results has been raised by the same authors as they question whether the effect is exposure to the anesthetic or related to an ischemia–reperfusion phenomenon [25].

## Susceptibility

In rats, although not undisputed [26], it has been shown that peak susceptibility to anesthesia-induced neuroapoptosis coincides with the time of peak synaptogenisis [5, 17]. This occurs on the seventh postnatal day and subsequently this is the age of rat that has been most extensively studied. Although rats are less susceptible before the first and after the fourteenth postnatal day [27], neuroapoptosis has been demonstrated in fetal rats of 21 days gestational age after high concentrations of isoflurane [28].

Various methods have been employed to correlate developmental events between different species [29] and this has led to differing predictions for the peak susceptibility of humans.

- The susceptibility period for humans is widely quoted to be between the third trimester and three years of age [5, 17, 30, 31].
- More recent estimates place the most vulnerable period at the 17th to 20th week [3] and 20th to 26th week of gestion [29].
- An alternative method of correlating developmental events between different species uses neuroinformatics [29]. This technique indicates that postnatal day seven in the rat correlates with 17 to 23 weeks gestation in the human and the susceptibility period is over before the human fetus reaches term.
- These varied estimates have resulted in anxiety about both pediatric anesthesia and anesthesia of the parturient. This would suggest that the impact of anesthesia is greater on the unborn child and premature neonate than on the term baby or infant.

## Anesthetic drugs and brain development in animal models

In an extensive review on the effects of general anesthetics on developing brain structure and neurocognitive function [3], the evidence for individual anesthetic agents causing neurodegeneration and functional impairment was discussed. This is summarized below.

### Benzodiazepines

- Diazepam and clonazepam resulted in neurodegeneration in neonatal rat pups in a dose-dependent manner, as well as in mice.
- Diazepam-induced neurodegeneration in mice, however, did not lead to impaired behavior or neurocognitive performance deficits in adulthood.
- Midazolam has not been found to induce neurodegeneration in rat pups or rat neuronal cultures, although at similar doses it triggers neuroapoptosis in neonatal mice.

### Barbiturates

- Pentobarbital and phenobarbital have both been shown to cause neurodegeneration in rat pups; however, thiopental administration to neonatal mice did not lead to neurodegeneration nor long-term behavioral or learning impairment.

### Ketamine

- Ketamine administration results in dose-dependent neurodegeneration in neonatal rats; however, with low doses resulting in plasma levels similar to those that would be measured during anesthesia in humans, there was no neurodegeneration detected. These data were also repeated in mice.
- In mice, only supraphysiological doses of ketamine resulted in neurodegeneration with subsequent abnormal behavior, impaired learning acquisition, and memory retention in adulthood.
- In non-human primates, prolonged exposure in prenatal and neonatal rhesus monkeys, using ketamine infusions with supraclinical doses, demonstrated time-dependent and dose-dependent increases in neuronal degeneration.

- Concomitant administration of non-injurious doses of ketamine and GABAergic anesthetics significantly increased neurodegeneration and led to learning impairment in adulthood.

## Propofol

- In mice, propofol increases neurodegeneration, leading to adult behavioral and learning impairment, at doses of 60 mg/kg alone, or at 10 mg/kg plus ketamine.
- With doses of 10 mg/kg or less, although there was increased neurodegeneration, there were no measurable neurological sequelae.
- There is no evidence that propofol, at clinically useful concentrations, leads to neuronal injury.

## Etomidate

- There are no studies on etomidate and neurodegeneration or neurocognitive performance.

## Halothane

- Prenatal halothane exposure in clinical doses leads to learning impairment in adulthood.

## Isoflurane

- In neonatal animal models, isoflurane has been linked to apoptotic neurodegeneration in newborn rats, mice, guinea pigs, and piglets.
- In rats, there were associated impairments in learning and memory retention later in adulthood; however, these deleterious effects were absent in mice.
- Co-administration of xenon and dexmedetomidine prevented isoflurane-induced neurodegeneration in neonatal rats.
- Interestingly, isoflurane was found to be protective during hypoxia–ischemia in both in vitro and in vivo animal models of the developing brain.

## Desflurane

- There are no studies on neurodegeneration; however, it has been show to be protective during episodes of hypoxia–ischemia in a hypothermic cardiopulmonary bypass brain ischemia model in piglets.

## Sevoflurane

- Data in neonatal mice suggest that sevoflurane protects developing neurons during brain ischemia, and no data exists on its impact on neurodegeneration.

## Nitrous oxide

- There is no significant increase in neurodegeneration in neonatal rats exposed to nitrous oxide alone, although high doses in combination with isoflurane resulted in increased neuroapoptosis.

- Nitrous oxide has been shown to be neuroprotective from excitotoxic neurodegeneration.

### Xenon

- Xenon at 0.5 MAC protected neonatal rats from neurotoxic affects of isoflurane plus nitrous oxide.
- There are no data on long-term neurocognitive function after neonatal exposure to xenon.

### Withholding anesthesia

- Neonatal animal studies have demonstrated the deleterious effects of painful stimuli or stress on increasing stress hormone levels, neuronal cell death, and abnormal behavior.

### Drug combinations

- Although not associated with neuroapoptosis when given in isolation, sodium thiopental has been shown to exacerbate neuroapoptosis when given with ketamine [6].
- Similarly, nitrous oxide is associated with neuroapoptosis when combined with isoflurane [32].
- The combination of midazolam, nitrous oxide, and isoflurane, termed the "triple cocktail," when given to infant rats, results in particularly pronounced neuroapoptosis with associated learning and memory deficits that persists into adulthood more so than with isoflurane alone, or isoflurane and nitrous oxide [8]. As mentioned above, neither nitrous oxide nor midazolam alone have been shown to cause neuroapoptosis in rats.

## Problems with the animal models

The experimental models used to administer the anesthetic agents are not without limitations and this has generated some controversy. The applicability of the animal data to the developing brain of a human fetus, neonate, or infant being exposed to a routine anesthetic is therefore questionable. Some of the issues that have been debated are as follows [17, 33–35]:

- There may be a species difference such that neuroapoptosis may not be demonstrable after anesthetic exposure in the developing human brain.
- Neurological development in humans takes years and is far more protracted than in rodents. Subsequently, the periods of anesthetic exposure studied in rats and mice would be the equivalent of days or weeks of anesthetic exposure in humans. This is clearly not a good reflection of the timeframe involved for intraoperative anesthetic exposure although could potentially be seen on neonatal or pediatric intensive care units. Nonetheless, as little as five hours of exposure to anesthesia results in neuroapoptosis in non-human primates [24]. These data indicate that more clinically relevant exposure periods may have similar results in humans.
- The doses of the anesthetic agents given to the animals were, at least in some studies, greatly in excess of those that would be given clinically.
- In the majority of the studies, fine control of the animal's physiological parameters under anesthesia was lacking. It is technically difficult to monitor and prevent hypercarbia, hypoxia, blood pressure changes, and hypoglycemia in rodents, although this was achieved in the guinea pig and monkey studies [9, 23, 24].

- In the animal experiments, anesthesia was given without surgery. In most of the studies there was an absence of painful stimuli and any associated stress response that would accompany surgery in a clinical setting. The interaction between the excitatory neuronal input from surgical stimuli and the inhibitory effect of anesthesia is a key factor that is missing in the experimental data from the animal models.

## Neurobehavioral data from animals

Multiple studies have demonstrated neurobehavioral deficits in animals following exposure to anesthesia in early life. Most of the early studies were in rats but similar positive findings have been reported in several studies with mice. The deficits have been elicited in a variety of different tests that assess various aspects of learning and memory. Two types of tests that have been used recurrently to show deficits are:

- circular water maze tests, in which rats are trained to find a platform in a circular water bath [7, 16, 26, 36]
- the radial-arm maze, a test in which there are eight arms leaving a central platform and food is placed at the end of the arms for the rats to learn to find [6, 7, 8, 36, 37].

Many published studies have used other tests of learning, behavior, and socialization, with several tests often being reported in a single publication [6–8, 16, 26, 36, 38–41].

- Mostly positive findings are reported in at least some of the tests, although in several studies non-significant differences were also reported.
- Some studies, however, did not show any negative impact on neurobehavioral development after anesthetic exposure [31].
- Indeed one study notably showed a protective effect [42]. In this study there were four experimental groups. These were (a) undisturbed control rats; (b) rats receiving painful 4% formalin injections; (c) rats receiving ketamine alone; and (d) rats receiving both ketamine and 4% formalin injections. With the radial-arm maze, formlin injections were shown to result in reduced exploratory behavior and an increased time to bait consumption. These effects on memory testing were avoided by the administration of ketamine. The results of this study suggest that even if anesthetic agents are causative of neurodevelopmental deficits in animals, the absence of such agents during painful stimuli results in a comparatively worse deficit.

## Human data supporting neuroapoptosis

The evidence for neuroapoptosis in animals is convincing but it remains to be established whether the phenomenon occurs in humans and if it does, whether it is clinically relevant.

For ethical reasons there is no histological evidence of neuroapoptosis in humans. Much of the data that suggests that the phenomenon occurs in humans comes from cohort studies of the pediatric population. These studies effectively demonstrate an association between anesthesia and neurodevelopmental problems.

- An association has been demonstrated between premature or extremely low birth weight babies having general anesthesia and sensorineural impairments [43].
- Extremely low birth weight babies, having received surgical treatment for necrotizing enterocolitis, have a higher incidence of neurodevelopmental impairment than either

infants having received medical treatment or infants without necrotizing enterocolitis [44, 45].

- Infants having had anesthesia for inguinal hernia repair are more likely to have developmental or behavioral problems than matched controls [46].
- Children receiving more than one anesthetic have shown an increased incidence of learning difficulties [47].

Not all studies have demonstrated a statistically significant association between anesthesia and neurodevelopmental impairment.

- Children having urological surgery before two years of age have a statistically non-significant tendency towards more behavioral problems [48].
- Pre-term infants have been shown to have a statistically non-significant increase in moderate or severe neurological disability if exposed to sedative medication for longer than seven days [49].
- Surgical ligation of a patent ductus arteriosis has not been associated with neurodevelopmental impairment [50].

Published studies predominantly support the association between anesthesia and neurodevelopmental problems in humans but none can demonstrate causality. The neonates and infants studied in these cohorts have multiple reasons for going on to have neurodevelopmental impairment. There are multiple confounders that could bias the results such as the medical condition requiring surgery, the surgical procedure itself, the effect of poor health on schooling, or the psychological impact of illness and having an operation.

One recent study in monozygotic twins would suggest that confounding factors play a large role in the association between anesthesia and neurodevelopmental problems [51].

- Twins, out of which only one had received an anesthetic, did not show any difference in either educational achievement or cognitive problems. This was apparent when the anesthetic was received before the age of three, thus at a time when the child might be at particular risk, or received at any time until the age of twelve at which point the study terminated. This result strongly suggests that anesthesia itself was not causative of learning difficulties.
- The study also demonstrated that both twins in a pair, out of which only one received an anesthetic, were at risk for learning difficulties. This was elucidated by comparison to twin pairs, out of which neither had received an anesthetic. This corroborates an association between anesthesia and learning difficulties but strongly suggests that anesthesia is not the causative factor. Indeed, it suggests that there may be a genetic predisposition to requiring surgery and thus anesthesia, which is also related to learning difficulties, or that the causative factor is environmental.

Although this study is important, it does have limitations [52]. The key concerns that have been raised are:

- Only 110 discordant pairs (in which only one twin had received an anesthetic) were studied for educational achievement and just 56 discordant pairs were studied for cognitive problems. It is therefore possible that the study was underpowered to find a difference between the discordant twins.

- The data does not differentiate between children having received one or multiple anesthetics. As this may be a factor in whether neurodevelopmental problems ensue [47], a difference between twins of a discordant pair, in which one received multiple anesthetics, may have been missed.

## Obstetric impact

If the neuroinformatic approach to extrapolating the timeframe of susceptibility in humans is correct then the developing fetus is far more at risk than the pediatric patient. Anesthetics given during pregnancy, and even intrapartum analgesics such as nitrous oxide, may promote neuroapoptosis.

- A study of a large birth cohort, with 5,320 children, demonstrated no significant difference in the incidence of learning disabilities at age 12 years, between those who had been delivered vaginally and those delivered by cesarean section under general anesthesia [53].
- Interestingly, in this study cesarean delivery under regional anesthesia appeared somewhat protective against the development of learning disabilities. The results were unchanged when cesareans of an emergent nature and children who had received anesthetics in early childhood were excluded.
- Children with severe learning disabilities had been excluded from the cohort and this may have altered the results.
- Time from induction of anesthesia to delivery of the neonate is usually short. General anesthesia for surgery other than cesarean section may have more impact.
- It is unclear which patients in this study used systemic labor analgesics. Although these are administered at sub-anesthetic levels, they could be used over several hours and may also be associated with neuroapoptosis. This would potentially influence the results, reducing any advantage of vaginal delivery over cesarean section under general anesthesia.

There have also been studies that explore early neurological problems in neonates who had been exposed to anesthesia in utero [54–58]. Some of these studies looked specifically at anesthesia exposure during delivery [56, 58]. Within these studies, multiple behavioral responses have been examined, some of which are known to correlate with later IQ. The majority of the studies, but not all [58], demonstrated poorer performance in those exposed to anesthesia. Few of these studies involved data collection on the neonates beyond four weeks of age. One, which collected data at 20 weeks of age, demonstrated that the earlier deficits were no longer statistically significant [56]. At this data collection point many of the infants had been lost to follow-up, which reduced the power of this result. A further study collected follow-up data when the children had reached four years of age [55]. In this study, the Peabody Picture Vocabulary Test IQ results revealed impairment in those who had been exposed to anesthesia in utero. However, this study combined the results from subjects exposed to either general or local anesthesia, with the majority only being exposed to local anesthesia.

Although data from the studies that look at early neurological outcome suggest that there is some impairment, there aren't any robust data to support the assertion that exposure to general anesthesia in utero results in any long-term neurological deficit. Equally there are insufficient data to refute the assertion.

## Proposed neuroprotective strategies

If anesthesia is proven to cause neurodevelopmental problems in humans then additional research will need to be undertaken in order to determine which anesthetic agents pose the least risk, and if there are any measures that can be taken to protect patients from the insult. To date, various agents and strategies have been suggested to ameliorate the adverse effects of anesthesia on the developing brain. The supporting evidence is limited but arises from animal experiments in which a reduction of anesthesia-induced neuroapoptosis has been achieved.

- Xenon has been shown to reduce the neuroapoptotic effect of isoflurane in rats [32]. The data in mice has been slightly less impressive, where although xenon reduced the adverse impact of isoflurane, neuroapoptosis was still evident histologically [59]. Interestingly, unlike in rats, when xenon was administered alone to mice, it actually produced some neuroapoptosis.
- Dexmedetomidine has been demonstrated in rats to reduce neuroapoptosis associated with isoflurane in a dose-dependent manner. Neuroapoptosis only becomes similar to controls at a dose of 25 μg/kg, administered on three occasions during a six-hour exposure to anesthesia. Nonetheless, when given at this dose, it also prevents the anesthesia-related neurocognitive deficit shown in controls [60].
- Lithium has been shown to abolish anesthesia-related neneuroapoptosis in mice but can also reduce natural neuroapoptosis to a level lower than seen in control animals [61].
- Melatonin reduces anesthesia-induced neuroapoptosis in rats in a dose-dependent manner. When 1 mg/kg is given subcutaneously it causes a 30 to 40% reduction, yet only at 20 mg/kg does it achieve a 75 to 90% reduction in damage [62].
- L-carnitine has also been proposed as an agent that could be useful in preventing anesthesia-induced neuroapoptosis [63].
- Hypothermia has also shown promise in preventing neuroapoptosis in mice [15].

## Future areas of study

Future work in the area needs to establish whether anesthesia-induced neuroapoptosis is of importance in humans. Several groups of researchers are in the process of conducting large studies in an attempt to clarify the risk associated with anesthesia. A recent series of three articles described four ongoing studies. These studies are:

- A prospective observational study of an existing cohort of children who were exposed to anesthesia under the age of three years. The IQ and neurocognitive function of these children will be compared to developmental age-matched siblings [64].
- A multicenter randomized controlled trial of general vs. spinal anesthesia for inguinal herniorrhaphy in neonates. The IQ at five years of age will be compared [65].
- An epidemiological study comparing the neurocognitive outcome of a large cohort of infants exposed to anesthesia before the age of one year to that of the general population [66].
- An epidemiological study using neurodevelopmental data that has already been collected on a cohort of children. A second data source is being used to stratify these children according to anesthesia exposure [66].

## Conclusions and key points

- There is considerable evidence for anesthesia-induced neuroapoptosis with associated neurodevelopmental deficits in animals.
- There is some data suggesting that the phenomenon may exist in humans, but it is not robust and multiple confounders exist. As a result there is insufficient evidence to alter current practice.
- Surgery cannot be ethically performed without anesthesia. Although it may be prudent to avoid unnecessary surgery in pregnant women, neonates, and infants, essential surgery must clearly be performed.
- Although there lacks sufficient evidence to produce clear guidelines about elective surgery in the prenatal and early postnatal periods, any elective surgery should include discussion with the pediatric surgeon, the anesthesiologist, and the parents regarding neurotoxicity and the potential impact on neurological development, as discussed in the editorial by Sanders and Davidson [67].
- With the current evidence, surgeries should proceed if the risk of not having the surgery outweighs the potential risk of harm to the fetus or neonate.

## Further reading


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Chapter 6

# Ultrasound guidance for epidural anesthesia

Dr M Kynoch, Dr K Rao, Dr M Hasan and Dr N Robinson

## Introduction

- Central neuraxial blockade (CNB) remains the gold standard technique of providing both analgesia and anesthesia in the obstetric population, a fact which is unlikely to change in the near future.
- Neuraxial blockade includes placement of epidural catheters, spinal injections, and combined spinal–epidurals. The technique is nicely summarized in this quote: "[it is] a complex amalgam of clinical judgment, technical skills, materials and equipment, drug delivery systems, patient supervision and care pathways" [1].
- Current techniques for implementing neuraxial blockade rely primarily on the clinician establishing the position of anatomical surface landmarks, which will guide them toward correct placement of the needle.
- This assessment of the spine involves a careful examination to assess vertical alignment of the spine, identification of the iliac crests to establish the level of L3/4 (Tuffier's line), palpation of the spinous processes and subsequently interspaces before the introduction of a needle into one of these interspaces.
- Ultimately this remains a blind technique and an invasive procedure, relying on correct assessment of surface anatomy. This means that current techniques for CNB, as well as providing effective analgesia and anesthesia, have the risk of leading to failure and complications leading to potential patient harm from inaccurate knowledge of exactly where the needle tip is placed.
- To that end we, as obstetric anesthesiologists, must continue to strive to ensure that our practice remains as safe as possible and utilizes any advances within medicine that may make this technique easier and or safer.
- The use of ultrasound to aid the placement of epidurals and spinal injections in the obstetric population was first published over 25 years ago, and has become an area of interest in the last decade, culminating in the UK's National Institute for Health and Clinical Excellence (NICE) supporting its use in catheterization of the epidural space by publishing guidelines to this effect in January of 2008 [2].

*Controversies in Obstetric Anesthesia and Analgesia*, ed. Ian McConachie. Published by Cambridge University Press. 

## The development of diagnostic ultrasound

- The human ear can sense audible sound waves in the frequency range of 20 Hz to 20 kHz. The term "ultrasound" refers to sound waves with a frequency greater than 20 kHz or 20,000 cycles per minute.
- An Italian biologist, Lazzaro Spallanzani, can be credited for first discovering ultrasound when in 1794 he demonstrated the ability of bats navigating accurately in the dark was through echo reflection from high-frequency inaudible sound [3].
- During World War I, the use of ultrasound as an application was seen with the development of sonar (sound navigation and ranging) for the purpose of the underwater navigation of submarines.
- During the 1930s, ultrasound began to be used in ship building, as a tool to look for any flaws in metal, and was particularly useful for the metal hulls of large ships or the armor plates of battle tanks.
- It was from here that two researchers are noted in the subsequent development of ultrasound in medical diagnostic use:
  - Dr Karl Dussik was an Austrian psychiatrist and neurologist, who first published a paper in 1941 entitled: "Uber die moglichkeit hochfrequente mechanische schwingungen als diagnostisches hilfsmittel zu verwerten" [On the possibility of using ultrasound waves as a diagnostic aid], based on his research of the use of transmission ultrasound of the brain.
  - Professor Ian Donald was a Scottish obstetrician who developed practical technology and application for ultrasound in the 1950s [3].
- Since then, its application within all aspects of medicine has grown and in the last ten years there has been increasing interest in its use for assessment of neuraxial anatomy and to aid CNB techniques. The two techniques that have been studied are using ultrasound as a pre-procedural tool or by using it for real-time imaging during the procedure, both of which are described in detail later in the chapter.

## The physics behind ultrasound

- Creating an ultrasound image is done in three steps:

  producing a sound wave
  receiving the echoes
  interpreting those echoes.
- Ultrasound waves are produced by making use of the piezoelectric effect of crystals acting as a transducer.
- Piezoelectricity is the ability of specific materials, notably crystals and certain ceramics, to generate an electrical charge after mechanical stress or movement is applied to them.
- Ultrasound waves are produced making use of the reverse effect, with the production of pressure or sound waves, following the mechanical movement of piezoelectric crystals after an electrical current is applied across them, causing the crystals to expand and contract as the polarity of the voltage changes.
- Most diagnostic ultrasound transducers use artificial polycrystalline ferroelectric materials such as lead zirconate titanate.

- The sound waves emitted from the crystal are similar to sound waves being emitted from a loudspeaker. The echo waves are the reflected ultrasound waves returning to the transducer.
- The ultrasound transducer oscillates between the two "modes" of first generating a sound wave and then followed by a pause enabling it to receive and analyze reflected echoes.
- When an echo is returned to the transducer it again exhibits the piezoelectric effect and causes the same crystals, which initially formed the sound wave, to then generate an electrical impulse in response to the mechanical movement from the returning sound wave (Figure 6.1).
- In order to form the image the machine needs to establish the direction of the echo, its strength, and the length of time taken for the echo to be received after the original sound wave was emitted. Using these three pieces of information it can form an image.
- When a sound wave encounters a material of different density it is reflected back and this is called "acoustic impedance." The time taken for this echo to return can be measured and used to calculate the depth of the tissue that caused the echo.
- Tissues of a high density, such as bone, are highly reflective and produce a strong echo represented on the image screen as a bright spot, as opposed to tissues that are poorly reflective, such as cavities containing liquid (e.g. blood, bile, and ascites), which are represented on the screen as a black spot.
- This is because tissues with a high water content allow passage of the waves away from the ultrasound probe well, rather than reflecting them back as an echo – just think of the great distances sound waves travel underwater allowing whales to communicate with each other over vast distances.
- The frequencies of the ultrasound waves used for medical imaging are in the range 2 to 15 MHz. Higher frequencies have smaller wavelengths and give higher quality, more detailed images. However, the sound waves at these higher frequencies are more attenuated than those at lower frequencies and therefore if a greater depth of penetration of tissue is required, then a lower frequency wave is used, such as 2 to 5 MHz, the trade-off being a less detailed image.

In practice remember that:

- To use ultrasound to help visualize a blood vessel just below the skin a *high* quality picture is required therefore the probe uses *high* frequencies. A lower frequency probe allows images to be seen at a deeper or *lower* level, but the images gained are equally of a *lower* quality.

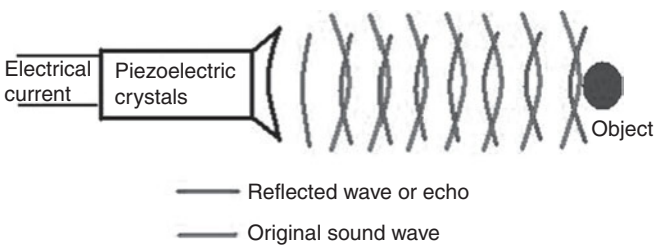


**Figure 6.1** Diagrammatic representation of the principles of sonar. Reproduced with the permission of *CPD Anaesthesia* (www.rila.co.uk).

- For ultrasound for the epidural space therefore the lower frequency probe of 2 to 5 MHz is used allowing deeper penetration of the ultrasound waves.

## How is ultrasound used for epidural space imaging?

- Epidural ultrasound is particularly challenging because the structures being imaged are surrounded by a bony encasement, which only allows a narrow acoustic window for the ultrasound beam.
- In addition, the structures are located deeper than those seen when using ultrasound for peripheral nerve blocks or placement of central lines.
- There are two useful acoustic windows for assessment of the lumbar spine anatomy and therefore only two patterns need to be recognized: one for the paramedian longitudinal approach and the other for the transverse approach [4].
- This makes ultrasound easier to use for this application than for peripheral nerve blocks where different sonographic patterns must be recognized.
- However, a thorough knowledge of lumbar spine anatomy is still required for the understanding of the sonoanatomy information being generated.
- The different pieces of anatomy visualized with ultrasound of the back are noted in Table 6.1.
- The anatomy noted in Table 6.1 should form a mental list of structures to locate for each of the two approaches, both of which are described later.
- Each of these approaches can be applied one of two ways: real-time visualization of the space while undertaking the procedure or pre-procedural visualization of the epidural space.

### The transverse approach

- To scan transversely, place the probe horizontally, perpendicular to the long axis of the spine, and try to identify the interspinous space as dictated by the different sonoanatomy seen in Figures 6.2 and 6.3.

**Table 6.1** Anatomy identifiable by lumbar ultrasound. Reproduced with the permission of *CPD Anaesthesia* (Rila.co.uk).

| Longitudinal approach | Transverse approach |
|---|---|
| Sacrum | Spinous process |
| Articular processes | Articular process |
| Facet joints, ligamentum flavum, and posterior dura mater | Ligamentum flavum and posterior dura mater |
| | Anterior dura, posterior longitudinal ligament, and vertebral body |

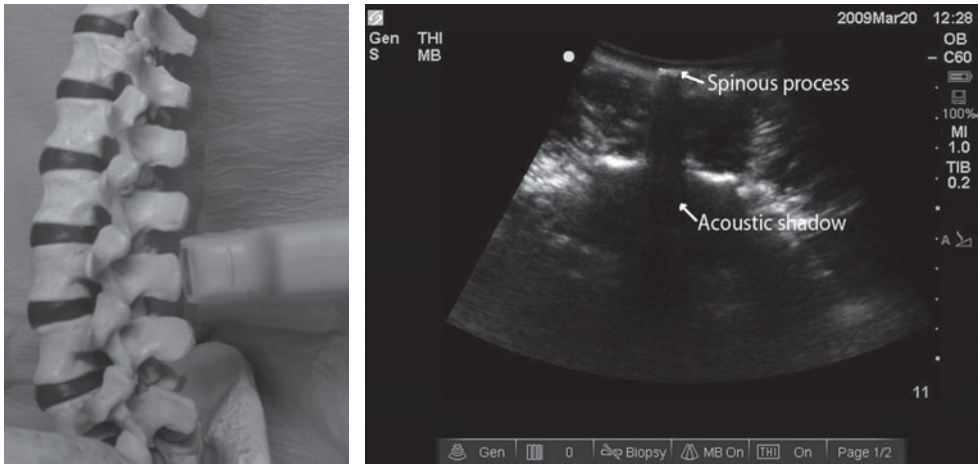


**Figure 6.2** (a) Probe position as related to the bony spine to give the ultrasound image seen in (b).
(b) Typical image seen with ultrasound when the probe is overlying the spinous process. The spinous process is seen as a hyperechoic signal close to the skin continuing as a vertical acoustic shadow fanning out below.

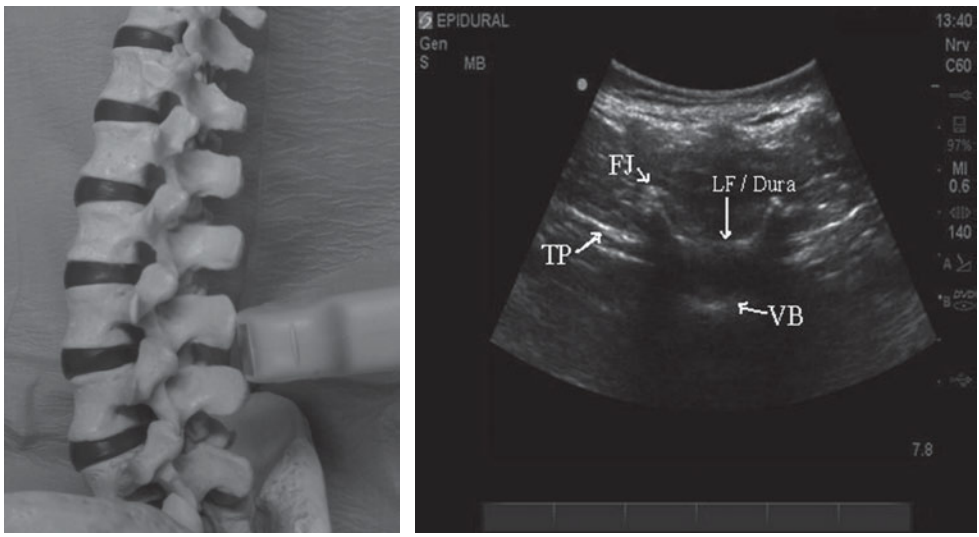


**Figure 6.3** (a) Probe position as related to the bony spine to give the ultrasound image seen in (b).
(b) Typical image seen with ultrasound in the transverse plane. Reproduced with the permission of *CPD Anaesthesia* (www.rila.co.uk).
TP = transverse process; FJ = facet joint; LF/Dura = ligamentum flavum and posterior dura mater; VB = vertebral body, posterior longitudinal ligament, and anterior dura mater.

- With this approach the spinous processes above and below the interspinous space appear as a small hyperechoic signal immediately under the skin, and continue as a long hypoechoic dark band corresponding to the acoustic shadow produced from the bony spinous processes above and below the space (Figure 6.2).

- On recognizing this appearance, the probe should moved to point slightly cephalad or caudad until the best image is obtained of the interspace (Figure 6.3).
- The image that we are aiming to obtain has been likened to that of a flying bat (Figure 6.4) [5].
- The "ears" of the bat correspond to the articular processes and the small round hypoechoic shadows produced below them.
- The hyperechoic band crossing the midline of the space between the articular processes, portrayed in the "bat analogy" as the top of the bat's head, corresponds to the ligamentum flavum and dorsal dura.
- Current resolution offered by portable ultrasound machines shows the ligament and dura as a single unit.
- Deeper down, a second hyperechoic band can be seen, parallel to the first one, corresponding to the anterior dura, the posterior longitudinal ligament, and the posterior aspect of the vertebral body.
- Once a satisfactory clear image of the interspinous space has been established with the transverse approach the image can be frozen on the ultrasound machine.
- With the probe held steady, the positions of the upper and lateral surfaces are marked on the skin. A puncture site is then defined by forming a cross from these marks when the probe is removed.
- Be aware that at this stage it would be wise to save the image on the machine before removing the probe to allow further analysis of the sonoanatomy later on.
- It is not easy to ensure correct angling of the needle during placement with pre-procedural scanning; however, logic would suggest trying to follow the same angle in which the probe was positioned when the clearest picture of the space was obtained.
- The frozen saved image can then be used to allow calliper measurement of the distances seen in the image to be made, such as the distance to the ligamentum flavum, and the antero-posterior diameter of the dural sac.

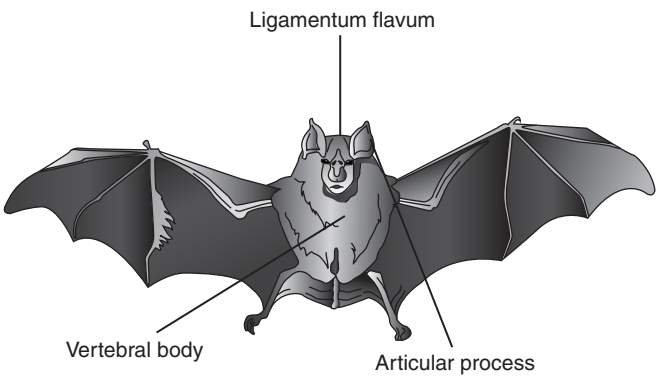


**Figure 6.4** Flying bat analogy of transverse approach image. Reproduced with the permission of *CPD Anaesthesia* (www.rila.co.uk).

## The paramedian longitudinal approach

- The paramedian longitudinal approach involves the probe being placed vertically, perpendicular to the long axis of the spine, 3 cm to the side of midline, and angled to target the center of the spinal canal.
- The probe is initially placed over the sacral area where a continuous hyperechoic (bright) line is seen representing the ultrasound image of the sacral spine (Figure 6.5).
- As the probe is moved cephalad a hyperechoic "saw like" image is seen.
- The "teeth" of the saw represent the articular processes, and the spaces between the "teeth," the interspaces.
- With the paramedian view of the interspaces, facet joints, ligamentum flavum, and posterior dura mater and traveling further posteriorly, the anterior dura mater, posterior longitudinal ligament, and vertebral body can all be seen.
- If the probe is then placed over the midline, but still in a longitudinal plane, the interspaces also include the supraspinous and interspinous ligaments.
- At this point the level of each interspace can then be marked on the skin as the probe is moved cranially away from the sacrum. This allows easier identification of the spaces for the transverse approach of the probe, or for identification of an entry point for epidural puncture.

## Real-time use

- There is very little published data regarding the use of ultrasound for real-time visualization of epidural puncture for neuraxial blockade.
- Two different techniques for real-time use of ultrasound have been described in the literature. The first, as described by Grau, is a sterile, two-person technique. This is carried out with one person placing the probe in the paramedian longitudinal position with the beam of the ultrasound aimed toward the midline, while the second person can

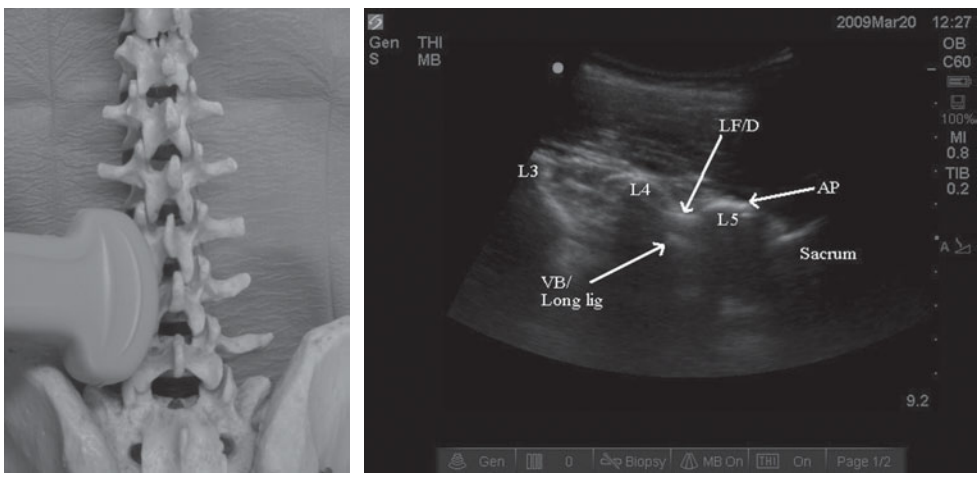


**Figure 6.5** (a) Probe position as related to the bony spine to give the ultrasound image seen in (b).
(b) Typical image seen with ultrasound when the probe is in the longitudinal plane, showing the lumbar spine and sacrum and longitudinal imaging of the articular process (AP); ligamentum flavum and posterior dura mater (LF/D); vertebral body and posterior longitudinal ligament and anterior dura mater (VB/Long lig).

undertake the epidural puncture using the conventional midline approach. In this study, Grau compared real-time ultrasound to pre-procedural scanning and also to conventional surface landmark assessment techniques and found that both real-time and pre-procedural ultrasound groups showed a reduced number of attempts, with the real-time group showing a small reduction on the number of attempts compared with pre-procedural scanning [6].

- Karmakar has more recently evaluated the use of real-time ultrasound scanning for epidural puncture, describing a technique with both ultrasound probe and epidural approach being in the paramedian position, therefore the needle being "in the same plane" as the ultrasound beam [7].
- In both studies an increased success rate for epidural puncture on the first attempt was observed with real-time ultrasound scanning. In each study there are also disadvantages highlighted with both techniques.
- Grau's technique requires a second person to do the scanning, who must also be trained to interpret the images gained in spinal sonography, while ensuring they keep their hands and the probe free from obstructing the person undertaking the epidural puncture.
- Karmakar, while describing a single-person technique, still requires the use of a special loss of resistance syringe, which contains an internal compression spring that applies constant pressure on the plunger. A false loss of resistance may occur with the use of this syringe if it is attached before the Tuohy needle is engaged in the ligamentum flavum.
- A further disadvantage is that this limits the individual undertaking the procedure, by leaving only one hand free to advance the epidural needle as far as the ligamentum flavum while keeping the probe correctly positioned with the other hand.
- Currently all real-time ultrasound scanning is also limited by needle design not producing a clear ultrasound image, therefore resulting in an inability to visualize the entire needle at all times. The position of the needle tip can only be inferred by movement of the needle producing a distortion of the surrounding tissues, which can be seen on the scan [7].

## Evidence-based medicine: the advantages of using ultrasound

- Several studies have been published looking at many aspects of the use of ultrasound in neuraxial blockade: from its ease of use or ability to improve visualization of underlying anatomy and therefore reduce the number of failed punctures, to more specific situations such as its use in the high body mass index (BMI) population (Table 6.2).
- Looking at each of these allows us to build up a picture of the evidence behind its use and in which clinical scenario is it best applied.

## Ease of use and learning tool

- As is shown above, with relatively little training, and appropriate amounts of time taken to teach the relevant sonoanatomy, ultrasound can be easily used to determine the desired vertebral interspace for placement of either an epidural catheter or spinal puncture. It has also been suggested that the use of ultrasound is advantageous as a teaching tool in

**Table 6.2** Clinical studies showing the use of ultrasound in obstetric anesthesia.

| Author | Date | Design | Summary statements | Findings |
|---|---|---|---|---|
| Grau [8] | 2003 | RCT | May improve success rates of junior trainees | Control group success 60% increasing to 84% after 50 epidurals<br>US group success 86% increasing to 94% ($p < 0.001$) |
| Grau [9] | 2002 | RCT | US can predict the depth of the epidural space with a high degree of accuracy reducing puncture attempts | Number of puncture attempts:<br>Control 2.2 +/− 1.1<br>US 1.3 +/− 0.6 ($p < 0.013$) |
| Broadbent [10] | 2000 | Obs | Ability of anesthesiologist to correctly identify L3/4 | Of 200 observations anesthesiologists successfully identified L3/4 in 58<br>102 were 1 space higher than expected<br>31 were 2 spaces higher<br>2 were 3 spaces higher<br>1 was even 4 spaces higher<br>6 were 1 space lower |
| Arzola [11] | 2007 | Obs | US in the transverse approach can provide reliable landmarks for labor epidurals | Successful identification of epidural space at pre-marked insertion point in 91.8% with statistically significant agreement between needle depth and ultrasound prediction |
| Balki [16] | 2009 | Obs | Pre-procedural US is an accurate tool to determine epidural depth and puncture site in obese parturients | 95% interval correlation between US measured and actual needle depth<br>76% epidural success at first attempt |
| Grau [14] | 2001 | RCT | US reduces the number of attempts in patients expected to be difficult epidural punctures | Number of punctures: US 1.5 +/− 0.9 compared to control 2.6 +/− 1.4 ($p < 0.001$) |
| Grau [8] | 2004 | RCT | Real-time vs. pre-procedural US scanning reduces puncture attempts | Significant reduction in attempts in both US groups compared to control ($p < 0.036$) |
| Lee [17] | 2008 | RCT | US helps identify abnormal ligamentum flavum present in patients who suffer dural puncture | Higher incidence of abnormal sonoanatomy of ligamentum flavum in dural puncture group |

Obs = observational
RCT = randomized controlled trial
US = ultrasound

improving learning curves related to epidural placement [8]. The use of ultrasound in this capacity, however, would seem a rather soft benefit. However, it is perhaps in patients who have more difficult landmarks that this technique of being able to use ultrasound may generate the greatest benefit.

- One of the advantages of using ultrasound in placement of epidurals and spinals that has been shown is that it is associated with fewer attempts at performing the procedure, greater chance of successful placement, and generally higher patient satisfaction when compared to the traditional palpation method [9].

- There are those who feel that the extra time taken to perform and set up the ultrasound makes the process unworkable. Although additional time is required for an ultrasound examination before performing an epidural or spinal, if in experienced hands this pre-procedural examination shortens the time taken for the actual procedure, especially in difficult cases.

## Accuracy of traditional palpation techniques

- Current practice to minimize failure and complications relies solely on the meticulous assessment of the surface anatomical landmarks and optimal positioning of the patient, either in the sitting or lateral position with their neck flexed and their back flexed to encourage the interspinous spaces to widen as much as possible.
- This position can be very difficult for patients to both understand and achieve, despite our best analogies to "curling up like a frightened cat," "a prawn," or "adopting the fetal position."
- Despite their best efforts clinicians have been shown to be incorrect in their assessment of puncture level when determined by palpation and, when compared with MRI assessment of the same patients, clinicians only managed to correctly identify the vertebral level in 30% of patients [10].
- Although this difference in palpated level with true vertebral level was typically only found to be a difference of one space, the maximal difference noted was up to four spaces adrift.
- Ultrasound has consistently been shown to not only identify the epidural space but also accurately predict the distance of skin to epidural space [11, 12].
- The risks of performing spinal puncture at a mistakenly high intervertebral space are well documented and feared by all anesthesiologists [13].

## High BMI and those with difficult anatomy

- The ability for ultrasound to aid central neuraxial blockade techniques has not only been shown in those patients felt to have spines that would facilitate easy placement of an epidural catheter, but also in those with spines considered to be difficult for epidurals, such as scoliosis, excessive lumbar lordosis, and kyphosis [14, 15].
- Bedside ultrasound scanning of those patients with rarer anatomical abnormalities may be of use, such as with patients with spina bifida occulta where pre-procedural ultrasound could help define where the bony and ligamentous abnormalities lie.
- In patients with a raised BMI, it stands to reason that there may not be as much concordance and accuracy between the ultrasound-measured distance to the epidural space and actual measured distance at the point of procedure. This is due to variability of skin pressure applied from the probe and will give variable measurements of distance. Images will be of a poorer quality as well, given the greater depth of image sought.
- Balki, however, has demonstrated that pre-puncture ultrasound scanning has been a reliable tool with good concordance for estimating depth to epidural space but also determining optimal needle insertion point in obese parturients [16].
- Ultrasound can also be employed when performing a blood patch. Lee *et al.* have suggested that when using ultrasound pre-procedurally defects in the ligamentum flavum can be seen. They note that a higher incidence of abnormal sonoanatomy of the ligamentum flavum is seen in patients who subsequently suffer dural puncture, and so, potentially, a pre-procedural scan may help avoid those particular interspaces where the ligamentum anatomy is abnormal [17].

## Guidelines

- Ultimately current practice still remains a blind technique, relying on correct assessment of surface anatomy, and therefore opens up the possibility of failure and complication from inaccurate knowledge of exactly where the needle tip is placed.
- In January 2008, NICE published guidelines on the use of ultrasound guidance in catheteriszation of the epidural space [2].
- They state that the evidence gathered to date supports the use of ultrasound for epidural catheterization as a "safe and useful aid to achieving correct placement of the epidural needle [. . .] especially in patients in whom palpation of the surface anatomy is challenging due to obesity or pregnancy or indeed unusual anatomy."
- CNB itself has been under the spotlight recently when the Royal College of Anaesthetists in 2009 published their Third National Audit Project (NAP3), which was undertaken to look at "Major Complications of Central Neuraxial Blockade" and attempt to establish, among other things, how often major complications leading to permanent harm occur in association with CNB [18]. In this, the largest number of CNB being undertaken by anesthesiologists was, unsurprisingly, shown to be in obstetrics, accounting for 45% of the total number of CNB reported.
- Reassuringly, the results showed that the incidence of complications resulting from CNB in the UK is much smaller than previously thought and the incidence of complications within obstetric anesthesia itself was very low accounting for fewer than 14% of all reports of permanent harm.

## Other uses of ultrasound in obstetric anesthesia

Ultrasound machines are slowly becoming more and more commonplace within an anesthetic and theater environment and have many other applications within obstetric anesthesia as well as its use in CNB.

### Abdominal wall local anesthetic infiltration

- There has been a recent increase in interest in the use of abdominal wall infiltration techniques when compared to standard epidural delivered analgesia.
- Ultrasound has been shown to increase accuracy when performing field blocks such as the transversus abdominis plane (TAP) block.
- The TAP block provides effective analgesia when used as part of a multimodal regime for abdominal surgery.
- The transversus abdominis plane runs between the internal oblique and transversus abdominis muscles and within this plane can be found afferents from nerve roots T6 to L1, which provide sensation to the anterior and lateral abdominal wall (Figure 6.6).
- Originally this was described as a landmark technique by depositing the local anesthetic within the lumbar triangle called the triangle of Petit situated above the iliac crest and posterior to the mid-axillary line.
- Randomized controlled trials using TAP blocks as part of a multimodal balanced analgesic regime have shown that patients score significantly lower on visual analogue scores with a consequent reduction in amounts of postoperative opiate use following

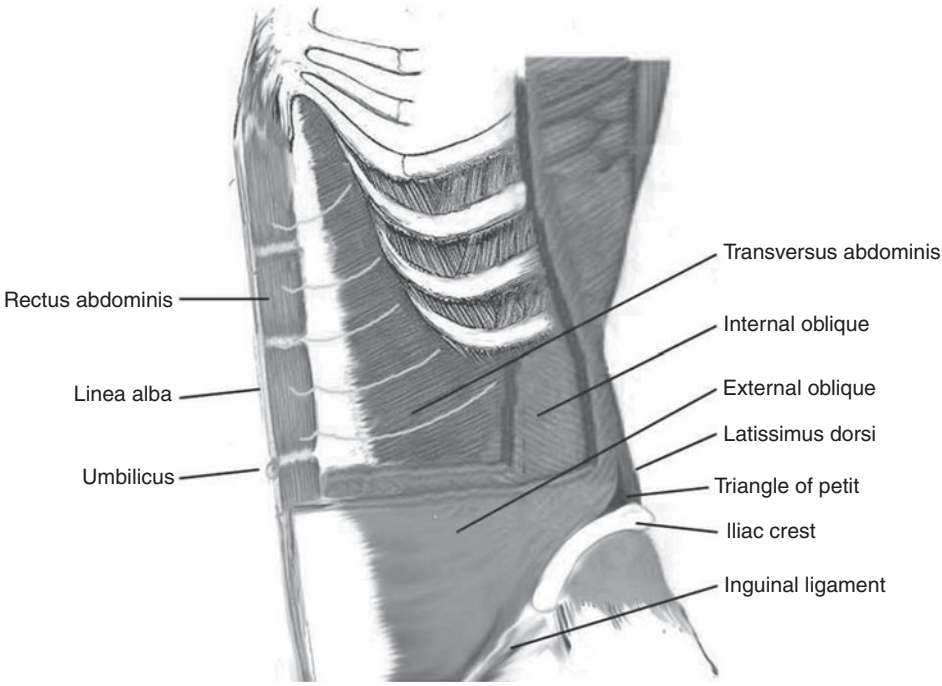


**Figure 6.6** Diagrammatic representation of the transversus abdominis plane.

Pfannenstiel incisions for cesarean sections [19]. The role of TAP blocks for analgesia following cesarean section is further discussed in the chapter on analgesia following cesarean section.

## Central venous access

- In 2002 NICE published guidance on the use of ultrasound scanning for placing a central venous catheter after a review of the literature at that time suggesting that the use of ultrasound was beneficial [20].
- As part of the technology appraisal process, NICE then commissioned a further meta-analysis of the literature, which further confirmed that ultrasound-guided venous catheter placement decreased the number of puncture attempts and decreased the rate of complications when compared to standard anatomical landmark techniques [21].
- In the third trimester it is not clear whether the anatomical changes of pregnancy will increase the potential complication rates for central venous cannulation; however, it is accepted that the head-down positioning is certainly not well tolerated. With these things in mind the use of ultrasound can help to place central venous catheters accurately with improved patient positioning for comfort, therefore tolerability of the procedure will also improve.
- In general, the growing trend from trainees based on NICE guidance is to use ultrasound to aid the placement of central venous catheters either with a pre-procedural scan and mark, or as a real-time tool.

- It should also be noted that in addition to central venous catheterization, ultrasound can also be used to help aid peripheral cannulation in patients who are obese or are simply proving to have difficult venous access.

## Other uses of ultrasound

- Transthoracic echocardiography (TTE) is now possible with portable ultrasound machines that are typically employed by anesthesiologists for regional anesthesia with the improvement in resolution of these machines.
- Appropriate training in performing TTE is obviously necessary before this can be usefully employed; however, it may be of value if used to help diagnose the cause of hypotension in a parturient whether it be hypovolemia or something more sinister picked up on the TTE, such as cardiomyopathy or pulmonary embolism.

# Cost

- There are inevitably cost implications for the acquisition and maintenance of a portable ultrasound machine, which currently limit its routine use in regional anesthesia.
- The most basic portable machines cost upwards of UK £10,000, these are appropriate for central venous cannulation but not of the quality required for visualization of the epidural space.
- The more multipurpose machines with better image quality, which come with at least two different probes and accessories as required in epidural imaging, cost substantially more at approximately UK £35,000 to UK £40,000.
- Once bought, any machine requires appropriate training and technical support and this inevitably adds to the cost of maintaining and preserving its use.
- Given the interest in this field and slowly increasing evidence for its use, the argument of cost and benefit is starting to become less of a challenge but still remains all the same.

# Summary

- The evidence supports the use of ultrasound to take the epidural catheterization and spinal injections away from being blind techniques, therefore aiming to help reduce the incidence of the potentially serious complications resulting from central neuraxial blockade.
- Overall the data so far have been limited to a small number of centers, with most procedures having been undertaken by experienced anesthesiologists, and so the use of ultrasound for aiding CNB is still just a guideline rather than the rule.
- Overall, the use of ultrasound in all aspects of regional anesthesia allows continual development and improvement of current techniques.

# Further reading

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Chapter 7

# Combined spinal–epidural anesthesia and continuous spinal anesthesia

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## Introduction

Neuraxial techniques have been used to provide pain relief during labor and anesthesia during cesarean section.

- When used for labor, combined spinal–epidural (CSE) techniques provide the advantages of intrathecal analgesia (rapid onset) with epidural analgesia (prolonged analgesia via an epidural catheter).
- When used for cesarean section, CSE may be useful when subarachnoid analgesia is inadequate or surgery is prolonged.
- Continuous spinal anesthesia (CSA) is rarely a first-choice technique in obstetrics but may be useful in certain clinical circumstances.

In this chapter, we describe the history and use of CSE techniques in laboring patients and for cesarean section. We then describe the advantages and disadvantages of these techniques compared to traditional spinal and epidural techniques. Finally, we outline the use of CSA in obstetric patients.

# Combined spinal–epidural

## History

- The CSE was first described by Soresi in 1937. The technique consisted of injection of local anesthetic (LA) into the epidural space and then advancing the needle into the subarachnoid space and injecting more drug.
- In 1981, Brownridge reported the use of CSE (using separate interspaces) for obstetric anesthesia.
- The needle-through-needle (NTN) technique was described in 1982 independently by Coates and Mumtaz for orthopedic surgery and in 1984 by Carrie for cesarean section. [1].
- In 1993, Morgan *et al.* described the use of CSE for labor analgesia using Brownridge's technique. Opioids were added to the LA, making it possible to decrease the total dose and the concentration [2]. This technique resulted in rapid analgesia without accompanying motor block. The epidural catheter could be used later to maintain analgesia.

*Controversies in Obstetric Anesthesia and Analgesia*, ed. Ian McConachie. Published by Cambridge University Press. 

## Description of the technique

The technique for CSE placement is the same regardless if it is intended for labor analgesia or for cesarean section. There are two main techniques for CSE placement: NTN and separate interspace.

- Of the two techniques, the NTN technique is the more commonly used. In this technique, the anesthesiologist identifies the epidural space in the usual fashion. A spinal needle, which is about 1 cm longer than the epidural needle is inserted through the epidural needle into the subarachnoid space. The medication is then injected into the subarachnoid space. When injecting, it is important to ensure that the spinal needle does not move. The operator holds the hubs of the spinal and epidural needles together to stabilize the spinal needle. Some CSE kits include a locking device to reduce movement, but this may only be helpful if the spinal needle is inserted to the hub. The operator then removes the spinal needle and inserts a catheter into the epidural space for future use.
- It is also possible to perform a separate interspace technique. A subarachnoid block is performed in the usual fashion, followed by an epidural catheter at a different interspace.
- Lyons *et al.* performed a randomized controlled trial (RCT) in 100 patients undergoing elective cesarean section to compare the double-space vs. NTN technique for CSE. There was a failure to establish the spinal block in 16% when using the NTN technique compared to 4% in the double-space technique [3].
- Later, the same group performed an RCT in 200 similar patients to study the performance of a new NTN kit against the double-space technique for CSE [4]. A successful block to T5 with the spinal component was more frequent in the double-space compared to the NTN technique, 80% vs. 54% respectively. Failure to enter the intrathecal space once the epidural space was located occurred in 29 patients in the NTN group.

Compared to Quincke type needles, pencil-point needles have a reduced incidence of postdural puncture headache, making the technique feasible for laboring patients. Some CSE kits include a special epidural needle with a back hole or channel for the spinal needle. This ensures that the dural puncture site is displaced from the epidural catheter and reduces the likelihood of friction between the two needles [5].

## Position of the patient

The optimal patient position to perform the CSE is still debated. It is possible that the sitting position makes location of the midline easier. In addition, the increase in cerebrospinal fluid (CSF) pressure may improve flow through the spinal needle [5].

- Norris *et al.* [6] performed a retrospective cohort study in which 506 patients of mixed parity received a CSE for labor. Positioning was chosen by the anesthesiologist. They reported a significantly higher first-pass success rate in patients in the sitting position, compared to the lateral position, 87.5% vs. 75.6% ($p < 0.05$) respectively. However, ultimately, the success rate was similar between the groups (96% vs. 92%).

This study shows that while both positions may result in success, the sitting position may be more suitable for some patients.

## Saline or air for loss of resistance?

The use of saline vs. air to identify the epidural space in the loss of resistance technique has been a source of controversy and is fully discussed in its own chapter.

- To address this issue with regard to the CSE technique, Grondin *et al.* [7] performed an RCT to compare the success of the spinal and the epidural component of the CSE using air vs. saline for the loss of resistance in 360 parturients in active labor. The spinal analgesia success (94.2% vs. 93.6%) and epidural catheter replacement (2.9% vs. 5.2%) were similar in the two groups.
- However, when epidural catheters were inserted in the absence of initial fluid returning through the spinal needle the replacement rate was 28.6% vs. 4.1% among those with initial fluid return ($p < 0.03$). These findings suggest that either method is suitable for epidural placement.

## Drugs for initiation and maintenance

Rapid onset of analgesia can be initiated with 1 or 2 mg of subarachnoid bupivacaine combined with 5 to 15 μg of fentanyl. Analgesia can be maintained with a continuous infusion of LA, with or without opioids, and supplemented with patient-controlled boluses. Less than 0.1% bupivacaine and 1 to 2 μg/ml of fentanyl (or equivalent doses of ropivacaine) can be used. Typical settings include a bolus dose of 4 to 12 ml, a lockout time of 10 minutes, and a continuous infusion of 2 to 10 ml.

- Okutomi *et al.* [8] performed an RCT in 144 nulliparous parturients undergoing induction of labor under CSE analgesia to determine the optimum time to begin an infusion via the epidural catheter. Initiation of an epidural continuous infusion was delayed by 3, 30, 60, and 90 minutes, depending on the group. The primary outcome was the number of patients who requested clinician boluses of epidural analgesia. The study showed that there was an increase in requests for clinician boluses in the 60- and 90- minute groups. The authors concluded that the epidural infusion should be started within 30 minutes of the spinal dose.

## Complications/side effects

Even though the CSE technique is useful, it also poses the risks of both epidural and subarachnoid techniques. In addition, the spinal and epidural components of the block may interact with each other [5]. The characteristics and side effects of epidural and CSE techniques are compared in Table 7.1 and discussed below.

## Maternal apnea

Respiratory depression after administration of lipophilic opioids in labor analgesia is a very infrequent, although potential deadly, event. Most of the reported cases typically occurred within 4 to 20 minutes after the administration of intrathecal sufentanil in dose of 10 to 15 μg, and were often associated with prior systemic opioid administration.

**Table 7.1** Side effects and characteristics of epidural and combined spinal–epidural techniques.

| Variable | Epidural (low dose) | Combined spinal–epidural |
|---|---|---|
| Maternal apnea | Extremely rare | 0.02% (95% CI: 0%–0.06%) [9] |
| Fetal heart rate abnormalities | 5.5 % [11] | 31.7 % [11] |
| Fetal bradycardia | 2 % [26]–4.7 % [10] | 8.3 % [10] |
| Meningitis | 0–3.5 per 100,000 [13] | 1 per 39,000 [12]<br>0–3.5 per 100,000 [13] |
| Epidural abscess | 0.2–3.7 per 100,000 [13]<br>3 per 100,000 [12] | Rare |
| Epidural hematoma | 1 in 168,000 [29] | 1 in 168,000 [29] |
| Nerve damage | 0.6 per 100,000 [13] | 3.9 per 100,000[13] |
| Pruritus | 29.5% [10] | 57.8% [10] |
| Hypotension | 2% [15] | 5% [15] |
| Postdural puncture headache | 0.21% [17]–1.6% [18] | 0.20% [17]–1.7% [18] |
| Onset | 10–20 min [15] | 5.5 min [15] |
| Motor block | CSE better preserves motor function during labor. This may be related to the decrease in the total dose of LA [21]. | |
| Catheter failure/replacement rates | 0.7% [18] | 0.8% [18] |
| Duration of 1st/2nd stage (+/– SD) in minutes | 526 (289)/105 (68) [16] | 530 (277)/102 (64) [16] |
| Maternal satisfaction | Excellent in both groups [19] | |

- Ferouz *et al.* retrospectively analyzed 4,870 laboring patients who received 10 μg of intrathecal sufentanil as part of a CSE technique for labor analgesia. The risk of respiratory depression was 0.02% (95% CI: 0%–0.06%) [9].

## Fetal bradycardia

Intrathecal opioids treat labor pain rapidly and reliably without motor block. Nonetheless, there is a concern that intrathecal opioids can increase the risk of fetal bradycardia.

- Mardirosoff performed a meta-analysis comprising 11 RCTs involving 1,340 patients [10]. Fetal bradycardia was reported in 8.3% of patients who received intrathecal opioids and in 4.7% of the controls who had not received intrathecal opioids. Although there was an increase in fetal bradycardia events in the intrathecal opioid group, there was no increase in the rate of cesarean section, operative deliveries, oxytocin usage, or Apgar score.
- Fetal bradycardia may reflect changes in uterine tone.
- Recently, Abrão *et al.* [11] randomly assigned 77 parturients to receive either epidural or CSE labor analgesia. The primary outcome was the baseline uterine tone. Uterine hypertonus and fetal heart rate (FHR) abnormalities were more frequent in the CSE

group than in the epidural group. The type of analgesia was the only independent predictor of uterine hypertonus (OR = 3.5, 95% CI 1.2–10.4).

In conclusion, there may be an additional risk of fetal bradycardia in patients who receive intrathecal opioids. This may possibly be due to an elevation in resting uterine tone caused by a rapid reduction in circulating maternal catecholamines. There appears to be no impact on the incidence of emergency operative delivery or on neonatal outcome, and so the clinical implications appear to be minimal.

## Central nervous system infection

- Reynolds *et al.* [12] reported a review of ten surveys. Epidural abscess and meningitis were infrequent complications of neuraxial techniques. While clusters of cases have been identified, the risk appears to be about 3 per 100,000 procedures.
- In 2009, the Royal College of Anaesthetists in the UK published the 3rd National Audit Project of the Major Complications of Central Neuraxial Block [13]. The projected incidence of bacterial meningitis after neuraxial block was 0 to 3.5 in 100,000 (95% CI).

Infective complications are extremely rare events; as such there are no clinical trials that demonstrate whether or not a particular intervention is preventative. However, most practitioners agree that meticulous aseptic technique should be observed.

## Nerve damage

The 3rd National Audit Project of the Major Complications of Central Neuraxial Block analyzed more than 320,000 obstetric procedures [13].

- The incidence of permanent harm after spinal anesthesia was 1.5 in 100,000, compared to 0.6 in 100,000 after epidural, and 3.9 in 100,000 after CSE.
- This is much less common than the 1% incidence of obstetric palsies, unrelated to neuraxial blocks [12].

## Paresthesias

Paresthesia with needle insertion may be more common with CSE techniques compared to epidural analgesia. This may be due to the diversion of the spinal needle from the midline or difficulty in stabilizing the needle.

- One retrospective study comprising 6,518 parturients found a high incidence of paresthesia in both the CSE and epidural groups. CSE was an independent risk factor for this complication (OR = 1.21, 95% CI 1.07 to 1.37) [14].

## Pruritus

Pruritus is the most common side effect of neuraxial analgesia. The incidence and severity is dependent on the opioid dose and the route of administration.

- It is more frequent with intrathecal opioids (58%) than with epidural opioids (30%) with a relative risk of 1.7 [10].
- The relative risk of CSE vs. epidural for pruritus is 1.62 [15].

The evidence suggests that pruritus produced by opioids is mediated through central μ-opioid receptors. Opioid antagonists or partial agonist–antagonists are effective treatment of pruritus from neuraxial opioids.

### Hypotension

- The incidence of hypotension after the initiation of neuraxial analgesia during labor is low. In a meta-analysis comparing low-dose epidural analgesia to CSE in parturients in labor, Simmons *et al.* found eight RCTs comprising 715 parturients. In this sample, the incidence of hypotension, as defined by the authors of the studies, was 2% in the epidural group and 5% in the CSE group ($p = 0.045$). However, there was sufficient heterogeneity in the results to question whether or not the difference is clinically significant [15].
- The COMET study comparing traditional epidural analgesia to CSE, did not find a difference in the incidence of hypotension [16].

### Postdural puncture headache

- Van de Velde *et al.* [17] retrospectively studied more than 17,000 obstetric neuraxial blocks. There was no difference in the incidence of accidental dural puncture (ADP) or postdural puncture headache (PDPH) between CSE and epidural analgesia.
- These results agreed with previous studies confirming the incidence of PDPH is similar for the two techniques [15].

## Combined spinal–epidural for labor

Combined spinal–epidural techniques have many of the characteristics of the "ideal analgesic technique" for labor. The rapid onset of action and minimal motor block are desirable.

- When compared to a low-dose epidural, CSE does not increase the incidence of cesarean section, operative vaginal delivery, or the duration of the first or the second stages of labor [15, 18].
- The epidural catheter allows LA to be administered throughout labor. The catheter can also be used to give sufficient LA to facilitate operative delivery.

### Onset of analgesia

- In their meta-analysis, Simmons *et al.* found three studies, comprising 289 patients in which the time to effective analgesia was compared between CSE and low-dose epidural analgesia. The mean time to analgesia was about ten minutes in the low-dose epidural group. The time of onset of effective analgesia was six minutes faster in the CSE compared to low-dose epidural group.
- In a randomized controlled trial, comprising 50 patients, all of the patients who received a CSE were comfortable within ten minutes of injection compared to 52% who received a low-dose epidural (relative risk 1.96). There was no difference in maternal satisfaction between both groups [15].
- These results have recently been confirmed [19].

Although analgesia can be accomplished within five to ten minutes with the CSE compared with ten to twenty minutes with the epidural block, the clinical importance is uncertain.

- In some settings it may take longer to prepare the required drugs and equipment to perform a CSE, compared to a standard epidural.
- In addition, contractions may be four to five minutes apart, reducing the advantage of a CSE to one contraction.
- Finally, the time saving is insignificant compared to the average duration of labor in nulliparous patients, which averages at about six hours.

### Analgesia in late labor

Abouleish *et al.* [20] initiated a CSE technique with 2.5 mg of subarachnoid bupivacaine and 10 μg of sufentanil in a case series of 38 patients of mixed parity in advanced labor. There was a rapid onset of sacral analgesia (<5 minutes) in all cases. Only one patient experienced mild lower extremity motor weakness (Bromage I), all the other patients retained full motor strength.

### Motor block

When compared to low-dose epidural infusions, CSE and intermittent bolus injections of epidural LA better preserve the motor function during labor. Motor function preservation is related to the decrease in the total dose of LA in the CSE group. Better motor function allowed greater mobility during the first stage of labor, but had no effect on the progress of labor [21].

### Catheter failure and replacement rates

While it is desirable to test the catheter for epidural placement, it may not be possible until the spinal block has receded. The spinal block has no effect on the test doses that are meant to detect accidental intravenous catheter placement, but tests of subarachnoid placement are problematic. It may also be possible to successfully place the spinal needle intrathecally, but then insert the catheter outside the epidural space.

The catheter appears to be at least as effective after CSE compared to epidural.

- In retrospective quality assurance data, Pan *et al.* [22] reported the failure rate for more than 12,000 neuraxial blocks. The failure rate was significantly lower after CSE than after epidural (10% vs. 14%, $p < 0.001$). Inadequate analgesia with the epidural catheter was reported in 8.4% of the epidurals and in 4.2% of the CSEs.
- In another retrospective study, Miro *et al.* [14] compared more than 6,000 parturient patients having epidural or CSE for labor analgesia. The incidence of catheter replacement was higher in the epidural group than in the CSE group (6.2% vs. 3.4%, $p < 0.001$).
- Norris *et al.* enrolled 2,183 laboring women in a quasi randomized clinical trial that compared CSE vs. epidural analgesia for labor [18]. The study found no difference in failed or replaced epidural catheters between CSE (0.8%) and epidural (0.7%).

## Combined spinal–epidural for cesarean section

Combined spinal–epidural is well suited for anesthesia for cesarean section. As outlined below, it may be possible to obtain rapid anesthesia and possibly reduce the incidence of side effects.

## Hemodynamic stability

Maternal hypotension is one of the most common side effects associated with spinal block. In some cases it is difficult to maintain normal blood pressure despite the prophylactic measures such as fluid loading, left uterine displacement, and vasopressors.

- Sequential CSE has been used in order to decrease the incidence and severity of hypotension. In this technique, a CSE is performed and a low dose (less than 7.5 mg bupivacaine) is injected intrathecally. The block is completed in a controlled fashion by injecting small aliquots of LA into the epidural space.
- This technique may be particularly valuable in high-risk patients when slow and controlled onset of sympathetic block is desirable, such as in patients with moderate to severe aortic stenosis. Conventionally, these patients are managed with slowly titrated epidural; however, the total dose of LA is much higher than with the sequential CSE.
- A sequential CSE takes longer to produce an adequate blockade compared to a full-dose single-shot spinal. Hence, it may be unsuitable if a rapid onset of surgical anesthesia is required.

## Duration of block

Compared to a single-shot spinal anesthetic, the presence of an epidural catheter may be useful to increase the duration of block when longer surgical times are expected. The CSE technique combines the rapid onset of spinal anesthesia with a prolonged block when necessary.

# Continuous spinal anesthesia

## History

- Continuous spinal anesthesia (CSA) was described in 1906, by Dean, who left a needle in the subarachnoid space and administered repeated doses of LA through it.
- In 1939, Lemmon left a malleable needle, attached to a rubber tube, in the subarachnoid space.
- In 1944, Edward Tuohy described CSA as a safe and useful technique without significant problems for lower body surgeries.
- In the early 1950s, Dripps reported a high incidence of PDPH, paresthesias, and low success rates, leading to a decline in the use of CSA.
- However, CSA was re-introduced in the mid-1980s as a technique that provided excellent control of segmental spread and decreased risk of cardiovascular side effects when compared to a single-shot spinal anesthetic.
- At about the same time, microcatheters were developed to reduce the incidence and severity of PDPH. Unfortunately, PDPH remained a significant clinical problem.
- In addition, microcatheters were associated with severe neurologic deficit when combined with high concentrations of hyperbaric LA. As a consequence, in 1992, the US Food and Drug Administration (FDA) banned the use of spinal catheters smaller than 24-gauge [23].
- Microcatheters are still used in some countries with no further reported neurological complications.

## Description of the technique

A general description of the technique can be found in Table 7.2. The main reason CSA is not used more frequently is because of the risk of PDPH.

- This risk is related to the large gauge of the needles and catheters currently available (i.e. epidural catheters and Tuohy needles).
- However, CSA may be an important option in a patient who has challenging anatomy and has already experienced an accidental dural puncture during epidural placement. For example, it might be prudent to pass a catheter into the subarachnoid space in a morbidly obese parturient rather than risk the failure of an epidural.
- If the patient has normal anatomy, the risks associated with a subarachnoid catheter, such as inadvertent overdose or infection, must be weighed against the potential benefit of leaving the catheter in place.
- If CSA is chosen, the catheter should be advanced about 3 cm into the subarachnoid space. Deeper placement may result in caudally positioned catheters and pooling of LA resulting in abnormal spread [23].

**Table 7.2** Recommendations for continuous spinal anesthesia and analgesia.

| |
|---|
| • Maintain meticulous aseptic technique |
| • Use an end-hole catheter |
| • Insert the catheter about 3 cm into the subarachnoid space |
| • Use a three-way stopcock to maintain sterility by reducing the number of catheter disconnections for medication injection |
| • Aspirate CSF with syringe to ensure intrathecal placement before injection |
| • Inject the LA in small increments and flush with 1 ml saline to compensate for the catheter's dead space between doses |
| • When using CSA for labor or cesarean section, ensure that all clinicians and nursing staff are aware of the subarachnoid placement of the catheter. In addition, label the catheter, infusion fluids, and pumps at multiple sites to ensure there is no confusion regarding the catheter type |
| • Do not exceed recommended doses for subarachnoid LA. If inadequate analgesia/anesthesia, change technique |
| • Suggested regimens:<br>*Labor*<br>▪ isobaric or hyperbaric LA can be used<br>▪ incremental doses of bupivacaine 1 to 3 mg<br>▪ may add up to 20 μg of fentanyl in the first bolus<br>▪ maintain with 1 to 3 mg increments or an infusion of 0.05% bupivacaine with 2 mμ/ml fentanyl at 2 to 5 ml/hour |
| *Cesarean section*<br>▪ isobaric or hyperbaric LA can be used<br>▪ initial dose of bupivacaine 5 mg<br>▪ increments of 2 to 3 mg bupivacaine to surgical level<br>▪ may add up to 20 μg of fentanyl and/or 200 μg of preservative-free morphine in the first bolus. |

- Sterile technique must be meticulous and every effort must be made to avoid the introduction of air into the intrathecal space as this will lead to severe PDPH.

## Conduct of anesthesia

Once the catheter has been placed and secured, but before any drug is given, the patient can be positioned in the supine position with a hip wedge. Starting the anesthesia in this position has some advantages.

- Firstly, it reduces the risk of unpredictable spread due to patient's position change.
- Secondly, it does not require discontinuation of the monitoring during the positioning change.
- Finally, it allows rapid treatment of hypotension [24].

## Complications/side effects

### Infection

Infectious complications are a potential risk with any neuraxial technique, but a CSA catheter provides a conduit for microorganisms to enter the subarachnoid space, whereas with the epidural the protective leaves of the dura mater are intact. Strict aseptic technique is of paramount importance during the performing of CSA.

- Data from Bevacqua *et al.* suggest that, in non-pregnant patients, the incidence of infection increases over time, but 72 to 96 hours of use is safe provided that the site is closely monitored and the CSF is analyzed for signs of infection [25].

### Neurological damage

Neurological damage may be caused by the drugs or by the catheters themselves.

- Slow flow rates of concentrated LA may cause pooling and damage neural elements. High dose (more than 100 mg) of hyperbaric lidocaine 5% and a 28-gauge catheter were used in a case series of 11 patients who suffered cauda equina syndrome [23].
- It is also possible to introduce microcatheters directly into the spinal cord, causing injury.
- Arkoosh *et al.* performed a multicenter RCT in 429 laboring patients to compare the safety and efficacy of a 28-gauge spinal catheter vs. the standard epidural catheters for labor analgesia. There was no occurrence of permanent neurologic damage associated with the use of either catheter. However, this study was too small to confirm the safety of the technique [26].

### Technical problems

- Smaller catheters seem to be useful for patients at high risk for developing spinal headache.
- A disadvantage of small catheters is that it is often not possible to aspirate cerebrospinal fluid to verify proper positioning.

- Microcatheters are difficult to thread, to remove, and might break easily.
- Arkoosh *et al.* reported an incidence of technical problems with microcatheters of 15% [26].

### Dural puncture headache

Obstetric patients are at a higher risk of PDPH than the general population. However, if an ADP has already occurred, some authors recommend leaving the catheter in the subarachnoid space.

- Ayad *et al.* [27] performed a quasi-randomized trial in which 115 parturients who had suffered ADP were assigned to one of three groups: group 1 – the needle was removed and the catheter inserted in a different interspace; group 2 – the catheter was threaded into the subarachnoid space and removed after delivery; and group 3 – the catheter was threaded into the subarachnoid space and removed after 24 hours. The incidence of PDPH was 81% in group 1, 31% in group 2, and 3% in group 3. These data suggest prolonged placement of a subarachnoid catheter may be beneficial.
- Other authors have not confirmed these observations and a recent meta-analysis done by Apfel *et al.* [28] does not support the benefit of long-term catheters.

The incidence of PDPH is quite high in parturients that received intentional CSA for cesarean section.

- Alonso *et al.* performed an observational study in 92 pregnant patients scheduled for elective cesarean using CSA with a 22- to 24-gauge catheter over a 27- to 29-gauge Quincke needle. The incidence of PDPH was 29% [24].
- In the study done by Arkoosh *et al.* using a 28-gauge catheter over a 22-gauge ramped Sprotte needle, the reported incidence of PDPH was 9% [26].

### Analgesic effectiveness

The overall analgesic effectiveness during labor was less with intrathecal catheters than with epidural catheters, 83% vs. 92% ($p = 0.031$) respectively [29].

## Summary

- Neuraxial analgesia techniques are commonly performed to relieve pain during labor and to provide analgesia during cesarean section.
- When CSE is used for labor analgesia it provides a faster onset with minimal motor block.
- The catheter appears to be at least as effective as with the epidural technique; however, CSE has a higher rate of complications (e.g. nerve damage, infection) and side effects (e.g. pruritus, FHR abnormalities) compared to epidural analgesia.
- Combined spinal–epidural does not affect the incidence of cesarean section or operative deliveries, and does not protect against ADP or PDPH.
- Combined spinal–epidural provides excellent hemodynamic stability (sequential technique) with the ability to extend the block.
- In contrast to CSE, CSA has no advantages compared to either CSE or epidural labor analgesia and should be reserved for patients who have suffered ADP.
- There is a high incidence of PDPH and technical problems with currently available equipment.

- In addition, there is a high failure rate.
- Meticulous attention must be paid to labeling the catheter and equipment to ensure all caregivers are aware of the subarachnoid location of the catheter.
- The theoretical advantages of hemodynamic stability and prolonged block can be easily achieved with other techniques such as CSE at much lower complication rates.

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Chapter 8

# Coagulation and regional anesthesia

**Dr S Morrison and Dr A Al-Areibi**

## Introduction

- Central neuraxial analgesia and anesthesia are major anesthetic techniques in managing labor pain and cesarean sections.
- Anesthesiologists, however, face a number of challenging scenarios where it becomes very difficult to choose and perform a neuraxial technique.
- One major challenge is the presence of a coagulation abnormality that may make these techniques carry a higher risk.
- In this chapter we will provide an overview of the normal changes in coagulation associated with pregnancy and discuss the most common challenges that face anesthesiologists in the coagulopathic pregnant woman.

## Coagulation changes in pregnancy

All aspects of the coagulation system are altered in pregnancy.

- The concentrations of most of the clotting factors are increased.
- There is a net decrease in the concentration of natural anticoagulants.
- Fibrinolytic activity is reduced.

The result is a hypercoagulable state that maintains placental function during pregnancy and protects the parturient from hemorrhagic complications during delivery but increases the risk of thromboembolism [1].

### Platelets

- A mild thrombocytopenia (<150,000) is the most common coagulation abnormality in pregnancy.
- Some studies suggest the incidence is about 8% of full-term pregnancies.
- In the non-hypertensive, asymptomatic patient this incidental thrombocytopenia is often benign.
- It can be attributed to hemodilution and a low-grade chronic intravascular coagulation within the uteroplacental circulation. Researchers agree this is part of the normal

*Controversies in Obstetric Anesthesia and Analgesia*, ed. Ian McConachie. Published by Cambridge University Press.  

physiological response to pregnancy and is compensated for by an increase in platelet production [1].

## Coagulation factors

The circulating levels of several coagulation factors change during pregnancy:

- Fibrinogen, factors VII, VIII, IX, X, XII and von Willebrand factor rise significantly.
- Concentrations can increase by 20 to 200%; however, factor VII may increase as much as tenfold.
- Von Willebrand factor and factor VIII are elevated in late pregnancy, when coagulation activity is about twice that in the non-pregnant state. Factors V and IX remain unchanged and factor XI levels decrease by 30% [1].
- Antithrombin and protein C levels appear to fluctuate during normal pregnancy but generally remain within normal non-pregnancy levels. Protein S activity and free protein S antigen decrease, due to estrogen-induced protein binding and other hormonal mechanisms. This fall seems to occur in the first to second trimester and remains depressed for the duration of pregnancy [1].

## Fibrinolysis

Fibrinolysis is reduced in pregnancy, remains depressed during labor and delivery, and then returns to normal almost immediately postpartum.

- This is attributed to decreased t-PA activity.
- Specifically, levels of plasminogen activator inhibitor proteins (PAI-1 and PAI-2) are increased. The placenta produces PAI-1 and is the primary source of PAI-2. At pregnancy week 35, PAI-1 values can be fivefold higher than in pregnancy week 12. PAI-2 levels at term are 25 times that of normal plasma [1, 2].

# Screening

Many medical centers still adopt the policy of routine complete blood count for all pregnant women who present to the labor and delivery suite, and this practice remains controversial although there is a general trend toward not to screen all pregnant women for low platelets. The controversy is mainly because we lack the evidence to support this practice.

- Supporters claim that the incidence of gestational thrombocytopenia is relatively high, and therefore platelet count should be ordered prior to performing any neuraxial technique, even in the previously healthy parturient.
- To date, there have been no reports of poor outcomes following the use of neuraxial techniques in the presence of gestational thrombocytopenia, and most authors consider it as a normal physiological phenomenon.
- The American Society of Anesthesiologists (ASA) Practice Guidelines state that the literature is insufficient to assess whether a routine platelet count can predict anesthesia-related complications in uncomplicated parturients. The literature suggests that a platelet count is clinically useful for parturients with suspected pregnancy-related hypertensive disorders, such as pre-eclampsia or HELLP syndrome, and for other disorders associated

with coagulopathy. The anesthesiologist's decision to order or require a platelet count should be individualized and based on a patient's history, physical examination, and clinical signs. A routine platelet count is not necessary in the healthy parturient according to ASA guidelines [3].

## Thrombocytopenia

- Thrombocytopenia affects 6 to 10% of all pregnancies [4] – up to 81% of which is gestational thrombocytopenia [5]. Other common causes are idiopathic or immune thrombocytopenic purpura (ITP) and pregnancy-induced hypertension/HELLP syndrome (see below). Less common causes include severe sepsis, drug therapies, and acute fatty liver of pregnancy.
- The diagnosis of gestational thrombocytopenia is made by exclusion of other disorders, and parturients are usually asymptomatic, have a normal platelet count in early pregnancy with no history of previous thrombocytopenia and no evidence of pre-eclampsia. The platelet count returns to normal post delivery.
- These patients are not at increased risk of hemorrhage, and there is no contraindication to neuraxial anesthesia [2, 6].
- ITP may present for the first time in pregnancy. This is an autoimmune disorder associated with production of antiplatelet immunoglobulin (IgG), resulting in platelet destruction in the reticulo-endothelial system. Despite the low platelet numbers, hemostasis is often normal. Intravenous immunoglobins and/or corticosteroids usually will raise the platelet count to enable neuraxial anesthesia.

Other more sinister causes of thrombocytopenia in pregnancy exist and must be respected by anesthesiologists.

- A platelet count at term <90,000 may indicate the presence of HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome, disseminated intravascular coagulation, immune thrombocytopenia, and other rare conditions coexisting with pregnancy [2]. The impact on hemostasis may be profound and represents a significant increase in the risk associated with neuraxial anesthesia.
- Additionally, questions have been raised about platelet function in pre-eclampsia [7, 8], but as these studies used bleeding time, their results are not considered definitive and the issue is not yet solved [9].

There is much debate over the minimum safe threshold for neuraxial anesthesia in the thrombocytopenic parturient. However, there is a slow trend toward performing these techniques in lower platelet count numbers, levels that were considered in the past as an absolute contraindication.

- The British Committee for Standards in Haematology guidelines for idiopathic thrombocytopenia recommends a platelet count of 80,000 for epidural anesthesia [10].
- However, many anesthesiologists, such as the authors, would do a neuraxial block (especially spinal anesthesia) in healthy, asymptomatic, idiopathic thrombocytopenia patients with platelet counts ≥50,000.
- This practice is based on the consideration that a platelet count ≥50,000 is considered sufficient for cesarean delivery in those patients [2].

- A platelet count from 70,000 to 100,000 in an otherwise healthy parturient should not contraindicate regional anesthesia [2].
- Most American anesthesiologists would insert an epidural in a healthy parturient with a platelet count ≥80,000 [11].
- A Canadian survey reported that 16.2% of university-based anesthesiologists would place an epidural if the platelet count were ≥50,000 in an otherwise healthy parturient [12].
- A recently published Canadian study has concluded that regional anesthesia can be safely administered in pregnant patients with platelet counts between 50,000 and 79,000, and their results are in keeping with other series in the literature. They suggested that in non-pre-eclamptic patients with stable platelet counts and no history or clinical signs of bleeding, the lower limit of platelet count for regional anesthesia should be 50,000 [13].
- The largest reported series [14] included 177 patients with a platelet count less than $100 \times 10^9$/L. Of those patients, 90% had platelet counts greater than $70 \times 10^9$/L. Seven had platelet counts between 50 and $60 \times 10^9$/L – only one was denied regional anesthesia. Four women who had platelet counts less than $50 \times 10^9$/L received regional anesthesia only after a platelet transfusion. The causes of thrombocytopenia were gestational thrombocytopenia, pre-eclampsia, and idiopathic thrombocytopenia. There were no other coagulation problems. No neurological complications were documented in any patients reviewed.
- However, even large series do not *prove* that it is safe to administer regional anesthesia to parturients with platelet counts less than $100 \times 10^9$/L.

The situation is more controversial in the setting of pre-eclampsia, including HELLP syndrome. In this situation, most anesthesiologists consider the platelet count, the clinical picture (i.e. hemorrhage risk and evidence of coagulopathy), and whether the thrombocytopenia is stable or decreasing [2].

- Vigil-De Gracia reported 12 cases of HELLP syndrome with a platelet count <50,000 who received uneventful epidural anesthesia [15]. In some cases a platelet transfusion was given immediately prior to neuraxial anesthesia.
- However, two cases of epidural hematoma have been reported in HELLP syndrome patients who were coagulopathic, one after spinal anesthesia and the other after epidural catheter removal [16].
- Studies using thromboelastography in women with pre-eclampsia suggest that coagulation is normal with a platelet count ≥75,000 [17, 18].

Note: If thrombocytopenia develops after an epidural catheter is sited, the catheter should not be removed until the platelet count normalizes to reduce the risk of bleeding and cord compression.

## von Willebrand disease (vWD)

- von Willebrand disease is the most frequent inherited bleeding disorder affecting 1% of the population.
- It is caused by either a quantitative (types 1 and 3) or qualitative (type 2) defect of von Willebrand factor (vWf) with autosomal dominant transmission. von Willebrand factor protects circulating factor VIII from proteolysis and is required for normal platelet

adhesion to the injury site. In vWD the marked reduction in factor VIII activity produces the clinical syndrome [2].

- Type 1 is the most common form, is usually mild, and characterized by a deficiency in vWf.
- Laboratory diagnosis involves measuring vWf, ristocetin cofactor A (RCoA), and factor VIII levels.
- Type 2 and subtypes involve abnormalities of binding to glycoproteins and factor VIII (qualitative defect). Thrombocytopenia occurs with type 2b.
- Type 3 is the most severe form and is the total absence of vWf.

Outcomes in pregnancy are generally good for vWD.

- Increases in fibrinogen, factor VII, factor VIII, factor X, and vWf during pregnancy are considered protective.
- Levels of vWf, RCoA, and factor VIII should be checked in early pregnancy and in the third trimester to ensure adequate levels for delivery.
- Postpartum hemorrhage (PPH) is a common complication and should be anticipated.
- Desmopressin (DDAVP) is considered safe for parturients with type 1 vWD. Its use results in immediate increases in vWf and factor VIII:RCoA ratio by 200 to 300%. Desmopressin is contraindicated, or the response is variable, in type 2 and ineffective in type 3 vWD [2].
- Most studies and case reports consider neuraxial techniques safe as long as the factor VIII levels are >50 IU $dL^{-1}$ [19, 20].
- Most anesthesiologists consider neuraxial block contraindicated in types 2 and 3 vWD, but there is a report of spinal anesthesia in a parturient with type 2M vWD whose coagulation was normal except for prolonged platelet adhesion and aggregation [21].

## Hemophilia

- Two main types of hemophilia exist, type A and type B.
- Both are rare in women because it is an X-linked recessive disorder.
- Type A is due to a deficiency of factor VIII. Interestingly, factor VIII does not change during pregnancy and in fact it may normalize in hemophilia type A patients because of the normal physiological increase in factor VIII during pregnancy.
- The current recommendations suggest that there is no contraindication to perform neuraxial techniques provided that the factor VIII level is ≥50 IU $dL^{-1}$, normal international normalized ratio (INR) and partial thromboplastin time (PTT), and no clinical evidence of bleeding or bruising [22].

Information on other rare coagulation disorders is available in the text cited in the section on further reading.

## Regional anesthesia in the presence of anticoagulation therapy

The discussion of this topic is beyond the scope of this chapter. It has been fully reviewed in recent evidence-based guidelines, e.g. the Scandinavian guidelines by Breivik *et al.* and the American Society of Regional Anesthesia (ASRA) by Horlocker *et al.* References for these guidelines are in the section on further reading.

## Regional anesthesia in the presence of a coagulopathic condition

- The question of whether to perform any neuraxial technique in a coagulopathic patient, and hence to violate the current regional anesthesia guidelines, still arises in many conflicting scenarios.
- Patients with comorbid disease that can make general anesthesia a very high-risk option may benefit from regional techniques, but the risk–benefit management should be individualized and case specific.
- When it comes to these difficult scenarios it is very hard to make the right decision, and it needs very careful analysis of all the factors and considerations before violating existing guidelines. This has been and can be justified by involving the patient, colleagues, and other professionals in the decision-making process.
- The incidence of spinal or epidural hematoma after neuraxial blockade (with or without altered hemostasis) is very difficult to determine, although it is widely reported that obstetric patients have a significantly lower incidence of complications than their elderly counterparts undergoing vascular or orthopedic surgery [16, 23].
- Spinal or epidural hematoma may occur spontaneously or after minor trauma, but mostly this rare phenomenon occurs in the presence of a coagulopathy or anticoagulant medication.
- Moen *et al*. reported [16] two spinal hematomas among 200,000 epidural blocks for pain relief in labor: one after a subarachnoid block and one after the removal of an epidural catheter. Interestingly, signs of severe coagulopathy were present in both patients. The authors reported the incidence of spinal hematoma after obstetric epidural blockade was 1:200,000, which was significantly lower than the incidence in elderly females undergoing total knee arthroplasty (TKA) (~1:3,600) [24].
- In an ASA closed-claims analysis of injuries associated with regional anesthesia published in *Anesthesiology*, Lee and colleagues found that neuraxial hematomas associated with coagulopathy remain sources of high-severity injury [25]. While rare, hematoma was the most common cause of neuraxial injuries, and the majority (72%) of these cases were associated with either intrinsic or iatrogenic coagulopathy.
- These results are consistent with the review of the literature by Vandermeulen *et al*. in which they found that 42 of 61 neuraxial hematomas (68%) were associated with impaired coagulation [26]. Of some reassurance was the fact that only 3 of the 36 cases involving hematomata and permanent nerve injury were in obstetrics.
- Among the published case reports of parturients who have experienced a spinal hematoma after neuraxial blockade, a significant proportion of patients had altered coagulation at the time of block placement or epidural catheter removal.
- To date, there have been no published cases of spinal hematoma in a parturient associated with antithrombotic therapy (with or without neuraxial block).

The risks of neuraxial anesthesia in the coagulopathic parturient must be weighed against the risks of the alternatives and the gravity of the situation. Airway and ventilation problems continue to be the leading cause of anesthesia-related maternal deaths [27].

## Spinal hematoma

- Spinal hematoma is the most feared and potentially catastrophic complication of neuraxial anesthesia [24].
- Bleeding in the epidural or subarachnoid space can lead to neurological impairment, which may be permanent.
- Recognition of early symptoms and signs is crucial. Four symptoms should alert all medical personnel of the possibility of a developing spinal hematoma:
  - new, severe back pain, often radiating
  - leg weakness paraparesis
  - sensibility disturbances unrelated to the block itself
  - bladder or bowel disturbances
- In some cases, an MRI has revealed a spinal hematoma where the only symptom was back pain.
- Too often, symptoms are mistakenly attributed to an ongoing epidural. This delays effective treatment (laminectomy) and may cause a permanent disability in a patient.

## If spinal hematoma is suspected

- Request an MRI scan (CT is less sensitive) and urgently consult a neurosurgeon or an orthopedic surgeon.
- In cases with an indwelling epidural catheter: try to evacuate as much blood as possible via the catheter. Leave the catheter in place: manipulations/extraction may increase bleeding.
- Try to reverse any possible hemostatic disorder, in order to reduce any ongoing bleeding.
- Avoid unnecessary patient transport and loss of time.
- The most effective treatment is decompressive laminectomy within 12 hours of the appearance of symptoms.

## Summary

- Normal pregnancy imparts an increased tendency toward thrombus formation, extension, and stability.
- Epidural or spinal hematoma are rare and devastating complications of neuraxial anesthesia in parturients.
- Their occurrence is almost invariably associated with clinical coagulopathy or the use of anticoagulants.
- Decisions regarding the most appropriate anesthetic management for obstetric patients can be difficult and fraught with pitfalls.
- The current state of literature is based primarily on case reports/series, expert opinion, and professional guidelines. There is a paucity of definitive evidence.
- Current evidence supports a platelet count of $80 \times 10^9$/L as a safe cutoff for placing/removing an epidural or spinal anaesthetic with the following caveats – non-pre-eclamptic

patients, stable platelet counts, and no history or clinical signs of bleeding. Regional anesthesia has been safely administered in pregnant patients with platelets between 50 and $79 \times 10^9$/L. The lower limit of platelet count for regional anesthesia could be $50 \times 10^9$/L and likely a graded risk exists, subject to individual risk–benefit analysis.

- There is no substitute for pragmatic assessment of risk and sound clinical judgment.

## Further reading


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Chapter 9

# Air vs. normal saline for the loss of resistance technique during epidural insertion

Dr A Hinova and Dr R Fernando

## Introduction

- Epidural anesthesia was introduced in 1901 by Sicard and Cathelin in France, who popularized the caudal approach. The technique has been subject to multiple modifications and updates since then.
- However, it relies essentially on correctly localizing the epidural space by means of a "blind" method known as the loss of resistance technique. This is followed by the insertion of an epidural catheter into the epidural space at an appropriate depth for the delivery of a combination of drugs, usually these days using a local anaesthetic/opioid combination, for example, for labor analgesia.
- The two most commonly used techniques in clinical use are the loss of resistance to air and to normal saline. The term loss of resistance refers to the subjective feel of a change in resistance while the epidural needle penetrates the interspinous ligament, the ligamentum flavum, and subsequently into the epidural space.
- Controversy surrounds the issue regarding the optimal medium used for loss of resistance – air or normal saline. This debate has been present for at least 30 years and the topic still generates discussion.
- Nowadays in the UK anesthesiology residents are being almost universally taught using the normal saline technique, although some anesthesiologists, often the ones with the greatest experience [1], still use air while arguing that in their hands loss of resistance to air is a perfectly safe and effective way to identify the epidural space.
- There are few good quality prospective randomized studies examining the differences between the use of air and saline. Most are in parturients [2–5], with only one study conducted in acute and chronic pain patients [6].
- This review attempts to evaluate whether, during the loss of resistance technique, air or saline used during epidural anesthesia influences either the efficacy of regional blockade or the incidence of complications such as accidental dural puncture rate and postdural puncture headache (PDPH).
- In addition we explore if one particular method should be used to train novice anesthesiologists.

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## Efficacy

Does each technique work and if so is one better than the other? Do we achieve better analgesia using air or saline as part of the loss of resistance technique?

- A survey of practice among obstetric anesthesiologists in the UK in 2006 examined 1,200 questionnaires, which showed that 74% used loss of resistance with saline and 25% used loss of resistance with air [7]. The main reason cited for the difference in practice was the superior safety features of the normal saline technique.
- Similarly, loss of resistance to saline is the preferred method among Canadian pediatric anesthesiologists [8], with 95% of the anesthesiologists questioned responding that they use loss of resistance to saline in all pediatric age groups.
- A retrospective study by Segal and Arendt [9] examined the effectiveness of both techniques. Out of almost 1,000 labor epidurals, 52% were performed using loss of resistance to air and 47% to saline. The primary outcome measure was an unsatisfactory block as evidenced by the absence of initial analgesia, block asymmetry, intravascular or intrathecal catheter, and catheter replacement. Since there were no differences in patient characteristics between groups, the authors concluded that when used at the anesthesiologist's discretion there is no difference in the success rate of the block whether using air or saline to locate the epidural space.
- In an audit of the analgesic efficacy of combined spinal–epidural (CSE) analgesia for labor using loss of resistance to saline vs. air, Leo *et al.* [10] examined data from 2,848 patients, with almost equal numbers of anesthesiologists using either air or saline (56% saline vs. 44% air). Both groups had similar complication rates and post-block side effects. The analgesic efficacy was measured by the incidence of breakthrough pain necessitating further local anaesthetic/opioid boluses. Patients in the air group had a higher incidence of breakthrough pain ($p = 0.023$).
- Their findings are similar to a single blinded randomized trial conducted by Valentine *et al.* [5] that compared analgesia obtained using 4 ml air or 4 ml saline to identify the epidural space. This group found that the use of air led to a greater number of unblocked dermatomes.
- Beilin *et al.* [4] also compared the quality of analgesia in a randomized study using air or saline to locate the epidural space and found that more parturients in the air group had incomplete analgesia 15 minutes after the last epidural dose of analgesic drug used to initiate labor analgesia, requiring additional epidural boluses.
- Similarly a paper by Evron *et al.* [3] compared the quality of analgesia, the ease of epidural catheter insertion, and the complication profile of air, lidocaine, or the combination of lidocaine and air as part of the loss of resistance technique for the identification of the epidural space. The 547 women were randomly allocated to three groups: (1) loss of resistance with 3 ml of air ($n = 180$); (2) loss of resistance with 3 ml of lidocaine ($n = 185$); and (3) loss of resistance with the sequential use of 3 ml of air followed by 3 ml of lidocaine ($n = 182$). Data collection included the ease of epidural catheter insertion and block quality. Inability to thread the epidural catheter occurred in 16% of the air, 4% of the lidocaine and 3% in the air/lidocaine group ($p < 0.001$). More patients from the air group had unblocked segments (6.6% vs. 3.2% and 2.2% respectively, $p < 0.02$). The authors also found a higher incidence of complications using air. This included more intravascular catheter placements

(17% vs. 6% and 8% respectively, $p < 0.02$) and dural punctures (1.7% vs. 0% in the other two groups $p < 0.02$). They concluded that there was no advantage of using air vs. lidocaine for the location of the epidural space while at the same time acknowledging the possibility of an inadvertent subarachnoid injection of lidocaine if lidocaine was utilized instead of saline for the loss of resistance technique. Interestingly, pain scores, time to onset of analgesia, upper sensory level, motor blockade, and PDPH incidence were comparable between the groups. A technique using loss of resistance to lidocaine, rather than saline, would today be regarded as an unusual technique, potentially causing more morbidity if lidocaine was injected into the subarachnoid space following an accidental dural puncture.

## Complications and safety profile

There are few prospective, controlled, randomized double-blind trials comparing the complications of air vs. saline in identifying the epidural space.

- A meta-analysis by Schier *et al.* looked at six outcome measures when looking at the complication rates between air and saline [11]. These were difficult catheter insertion, paresthesia, intravascular catheter insertion, accidental dural puncture, PDPH, and partial block. The authors found no difference in these outcomes in obstetric patients, but a small but statistically significant reduction in PDPH when saline was used instead of air in chronic pain patients.
- In a comprehensive review Saberski *et al.* [12] examined all published reports between 1966 and 1995 of complications related to using air. These included pneumocephalus, spinal cord and nerve root compression, retroperitoneal air, subcutaneous emphysema, and venous air embolism. Additionally transient and even permanent neurological sequelae, including paresthesiae, have been reported with the use of air in the epidural space.

### Pneumocephalus

Most headaches associated with dural puncture typically occur one to three days after the epidural/spinal block and persist for one to five days.

- Abram *et al.* [13] reported a different kind of headache observed in 8 of 604 patients undergoing epidural analgesia. These headaches occurred shortly after the procedure when air was used and only when the patients sat up. The headaches were partially relieved by reclining. In all cases the headache was secondary to dural puncture following an attempt to locate the epidural space using loss of resistance to air.
- Saberski identified 13 similar case reports of pneumocephalus using air for the loss of resistance technique. The amount of air used was 2 to 20 ml. Pneumocephalus was radiologically demonstrated in most cases by means of a CT scan of the head. While some of the patients were asymptomatic [14] others suffered from severe headache, nausea/vomiting, generalized seizures, and/or hemiparesis [15].
- In a case described by Katz [16] pneumocephalus was believed to be responsible for the delayed awakening in a patient who had a total spinal after an attempted epidural with loss of resistance to air and in whom nitrous oxide was thought to have caused expansion of an entrapped air bubble. Headache due to pneumocephalus typically occurs earlier than one after an accidental dural puncture and the treatment is symptomatic.

Administering 100% oxygen improves it, whereas nitrous oxide may make the headache worse by increasing CSF pressure [17].

- Another case report by Laviola [18] described the development of acute severe bifrontal headache and left-sided pupillary dilatation following epidural insertion using loss of resistance to air after an accidental dural puncture in a young woman undergoing an elective cesarean delivery. The operator injected inadvertently 5 ml of air into the epidural space after which the epidural catheter was resited at a different interspace. Fifteen minutes later the patient developed an acute severe headache with unilateral pupillary dilatation. A CT scan demonstrated both subarachnoid and intraventricular air, causing direct compression of the oculomotor nerve. The authors concluded that while there is not sufficient evidence to stop using loss of resistance to air in all cases, the technique should definitely not be used after an inadvertent dural puncture.
- Panni *et al.* [19] described a case of a postpartum patient who developed a prolonged dense persisting motor and sensory block (to T6) for a number of hours post partum, which was due to air in the epidural space compressing the thecal sac, as demonstrated on CT scan. At the recommendation of the neurologist the patient needed hyperbaric chamber therapy and recovered uneventfully.

## Spinal cord and nerve root compression

Neurologic defects following epidural anesthesia are fortunately rare but they can occur due to spinal cord compression from a hematoma, trauma to the spinal cord or nerve roots, and vascular compromise. There are case reports of spinal cord compression as a result of the use of air to identify the epidural space [20–22]. Patients had a variety of symptoms ranging from excruciating pain to motor weakness, loss of sensation, and paraplegia. Computed tomography scans have showed air impinging on the spinal cord at a level corresponding to the pattern of the neurological deficit.

- Kennedy *et al.* [23] described a case of nerve root compression from accumulation of air in the epidural space in a patient receiving continuous epidural infusion. The patient had repeatedly silenced the alarm signaling the presence of air in the system and had purged air through the epidural catheter.
- Cuerden *et al.* [24] described delayed recovery due to neurological complications in four obstetric patients in whom loss of resistance to air was used to identify the epidural space. The deficits included sensory loss, paresthesiae, motor weakness, decrease in muscle tone, and decreased tendon reflexes in the lower limbs. The authors felt that the deficits were consistent with spinal cord compression from air, which was reabsorbed in the following 24 to 48 hours leading to complete resolution. However, no imaging was performed in order to demonstrate the presence of air.
- The use of air in identifying the epidural space may have contributed to the development of a cauda equina syndrome in a patient who subsequently received nitrous oxide as part of a general anesthetic for a prostatectomy [25]. Neurological symptoms were present 12 months postoperatively. The MRI scan was inconclusive although the air, which could have been responsible, may well have been reabsorbed at the time of imaging.

Despite the lack of a sufficient number of formal randomized studies demonstrating the increased incidence of pneumocephalus and other neurological complications with the use of

air as part of a loss of resistance technique, there is an increasing amount of evidence from case reports to indicate that using air can cause more morbidity.

## Subcutaneous emphysema

There have been several case reports of subcutaneous emphysema as a result of the loss of resistance to air technique used to identify the epidural space [7, 26–30]. Emphysema has been described in the supraclavicular, cervical, thoracolumbar, and abdominal regions. Common factors in all cases were multiple attempts using upwards of 20 ml of air before identifying the epidural space. Crepitus was the commonest presentation. In all cases the subcutaneous air was reabsorbed over a number of days. Potential clinical problems arising from subcutaneous emphysema could include extrinsic airway compression and air embolism, both of which become more serious with the use of nitrous oxide.

## Venous air embolism

Venous air embolism (VAE) is a well recognized complication of many surgical and diagnostic procedures. The epidural space is occupied by a rich plexus of veins lateral and anterior to the spinal cord. These veins are valveless so when a patient is in the lateral position, the epidural pressure closely approximates central venous pressure [31]. Factors predisposing to development of venous air embolism include a tear in a vein and a perivascular pressure that is higher than the central venous pressure. Therefore an epidural venous puncture with rapid injection of air used for loss of resistance may result in VAE.

- There have been two pediatric case reports of VAE in the course of using loss of resistance technique to identify the epidural space [31, 32]. The children were administered approximately 0.4 ml and 0.2 ml air. In both cases there was a rapid onset cardiovascular collapse following a forceful injection of air through a misplaced needle and catheter in an epidural vein. Prompt cardiovascular resuscitation prevented both children from further deterioration.
- Naulty *et al.* demonstrated Doppler evidence of intracardiac embolism in 8 out of 17 patients (46%) in whom loss of resistance to air was used [33].
- The volume of air or the rate of administration necessary to produce significant physiological alterations in humans are not known; however, it has been demonstrated in animals that 0.5 ml/kg/min can produce cardiovascular instability. Although a large amount of air is necessary in order to produce right ventricular dysfunction and hemodynamic changes, a relatively smaller volume of air reaching the arterial circulation through an intracardiac defect could potentially occur. The use of nitrous oxide in the context of VAE could more than double the volume of an air embolus resulting in significantly more cardiovascular problems.

The exact incidence of complications associated with the use of air as part of the loss of resistance technique for identifying the epidural space is not known. Although rare, some complications are serious and potentially life threatening. In addition, it is likely that a significant number of subclinical problems occur that often are not detected or reported.

In light of the evidence outlined and considering the significant proportion of patients with asymptomatic intracardiac communication, it appears that the risks of using air instead of saline as part of a loss of resistance technique outweigh the benefits.

## Accidental dural puncture

There is a suggestion that using normal saline has an additional safety aspect over the use of air. It is thought, although unproven, that using saline as part of a loss of resistance "pushes away" the dura, leading to a reduction in the risk of dural puncture. This is because the air technique requires intermittent advancement of the epidural needle, which theoretically means that with each movement the epidural needle may exit the ligamentum flavum and penetrate the dura. On the other hand, since the saline technique requires continuous pressure, the moment the epidural space is entered the syringe plunger moves injecting a small volume of saline that may push the dura away.

- Stride and Cooper [34] reviewed the records from 34,819 obstetric epidurals performed in the Birmingham Maternity Hospital in the UK between 1969 and 1988. The overall accidental dural puncture incidence during that period was 1.3% (460 dural punctures). Of the methods used to identify the epidural space, loss of resistance to saline was associated with the lowest incidence of dural puncture (0.6%). The incidence of typical PDPH when managed conservatively was 86%. A blood patch provided complete relief of headache in 68% of patients in which it was performed (93 out of 135), with a further 23 patients (16%) obtaining partial relief.
- The National Obstetric Anaesthesia Database (NOAD) in the UK published detailed data in 1999 on postpartum headache from a database of over 65,000 women who had received an anesthetic intervention [35]. Although 80% of epidural procedures were performed using loss of resistance to saline, significantly more women overall were likely to suffer a PDPH when air was used.
- Paech *et al.* [36] similarly showed in a retrospective audit that although the incidence of dural puncture was not influenced by the technique, an earlier onset of headache occurred if air was used.

However, most randomized studies show that there is no difference in the rate of accidental dural puncture with air or saline [2–5].

## Disadvantages of using saline over air

It has often been stated that, when using loss of resistance to air, any fluid seen in either the needle or catheter is cerebrospinal fluid (CSF) and thus the use of air aids the diagnosis of accidental dural puncture. It could be argued, however, that it is better to use a technique that reduces the incidence of a complication rather than one that facilitates its diagnosis [37]. Moreover, the assumption that any fluid is indeed CSF is flawed as local anesthetic or edema fluid may both be observed in the absence of dural puncture [38]. Furthermore, El-Behesy and colleagues demonstrated that saline and CSF are easily distinguishable by their glucose and protein content and temperature [39] – while the difference in volume (observed exiting the epidural needle at the moment of dural puncture) is usually obvious.

## Ease of use and training

Nowadays the majority of UK anesthesiologists use saline for the loss of resistance method with only a minority using air, while novice anesthesiologists are universally taught to use saline [7]. There may be more experienced anesthesiologists who still continue to use air

claiming the procedure is safe in their hands. This probably represents more their high level of experience rather than the superiority and safety of using air as part of the loss of resistance technique for locating the epidural space.

Locating the epidural space through the loss of resistance method, whether we use saline or air, is still a blind procedure and the success and complication rates are intricately related to operator experience. Finding the most effective and safest way of teaching the loss of resistance technique has prompted the creation of new devices such as the Episure® loss of resistance syringe.

The Episure® syringe (Indigo Orb, Santa Clara, CA) is a spring-loaded syringe with a coaxial compression spring that provides a force to the syringe plunger. The aim of this design is to provide a more objective sign when the epidural space is identified compared with the traditional subjective, operator-dependent loss of resistance technique. This device has been tested in both laboratory and animal models as well as in a clinical setting [40, 41]. Riley *et al.* [41] evaluated the use of the Episure® in animal models and found that it was potentially useful as a tool to identify the epidural space. However, realistically less than half (48%) of the questioned anesthesiologists would have been happy to change their technique. Where the new device might be more helpful would be as a teaching aid to help trainees recognize the loss of resistance feel while using simulation models such as commercially available epidural trainers.

Douglas, debating this issue, maintains that instead of focusing on the loss of resistance technique we should be focusing on other factors that are known to influence the dural puncture rate [42], which is the most common cause of morbidity in parturients following epidural blockade. These include the increased incidence at night [43], the inverse relationship with the number of epidurals performed annually [6], and the higher incidence in trainees [43].

## Conclusion

- Using saline as part of a loss of resistance technique to identify the epidural space is probably the most widely accepted practice worldwide among anesthesiologists.
- A minority use air and there is no evidence that this technique should be discarded altogether.
- Reviewing the literature leads to the conclusion that using saline is a better standard of practice in terms of providing a better quality block with fewer complications.
- Therefore this should be the only technique residents should be taught.

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Chapter

10

# Ambulatory and patient-controlled epidural analgesia

**Dr M Gros and Dr B J Morrell**

## Introduction

- Epidurals have proven themselves to be the most effective form of analgesia for the laboring parturient; however, pain relief has come with potential risks.
- Traditional epidurals utilize a higher concentration of local anesthetic solution (at least 0.25% bupivacaine) and result in a dense motor block.
- While traditional epidurals do not affect cesarean section rates, they are still associated with increased instrumented deliveries, a prolonged second stage of labor, and the use of oxytocin for augmentation [1] – see also chapter on Epidurals and outcome.
- Since the 1990s obstetrical epidurals have evolved from their traditional form to lower dose local anesthetics in combination with narcotics, and in various delivery methods including patient-controlled epidural anesthesia (PCEA).
- Often these techniques are referred to as "mobile," "ambulatory," or "walking" epidurals as the patient's balance and motor strength are unimpaired and the potential for safe ambulation exists.
- The ultimate goal is to find the safest technique without compromising pain relief or maternal satisfaction.

## Techniques

The two most commonly employed low-dose techniques are combined spinal–epidural (CSE) and continuous low-dose epidural infusion.

- The CSE involves an injection of medication into the intrathecal space followed by placement of the epidural catheter. This is fully discussed in its own chapter.
- Low-dose epidural solutions usually consist of both a reduced concentration of local anesthetic (less than 0.125% bupivacaine or ropivicaine) with a narcotic, such as fentanyl (approximately 2 to 2.5 μg/ml) or sufentanil (approximately 0.25 μg/ml).

Ongoing maintenance of analgesia may be with any number of techniques, which include but are not limited to continuous infusions, patient-controlled epidural analgesia, and programmed intermittent epidural boluses.

*Controversies in Obstetric Anesthesia and Analgesia*, ed. Ian McConachie. Published by Cambridge University Press. 

## Comparison of CSE and low-dose infusions

Advantages of CSE:

- CSE offers faster onset of analgesia, in particular sacral analgesia [2].
- CSE is associated with less urinary retention [3].
- CSE technique may decrease epidural failure rate [4].

Disadvantages of CSE:

- CSE is associated with a higher incidence of pruritus (due to intrathecal vs. epidural opioids) [5].
- It may be unclear for one to two hours if the epidural catheter is providing effective analgesia.
- Neonatal outcomes as measured by neonatal unit admission or Apgar scores are no different, and statistically significant umbilical artery pH differences are not considered clinically significant compared to traditional epidurals [3].
- Overall maternal satisfaction is equivocal [6, 7].
- There are conflicting studies with regard to CSE techniques having less need for rescue analgesia [8, 9].
- Despite dural puncture with the CSE technique, there is no increased incidence of dural puncture headache, blood patch, or maternal hypotension [10].

# Low-dose ambulatory epidurals compared to traditional epidurals

- The risk of instrumental delivery seems to be reduced [6, 7].
- Maternal perception of "retaining control" is improved. According to surveys, maintaining control is an important factor for a positive childbirth experience [11].
- Ambulatory epidurals promote the retention of urinary function and reduce the risk of urinary catheterization during labor [12].
- The quality of analgesia does not seem to be compromised [6, 7].

## Is it safe to ambulate?

Importantly, balance in mothers with low-dose epidurals seems equal to that of non-epidural pregnant ladies – a least in the initial stages of the epidural [13].

Protocols usually include [14]:

- exclusion criteria based on obstetric problems or complications
- 20 to 45 minutes of monitoring for maternal hypotension and fetal heart rate post-analgesia administration
- maternal vital signs confirmed to show no orthostatic instability
- motor assessment (based on modified Bromage scales with the ability to raise an extended leg from the supine position, ability to flex the knee, flex and extend the ankle, and perform deep knee bends)
- clinical balance assessment

- ambulation with the patient's infusion pole on one side and a support person (nurse or partner) on the other side.

There is one published report of a patient falling while walking after epidural placement [15]. While the incidence may be rare, the resulting medical and medico-legal implications could be catastrophic.

## Do parturients with walking epidurals actually walk? Does ambulation per se matter?

Most women prefer to rest or sleep once adequate analgesia is established [14].

- Of those who do walk, on average they only do so for 40 to 60 minutes of the duration of the first stage labor.
- Very few continue to ambulate in the second stage of labor.

Another advantage is that maintaining ambulation does promote spontaneous voiding with less need for urinary catheterization [12]:

- reduced catheterization has only been shown in labor and has yet to show a difference in postpartum catheterization rates
- a proposed potential benefit, in addition to maternal satisfaction, might include reducing bacteriuria.

A number of studies have failed to demonstrate that ambulation or an upright position in the first stage of labor alters outcomes [16]. While some evidence suggests an upright position in the second stage of labor may be beneficial, ambulation alone has not been clinically significant in altering labor outcomes [17]. Well designed studies are required to investigate this potential benefit further.

## If not ambulation, what are the possible theories for reduced instrumental deliveries with the "walking" epidural?

- Preservation of lower body motor function may be enough to assist voluntary and involuntary maternal efforts to expel the fetus in the second stage of labor.
- Low dose means low concentration. The total dose of bupivacaine is not necessarily reduced, implying that it is the concentration of bupivacaine administered that is important. That is, it is high *concentrations* of bupivacaine as opposed to high *doses* in mg that are implicated in the motor weakness experienced with traditional epidurals [6, 7].

# Maintenance of labor analgesia with patient-controlled epidural analgesia

Patient-controlled epidural analgesia (PCEA) for labor was first introduced into clinical practice in 1988 by Gambling *et al.* [18].

The potential benefits of PCEA are:

- use of less local anesthetic
- decreased lower limb weakness

- more effective pushing in the second stage of labor
- improved maternal satisfaction as a result of increased control
- decreased clinician intervention.

Patient-controlled epidural analgesia has proven to be both safe and effective; however, there remain many unanswered questions and more studies are required to further refine the technique. The remainder of this chapter will focus on presenting the most current literature addressing some of these controversies.

## Background infusion or not?

- Several randomized controlled trials have compared PCEA with and without background infusions.
- These trials generally have been performed in low-risk pregnancies in mothers of mixed parity. This may limit their broader extrapolation.
- The background infusion rates have tended to be low, with most being <5 ml/h.
- One early study found a difference in analgesia. The "no infusion" group had a higher incidence of pain scores (>4/10) than the "infusion" group [19].
- There was no difference in the incidence of significant motor block between the groups.
- There were more clinician interventions in the "no infusion" groups, implying greater workload for the clinician.
- A recent study found increased maternal satisfaction and improved analgesia with background infusions [20].
- There are no reports of toxicity.
- The American Society of Anesthesiologists' practice guidelines for obstetric anesthesia support the use of a background infusion based on a meta-analysis of five studies [21].

Based on the available studies, there may be a benefit to using a continuous background infusion as it may improve analgesia. At the very least, none of the outcomes were better in patients who did not receive an infusion. It appears that the most consistent outcome is a decreased workload for the clinician, which may have the most benefit in busy settings where the clinician can't readily attend to the patient for "rescue" dosing.

## Bolus dose volume and lockout interval

- There are wide variations in PCEA settings between different centers.
- There have been six randomized, controlled trials comparing various settings, solutions, etc.
- For example, the different solutions include bupivacaine 0.0625 to 0.125% or ropivicaine 0.1 to 0.2% with the addition of fentanyl or sufentanil.
- Bolus volumes have varied from 2 to 20 ml with lockout intervals from 5 to 30 minutes.
- Three studies have used background infusions in their protocols.
- One study compared a 4-ml bolus and a lockout of 8 minutes with a 12-ml bolus and a lockout of 25 minutes, using 0.125% bupivacaine with sufentanil, and no background infusion. They found significantly better analgesia in the larger bolus group and

improved maternal satisfaction. There was no difference in clinician workload, and motor block was not measured [22].

- Another study found a shorter lockout interval (5 minutes versus 15 minutes both with a bolus dose of 5 ml) resulted in improved success:demand ratio. However, this did not translate into improved analgesia, improved maternal satisfaction, or decreased clinician rescue boluses [23].
- The remainder of the studies did not find any differences in any outcomes, including analgesia, maternal satisfaction, motor block, or clinician rescue boluses. There were also no reports of toxicity or increased side effects with larger bolus volumes.

The available data suggest that there are no known "optimal" PCEA settings for labor analgesia. Most studies are underpowered to show even modest outcome differences. It has previously been shown with labor epidurals that large bolus doses do in fact improve the spread of local anesthetic within the epidural space [24]. Therefore it makes sense to use larger bolus doses with longer lockout intervals. It also remains unclear whether a background infusion should be included with these large bolus doses.

## Drug choice

Another ongoing debate is which is the optimal drug to use – bupivacaine or ropivacaine? Many studies have investigated this debate.

- Different studies have investigated a wide range of settings with concentrations of bupivacaine 0.05 to 0.125% or ropivacaine 0.05 to 0.20%.
- Labor analgesia, in general, is similar between different choices of drugs.
- Five studies report an increased incidence of motor block with bupivacaine, which is consistent with previous data obtained using continuous epidural infusions.
- One study found greater maternal satisfaction with analgesia for delivery in the bupivacaine groups. The same study found that maternal satisfaction while mobilizing was higher in the ropivacaine group [25].
- Fischer found no difference in analgesia, but greater maternal satisfaction in the bupivacaine group [26].
- One study found increased clinician rescue boluses were required in the first stage of labor in the bupivacaine group, and increased boluses in the second stage in the ropivacaine group [27]. The remainder of the studies didn't find any significant differences between the different drugs.

Therefore, based on the available studies, both bupivacaine and ropivacaine are well suited to PCEA. The most consistent benefit appears to be decreased motor block with ropivacaine; however, there are so many different options for the PCEA settings, that any advantage that one drug may have can be overcome by adjusting these parameters.

### Drug concentration

The factors influencing the distribution, intensity, and duration of action of local anesthetics remain unclear.

Potential benefits of dilute local anesthetics include:

- improved analgesia
- improved maternal satisfaction
- decreased motor block
- improved ambulation
- improved outcomes.

There have been several studies comparing different concentrations – either bupivacaine 0.0625 to 0.25% or ropivacaine 0.1 to 0.2%. Findings include:

- Increased local anesthetic use and uptake in the concentrated groups.
- Increased maternal motor block in the concentrated groups.
- One study found improved maternal satisfaction scores in the dilute group (93 vs. 82, $p = 0.04$). However, the dilute solution group used larger volumes, which may improve analgesia as a result of more uniform spread in the epidural space. This study also found a >50% increase in the number of boluses in the concentrated group ($p = 0.001$) and a >200% increase in failed attempts at boluses in the concentrated group ($p = 0.05$) [28].
- No differences have been seen in the duration of the first or second stages of labor, the incidence of non-reassuring fetal heart rate, adequacy of pushing, incidence of instrumental delivery, or Apgar scores.
- It seems that dilute solutions with larger boluses may decrease clinician workload because of the need for fewer rescue boluses.

Therefore, the available studies suggest that larger volumes of more dilute solutions be used to decrease the total dose used, decrease the incidence of motor block, and potentially improve maternal analgesia and satisfaction. Bupivacaine 0.25% and ropivacaine 0.2% are no longer appropriate for PCEA for labor.

## Patient-controlled epidural analgesia regimes in some major academic centers in North America

Recently, six faculty members from the University of Washington visited six North-American academic centers with an active obstetric anesthesia division to determine obstetrical anesthesia practice in those academic centers. A summary of their findings for the six visited centers and their own center was published in the Society for Obstetric Anesthesia and Perinatology (SOAP) Winter 2011 newsletter [29].

- All centers use PCEA for labor analgesia.
- All centers use bupivacaine as the drug of choice.
- Drug concentration varied from 0.0625% (four centers), 0.08% (one center), 0.1% (one center), to 0.125% (one center).
- Six centers add fentanyl to the infusion, and one center adds sufentanil.
- All centers use basal infusions ranging from 5 to 12 ml/h.
- Bolus doses range from 5 to 12 ml.
- Lockout intervals range from 8 to 15 minutes.

# Future possibilities for patient-controlled epidural analgesia

## Computer-integrated PCEA

- The device automatically adjusts the background infusion rate based on the number of demands and, therefore, responds to the patient's analgesic requirements.
- This potentially improves efficacy while minimizing the dose of local anesthetic.
- One study compared this with traditional demand-only PCEA and found improved maternal satisfaction in the computer-integrated PCEA group [30].
- These findings were subsequently repeated [31], that is, there were higher maternal satisfaction scores with a higher infusion rate during the second stage of labor without prolonging the second stage.
- This system is not currently commercially available, but its implementation into clinical practice may be seen in the near future.

## Programmed intermittent epidural boluses

- The same total hourly amount of local anesthetic is administered as would have been with continuous epidural infusion but this is administered as intermittent mandatory boluses.
- For example, two boluses of 6 ml every 30 minutes, instead of 12 ml/h continuous infusion.
- The proposed mechanism of any benefit would be a more uniform spread of local anesthetic in the epidural space when large volumes with high injectate pressures are delivered.
- Several studies have found that, compared to continuous epidural infusion, intermittent boluses result in similar analgesia, higher maternal satisfaction, less need for rescue boluses, and less local anesthetic use [32–34].
- Most recently, Leo in 2010 [35] found that PCEA with automated mandatory boluses, when compared to PCEA with a basal infusion, confers greater patient satisfaction and a longer duration of effective analgesia after CSE, despite overall reduced analgesic consumption.
- This is also currently not available but will likely be incorporated into future epidural devices.

# Summary

- Mobile epidurals reduce the risk of instrumental deliveries and provide uncompromised analgesia when compared to traditional epidurals.
- Whether initiated or not with a CSE, ongoing analgesia with low-dose infusions or PCEAs confers these same benefits.
- Evidence suggests PCEA protocols that use a low-dose background infusion (approximately 5 ml/h) in combination with larger boluses with longer lockout intervals may be superior.
- There is little evidence to support the choice of one local anesthetic (bupivacaine or ropivicaine) over another.
- Automated mandatory boluses seem promising for the future.

## Further reading


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Chapter 11

# Hypotension following spinal anesthesia

Dr C Delbridge and Dr I McConachie

## Introduction

- Hypotension following spinal anesthesia in obstetric patients is commonplace. Less commonly this can occur following epidural analgesia. The resulting distress to the patient is not in dispute but controversy still surrounds the exact clinical implications of this hypotension especially with regard to fetal outcomes.
- Hypotension as a result of spinal anesthesia will be mainly discussed here but many of the principles will also apply to hypotension following epidural analgesia.
- The controversies arise during discussion of the best approaches for preventing and/or managing this complication. A large part of this discussion centers around the choice of phenylephrine or ephedrine for this purpose.

## Mechanisms of spinal-induced hypotension

The hypotension produced by spinal anesthesia in obstetric patients is multifactorial.

- Spinal anesthesia induces a sympathectomy, leading to vasodilation, increased venous capacitance, and decreased venous return. High levels of sympathetic blockade can decrease maternal cardiac output although with lesser height and degrees of sympathetic blockade a compensatory increase in cardiac output may be seen secondary to reductions in cardiac afterload.
- Pregnant women have an elevated resting sympathetic tone and thus increased effects of sympathetic blockade.
- This also leads to decreased sensitivity to vasopressors, secondary to downregulation of adrenergic receptors and increased synthesis of endothelium-derived vasodilators during pregnancy.
- Spinal anesthesia abolishes labor pain, which can decrease maternal blood pressure.
- Pregnant women have increased sensitivity (i.e. increased peak block height and block duration) to spinal anesthesia, due to a combination of reduced volume of spinal cerebrospinal fluid (CSF), enhanced neural susceptibility to local anesthetics, and changes in vertebral anatomy during pregnancy.
- Aortocaval compression by the gravid uterus, if present, further contributes to hypotension.

*Controversies in Obstetric Anesthesia and Analgesia*, ed. Ian McConachie. Published by Cambridge University Press. 

## Incidence and risk factors

In a recent retrospective study 46% of cesarean section patients who received regional anesthesia had a decrease in blood pressure (BP) of 30% or more [1] but with no measurable differences in fetal outcome.

Risk factors associated with spinal-induced hypotension include [1, 2]:

- increasing age
- spinal anesthetic factors, e.g. dose of local anesthetic, height of resultant block
- pre-existing hypertension
- higher infant birth weight
- obesity.

## Is hypotension secondary to spinal anesthesia harmful?

It would be hard to imagine that hypotension secondary to spinal anesthesia could be beneficial! Certainly, hypotension is commonly accompanied by distressing maternal symptoms including nausea, vomiting, and syncopal symptoms. Spinal anesthesia has been implicated as a factor in several cases of maternal mortality – in part due to cardiovascular effects. Sustained, severe hypotension would clearly be detrimental to the function of several maternal organs. Thus its prevention and/or management seems clearly warranted from a maternal point of view.

From a fetal point of view:

- Chronic hypotension, especially if accompanied by decreased cardiac output, may reduce placental perfusion and impair fetal oxygenation.
- Effects on the fetus of transient hypotension are less clear.
- In animals, acute reductions in oxygen delivery of up to 50% are well tolerated and compensated for, in part, by an increased oxygen extraction ratio by the fetus [3]. This assumption may not hold true in situations of placental pathology.
- An acute fetal acidosis rarely causes fetal problems as opposed to long-term chronic acidosis. The influence and significance of fetal acidosis associated with the use of different vasopressors will be further discussed below.

## Survey of prophylaxis methods

A variety of strategies are employed to prevent hypotension associated with spinal anesthesia. A recent survey [4] found the following methods were used:

| Method | Percentage of respondents |
|---|---|
| Fluid preloading | 33 |
| Fluid coloading (see below) | 11 |
| Fluid preloading and vasopressors | 32 |
| Fluid coloading and vasopressors | 21 |
| None of the above | 1 |

The choice of vasopressor is also variable according to that survey:

| Drug | Prevention % | Treatment % |
|---|---|---|
| Ephedrine alone | 32 | 32 |
| Phenylephrine alone | 26 | 23 |
| Phenylephrine and ephedrine | 8 | 4 |
| Phenylephrine or ephedrine depending on heart rate | 33 | 41 |
| Other α agonist | 1 | 1 |

# Miscellaneous methods to prevent hypotension

- Tilting the patient by means of a wedge to limit aortocaval compression by the gravid uterus is standard practice – though if fully effective would negate the need for this chapter. A recent study [5] found that placing the wedge under the right lumbar area as opposed to under the right hip resulted in a lesser incidence of maternal hypotension.
- The use of a lower dose of local anesthetic such as bupivacaine with the resultant lesser extent of sympathetic block will result in less hypotension – but at the potential cost of reduced block duration and increased maternal discomfort during cesarean section. A full discussion of the factors involved in the choice of local anesthetic dose for spinal anesthesia is outwith the scope of this chapter.
- Wrapping of the legs (to decrease bood pooling in the legs and increase venous return) is as effective as phenylephrine in maintaining blood pressure after epidural anesthesia for cesarean section [6] but is not widely practiced.
- Transcutaneous electrical nerve stimulation (TENS) applied on two traditional acupuncture points has been shown to be effective in maintaining blood pressure in patients undergoing cesarean section under spinal anesthesia and reduces the requirement for ephedrine [7]. The mechanism is unclear but TENS may increase sympathetic tone. This method of preventing hypotension after spinal anesthesia is likely not widely practiced in the Western world.

# Fluid therapy

## Preloading

- "Preloading," that is, giving intravenous fluids prior to induction of spinal anesthesia with the intent of increasing the circulatory volume and cardiac preload, used to be standard practice.
- A systematic review in 2001 [8] showed that crystalloid preload was inconsistent in preventing hypotension, whereas colloid was slightly more effective.
- Even volumes of crystalloid as high as 30 ml/kg do not significantly alter maternal hemodynamics or ephedrine requirements after spinal anesthesia suggesting that crystalloid preloading may have no benefit [9].
- It has been suggested that crystalloid preloading is not necessary when metaraminol (a pure α1 agonist) is given in the immediate postspinal period [10].

## Coloading

- "Coloading," that is, giving intravenous fluids concurrent with the onset of the spinal anesthetic block, is a more recent practice attempting to prevent hypotension secondary to spinal anesthesia.
- 20 ml/kg crystalloid 20 minutes prior to spinal anesthesia (preload) was compared with 20 ml/kg by rapid infusion immediately after induction (coload) [11]. Significantly greater numbers of patients in the coload group did not require vasopressor therapy to maintain blood pressure.
- A recent meta-analysis [12] found no significant difference in the incidence of hypotension between preloading and coloading and concluded that there was no need to delay spinal anesthesia to permit prior administration of intravenous fluids. They noted that, with either fluid strategy, the incidence of hypotension was high resulting in significant need for vasopressor therapy.

## Crystalloid versus colloids

- Colloid preloading is more effective than crystalloid preloading for decreasing the incidence and severity of spinal-induced hypotension [13]. However, neither were completely effective.
- Colloid preloading and coloading have been shown to result in a similar low incidence of hypotension and similar requirement for vasopressors [14].
- There has been recent interest in measuring cardiac output (CO) in patients undergoing cesarean section under spinal anesthesia. A recent study [15] showed that crystalloid and colloid preloading increased CO equally but hypotension still occurred. This study suggests that increasing preload and CO does not fully compensate for the vasodilation that occurs with spinal anesthesia.
- The reduced incidence (but not complete abolition) of hypotension with colloids compared with crystalloids must be set against the increased costs and slightly increased risk of allergic reactions associated with colloids.

## Why are fluids not more effective?

- Crystalloids equilibrate through the various fluid compartments within the body such that after 30 minutes only 28% of crystalloid remains in the intravascular volume compared with 100% of the colloid [16]. This explains the relatively greater efficacy of colloids in the prevention of hypotension following spinal anesthesia.
- Further confounding our efforts with IV fluids, an interesting study [17] demonstrated that the concentration of atrial natriuretic peptide (ANP) in plasma increases during crystalloid infusion with greater increases during colloid infusion during spinal anesthesia for cesarean section. A slight decrease in endothelin-1 levels was also found during colloid infusion. It is suggested that the increase in the release of ANP in response to volume load may decrease vascular tone and initiate diuresis, thereby limiting the effect of efforts to increase preload during elective cesarean delivery.
- The situation is therefore different from that of resuscitation from trauma, for example, where there is an actual reduction in vascular volume. Fluids infused in this situation will

presumably restore blood volume without stretching of the atrial wall. In the obstetric patient there is no hypovolemia during crystalloid preloading prior to spinal anesthesia resulting in the above responses aimed at acutely limiting our desired increases in blood volume. Coloading would, therefore, be expected to be more effective at prevention of hypotension secondary to spinal anesthesia as the fluid is being infused as the vasodilation occurs. Thus, there is no hypervolemia to stimulate the release of ANP.

Thus, opinion and evidence favors the use of vasopressor drugs as the mainstay of prevention and management of hypotension following spinal anesthesia. Note, however, that fluid therapy is crucial in the presence of hypovolemia, e.g. following hemorrhage.

## Basic science of vasopressor drugs

### Ephedrine

- Synthetic non-catecholamine.
- Has both indirect and direct effects on the sympathetic nervous system. Its principal action is indirect causing the release of endogenous norepinephrine. There is some direct stimulant effect on adrenergic receptors.
- Both α and β agonist stimulation. Intravenous administration results in increased systolic and diastolic blood pressure, heart rate, and cardiac output.
- Cardiovascular effects are partly due to α receptor mediated peripheral arterial and venous vasoconstriction, but are mostly due to increased myocardial contractility as a result of activation of β1 adrenergic receptors.
- Ephedrine crosses the placenta.

### Phenylephrine

- Synthetic non-catecholamine.
- Mimics norepinephrine but is less potent and longer acting.
- Predominantly direct α1 agonist activity. The primary effects are peripheral vasoconstriction, raised systemic vascular resistance, and raised arterial blood pressure.
- Baroreceptor-mediated reflex bradycardia can reduce cardiac output.
- Phenylephrine crosses the placenta.

## Ephedrine versus phenylephrine for obstetric patients

Many studies have been carried out to determine the role of ephedrine and phenylephrine during spinal anesthesia for cesarean section.

### Historical perspective

- Using ephedrine as the first-line vasopressor for spinal-induced hypotension in cesarean section is based on animal studies demonstrating that ephedrine preserves uterine blood flow; in contrast, drugs with increasing alpha-adrenergic activity such as phenylephrine decrease uterine blood flow.
- In the 1990s, studies of prophylactic ephedrine use to prevent hypotension revealed that large doses were required, and that these doses led to decreased umbilical cord blood pH.

- In a dose–response study, the smallest effective dose of prophylactic ephedrine to reduce the incidence of hypotension was 30 mg iv [18]. However, the mean systolic blood pressure was still only 87% of baseline (range of 58 to 105%) in the 30 mg IV group while reactive hypertension occurred in 45% of patients. Fetal acidosis (pH < 7.2) occurred in 42% of neonates in the 30 mg group.
- In 2002, Lee published a meta-analysis of randomized controlled trials from 1976 to 2001 comparing prophylactic ephedrine to placebo or no ephedrine to assess the effectiveness and safety of ephedrine to prevent hypotension during spinal anesthesia for cesarean section [19]. They found that ephedrine is more effective than placebo/control for preventing hypotension; however, the overall benefit of prophylactic IV ephedrine was small and may be better if used once hypotension has occurred. There was no difference in maternal nausea and vomiting or neonatal outcome with respect to Apgar scores and fetal acidosis between ephedrine and placebo/control.
- Ephedrine has the unwanted side effect of increased heart rate and is not completely effective at reducing hypotension with typical doses of 5 to 10 mg IV. Appreciations of the limitations of ephedrine led to renewed interest in phenylephrine as an alternative vasopressor.
- In 2002, Lee also published a systematic review of seven randomized controlled trials comparing the efficacy and safety of ephedrine to those of phenylephrine for the prevention and treatment of hypotension during spinal anesthesia [20]. There was no difference in efficacy to treat hypotension and neither group reported increased hypertension but phenylephrine increased the risk of bradycardia. The phenylephrine group had higher neonatal umbilical arterial (UA) pH, but the Apgar scores were similar between groups. However, they also pointed out that the data did not support ephedrine as the preferred choice for the management of hypotension.

## Combinations of ephedrine and phenylephrine

- Combinations of ephedrine and phenylephrine have been used in the past.
- Cooper *et al.* [21] in 2002 observed that a combination of phenylephrine and ephedrine as first-line vasopressors reduced the incidence of fetal acidosis at delivery. Their study compared infusions of ephedrine, phenylephrine, or a combination of the two, and assessed systolic arterial blood pressure (SBP) and maternal nausea and vomiting. Their conclusions were similar to the previous meta-analysis (i.e. similar mean SBP between the groups); however, the lowest systolic blood pressures were seen in the ephedrine group. The phenylephrine infusions were associated with the lowest incidence of fetal acidosis (although no group had UA pH value < 7.2) and maternal nausea and vomiting. However, they suggested no advantage in combining phenylephrine and ephedrine infusions, as adding ephedrine increased maternal nausea and vomiting and did not further improve fetal blood gases, compared to phenylephrine alone.
- Ngan Kee *et al.* [22] used equipotent IV phenylephrine and ephedrine, combined in varying concentrations to maintain SBP near baseline until uterine incision. As the proportion of phenylephrine decreased and ephedrine increased, they noted reduced hemodynamic control and significantly compromised fetal acid–base status (UA pH < 7.2). They also noted the following trends:

  - increased nausea and vomiting
  - increased incidence of hypotension
  - increased maternal heart rate
  - decreased umbilical arterial oxygen content.
- The incidence of phenylephrine-related maternal bradycardia may be decreased when phenylephrine is used prophylactically and ephedrine is used as rescue.

## How to dose?

- Ephedrine is commonly given as intermittent boluses. The smallest effective prophylactic dose of ephedrine to prevent hypotension during spinal anesthesia for cesarean delivery was 30 mg IV [18] as mentioned earlier.
- Phenylephrine 100 μg IV and ephedrine 6 mg IV had similar efficacy when treating maternal hypotension during spinal anesthesia, but the neonates in the phenylephrine group had higher UA pH (no neonate had UA pH < 7.2) and base excess and had similar Apgar scores compared with the ephedrine group [23].
- Since phenylephrine has a short duration of action, some authors suggest that continuous IV infusion is the best technique for administration.
- Maintaining maternal blood pressure at 100% of baseline with a phenylephrine infusion of 100 μg/min IV was associated with fewer episodes of hypotension, less nausea/vomiting, and a higher UA pH compared to maintaining maternal blood pressure at 90% and 80% of baseline. All neonates had a UA pH > 7.2 and base excess was similar between groups [24].
- Combination of high-dose phenylephrine infusion (100 μg/min IV) combined with rapid coloading of up to two liters of crystalloid was an effective technique of preventing spinal-induced hypotension for cesarean delivery, and was associated with less nausea/vomiting, less phenylephrine use, and no adverse neonatal outcomes [25].
- The data for optimal bolus dosing of phenylephrine is unclear. One study found the 90% effective dose (ED90) of phenylephrine to be 147 μg IV (95% CI 98 to 222 μg) by using up-down sequential allocation for the treatment of spinal anesthesia-induced hypotension [26]. However, another study found that the 95% effective dose (ED95) of phenylephrine was 135 μg IV (95% CI 106 to 257 μg) to prevent spinal-induced hypotension alone and 159 μg IV by using up-down sequential allocation for the prevention of hypotension and nausea [27].
- The most recent study of phenylephrine infusions [28] compared placebo or prophylactic phenylephrine infusions at 25, 50, 75, or 100 μg/min plus 2 L crystalloid coload after spinal anesthesia. They found more hypotension in the control group compared with all phenylephrine groups but phenylephrine 75 and 100 μg/min groups were associated with more hypertension compared with control groups.

## Intramuscular (IM) vasopressors

- Ephedrine 37.5 mg IM given before spinal anesthesia for cesarean section was not associated with increased reactive hypertension and provided delayed but sustained cardiovascular support. Early hypotension was not reduced [29].

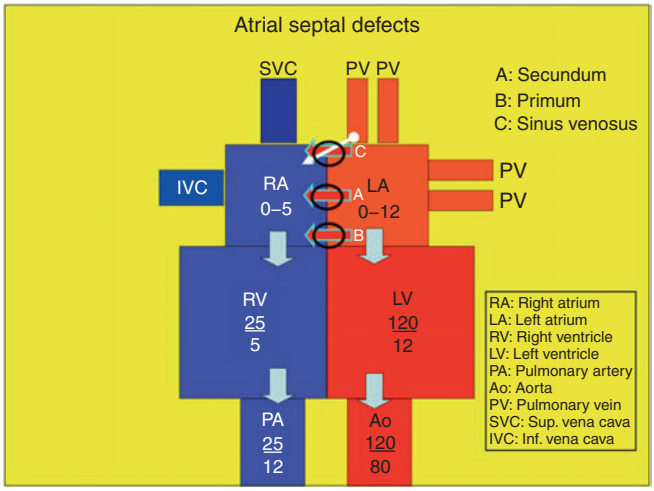


**Figure 2.1** Atrial septal defects.

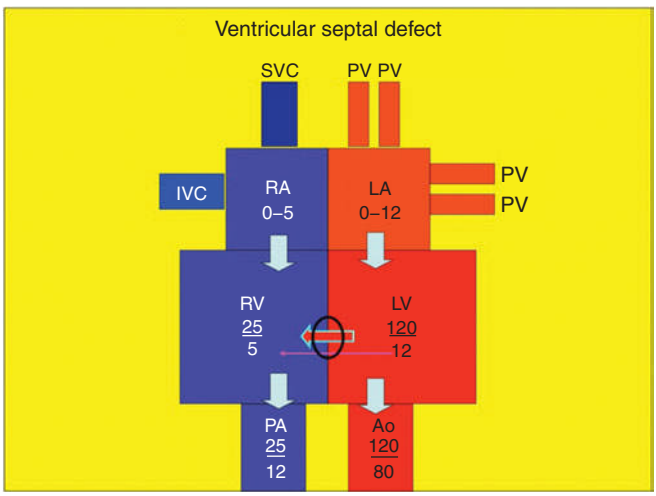


**Figure 2.2** Ventricular septal defect.

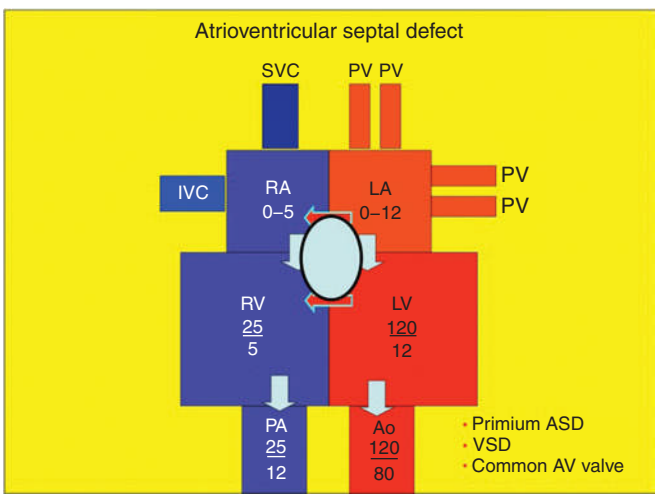


**Figure 2.3** Atrioventricular septal defect.

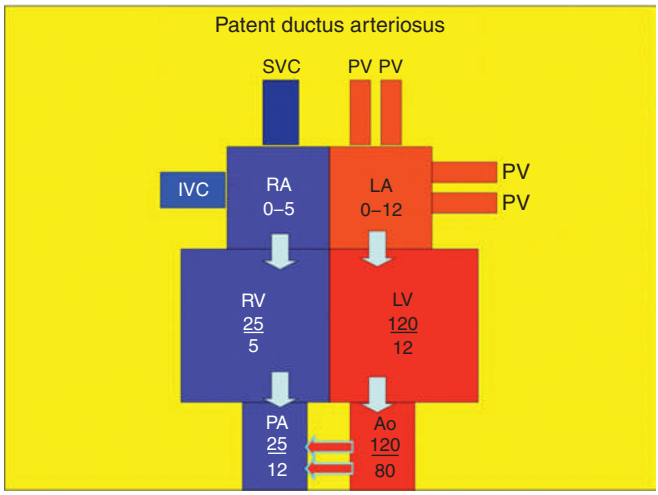


**Figure 2.4** Patent ductus arteriosus.

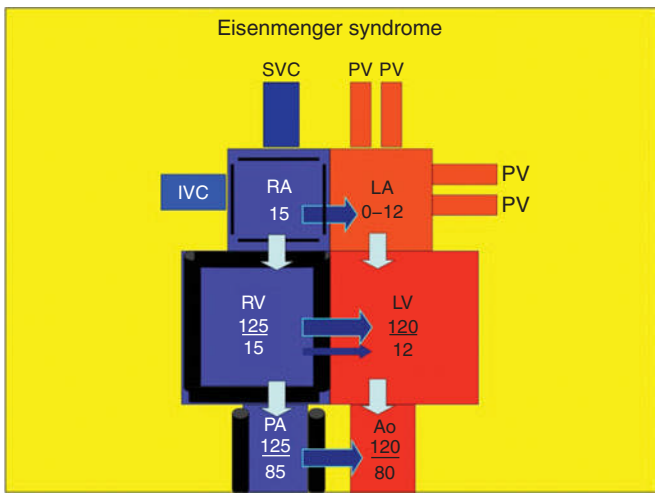


**Figure 2.5** Eisenmenger syndrome.

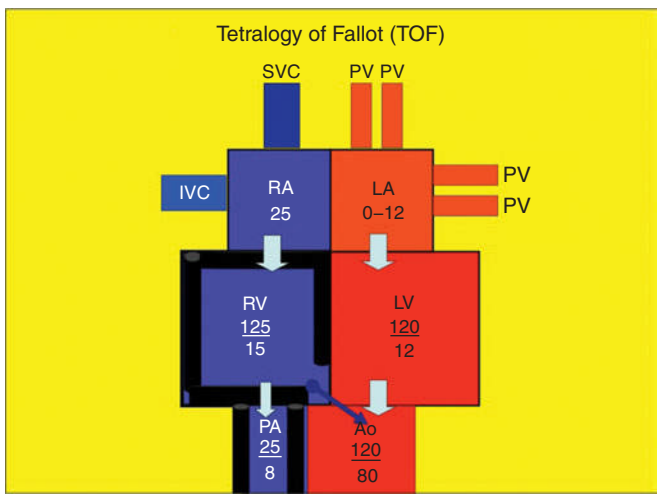


**Figure 2.6** Tetralogy of Fallot (TOF).

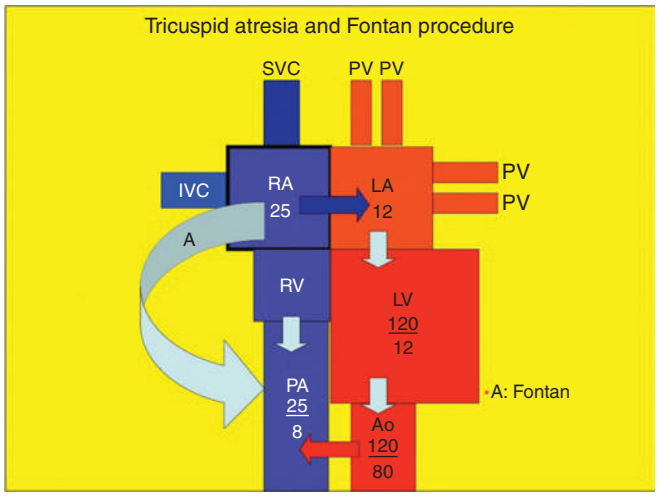


**Figure 2.7** Tricuspid atresia and Fontan procedure.

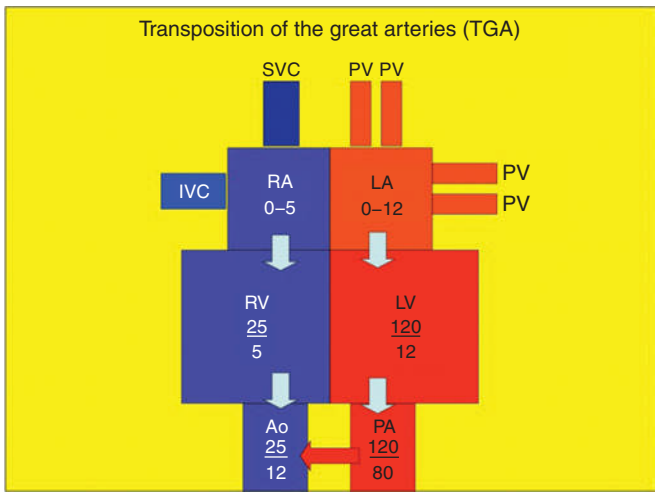


**Figure 2.8** Transposition of the great arteries (TGA).

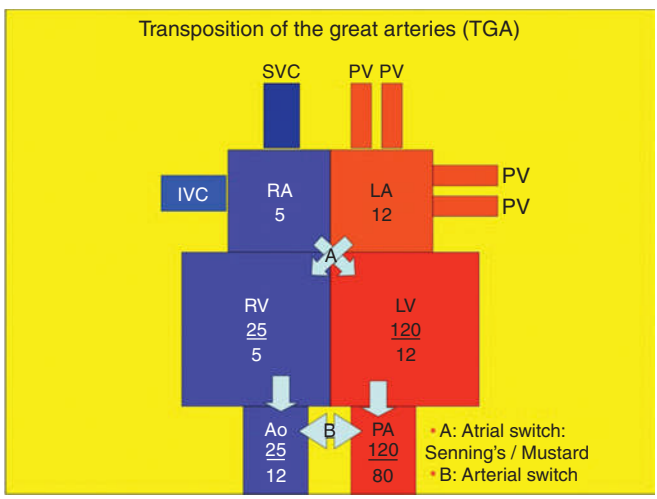


**Figure 2.9** Transposition of the great arteries (TGA).

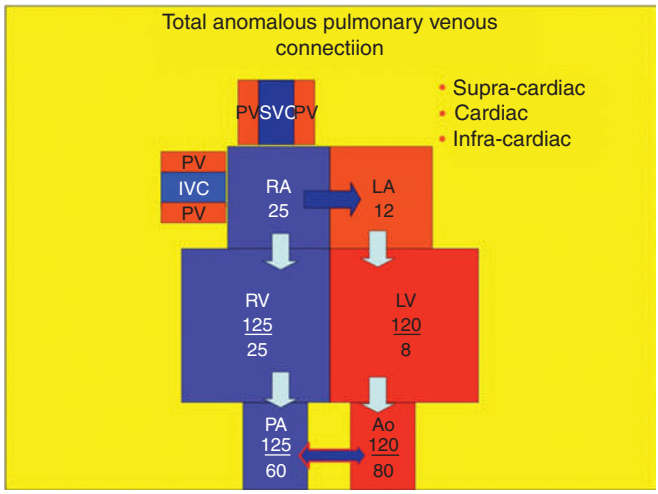


**Figure 2.10** Total anomalous pulmonary venous.

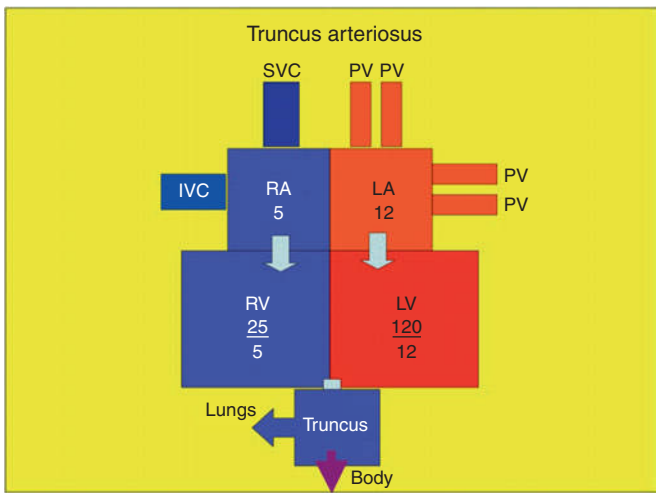


**Figure 2.11** Truncus arteriosus.

- A similar study comparing pre-emptive IM ephedrine and phenylephrine found that 4 mg phenylephrine and 45 g ephedrine reduced the severity of hypotension and the requirement for rescue IV ephedrine during spinal anesthesia for cesarean section. Neither drug was completely effective in preventing hypotension [30].
- The place of IM vasopressors is not entirely clear but is difficult to recommend as routine practice.

## Maternal hemodynamic responses to phenylephrine and ephedrine

Given that both ephedrine and phenylephrine may be successfully used to prevent and treat hypotension, more recent studies have focused primarily on more detailed investigations of the hemodynamic effects, high-risk patients, and implications for fetal acid–base status.

- The vasodilation produced by spinal anesthesia would imply that vasopressors such as phenylephrine would be logical therapies to treat the resultant hypotension.
- Time to peak increase in mean arterial pressure (MAP) after vasopressor administration is significantly reduced with phenylephrine [31].
- However, phenylephrine bolus (80 μg IV) and low-dose phenylephrine infusions (0.25 μg/kg/hr) reduce maternal heart rate and cardiac output (CO) compared to the increases in HR and CO seen from giving ephedrine 10 mg IV. Phenylephrine increases systemic vascular resistance more than ephedrine, while ephedrine increases stroke volume and heart rate more than phenylephrine [31, 32].
- The decrease in HR correlates with the decrease in CO, i.e. the fall in HR with phenylephrine is potentially bad from the point of view of maternal CO but with no obvious fetal consequences.
- The most recent examination of CO changes following phenylephrine infusion in spinal anesthesia patients showed that 100 μg/min of phenylephrine led to maternal CO falling to less than baseline when compared with 25 or 50 μg/min infusions [33].

# Fetal acidosis and its mechanisms

- Uterine artery blood flow is not autoregulated so is essentially pressure dependent. Ephedrine increases blood pressure without causing uterine artery vasoconstriction, whereas phenylephrine potentially causes uterine artery vasoconstriction. This difference may, in part, be due to ephedrine stimulating the release of nitric oxide in the uterine artery leading to uterine arterial vasodilation, despite causing systemic arterial vasocontriction. Release of nitric oxide synthase by ephedrine, more than other vasopressors, accounts for its beneficial effect of preserving uterine blood flow.
- However, studies show that ephedrine impairs fetal acid–base status more than phenylephrine (i.e. is associated with lower UA pH and higher base deficits).
- This seems hard to reconcile with suggestions that the mechanism for production of fetal acidosis is vasoconstriction of the uterine artery impairing placental oxygenation.
- However, Ngan Kee [34] using ephedrine and phenylephrine infusions, showed that ephedrine crosses the placenta to a greater extent than phenylephrine and undergoes less early metabolism, as evidenced by significantly greater umbilical vein and maternal arterial plasma concentrations in the ephedrine group. Clearly, ephedrine has in utero effects, including fetal tachycardia and increased heart rate. Thus, the higher fetal

concentrations of lactate, glucose, catecholamines, and umbilical vein (UV) $PCO_2$ found in the ephedrine-treated group support the hypothesis that increased metabolic demand results from fetal beta-adrenergic receptor stimulation [34].

- Previously it had also been suggested that the higher incidence of fetal acidosis in studies involving ephedrine relates to higher fetal metabolic rate secondary to the beta-adrenergic effects of ephedrine, as evidenced by a greater arteriovenous $PCO_2$ difference. Umbilical artery $PCO_2$ was higher in the ephedrine group than the phenylephrine group suggesting a higher fetal metabolic rate in the ephedrine group [21].
- Vasopressor choice may therefore influence the chance of development of fetal acidosis. A multivariate analysis found that the use of ephedrine, longer time from uterine incision to delivery, greater decrease in systolic arterial pressure, and the interaction of ephedrine use and duration of hypotension are the significant factors contributing to lower UA pH. The use of ephedrine and the interaction of ephedrine use and duration of hypotension were the most significant factors predicting UA base excess [35].
- Phenylephrine treatment leads to lower UV $pO_2$ compared to ephedrine treatment [34]. Is this related to the greater vasoconstricting effect of phenylephrine on the uteroplacental circulation? Animal studies show that although uterine blood flow varies, fetal oxygen uptake remains fairly constant, implying that fetal oxygen extraction increases as uteroplacental flow decreases. Therefore, phenylephrine may decrease placental blood flow, leading to increased oxygen extraction and thus a lower UV $pO_2$. However, since fetal acidosis is not increased with phenylephrine in healthy women undergoing non-urgent cesarean section, this effect on uteroplacental blood flow does not appear detrimental. Dosage of phenylephrine may also be important – greater doses of phenylephrine may cause actual vasoconstriction while lesser doses merely reverse the abnormal vasodilation produced by spinal anesthesia.

## High-risk patients

To date, many of the studies comparing ephedrine with phenylephrine have evaluated healthy women undergoing non-elective cesarean section. There is very little evidence comparing the use of phenylephrine or ephedrine in the high-risk patient.

- Understanding of the hemodynamic effects and implications of phenylephrine and ephedrine in the pregnant patient undergoing spinal anesthesia for cesarean section is especially important in the pregnant patient with cardiac disease, e.g. reductions in maternal cardiac output with large doses of phenylephrine.
- A recent retrospective study by Cooper [36] evaluated the UA pH in 385 women who underwent high-risk cesarean section under spinal anesthesia. Interestingly, they found the UA pH to be similar between the ephedrine and phenylephrine groups (with bolus and infusion administration), a result that differs from that of studies of neonates from low-risk cesarean section. Cooper found that, in the high-risk group, the doses of ephedrine used to treat hypotension were lower than those associated with poor acid–base status. Also, the high-risk nature of the cesarean section may have been associated with a reduced spinal-to-delivery time, thus decreasing the ephedrine doses, fetal exposure, and fetal metabolic effects. Prematurity or being in labor prior to cesarean section were also associated with a lack of vasopressor requirement, supporting previous reports that indicated spinal-induced hypotension is less likely in these groups.

- Ngan Kee in 2008 [37] investigated non-elective cesarean sections in healthy parturients with potential fetal compromise, and found that UA pH, UV pH, and base excess were similar between phenylephrine (100 μg IV bolus) and ephedrine groups (10 mg IV bolus). The UA and UV lactate were higher in the ephedrine group, but neonatal clinical outcomes were similar. Phenylephrine was associated with less maternal nausea and vomiting.
- Studies suggest that spinal-induced hypotension is less frequent (two- to threefold less) in severely pre-eclamptic patients and requires less ephedrine compared with healthy parturients [36–38].

One should be cautious about extrapolating results and implications for therapy from studies of low-risk elective patients to other sicker or more urgent groups of patients.

In particular, the implications for hypotension secondary to spinal anesthesia may be different in patients with placental pathology.

However, based on these studies, it may be reasonable to consider both phenylephrine and ephedrine as suitable choices in high-risk non-elective cesarean section.

## Clinical significance of fetal acidosis

Are these differences in fetal acidosis between ephedrine and phenylephrine clinically significant? After all, many studies report statistically significant (though minor) differences in UA pH but neonatal Apgar scores have not differed significantly and, more recently, neurobehavioural scores do not appear to be adversely affected in the first 48 hours of life.

It is unlikely that transient hypotension that is promptly treated would result in significant reductions in fetal oxygenation or increases in fetal acidosis given the normal fetal compensatory increases in oxygen extraction already discussed. Rarely would this acute acidosis in previously normal fetuses result in long-term damage [39].

A consensus report of the Australian, New Zealand, Canadian, and American obstetrical societies contained a template for defining a causal relation between acute intrapartum events and cerebral palsy [40], their conclusions included:

1. Metabolic acidemia is relatively common at birth, and the vast majority of infants do not develop cerebral palsy.
2. "A realistic cut off for defining pathological fetal acidaemia that correlates with an increasing risk of neurological deficit has been found to be a pH of < 7.00 and a base deficit of more than 16 mmol/L. It is unlikely that acute acidosis of lesser severity under these levels could be directly associated with cerebral palsy."

It should be noted that such severe degrees of acidosis are worse than those found in the studies quoted in this chapter.

Nevertheless, there may be no room for complacency:

- Severe or longstanding maternal hypotension may be less well tolerated by the fetus.
- Placental pathology may result in less tolerance for the hypotension associated with spinal anesthesia.
- Reynolds [41] challenges the conventional wisdom that a spinal anesthetic results in better fetal well-being than a general anesthetic. Despite the transient fetal depression produced by placental transfer of anesthetic drugs, meta-analysis has shown that fetal

acidosis is greater with spinal anesthesia than general anesthesia. Epidural anesthesia also results in less fetal acidosis than does general anesthesia. Again, it must be stated that mild fetal acidosis at birth may not result in long-term poor outcome but might the differences here be due to the greater hypotension with spinal anesthesia compared to epidural or general anesthesia?

- A large, prospective, cohort study in France of outcome in premature neonates examined the influence of mode of anesthesia for maternal cesarean section. Although other factors such as gestational age and complications of pregnancy were more significant influences on outcome, spinal anesthesia was associated with a higher risk of neonatal death after premature birth than general anesthesia [42]. The authors speculate that the hemodynamic effects of the spinal anesthetic on placental perfusion may possibly be a factor explaining this apparent difference in outcome. The study period was in 1997 and the authors comment on the many changes in practice regarding spinal anesthesia between the study period and publication in 2009, e.g. fluid coloading and the increasing use of ephedrine compared to phenylephrine.

## Conclusions and clinical perspective

- Hypotension secondary to spinal anesthesia is common.
- Hypotension causes maternal distress.
- Fetal adverse effects from transient hypotension are less clear.
- First avoid aorta caval compression and correct hypovolemia. "Coloading" is probably better than "preloading." Colloids are possibly more effective than crystalloids.
- Benefits of ephedrine are that it is a well-established drug with few reported adverse clinical outcomes for both mother and neonate.
- Drawbacks to ephedrine include variable efficacy at prophylaxis of hypotension secondary to spinal anesthesia in low doses or in doses normally used in the clinical setting; fetal acidosis is more prevalent with increasing doses of ephedrine (though the clinical significance of this is unclear). Also, ephedrine works primarily via beta-adrenergic stimulation. Therefore maternal tachycardia can be an issue.
- Benefits to phenylephrine include fast-acting potent vasoconstrictor, associated with better neonatal acid–base status and associated with less maternal nausea and vomiting.
- Drawbacks to phenylephrine include increased risk of maternal bradycardia and reduced cardiac output.
- Effective prophylactic doses of phenylephrine and ephedrine are large. More research is needed to determine if these large doses are safe.
- Rescue dosing for spinal-induced hypotension are lower, and both ephedrine and phenylephrine appear effective.
- Varying combinations of phenylephrine and ephedrine by infusion do not appear to be more effective at preventing hypotension than phenylephrine alone.
- Ephedrine placental transfer is greater than that of phenylephrine, most likely based on ephedrine's greater lipid solubility.
- Use ephedrine if maternal heart rate is low.
- Very large doses of either drug are potentially harmful.

- Use other drug if first-choice agent not achieving its desired effect.
- Optimum drug choice and dosing, and the significance of hypotension and fetal acidosis, remain controversial.

## Further reading


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Chapter

12

# Prevention and management of postdural puncture headache

Dr L Wakely, Dr S Singh and Dr I McConachie

## Introduction

- Postdural puncture headache (PDPH) is a recognized and, unfortunately, not uncommon complication of neuraxial anesthesia in obstetric patients.
- It can occur after spinal anesthesia as well as accidental dural puncture (ADP) during epidural anesthesia.
- It may be debilitating for patients and result in delayed discharge or repeat hospital visits [1]. The ability of the new mother to care for her baby is also reduced [2].
- Postdural puncture headache also poses challenges to the clinician regarding diagnosis and management.

This chapter will discuss the clinical management of PDPH in obstetric patients and suggest recommendations based on current, relevant evidence.

## Diagnosis

Headaches are common in the postpartum period. A prospective cohort study of 985 postpartum women revealed a headache incidence of 39% and tension and migraine headaches were the most common causes [3]. According to the International Headache Society, PDPH is defined by the following criteria:

- Headache that worsens within 15 min after sitting or standing and improves within 15 min after lying, with at least one of the following symptoms:
  1. neck stiffness
  2. tinnitus
  3. hypoacusia (decreased auditory sensitivity)
  4. nausea
  5. photophobia.
- Dural puncture was performed.
- Headache develops within five days after dural puncture.
- Headache resolves either:
  1. spontaneously within one week
  2. within 48 hours after an epidural blood patch

*Controversies in Obstetric Anesthesia and Analgesia*, ed. Ian McConachie. Published by Cambridge University Press. 

There are many case reports of delayed presentation of PDPH in obstetric patients and also reports of prolonged symptoms that would not fall within a strict interpretation of these definitions.

The postural element to the headache helps differentiate it from other headaches such as migraine. The presence of focal neurological signs may point toward other neurological problems and prompt further investigations and assessments. Similar headaches have been reported following the administration of ondansetron with obvious implications for those patients [4].

## Pathophysiology

The pathophysiology of PDPH is not completely understood, although imaging studies have provided the most likely course in its development. Puncture of the dura allows excessive leakage of CSF, as confirmed by radionuclide cisternography, which results in intracranial hypotension. The low CSF volume causes a drop in subarachnoid pressure. Magnetic resonance imaging studies demonstrate sagging of intracranial structures and meningeal enhancement from vasodilation of the meningeal vessels [6]. It is thought that:

- low CSF pressure causes traction on pain-sensitive intracranial structures in the upright position, and/or
- loss of CSF produces compensatory vasodilation of the cerebral venous blood vessels.

In addition, if air is used during a loss of resistance (LOR) technique for epidural insertion and ADP occurs, with the injection of air into the CSF there is a much higher likelihood of headache developing [7]. In those patients who developed headache after using air for the LOR, CT scanning demonstrated the presences of supraspinal gas bubbles within the CSF. This headache was of faster onset but shorter duration than the "classic" PDPH.

## Incidence

The incidence of PDPH in obstetric patients is relatively high due to the effects of gender and young adult age. It is also related to the size and design of the needle used and the experience of the anesthesiologist carrying out the procedure.

There are two scenarios:

- Following ADP during epidural analgesia. The incidence of ADP in obstetric patients during epidural catheter placement for labor analgesia approximates 1% when performed by experienced practitioners. However, the actual incidence will be higher in an institution that trains residents. For parturients in whom dural puncture occurs with an epidural needle, up to 80% will develop PDPH [5].
- Following puncture of the dura with a spinal needle for anesthesia for cesarean section or as part of a combined spinal–epidural (CSE) technique. The incidence of PDPH after spinal anesthesia is much lower than following ADP due to the use of small-gauge, pencil-point spinal needles.

## Prevention

## Prevention of ADP

Various techniques have been utilized to reduce the overall incidence of ADP during epidural catheter placement.

### Air versus saline

A postal survey of all UK members of the Obstetric Anaesthetists' Association revealed that in obstetric patients, the single most common technique to identify the epidural space (used by 58% of anesthetists) was continuous advancement of the epidural needle and LOR with saline, followed by intermittent needle advancement with air (21%) [8].

A meta-analysis in 2009 compared complications between air vs. liquid as the medium for LOR during epidural catheter placement. This analysis reported that a number of small studies do exist suggesting LOR with air is associated with increased complication rates, but also stated that larger studies that overcome heterogeneity and infrequent occurrence rates are required to determine the optimal medium for LOR during epidural catheter placement [9].

The incidences of both ADP and headache with LOR to air vs. saline are fully explored elsewhere in this text.

### Needle type

A prospective, double-blinded, randomized trial comparing the 18G Sprotte with 17G Tuohy needle was performed [10]. The trial included 1,077 laboring parturients across three tertiary obstetric centers who were followed for seven days by assessors to determine if neckache or headache occurred as per PDPH criteria. No significant difference in the incidence of ADP was noted between the two needle types.

### Ultrasound guidance

No studies to date have revealed a decrease in the incidence of ADP with ultrasound guidance for epidural catheter placement.

### Combined spinal–epidural

A systematic review of 19 trials (2,658 women) demonstrated no difference in the overall incidence of PDPH when CSEs were performed in comparison to epidurals alone [11].

## Prevention of headache following accidental dural puncture

### Needle type

In the comparison of the 18G Sprotte vs. 17G Tuohy epidural needles mentioned previously, a significant difference *was* detected in the incidence of PDPH [10].

- Dural puncture headache occurred more frequently after ADP in the 17G Tuohy group (100% vs. 55.5%); however, the 18G Sprotte needle was found to be more technically challenging in placing epidural catheters.
- Further, audit of a large UK database suggests that the use of an 18G Tuohy needle reduces the incidence of headache despite no difference in the incidence of ADP [12].

### Needle orientation

It does not seem that there is any difference in either ADP rate or headache with lateral or cephalad Tuohy needle orientation during epidural placement [13].

## Intrathecal catheters

Following ADP, the placement of intrathecal catheters was postulated as a means to induce inflammation of the dural tear, hastening its closure and reducing the incidence of PDPH.

- A small study found no difference in the incidence of headache following ADP when an intrathecal catheter was inserted for continuous spinal anesthesia during labor and delivery [14].
- A larger clinical trial showed a significant decrease in PDPH following ADP when intrathecal catheters were left in situ [15]. The trial compared outcomes following ADP when intrathecal catheters were removed immediately after delivery or 24 hours after delivery, vs. re-siting the epidural at another level following ADP. The incidence of PDPH was 91.1% in the re-site group, 51.4% in the immediate-removal group, and 6.2% in the delayed removal group.

The use of intrathecal catheters for this purpose may be increasing but there are concerns regarding the possible inadvertent administration of unintended drugs into this catheter postdelivery, and there are reports of the development of such complications as meningitis.

## Management of the second stage of labor

It has been suggested that an association exists between the duration of the second stage of labor (bearing down) and PDPH, following an observed ADP; however, this has only been documented in a chart review of 33 parturients at a single institution [16]. No other evidence has been found to support this theory.

## Prophylactic epidural blood patch

Epidural blood patch (EBP) is discussed fully in the sections on therapy for PDPH. The use of EBP as prophylaxis following ADP remains uncertain. However, a significant difference was *not* found in one double-blinded, randomized, clinical trial in which a prophylactic EBP was compared to a "sham patch" [17].

A 2010 Cochrane review of epidural blood patching for prevention and treatment of PDPH concluded that "Further, adequately powered, randomized trials are required before reliable conclusions can be drawn about the role of epidural blood patching in the prevention of PDPH" [18].

## Epimorph injection

Following an inadvertent dural puncture, two injections of 3 mg preservative-free morphine (epimorph) 24 hours apart, in the epidural space may reduce the incidence of PDPH. This was demonstrated in a single recent prospective randomized controlled trial [19]. The author concluded that epimorph is a simple and effective intervention for preventing PDPH after ADP, and could also reduce the requirement for EBP. However, the safety of this procedure needs to be established.

## Cosyntropin administration

A recent randomized controlled trial found a significant reduction in PDPH following ADP with administration of IV cosyntropin [20]. This also reduced the requirement for EBP. The

mechanism of this adrenocorticotrophic hormone (ACTH) analogue in the treatment of PDPH is unclear as the exact pathogenesis of dural puncture headaches remains unclear. Analogues of ACTH are known to increase aldosterone, thus affecting sodium and water absorption to cause an overall increase in circulating blood volume. Perhaps this increase in volume causes dural edema and possibly dural repair? There is also a suggestion that cosyntropin might have an effect on opioid receptors, thus decreasing the severity of PDPH.

### Prophylactic epidural or intrathecal saline

Prophylatic infusions of saline into the epidural space once the effects of the local anesthetic have worn off does not seem to be of benefit in preventing PDPH, but intrathecal injection of 10 ml of saline in a non-randomized study did seem to reduce the incidence of PDPH [21].

## Prevention of headache following spinal anesthesia

### Needle type

A meta-analysis [22] confirmed the clear associations between needle size and design and the incidence of PDPH.

- Small needles have a lower incidence of PDPH than large needles.
- Pencil-point "non-cutting" needles, such as Sprotte and Whitacre needles, have a lower incidence of PDPH than "cutting" spinal needles, such as the Quincke needle, and are generally recommended.

### Bed rest

Bed rest used to be recommended to prevent the development of PDPH after ADP (certainly the supine position is effective in relieving the symptoms of PDPH once established). After spinal anesthesia, 4 hours of bedrest or 24 hours of bedrest result in the same incidence of headache [23]. However, there are no similar data examining the role of bedrest in preventing PDPH after ADP with an epidural needle.

### Needle orientation

Some studies have shown that perpendicular rather than parallel direction of the bevel of the needle, relative to the orientation of the fibers within the dura mater, leads to a decrease in the incidence of PDPH after spinal anesthesia when using cutting spinal needles. This is controversial because there are conflicting studies on the anatomical fiber orientation within the human dura mater. Needle orientation is of minor concern when the recommended non-cutting pencil-point spinal needles are used.

## Therapy for postdural puncture headache

### Conservative therapy and miscellaneous interventions

For parturients who suffer from PDPH, a trial of conservative management including bedrest, hydration, and caffeine therapy has traditionally been suggested although there is little evidence to support these therapies. Often, with time, the dural defect will resolve and symptoms will abate spontaneously. If this does not occur or symptoms are severe, then an EBP should be considered.

- Angle [1] examined length of hospital stay and emergency room visits in parturients with diagnosed PDPH who were managed conservatively. Expectant management increased the length of hospital stay by 24 hours compared with patients without dural puncture and increased the risk of the patient returning to the emergency room with the complaint of PDPH.
- A small study [24] examined a cohort of 25 patients who developed PDPH following spinal anesthesia for cesarean delivery. These patients were treated with oral methergine. Twenty-four patients showed improvement within 24 hours and only one patient required an EBP. However, this series only included PDPH following spinal anesthesia not epidural anesthesia.
- Despite its historical popularity, the use of caffeine has been recently questioned [25].
- In an attempt to avoid the risks of EBP, alternative techniques have been tried when conservative measures fail. A study of 50 patients compared occipital nerve block to conservative management [26]. There were improvements in analgesia and shorter hospital stay in the occipital nerve block groups. Case reports have also demonstrated successful management of PDPH with acupuncture [27].
- If conservative management fails, intervention is indicated to improve maternal symptoms and to prevent possible long-term complications of PDPH. For example, case reports raise concerns that untreated PDPH may lead to subdural hematoma [28].

## Epidural blood patch

In 1960, Gormley noted that patients undergoing lumbar puncture had a lesser chance of developing a headache if there was evidence of blood. He reasoned that blood could serve as the sealing material. In his series of seven cases of PDPH the injection of 2 to 3 ml of blood at the site of dural puncture was effective in relieving the headache [29].

There are two main theories regarding the mechanism of action of EBP in the treatment of PDPH:

- The injected blood forms a clot that adheres to the dura, patches the hole, and reduces the CSF leak.
- The injected blood increases the pressure in the spinal space reducing traction of pain-sensitive brain structures, which relieves symptoms.

Magnetic resonance imaging has confirmed the presence of the EBP as a large extradural collection spreading over several intervertebral spaces with anterior displacement of the thecal sac [30]. The tamponade effect of the blood patch was observed with immediate resolution of symptoms.

The optimal volume of autologous blood to be injected for an EBP has not been determined.

- It is common clinical practice to inject between 10 to 20 ml, or until symptoms of backache or pain in the legs occur during injection based on the study by Crawford [31].

The success rate of EBP is high.

- In the largest series of over 500 patients, 75% reported complete relief of headache. Only 7% had no improvement in symptoms [32].

- Other studies have found less impressive results and there are lower success rates if the PDPH is as a result of dural puncture with a larger bore needle [33] (as occurs after ADP during epidural placement).

The success of the EBP may be affected by timing, with higher success rates reported if performed >48 hours after dural puncture.

- An early series demonstrated an increase in the failure rate when EBP was performed within 24 hours of the ADP [33].
- In the largest series to date the failure rate increased if EBP was performed within three days of dural puncture [32].
- In a prospective audit of 58 parturients who had therapeutic EBP, 67% experienced complete relief following an EBP. There was no difference in the initial rate of resolution of the headache when performed within 48 hours of the ADP compared with after 48 hours. Unfortunately, 31% had recurrence of headache and 28% required a second EBP. The recurrence of headache was significantly higher in those women who had EBPs performed <48 hours vs. >48 hours following ADP [34].

## Risks and complications of EBP

- Repeat dural puncture is possible.
- Transient, mild back or leg pain is common.
- It is generally recommended not to perform EBP if the patient is febrile due to the risk of hematogenous bacterial seeding of the blood clot leading to epidural abscess.
- During performance of an EBP, blood may spread intrathecally giving rise to symptoms of meningeal irritation or arachnoiditis [35]. These symptoms are usually temporary. Magnetic resonance imaging may be useful if symptoms are prolonged.
- Large volumes of blood probably should not be injected due to reports of significant complications [36].
- Epidural analgesia in subsequent pregnancies does not seem to be compromised by the performance of a prior EBP.
- Repeat EBP may be necessary. However, it is important to consider and rule out other pathologies before performing a repeat EBP. A multidisciplinary approach involving radiology and neurology may be helpful. Magnetic resonance imaging of the brain, particularly if the patient has focal symptoms, should be considered.

Many questions remain unanswered regarding EBP: What is the mechanism of action? What is the success rate? When should it be performed? What volume is ideal? What complications are associated? When should it be repeated?

Alternatives to EBP have been suggested, including the injection of dextran or fibrin glue to seal the dural puncture. These should be considered experimental therapies at present.

# Surveys of practice

- Interestingly, a survey of UK anesthesiologists in 2005 revealed that many are placing intrathecal catheters for the management of ADP [37].
- In Australia it seems the more common practice is to re-site the epidural. Concerns regarding the safety of intrathecal catheters were cited [38].

- American practitioners prefer to re-site the epdidural [39]. When intrathecal catheters are used they are commonly removed after delivery.
- Most units in the UK responding to the survey had written protocols for the management of ADP and PDPH [37]. Protocols were uncommon in the US centers [39].

## Summary

- The prevention and management of PDPH in the obstetric patient continues to challenge the anesthesiologist.
- The techniques that might prevent PDPH include: use of small-gauge needles, use of pencil-point needles, epidural morphine injection, intrathecal catheters, and IV cosyntropin, although further investigations are required.
- The treatment of choice for PDPH is EBP, although success is limited. Presently, evidence would suggest that the success rate of EBP increases if performed longer than 24 hours after dural puncture.
- In the future, well-designed, larger randomized controlled trials may help provide insight into the optimal use of the EBP and other treatments. Such trials will be difficult to perform due to the low incidence of ADP and PDPH.

## Further reading


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Chapter 13

# Epidurals and outcome

Dr C Miron, Dr C Bradbury and Dr S Singh

## Introduction

- Epidurals are the most effective mode of analgesia for labor pain [1].
- Significant negative outcomes following epidural analgesia are thankfully rare. Nonetheless, there are many minor side effects and some rare serious complications that can occur.
- There is controversy over whether epidurals are associated with an increased incidence of assisted and operative deliveries or an increase in the incidence of backache. Neurological damage is an uncommon but potentially serious sequela of epidural analgesia and also warrants discussion.
- Not all of the potential complications of epidurals will be included in this chapter and postdural puncture headaches will be covered in a separate chapter.

## Effect on mode of delivery

- It has been reported that epidurals reduce the effectiveness of uterine contractions, particularly in the second stage [2].
- This may be related to the decreased surge in oxytocin that would normally accompany the second stage and that appears to be mediated via parasympathetic fibers when the birth canal is stretched [3].
- The reduced uterine contractions, along with relaxation of the muscles of the pelvic floor, increase the likelihood of malposition of the fetal head and prolong labor, increasing the need to use oxytocin [1, 2, 4].
- Ineffective pushing, secondary to a diminished bearing-down reflex, motor block, and malposition of the fetal head, especially in the context of a prolonged second stage, could lead to maternal exhaustion [4].
- The overall result of these factors may be an increased risk of instrumental deliveries and cesarean sections. Studies have often been conflicting. Nonetheless, many of the studies are suitable for meta-analysis and more than one publication has embarked upon this [5–7].

### Prolongation of labor

- Studies have shown a tendency toward the first stage of labor being prolonged in parturients receiving epidural analgesia. However, even when the results are

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meta-analyzed, the tendency does not reach statistical significance [6]. Unfortunately the studies that have been done have not used the same definition and have therefore not measured the first stage of labor in the same way. This means that the meta-analysis is of a heterogenous group and this reduces the strength of the conclusions that can be drawn. It may be that epidurals do increase the duration of the first stage of labor but there is insufficient power to detect it.

- By contrast, the second stage of labor is clearly prolonged in parturients receiving epidurals [5–7]. A review of 11 studies, incorporating 3,580 parturients, revealed a weighted mean difference of 15.55 min (95% CI 7.46 to 23.63 min) [6]. Prolongation of the second stage was also found to be statistically significant in a review that only meta-analyzed data from studies that used low-dose epidurals [5].
- The prolongation of the second stage means that the normal timeframe of labor is no longer adhered to, and this could result in altered management of the labor. Instrumental deliveries or cesarean sections, particularly if performed for failure to progress, could result directly from the epidural analgesia.
- It has also been demonstrated that there is an increased use of oxytocin to augment contractions in those receiving epidural analgesia [6]. It may be that the use of oxytocin prevents what would otherwise be a statistically significant increase in the duration of the first stage. It has certainly been suggested that exogenous oxytocin improves the efficiency of the second stage of labor and reduces the need for instrumental delivery [3].

## Instrumental delivery

An association has been shown to exist between epidural analgesia and instrumental deliveries [5–7]. This phenomenon had been suggested to occur because of parturients requesting epidurals as a result of a longer, more difficult labor. Indeed, a request for an epidural is associated with prolonged pre-epidural progression and is a marker of an increased risk of dystocia [7, 8]. Use of randomized controlled trials should prevent this selection bias, and following an intention-to-treat analysis ensures that an observed difference is not due to patients with a more difficult labor crossing over to the epidural group because other forms of analgesia had proven inadequate.

- A meta-analysis of 17 studies, incorporating 6,162 parturients, showed a relative risk of 1.38 (95% CI 1.24 to 1.53) [6].
- Statistical significance was still found in a review in which only studies of low-dose epidurals were used in the meta-analysis [5]. In this review, all the included studies used concentrations of bupivacaine of 0.125% or less and continued this into the second stage – reflecting modern practice. The exclusion of studies using higher-dose epidurals is important because such epidurals have previously been shown to be associated with more instrumental deliveries than low-dose epidurals [9]. The association with instrumental deliveries still exists with low-dose epidurals, although once inductions and elective instrumental deliveries were removed from the analysis, this lost statistical significance [8]. A trend, however, still remained.
- However, it is plausible that obstetricians have a lower threshold to perform an instrumental delivery on a parturient with an epidural.

## Cesarean section

The link between epidural analgesia and cesarean section is yet more controversial. Meta-analyzed data, in several publications, have been unable to demonstrate a statistically significant association but each has shown a trend towards more cesarean sections [5–7]. It is possible that an association exists but that the meta-analyses are of insufficient power to detect the difference.

- The largest meta-analysis, of 20 trials and 6,534 patients, showed a relative risk of just 1.07. However, the 95% confidence intervals were from 0.93 to 1.23 [6]. The true relative risk could therefore reveal anything from a 7% reduction in risk to a more clinically significant 23% increase in risk of cesarean section.

The confidence intervals for the data are relatively wide and a clinically significant increase in cesarean section could exist but the data cannot support the association or disprove a clinically significant association.

## Discontinuation during the second stage

As a result of the effect of epidural analgesia on increasing both the duration of labor and the incidence of instrumental deliveries, many centers adopt an approach of discontinuing the epidural during the second stage of labor. The evidence for this practice has been reviewed.

- When meta-analyzed, a trend towards a reduction in instrumental deliveries has been found but was not statistically significant. The relative risk was 0.84 (95% CI 0.61 to 1.15) [10]. The true relative risk could therefore demonstrate a clinically significant reduction of 39% to an increase of 15% risk in instrumental delivery. Unfortunately the meta-analysis has insufficient power to determine whether there is a beneficial impact from stopping the epidural in the second stage but currently there is no evidence to support this.
- Meta-analyses of other outcomes were unable to show an impact on the duration of second stage or rate of cesarean section. Moreover, an increased rate of inadequate pain relief, with a relative risk of 3.68 (95% CI 1.99 to 6.8) was revealed [10].

## Delayed pushing

An alternative approach to reduce the number of instrumental deliveries associated with epidural analgesia is to delay maternal pushing in the second stage.

- In a meta-analysis of randomized controlled trials, delayed maternal pushing resulted in a reduction in the number of rotational or mid-pelvic instrumental deliveries with a relative risk of 0.69 (95% CI 0.55 to 0.87) [11].
- However the meta-analyses for overall instrumental delivery and for second stage cesarean section simply showed a non-significant trend towards reduced incidence with delayed pushing [11].
- Although there is no evidence that delayed pushing is harmful, the evidence that it reduces the impact of epidurals on the risk of instrumental delivery is limited.

# Neurological complications

Neurological complications, although rare, remain one of the most important causes of anxiety in the parturient and it is important to provide reassurance while providing accurate

data for informed consent. The issue, however, remains difficult to address for a multitude of reasons, despite numerous studies dating as far back as 1935.

Historically, obstetric nerve palsies as well as other mononeuropathies were attributed to neuraxial procedures. Today, there is a much clearer understanding of obstetric palsies and our ability to diagnose them. It is of note that most neurologic complications following childbirth are of obstetric origin.

Central nervous system (CNS) lesions secondary to epidural analgesia are very rare. They can be classified into four etiologies: traumatic, ischemic, infective, or chemical, or can sometimes be a combination thereof.

## Trauma

Trauma to nerve roots originates from the insertion of epidural catheters and has been associated with level of insertion. The spinal cord usually terminates at L1 but may, on occasion, terminate lower. Furthermore, studies have shown that anesthesiologists commonly access the epidural space at least one space higher than anticipated.

- One MRI study found that only 29% of anesthesiologists identified the correct interspace and 51% of the time the space identified was one level higher than intended [12].

Trauma may occur with uncontrolled advancement of the epidural needle, such as with an inexperienced provider or an uncooperative patient. Distortions of the anatomy such as unrecognized spina bifida occulta, a tethered cord, or spinal surgery in an otherwise healthy patient might also lead to complications. Pain or paresthesia are frequent indicators of trauma and should incite the operator to reposition or remove the needle/catheter.

## Epidural hematoma

The exact incidence of epidural hematoma is unknown.

- A British retrospective study of 505,000 patients described only a single case between 1982 and 1986 [13], while another review of over 200,000 epidural blocks in Sweden revealed two cases between 1990 and 1999 [14].
- A recent audit (2006–7) by the British Royal College of Anaesthetists found no cases in the obstetrical population [15].

It is of note that multiple studies describe higher incidences of epidural hematoma in the general surgical population compared to the obstetrical population and the hypercoagulability of the pregnant patient has been cited as a protective factor [14, 16, 17].

Epidural hematoma can arise from trauma to vessels, in conjunction with coagulopathy. This is an issue at catheter removal as well as at insertion.

## Coagulopathy

- Coagulopathy has played a part in at least seven of sixteen cases of epidural hematomas described in the literature since 1981, under the form of thrombocytopenia, altered aPTT, or HELLP syndrome [16].
- The literature does not quote a "safe" cutoff value for platelets in the laboring patient. A recent review in the *British Journal of Haematology* looked at 17 national and international guidelines, including those from the American Society of Anesthesiologists,

and of those, only four gave direct guidelines concerning epidurals. The minimum platelet count suggested by three of those (France, Britain, and the American Red Cross) was $80 \times 10^9$/L whereas the Australian and New Zealand College of Anaesthetists in 2008 suggested a safe platelet count of $>100 \times 10^9$/L and proposed that a count of $>80 \times 10^9$/L is safe when there are no risk factors and the platelet count is not falling [17].

- Clinical judgment should be used regarding the insertion of an epidural catheter in a patient with a rapidly falling number of platelets, even if the value is within the normal range.
- The issues around platelet counts and epidurals are fully discussed elsewhere in this text.

Signs and symptoms of epidural hematoma include acute onset of back and radicular leg pain, lower extremity weakness and numbness, as well as bladder and bowel dysfunction. If hematoma is suspected, prompt clinical evaluation and MRI is indicated. Adverse neurologic outcome is directly related to the duration of symptoms. For best recovery of neurologic function the hematoma should be decompressed within 6 to 8 hours of onset of symptoms [18].

## Ischemia

The blood supply to the spinal cord is twofold. A single anterior spinal artery (artery of Adamkiewicz) irrigates the anterior two-thirds of the cord whereas the bilateral posterior arteries supply the posterior columns. While the posterior arteries receive regular support from the radicular arteries, the anterior spinal artery only receives consistent support from the internal iliac arteries in 15% of patients. This inconsistency creates vulnerability to ischemia with hypotension or extrinsic compression. Incidence in the obstetrical population is extremely rare. One such case was described in a retrospective study of 505,000 cases in the UK [13].

Anterior spinal artery syndrome is characterized predominantly by a motor deficit, with or without loss of pain and temperature sensation, but with sparing of vibration and joint sensations. These characteristics help differentiate ischemia from epidural hematoma.

## Infections

The potential infective complications of epidural anesthesia manifest as epidural abscesses or meningitis.

- In an analysis of the ASA Closed Claims Project database from 1980 to 1999, meningitis and abscess accounted for 46% of neuraxial injuries associated with neuraxial procedures in obstetric patients [19].
- Multiple studies, such as a Swedish retrospective study from 1990 to 1999, and a more recent audit by the British Royal College of Anaesthetists from 2006–2007 have shown a greater incidence of both epidural abscess and meningitis in the general surgical population than in the obstetrical population [14, 15].

## Epidural abscess

The incidence of epidural abscess is low. A recent review of ten studies, estimated an incidence of 1 in 302,757 [20].

- Skin-originating *Staphylococcus aureus* is the most common organism implicated in epidural abscess formation [18].

- Risk factors include prolonged catheterization (one to four days), poor aseptic technique, multiple attempts, and immunocompromised patients. Racemic bupivacaine and lidocaine, in concentrations appropriate for epidural analgesia, have antibacterial effects, and as such infusion with opioids devoid of local anesthetics may also be a risk factor.
- Clinical presentation includes severe backache and local tenderness, and fever with or without root pain. Stiff neck, fever, and inflammatory markers on laboratory results serve to differentiate between abscess and hematoma.
- Treatment of epidural abscess requires urgent laminectomy for evacuation of the abscess and appropriate antibiotic therapy for two to four weeks. Prognosis improves if evacuation is done before neurological signs develop.

### Meningitis

The incidence of meningitis from spinal anesthesia has been quoted as 1 in 39,000 [20]. It is thought that meningitis requires dural puncture and, as such, the incidence from uncomplicated epidurals is extremely low.

- The most common organism implicated is *Streptococcus viridans*, either from the oropharynx of the operator or vaginal flora.
- Clinical presentation occurs 12 hours to several days post procedure.
- Symptoms of meningitis include fever, headache, photophobia, nausea, vomiting, and neck stiffness. Confusion, drowsiness, or a positive Kernig's sign (inability to straighten the knee when the hip is flexed) may also be present.
- Diagnostic lumbar puncture reveals an elevated CSF protein level and white blood cell count, and a CSF glucose level that is lower than the plasma glucose concentration.
- Treatment should be initiated immediately with broad spectrum antibiotics while waiting for culture results.

### Chemical

Chemical injury may result from erroneous injection through an epidural catheter or spinal needle.

- Injection of toxic substances into the epidural space is relatively well tolerated because of the protection afforded by the dural cuff layers, dura, arachnoid, and pia mater, covering the nerves. Additionally, blood flow into the epidural space helps cleanse toxins.
- There are many reports of accidental injections of substances into the epidural space (e.g. thiopental, potassium chloride, and antibiotics) without permanent sequelae [18].

## Prevention

- Prevention of neurologic complications implicates the healthcare team as a whole.
- Patients at risk for complications (i.e. history of previous complications with neuraxial procedures, neurological or spine pathology, anticoagulated patients, immunocompromised patients) should be evaluated ahead of time as much as possible by an anesthesiologist in the pre-admission clinic or equivalent.
- Aseptic technique should be rigorously followed with each patient receiving an epidural.

- Meticulous attention should be paid to pain or paresthesias on insertion of the epidural catheter, prompting adjustments until symptoms resolve.
- Patients with neurological complaints should be evaluated promptly by a member of the anesthesia team as time is of the essence if neurological complication is suspected.
- Meticulous attention should be paid to labeling drugs injected into the epidural space by physicians or nursing staff.

## Back pain

Back pain after delivery is not uncommon, with an incidence of up to 70% [21]. Surveys performed in the UK in the 1990s suggested an increased incidence of chronic backache after delivery in women having epidural labor analgesia.

- MacArthur *et al.*, reviewed charts and questionnaires of 11,701 women and found that women who had chosen epidural analgesia had a 19% incidence of new long-term backache compared to an 11% incidence in women who had no epidural analgesia [22]. They suggested that back pain from epidural analgesia may have been related to pain relief and prolonged stressed posture.
- Russell *et al.* found a similar association in their survey of 1,615 women – 17.8% of women who had epidural analgesia had back pain after delivery [23].

However, both these studies had low response rates and were subject to recall bias and selection bias.

All prospective reports and systematic reviews have shown no significant relationship between epidural labor analgesia and chronic back pain.

- A prospective survey of 599 women with a 75% response rate by Russell *et al.* found no increased incidence of chronic back pain in women who had epidural labor analgesia [24].

Randomized controlled trials that have compared women randomized to receive epidural or non-epidural analgesia techniques have shown that epidural labor analgesia is not associated with an increased incidence of new onset chronic low back pain.

- Howell *et al.* randomized 184 women to epidural analgesia and 185 to non-epidural analgesia with primary outcome measures as backache three and twelve months after delivery. They found no significant differences at three months (35% vs. 34%) or 12 months (35% vs. 27%) [25].
- A follow-up study at 26 months found no significant difference between groups, with still 30% in each group having low back pain [26].
- Orlikowski *et al.* conducted a secondary analysis of a randomized controlled trial in which 690 women received epidural analgesia and 302 women received other forms of analgesia. They found that back pain was common in both groups and that risk factors for back pain at six months were back pain before pregnancy and back pain at two months after delivery. Epidural analgesia was not found to be a significant risk factor [27].
- A Cochrane review to assess the effects of epidural vs. non-epidural or no analgesia in labor concluded that epidural labor analgesia does not increase the risk of postpartum chronic back pain [28].

In conclusion, high-quality evidence supports that there is no causal relationship between epidural labor analgesia and the development of new chronic back pain.

## Breastfeeding

It has been suggested that epidural labor analgesia has an adverse effect on breastfeeding.

- It is known that epidural medications, especially opioids, cross the placenta.
- A retrospective review by Jordan *et al.* first suggested a negative relationship between epidural fentanyl and breastfeeding [29]. They reviewed the charts of 425 women and the primary outcome was method of infant feeding at discharge. A logistical regression model used for data analysis suggested that intrapartum fentanyl at high doses could deter breastfeeding. The authors concluded that breastfeeding rates could be improved by removing fentanyl from labor epidural solutions.
- A prospective cohort study of 1,280 women found that women who had epidural analgesia with bupivacaine and fentanyl were twice as likely to stop breastfeeding in the first 24 weeks postpartum [30].
- However, a recent small prospective cohort study of 105 multiparous woman who had previously breastfed noted high breastfeeding success rate (>95%) at six weeks despite the use of epidural fentanyl during labor [31].
- Beilin *et al.* carried out the first randomized controlled trial (RCT) to study the effect of epidural fentanyl on breastfeeding. One hundred and eighty women were assigned to one of three groups, based on the total amount of fentanyl to be administered during labor: no fentanyl, an intermediate fentanyl dose (1 to 150 μg), or high-dose fentanyl (>150 μg). Women having >150 μg of fentanyl were more likely to have problems breastfeeding at 24 hours and six weeks postpartum [32]. However, it is important to note that more than 10% of participants were lost to follow-up in this study.
- A recent secondary analysis of another RCT of 1,054 nulliparous women randomized to high-dose epidural, or CSE, or low-dose epidural analgesia did not support an effect of epidural fentanyl on breastfeeding initiation [33].

Successful breastfeeding depends on many factors (motivation to breastfeed, parity, age, local culture, social class, education, delivery type, and the level of support offered). More studies are needed before removing fentanyl from epidural solutions. The removal of fentanyl would mean an increase in local anesthetic concentration to provide adequate analgesia and would likely increase the risk of instrumental delivery.

## Maternal fever

An association between epidural analgesia for labor and maternal fever was first reported by Fusi *et al.* [34]. The non-epidural group maintained a normal temperature through labor. However, the epidural group developed a significant increase in temperature after six hours of labor. The authors concluded that patients receiving epidural analgesia for labor were at increased risk for developing fever. They suggested that vascular and thermoregulatory changes may be responsible for the increase in temperature.

Lieberman *et al.* evaluated the impact of labor epidural analgesia on the rate of maternal fever, neonatal sepsis evaluations, and neonatal antibiotic treatment [35].

- They studied 1,657 nulliparous women who were afebrile at admission for labor. Their results showed that 14.5% of women with epidurals developed a fever during labor compared to 1% of patients without an epidural. The neonates born to mothers having epidurals underwent sepsis evaluations 34% of the time vs. 9.8% in the other group. These babies also received antibiotics more often (15.4% vs. 3.8%). The authors concluded that epidural analgesia during labor was strongly related to maternal fever, neonatal sepsis workups, and neonatal antibiotic treatments.
- Maternal fever has been shown in a retrospective analysis of 1,233 nulliparous women to be associated with an increased risk for cesarean delivery and assisted vaginal delivery [36]. The authors concluded that more frequent temperature increase in women with epidural labor analgesia may explain the increased rates of cesarean and assisted vaginal deliveries seen with epidural use.
- Epidural-related fever in another study of 1,235 nulliparous women was found to be associated with increased maternal antibiotic treatment for presumed chorioamnionitis [37].

Selection bias may confound the relationship between epidural labor analgesia and maternal fever because women at increased risk for fever (those with prolonged rupture of membranes, longer labor, more frequent cervical examinations, etc.) are more likely to request epidural analgesia. However, RCTs have also shown an increased incidence of fever in women having epidural analgesia, suggesting a causal relationship. But on closer examination of these trials, women randomized to epidural analgesia may have undergone artificial rupture of membranes and more frequent cervical examinations. It is possible that different obstetrical management may have confounded these RCTs.

- The mechanism of maternal fever is unclear.
- Although thermoregulatory effects were first proposed, more recently it has been suggested that inflammation may be an important source.
- In a review of three groups of patients: those without epidural analgesia and with clinical chorioamnionitis, those with epidural analgesia and without clinical chorioamnionitis, and women with epidural analgesia and clinical chorioamnionitis, it was found that epidural analgesia without clinical chorioamnionitis was not associated with maternal fever [38].

Prophylactic treatment for maternal fever associated with epidural analgesia is controversial.

- Acetaminophen has not been found to be effective [39].
- High-dose methylprednisolone was found to be effective in preventing maternal fever in women having epidural analgesia but was associated with an increased risk of neonatal bacteremia [40].
- Recently, epidural dexamethasone has been shown to decrease maternal temperature elevation in an RCT of 60 nulliparous women in labor [41].

In summary, women who labor with epidural analgesia experience an increase in temperature that is associated with administration of antibiotics to both mother and babies, increased neonatal sepsis workups, as well as possibly increased operative deliveries. The mechanism of fever may be related to inflammation and to thermoregulatory effects.

## Conclusions and key points

- Epidural analgesia is associated with a prolonged second stage of labor and an increased risk of instrumental delivery.
- There is insufficient evidence to support an association between epidurals and an increased risk of cesarean section.
- Epidural hematoma in the obstetric population is rare. If hematoma is suspected this should be investigated and treated promptly.
- Infectious complications of epidurals are low but practitioners should be vigilant and investigate and treat complications promptly.
- High-quality evidence supports that there is no causal relationship between epidural labor analgesia and the development of new chronic back pain.
- High-dose epidural fentanyl may be associated with an adverse effect on breastfeeding. More studies are needed before removing fentanyl from epidural solutions.
- Women who labor with epidural analgesia experience an increase in temperature, which is associated with administration of antibiotics to both mother and babies, increased neonatal sepsis workups, as well as possibly increased operative deliveries.

## Further reading


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Chapter 14

# Epidural and intrathecal opiates and outcome

**Dr P Batohi and Dr J Parkin**

## Introduction

- Since the discovery of opioid receptors within the dorsal horn of the spinal cord and the first reported clinical use in humans by Wang in 1979 [1], the use of epidural and intrathecal opiates has become a standard part of present-day obstetrical anesthesia practice.
- Over thirty years of research and clinical use has answered many of the questions practitioners have had concerning the drugs, routes of delivery, and doses to use for optimal effect in the obstetrical patient while minimizing side effects in the mother and fetus.
- Controversies remain, particularly related to the dosage and side effects of epidural and intrathecal opiates and with regard to the role of epidural opiates in fetal outcome.

## Pharmacology of neuraxial opiates

- By producing an analgesic action in the absence of associated motor block or reduction in sympathetic tone, neuraxial opiates are an ideal component of the list of analgesic medications available for use by the obstetrical anesthesiologist. The mechanism of action of these drugs, as well as the pharmacology of individual agents, has been widely studied.
- Pharmacologic action results from binding of the drug to opioid receptors in the dorsal horn of the spinal cord.
- Lipid solubility determines the ability of the drug to cross the dura and meninges if administered epidurally. Drugs that are more lipid soluble (fentanyl, sufentanil) diffuse into the CSF more rapidly than do hydrophilic agents (e.g. morphine) and consequently have a faster onset of action. Similarly, once in the CSF, either by diffusion from the epidural space or following direct injection, diffusion into the spinal cord to the site of action is more rapid with lipophilic agents.
- When administered epidurally, systemic absorption of lipophilic opioids will also occur. Measurable systemic levels are produced with this group [2, 3], and the predominant site of action has been debated. Several investigators have shown the site of action to be predominantly at the spinal level [4, 5]. The analgesic effect produced by hydrophilic opioids is also predominantly the result of the action at the spinal cord level.

*Controversies in Obstetric Anesthesia and Analgesia*, ed. Ian McConachie. Published by Cambridge University Press. 

- Duration of action is also determined by the physicochemical properties of the individual drug. Lipophilic agents, as might be expected, have a shorter duration of action than do hydrophilic agents due to more rapid clearance from their site of action.
- Neuraxial opiates may be effective for visceral pain during the first stage of labor, but are relatively ineffective for the somatic pain produced by descent of the fetal presenting part during the latter part of the first stage and second stage of labor. As a result, these drugs are optimally combined with a local anesthetic when used for labor analgesia.
- A dose-dependent reduction in the local anesthetic required to provide effective labor analgesia results when an opioid is added. The synergistic action of the combination has been clearly demonstrated. The obvious advantage of smaller doses of each being required to produce effective analgesia also results in reduced motor block and less potential for undesirable side effects.
- The speed of onset, quality of analgesia produced, and duration of analgesic action are all improved with the addition of a lipophilic opioid to the local anesthetic at the time of initiation of epidural analgesia for labor [6, 7].
- The combination of a lipophilic drug, hydrophilic drug, and local anesthetic is commonly used for cesarean section anesthesia. The lipophilic drug improves the quality of intraoperative analgesia, while the hydrophilic drug's slower onset and prolonged duration of effect provides effective postoperative analgesia.
- Findings in early studies suggested that adverse interactions might occur when combinations of opioids are used [8]. Cohen *et al.* reported that the use of epidural fentanyl might lead to a decreased analgesic effect of subsequently administered epidural morphine. They speculated that fentanyl either accelerated the systemic absorption of morphine thereby reducing the analgesic action at the spinal cord level, or competed with morphine for spinal cord opioid receptors, also decreasing the resulting analgesia. Interestingly, epidural morphine doses used in the study were 4 to 5 mg in the group receiving morphine alone and 2.5 to 3 mg in the morphine plus fentanyl group. Several studies that followed failed to substantiate the findings of Cohen's group, and current practice includes the use of lipophilic/hydrophilic neuraxial opioid combinations as part of a multimodal post cesarean section pain management plan.

## Individual agents

The role of neuraxial opiates for post cesarean section analgesia is further discussed in the chapter on Analgesia post cesarean section.

### Morphine

- A hydrophilic opioid – among the first to be used for postsurgical analgesia when administered by epidural or intrathecal route.
- A preservative-free preparation is available for clinical use.
- A slow onset of action limits its usefulness for labor analgesia. Following epidural administration, the first noticeable effect is seen after approximately 30 minutes, with peak action achieved after 60 to 90 minutes. Slightly faster onset of peak effect of approximately 40 to 60 minutes when administered intrathecally.

- Morphine's hydrophilic properties result in a prolonged duration of action of up to 18 to 24 hours. Conversely, the hydrophilic nature of morphine allows for rostral spread within the CSF with the potential for delayed respiratory depression when the drug reaches the brainstem respiratory centers.
- The usual epidural morphine dose for post cesarean section analgesia is 2 to 3 mg. Studies have failed to demonstrate improved analgesia with larger doses, which potentially lead to an increased incidence of side effects in the mother.
- Intrathecal administration for obstetrical anesthesia use is generally reserved for post cesarean section analgesia. Most recent studies suggest 100 to 150 μg as the ideal dose for intrathecal use. Larger doses provide no advantage in terms of improved analgesia while exposing the parturient to a higher incidence of side effects.
- There are now several reports of the use of sustained-release epidural morphine (DepoDur®) in post cesarean section patients. This formulation allows for a prolonged period of postoperative analgesia, particularly in the period from 24 to 48 hours after surgery. Carvalho *et al.* demonstrated superior and prolonged analgesia in their patients using 10 mg of extended release morphine as compared to a standard 4 mg dose of "conventional" morphine [9]. Approved for use in the US by the FDA in 2004, this preparation is becoming available in several countries, and may become a viable option for post cesarean section analgesia. The potential for late respiratory depression and the resulting need for extended monitoring on the postpartum ward may represent an obstacle in some practices.

## Hydromorphone

- The lipid solubility of hydromorphone is between that of lipid soluble fentanyl and hydrophilic morphine.
- Studies have suggested that there is a reduced incidence of pruritus with hydromorphone as compared with morphine when used for postoperative analgesia, but clinical trials involving obstetrical patients are limited. Halpern *et al.* demonstrated no clinical benefit for hydromorphone as compared to epidural morphine for post cesarean section patients in terms of either the analgesia produced or the incidence of side effects [10].
- The suggested epidural dose for post cesarean section analgesia is 0.4 to 0.8 mg, which produces analgesia of duration similar to morphine.

## Fentanyl

- Fentanyl is a highly lipid soluble opioid with a resulting rapid onset and short duration of action.
- Fentanyl's rapid uptake into the systemic circulation after epidural administration led to initial speculation that this played a significant role in the analgesia produced. However, several subsequent studies have clearly demonstrated that the primary site of analgesic action is at the spinal cord level.
- 50 to 100 μg is the suggested epidural bolus dose for induction of labor analgesia when combined with a long-acting amide local anesthetic, with a lower dose indicated for patients in early labor.

- For continuous epidural infusion in combination with an amide local anesthetic, an optimal fentanyl dose range of 1.5 to 3.0 μg/ml of the infusion solution has been suggested.
- Intrathecal fentanyl is effective as the sole agent, or in combination with low-dose local anesthetic as the initial dose for, or as part of, a CSE technique. The onset of action is rapid. The clinical onset is within 5 minutes, with peak effect achieved by 20 minutes.
- When used alone in early labor, 25 μg generally produces satisfactory analgesia when given intrathecally. If combined with a local anesthetic the fentanyl dose can be reduced, with most studies suggesting 10 to 15 μg as the required dose.
- Fentanyl is useful as a component of neuraxial anesthetic for cesarean section when given as part of an epidural "top up" or as an adjunct for spinal anesthesia. When given in this manner, fentanyl provides useful intraoperative analgesic action, but a short duration of action of approximately four hours limits its usefulness for postoperative analgesia.

## Sufentanil

- Sufentanil is also highly lipid soluble with resulting rapid onset and short duration of analgesic action.
- Sufentanil is an analogue of fentanyl with higher lipid solubility, which results in a slightly faster onset of peak effect.
- Sufentanil exhibits a high degree of protein binding once absorbed into the systemic circulation leading to a lower plasma concentration when compared to fentanyl. There appears to be a greater degree of transfer of sufentanil across the placenta when compared to fentanyl, but the lower plasma concentration of sufentanil in the maternal circulation results in less fetal exposure to the drug. Further study is needed to determine if this is clinically significant in the newborn.
- Similar to other opioids, sufentanil provides relief from the visceral pain of the first stage of labor, but is ineffective alone as labor progresses and somatic pain becomes more prominent.
- Thus, sufentanil is most commonly used in combination with a low concentration of a long-acting amide local anesthetic.
- Its potency is between five to ten times that of fentanyl. The corresponding dose if used with local anesthetic at initiation of epidural analgesia for labor is 5 to 10 μg.
- When used alone as part of CSE technique the suggested dose is 5 to 10 μg. If combined with a local anesthetic the dose can be reduced by approximately 50% (suggested dose 2 to 5 μg).
- Sufentanil can be used as an adjunct to local anesthetic for cesarean section anesthesia. Similar to fentanyl, the high lipid solubility generally limits the beneficial effect to the intraoperative and early postoperative period. A hydrophilic opioid is usually added to provide prolonged postoperative analgesia.
- The commercial preparation available in North America contains 50 μg/ml. Potentially the relatively small dose used clinically for neuraxial administration increases the possibility of dosing errors.

## Diamorphine

- Diamorphine (diacetylmorphine also known as heroin) is a highly lipid soluble opioid currently available for use in several countries including the UK, but unavailable for use in North America.
- Diamorphine can be used as an adjunct to local anesthetic for labor analgesia, intrathecally as part of a CSE technique, or for cesarean section.
- Diamorphine's high lipid solubility leads to rapid movement of the drug into the CSF and to the site of action in the dorsal horn of the spinal cord. There is a relatively rapid onset of effect (similar to fentanyl), which may be beneficial if used for labor analgesia or as part of an anesthetic for cesarean section.
- The clinical effect is produced by the active metabolites morphine and monoacetyl morphine.
- The suggested dose used for post cesarean section analgesia (National Institute for Health and Clinical Excellence, UK) is 0.3 to 0.4 mg if used intrathecally and 2.5 to 5.0 mg when given by the epidural route [11]. The time to first maternal request for supplemental analgesia is dose dependent. The average duration of analgesia produced is approximately ten hours.

## Meperidine

- Meperidine (also known as pethidine in some countries) is a lipid-soluble opioid with chemical structure similar to local anesthetics. Meperidine was the first synthetic opioid – synthesized in 1932. Meperidine is unusual among opioids in that it has significant, intrinsic local anesthetic properties and also anticholinergic properties. Because it has local anesthetic properties, meperidine potentially may be used as a sole agent when given by the intrathecal route for cesarean section or as an adjunct to local anesthetic for labor analgesia or cesarean section.
- The neuraxial block produced when administered intrathecally in a dose of 1 mg/kg body weight is similar to that seen with local anesthetics. However, the block produced is less reliable in terms of intensity and duration, and the drug is more commonly used as an adjunct to local anesthetic in a dose of 10 mg. The duration of postoperative analgesia (four to five hours with the usual dose) is less than that produced by morphine.
- The higher incidence of both intra- and postoperative nausea and vomiting is a limiting factor when considering meperidine for neuraxial use.
- The addition of meperidine (0.2 mg/kg) to a standard intrathecal bupivacaine/morphine mixture for cesarean section has been shown to decrease the incidence and intensity of shivering associated with spinal anesthesia for cesarean section [12].

# Side effects of neuraxial opioids

The beneficial effects of neuraxial opioid administration are associated with potential complications or side effects, both in the mother and in the fetus.

## Respiratory depression

- This is the most serious side effect of neuraxial opioid administration.
- The physiologic increase in respiratory drive during pregnancy is protective, but does not eliminate the possibility of respiratory depression with opioid administration.
- All opioids can cause respiratory depression, irrespective of the route of administration.

The risk of respiratory depression in neuraxial administration is affected by:

- the agent chosen
- the dose given
- concomitantly administered CNS depressant medications [13].

The onset of respiratory depression with intrathecal administration is most influenced by the lipid solubility of the agent used [14].

- Lipophilic agents (e.g. fentanyl, sufentanil) can cause respiratory depression within minutes but, due to fast elimination and clearance, have a short window in which to cause respiratory depression.
- With hydrophilic agents (e.g. morphine, hydromorphone) respiratory depression may occur early (within minutes to hours) or late (6 to 12 hours later). This is due to the agent remaining in the CSF for many hours, combined with rostral spread and absorption into the respiratory centers.

The onset of respiratory depression with epidural administration is likewise influenced by lipid solubility of the agent used.

- Lipophilic agents can cause respiratory depression within minutes. The window in which respiratory depression can occur is up to three hours.
- Hydrophilic agents can cause respiratory depression for up to 24 hours. Early (<12 hours) respiratory depression is far more common than late (>12 hours) respiratory depression.

Practice guidelines from the American Society of Anesthesiologists (ASA) [15] recommend that all patients who receive neuraxial opioids are monitored for:

- adequacy of ventilation (e.g. respiratory rate, subjective appearance of tidal volume)
- oxygenation (oxygen saturation)
- level of consciousness.

This monitoring should be maintained for at least two hours after administration of a lipophilic agent, and 24 hours after use of a hydrophilic agent.

## Nausea and vomiting

- Nausea and vomiting are very common during pregnancy. Anesthetic and analgesic causes are only part of this problem.
- The causes are multifactorial.
- The scenario with the highest rate of nausea or vomiting is when intrathecal opioids are used for cesarean section.

- Prophylaxis and/or treatment can be with any of the antiemetics commonly used in anesthesia (metoclopramide, ondansetron, droperidol, cyclizine, dexamethasone). Combination therapy may be appropriate.

## Pruritus

- Pruritus is the commonest side effect of neuraxial opioids, with it being most common after intrathecal use [16].
- The onset of pruritus is shortly after analgesia develops, and decreases with the resumption of pain.
- Pruritus after neuraxial opiates can be more distressing to the patient than the pain itself and should be promptly treated.
- Lower doses of neuraxial opioids cause less pruritus.
- The co-administration of local anesthetic agents reduces the incidence of pruritis [17].
- Pruritus appears unrelated to histamine release.

Treatment may be with:

- naloxone (40 to 100 μg IV, repeated as required)
- nalbuphine (2.5 to5 mg IV or 10 mg IM) – nalbuphine may be less likely to reverse the analgesia than naloxone
- 5-hydroxytryptamine-3 (5-HT3) antagonists (e.g. ondansetron) – most studies have shown 5-HT3 antagonists to be effective though some have not
- propofol (10 mg IV)
- diphenhydramine (25 mg) – while not considered a logical treatment, the sedation produced draws attention away from the pruritus.

## Urinary retention

- Urinary retention is thought to de due to the rapid onset of detrusor muscle relaxation produced by a local sacral action of spinal opioids [18].
- Urinary retention is relieved by urinary catheterization.
- Alternatively, it is possible to treat urinary retention with low-dose naloxone.

## Delayed gastric emptying

- Delayed gastric emptying is common in labor. The majority of this is hormonal, pain induced, or mechanical, i.e. the effect of increased intra-abdominal pressure from the gravid uterus.
- Epidural opioids have a minimal effect on gastric emptying.
- Intrathecal opioids have a greater effect than epidural opioids.
- It is possible that this increases the incidence of nausea and vomiting.

## Recrudescence of oral herpes simplex virus (HSV) infections

- It is possible that pregnancy may reactivate HSV.
- Exposure to ultraviolet light, immunosuppression, trauma and fever are other factors implicated in HSV reactivation.

- Earlier studies point to intrathecal opioids as a further factor [19].
- The scope of the problem appears to be very small.

# Effects on the fetus

## Neonatal depression

- Systemic opioid administration can result in neonatal respiratory depression.
- Despite the rapid uptake of intrathecal or epidural opioids, the much lower total dose and lower maternal plasma levels result in much less neonatal depression compared to systemic opioids [20].
- In mothers who received epidural fentanyl infusions, a slight reduction in neonatal neurologic and adaptive capacity scores was seen at 24 hours of age [21].
- There seems to be a lesser effect when epidural sufentanil is used.
- However, the overall feeling is that neuraxial opioids produce superior analgesia, with better neonatal outcomes, when compared to systemic administration [22].

## Epidural fentanyl and breastfeeding

- Concerns have been raised regarding the influence of epidural fentanyl on successful breastfeeding. This is fully discussed in the chapter on Epidurals and outcome.

## Fetal bradycardia

- There are reports of significant fetal bradycardia or late decelerations with the administration of intrathecal fentanyl or sufentanil. This is commonly seen when intrathecal fentanyl is administered as part of a combined spinal–epidural (CSE) technique and, as such, is also discussed in the chapter on CSE.
- The incidence is thought to be 15 to 20%.
- This is possibly due to the sudden onset of good analgesia, with consequent steep reduction of circulating epinephrine. Epinephrine has tocolytic effects, and the sudden reduction may result in increased uterine tone, or even uterine hypertonus. Norepinephrine, which is known to stimulate the uterus, is unchanged. This may also contribute to the hypertonic uterus [23].
- However, equivalent analgesia produced by a combination of a smaller dose of opioid and local anaesthetic resulted in a much lower incidence of fetal heart rate abnormalities [24].
- Interestingly, intrathecal fentanyl is reported to increase the success rate of external cephalic version due to its presumed tocolytic effects – without any evidence in this series of bradycardia [25].
- In consideration of the reports of bradycardia, it is prudent to monitor the fetal heart rate when neuraxial analgesia is administered to laboring women.
- Even if there are changes in the fetal heart rate, conservative measures are usually sufficient, as the changes are most often self-limiting.

Management includes:

- supplemental oxygen
- position to relieve aortocaval compression
- treat hypotension
- stop oxytocin
- consider tocolytic agents, such as nitroglycerin IV 50 to 100 μg or terbutaline IV 0.25 mg
- emergency cesarean section may be required if conservative measures fail.

In the treatment of persistent uterine hypertonus, nitroglycerine is preferred initially as:

- it has a short duration of action
- there is a low chance of hypotension, and it is easy to treat if it occurs
- there is a high rate of success.

## Summary

- Neuraxial opioids are an essential component of the pharmacologic options available for use in present-day obstetrical anesthesia practice.
- A variety of agents is available for clinical use.
- Lipophilic agents form an important part of the commonly used techniques for labor analgesia, and are often used as adjuncts when providing anesthesia for cesarean section.
- Hydrophilic drugs (most commonly morphine) are primarily used as part of a multimodal analgesia plan for postoperative pain management following cesarean section.
- All have the potential for significant side effects in both the parturient and the fetus, and the obstetrical anesthesiologist must weigh the risks of these against the benefits provided when formulating a plan of management for each individual patient.

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Chapter 15

# Remifentanil infusions and patient-controlled analgesia

Dr P Foley and Dr D Hill

## Introduction

- Remifentanil is an opioid with μ-specific activity, low volume of distribution, low lipid solubility, and a context-sensitive half-life of 3 to 5 minutes. Blood–brain equilibrium occurs in 1.2 to 1.4 minutes and it is rapidly metabolized by plasma and tissue esterases to an inactive metabolite [1]. Metabolism is independent of renal and hepatic function and there is no accumulation with prolonged infusion [2].
- Remifentanil readily crosses the placenta; however, there is rapid metabolism, redistribution, or both in the neonate [3]. The pharmacokinetics of remifentanil when used for postoperative pain relief in neonates are similar to those for older children and adults [4].
- Remifentanil's safety profile in neonates combined with rapid onset and offset means that it offers potential not only as a labor analgesic, when administered as patient-controlled analgesia (PCA), but also as an adjunct to general anesthesia, particularly in high-risk obstetric patients.

## Suitability of remifentanil as a labor analgesic

Neuroaxial analgesia provides excellent analgesia; however, alternatives are needed when these techniques are contraindicated. Obstetric anesthesia has had a long, albeit uncomfortable, relationship with systemic opioids. Sedation, nausea, delayed gastric emptying, respiratory and neonatal depression, combined with doubtful efficacy as a labor analgesic, have limited their use [5].

An ideal intravenous opiate should have an onset and offset that can match the time course of uterine contractions, while preserving uterine contractility and a reassuring cardiotocograph (CTG). The analgesia experienced should be considered worthwhile and there should be minimal maternal and neonatal effects, allowing administration up to and during delivery.

The rapid onset and rapid elimination of remifentanil suggest that it could be suitable for the cyclical pain of uterine contractions.

- A study recording effects on ventilation in volunteers following a 0.5 μg/kg bolus over 5 seconds reported onset of effect at 30 seconds and peak effect at 2.5 minutes [6]. This suggests that it would be difficult, if not impossible, to coincide peak effect with each uterine contraction. It is more likely that the peak effect would coincide with the second or subsequent contraction.

*Controversies in Obstetric Anesthesia and Analgesia*, ed. Ian McConachie. Published by Cambridge University Press. 

- This may explain why the first published attempt to use remifentanil for labor analgesia fell short of expectations [7]. Its use in four women was reported. However, the bolus doses of remifentanil were manually administered by a third party, inevitably leading to delay in dosing. The investigators concluded that remifentanil was ineffective. It is likely that the peak effect occurred in the period between contractions.

## Optimal dosing regimen

Early studies focused on determining efficacy and the optimal dosing regimen for remifentanil PCA in labor. The wide variation in dosing regimens is illustrated in Table 15.1. These include two dose-finding studies [8, 9], one observational study employing a fixed PCA dose [10], and one comparing two regimes of background infusion plus PCA [11].

All four studies reported analgesia with remifentanil.

- In the feasibility study of Blair and colleagues [8], the median reduction in pain score was 30 mm compared with baseline with a bolus dose range of 0.25 to 0.5 μg/kg.
- The dose-finding study of Volmanen *et al.* [9] reported a median reduction in pain scores of 42 mm with a median dose of 0.4 μg/kg.
- The observational study of Volikas *et al.* [10] administered a fixed dose of 0.5 μg/kg and reported a mean reduction in pain scores from baseline of 26 mm.
- The remaining study compared a fixed background infusion dose and an escalating PCA bolus dose with a fixed bolus dose and an escalating background infusion dose and reported a mean reduction in pain scores from baseline of 30 mm [11].

There is no consensus on the optimal regimen for remifentanil. Each study has used its own dosing schedule with a bolus dose range of 0.2 to 0.93 μg/kg. The most popular dose is 0.5 μg/kg. Some investigators have commented on the wide individual variation of bolus dose

**Table 15.1** Remifentanil PCA dosing details for labor analgesia.

| Reference | Bolus dose | Lockout time | Background infusion | Conversion to regional analgesia |
|---|---|---|---|---|
| Blair *et al.* [8] | 0.25–0.5 μg/kg | 2 min | No | 4 of 21 |
| Volmanen *et al.* [9] | 0.2–0.8 μg/kg | 1 min | No | Not reported |
| Volikas *et al.* [10] | 0.5 μg/kg | 2 min | No | 5 of 50 |
| Balki *et al.* [11] | 0.25 μg/kg | 2 min | Yes | 1 of 20 |
| Evron *et al.* [16] | 0.27–0.93 μg/kg | 3 min | No | 4 of 43 |
| Blair *et al.* [18] | 40 μg | 2 min | No | 2 of 20 |
| Douma *et al.* [19] | 40 μg | 2 min | No | 7 of 52 |
| Thurlow *et al.* [20] | 0.2 μg/kg | 2 min | No | 7 of 18 |
| Volmanen *et al.* [23] | 0.4 μg/kg | 1 min | No | Not reported |
| Volmanen *et al.* [24] | 0.3–0.7 μg/kg | 1 min | No | Not reported |

required to achieve effective analgesia [9]. This would suggest a fixed-dose regime could underdose and lead to failure, or could overdose and lead to maternal oxygen desaturation.

### Lockout times

Reported lockout times have also varied, some described lockout times of two minutes while others describe a bolus dose delivered over one minute with a one-minute lockout time. With an average uterine contraction time of 70 seconds [12], it would seem prudent to allow a dose every two minutes.

### Background infusions

- In the dose-finding study of Blair *et al.* [8], who recommend a PCA bolus dose of 0.25 to 0.5μg/kg, the introduction of a background infusion of remifentanil did not improve analgesia, but caused excessive maternal sedation and oxygen desaturation.
- In contrast, Balki *et al.* has recommended a PCA bolus of 0.25 μg/kg with a background infusion of 0.025 to 0.1 μg/kg/min [11]. The investigators claimed a conversion rate to regional analgesia of 5% compared with the 10% rate of other studies without a background infusion.

### Timing

Several investigators commented that timing of dosing was critical [13].They reported that "with tutoring, the patient can learn to anticipate the next contraction and to make an early effective demand" [14]. More work needs to be done to define the optimal dosing regimen before a background infusion can be recommended.

## Analgesic efficacy compared with alternative labor analgesia

### Pethidine (meperidine)

Pethidine remains the most commonly used opioid for systemic labor analgesia, available as an option in 95% of UK units [15].

- Evron *et al.* [16] compared remifentanil PCA with pethidine infusion in early labor and found lower pain scores, higher maternal satisfaction, and lower epidural conversion rates in the remifentanil group.
- Volikas *et al.* [17] compared remifentanil PCA (0.5μg/kg bolus, two-minute lockout) with pethidine (10 mg bolus, five-minute lockout) and found pain scores were lower in the remifentanil group; however, the study was terminated early due to concerns regarding low Apgar scores in the pethidine group.
- Blair *et al.* [18] found pain scores were similar for remifentanil PCA (40 μg bolus, two-minute lockout) and pethidine PCA (15 mg bolus, ten-minute lockout); however, maternal satisfaction with analgesia was higher in the remifentanil group compared.
- Douma *et al.* [19] also compared remifentanil PCA (40 μg bolus, two-minute lockout) with pethidine PCA (49.5 mg loading dose, 5 mg bolus, ten-minute lockout). The pain scores were lower in the remifentanil group but this was only statistically significant during the first hour after initiation of therapy. However, like the earlier study, maternal satisfaction was higher in the remifentanil group.

- Thurlow *et al.* [20] found that remifentanil had significantly reduced pain scores when compared with intramuscular pethidine.

### Fentanyl

- Fentanyl has been reported to provide worthwhile analgesia with peak effect at three to four minutes [21], but can cause measurable neonatal effects with one study reporting naloxone administration was required for 37% of neonates at birth with neurobehavioral effects lasting up to seven days post delivery [22].
- Douma *et al.* [19] also compared remifentanil PCA (40 μg bolus, two-minute lockout) with fentanyl PCA (50 μg loading dose, 20 μg bolus, five-minute lockout) and found lower pain scores in the remifentanil group – again this was only statistically significant during the first hour after initiation of therapy.

### Nitrous oxide

- Remifentanil compared favorably with nitrous oxide in a crossover study by Volmanen *et al.* [23]. Remifentanil PCA (0.4 μg/kg bolus, one-minute lockout) and intermittent inhaled 50% nitrous oxide were compared in 20 minute cycles. Parturients reported better pain relief with remifentanil.
- Blair and colleagues reported that 19 of 19 women in the pethidine group and 18 of 20 in the remifentanil group used nitrous oxide [18]. It appears that, if given the choice, women would opt for nitrous oxide despite using remifentanil.

### Epidural analgesia

- In another study by Volmanen *et al.* [24], 52 parturients were randomized in early labor to receive either epidural analgesia (20 ml 0.625% levobupivacaine and fentanyl 2μg/ml) or remifentanil PCIA with a variable dose administered over one minute with a one-minute lockout. Pain scores were significantly lower in the epidural group; however, the pain relief was rated similar for both groups.

## Efficacy and maternal satisfaction

It appears that the analgesia provided by intravenous PCA remifentanil is not complete. Nevertheless a common theme is high maternal satisfaction, implying that this modest analgesia is worthwhile. Analgesia is only one component of a satisfactory birth experience, and complete analgesia has not been reported as figuring high in the birthing process for the majority of women. In a review of 137 reports involving the views of 14,000 women from nine countries, the important factors were: personal expectations, support and coping skills, quality of the caregiver–parturient relationship, and involvement in decisions [25].

Several studies also report that dissatisfaction with analgesic care is more related to non-availability of analgesia [26]. This is where PCA remifentanil has an advantage as it can be readily initiated.

## Maternal effects

Of major concern is the potential for maternal respiratory depression and oxygen desaturation. All studies report episodes of maternal oxygen desaturation but comment that they were transient and easily corrected with nasal oxygen or reduction in dose.

When we look at the detail:

- Blair *et al.* [8] reported 4 out of 21 women with saturation of oxyhemoglobin below 90% for 15 seconds and the lowest respiratory rate was eight breaths per minute.
- Balki *et al.* [11] reported a range of oxygen saturations, the lowest being 85%.
- Volmanen and colleagues [9] reported 10 out of 17 women with oxygen saturations below 94%.
- The comparative study by Douma *et al.* [19] found more episodes of desaturation ($SpO_2$ < 95%) in the remifentanil group (74%) when compared with both the pethidine PCA group (33%) and the fentanyl PCA group (56%). Sedation was noted to be significantly higher in the remifentanil group. Supplemental oxygen was required in 12% of parturients in the remifentanil group.

Therefore we cannot be complacent and, on balance, women receiving PCA remifentanil should have one-to-one nursing care, availability of oxygen saturation monitoring, and oxygen supplementation if required.

## Fetal and neonatal effects

- The comparative study of remifentanil PCA with pethidine PCA found fewer non-reassuring CTGs and better neurobehavioral scores in the remifentanil group [18].
- Douma *et al.* [19] noted no differences in CTG traces, Apgar scores, Neurologic and Adaptive Capacity Score (NACS), and fetal cord blood between the remifentanil, pethidine, and fentanyl PCA groups.

## Practical experience

In the author's institution, remifentanil PCA is offered for routine use as a labor analgesic. The dosing regime is a fixed bolus of 40 μg delivered over ten seconds with a two-minute lockout. Supervision is by trained midwives who provide one-to-one care. After initiation of analgesia, maternal oxygen saturation is measured continuously. Hourly respiratory rate and oxygen saturation are measured during remainder of use. Other aspects of antepartum care are normal, with intermittent monitoring of CTG unless otherwise indicated. There is a high maternal satisfaction rate with 95% of mothers either satisfied or very satisfied with analgesia [27].

## Remifentanil analgesia for anesthesia interventions

- Remifentanil can offer sedation and analgesia for the anxious patient without the risk of persistent opioid effects.
- Remifentanil has been reported to facilitate initiation of spinal anesthesia in a morbidly obese, needle-phobic parturient [28] and to facilitate epidural catheter placement in a parturient unable to keep still because of painful contractions [29].
- In the former report, remifentanil was infused at 0.05 to 0.1 μg/kg/min and in the latter report it was infused at 0.1 to 0.25 μg/kg/min. In both cases, verbal contact was maintained and the intended procedure was performed with patient cooperation.

## Remifentanil supplementation of epidural anesthesia

Systemic opioids are the mainstay of managing discomfort during epidural anesthesia for cesarean section, yet there are few published reports of remifentanil for this purpose.

- Kan *et al.* [3] infused 0.1 μg/kg/min of remifentanil to 19 women undergoing epidural anesthesia. The purpose of the study was to investigate placental transfer and neonatal effects. In this study, anesthesia was provided by 2% lidocaine with epinephrine (1:200,000). Episodes of discomfort were not reported, but one woman had a rescue bolus of remifentanil. The remifentanil infusion rates were decreased in three women before delivery because of hypotension. The infusion rates were decreased in five more women after delivery of the infant because of dizziness in one woman and excessive sedation in four women.
- One study has investigated intravenous remifentanil as an adjunct to epidural anesthesia for cesarean section [30]. The investigators compared epidural bupivacaine 0.5% supplemented with either epidural fentanyl or intravenous remifentanil. The investigators found intravenous remifentanil as effective as epidural fentanyl. Considering the adverse neonatal effects of alfentanil [31] and fentanyl [22], remifentanil seems a preferable choice for maternal discomfort during epidural anesthesia. The expected dose would be below 0.1 μg/kg/min with a low potential for neonatal effects.

Further studies are needed.

## General anesthesia with remifentanil for cesarean section

Although the use of general anesthesia is in decline in obstetric patients, there will always be a role in high-risk women where regional anesthesia is not appropriate. Opioids are generally withheld in obstetric general anesthesia until after the delivery of the neonate to avoid the potential for respiratory depression. However, the risk/benefit ratio can favour opioids in circumstances where maternal hemodynamic stability and blunting of responses to airway manipulation and surgical stimulation are deemed important.

- Ngan Kee *et al.* [32] compared a 1 μg/kg bolus of remifentanil with a saline injection at induction of general anesthesia for elective cesarean section. The remifentanil group had an improved hemodynamic response to laryngoscopy and intubation but seven out of twenty infants required bag-and-mask ventilation and two received naloxone, compared with four infants in the control group requiring mask ventilation and none requiring naloxone.
- Yoo *et al.* [33] compared the hemodynamic response to intubation in severe pre-eclampsia patients undergoing general anesthesia for cesarean section. They found that remifentanil bolus (1 μg/kg) compared with saline control effectively attenuated the hemodynamic response to intubation. However, this was associated with significant yet transient neonatal depression with 6 out of 21 infants requiring bag-and-mask ventilation in the remifentanil group versus 1 out of 21 in the control group. Apgar scores and cord blood gas analysis were similar for the two groups after five minutes.
- Draisci *et al.* [34] determined whether a remifentanil bolus dose (0.5 μg/kg) followed by an infusion (of 0.15 μg/kg/min) until peritoneal incision, could control the neuroendocrine response during general anesthesia for cesarean section. Although there was evidence of a partial reduction in the hormonal stress response, three (14%) neonates required intubation for respiratory depression, but all recovered at five minutes without naloxone.

In general, it appears that the higher the maternal dose of remifentanil, the more neonatal effects are observed.

- Kan *et al.* [3] infused IV remifentanil at a dose of 0.1 μg/kg/min to awake patients during epidural anesthesia for cesarean section. No adverse neonatal effects were reported.
- However, Van de Velde *et al.* [35] reported a 50% incidence of respiratory depression at birth requiring intervention by a neonatologist, although the incidences were brief and self-limiting. In this study, anesthesia was maintained with target-controlled infusions of propofol and remifentanil at an infusion dose of 0.2 μg/kg/min.
- Neonatal chest wall rigidity was reported at birth in an infant whose mother had received remifentanil at an infusion dose titrated between 0.1 and 1.5 μg/kg/min [36].
- Richa *et al.* [37] interrupted the remifentanil infusion immediately after hysterotomy until delivery of the infant and reported no adverse neonatal effects.

It seems prudent to anticipate the need for neonatal resuscitation at delivery when remifentanil is used in high-risk women at high doses. If contemplating the use of remifentanil in healthy women, it would seem reasonable to either avoid remifentanil until after delivery of the infant or restrict the infusion dose to at or below 0.1 μg/kg/min until delivery of the infant. A physician experienced in neonatal resuscitation should be available when remifentanil is used as an adjunct to general anesthesia in obstetric patients, even if the effects are short lived.

Remifentanil has also been reported as an adjunct to general anesthesia in patients with coagulation factor and platelet deficits [36]; haemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome [37]; pre-eclampsia [38]; severe cardiac disease [39]; intracranial disease [40]; and Marfan's syndrome [41].

## Off-label use (UK)

- Remifentanil is not licensed for use in obstetric patients. The administration of drugs outside their product license is common in obstetric anesthesia.
- All opioids by the spinal and epidural route, as well as all self-prepared mixtures of drugs, are not licensed uses.
- Propofol and doses above 250 mg of thiopentone (thiopental) are not licensed either.
- Most of us are content to use drugs outside the product license.
- Almost all of the 169 members of the Obstetric Anesthesiologists Association surveyed in 1997 [42] admitted to using drugs outside the product license in obstetric anesthesia.
- It is unlikely that the manufacturers of remifentanil would invest in the cost of obtaining a license for obstetric use.
- The onus remains on each clinician to assess the risk/benefit ratio.
- Currently, remifentanil is more suited than any other systemic opioid to obstetric anesthesia. Time will tell whether its use will become routine.

## Summary

- Remifentanil is currently the most suitable systemic opioid for obstetric use.
- While it has a rapid onset and offset, the timing of onset and offset cannot be matched to that of a single uterine contraction. Nevertheless, remifentanil has been shown to provide effective analgesia, especially during the first stage of labor.

- We should continue to appraise and study its unique properties, bearing in mind that it is an opioid with all the attendant problems that opioids can bring.
- An appropriate PCA dose regime is a 40 μg bolus with a two-minute lockout.
- Systems should be in place to ensure one-to-one monitoring with trained caregivers.
- Maternal desaturation occurs in approximately 10% of women.
- PCA remifentanil is a viable alternative for those who do not want or are unable to have regional analgesia. It is only after experience in this group of women that it may be rolled out for routine use.
- In high-risk obstetric patients requiring general anesthesia, remifentanil is successful in providing hemodynamic stability at intubation and during surgery.
- High doses of remifentanil with general anesthesia have unpredictable neonatal effects, making attendance by a physician trained in neonatal resuscitation mandatory.
- Remifentanil has a place in obstetric anesthesia and analgesia. With experience and training, this will be a safe place.

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Chapter 16

# Nitrous oxide

Dr R Smith and Dr I McConachie

## Introduction

- There are two common uses for nitrous oxide in modern anesthetic practice: as a carrier gas for more potent volatile anesthetics during general anesthesia and as an analgesic during labor and childbirth. This discussion will focus mainly on the latter use.
- Despite its long history of use for this purpose, controversy persists regarding its efficacy.
- This is especially pertinent in view of recent concerns regarding side effects, potential for abuse among healthcare workers, and environmental effects.

## History

Nitrous oxide ($N_2O$) was observed in the early nineteenth century to have both anesthetic and analgesic properties when inhaled. Nitrous oxide was first used as an anesthetic gas by Horace Wells in 1844 and has been commonly used in anesthetic practice for more than 160 years. Few drugs can claim such longstanding use.

The use of inhalational analgesia during labor and childbirth has a history almost as long as the specialty itself:

- James Simpson used ether in Edinburgh in 1847 for labor analgesia shortly after its first use as an anesthetic in Boston, USA in 1846.
- Inhalational anesthetics became more commonly used during the birthing process after John Snow administered chloroform to Queen Victoria during labor in the 1850s.

Although most inhalational anesthetic agents have been trialed as analgesics during labor and childbirth, only nitrous oxide has persisted in common usage.

## Pharmacology

Nitrous oxide is a sweet-smelling, colorless gas that is administered by inhalation. Although it is relatively insoluble in blood (blood:gas partition coefficient of 0.46, similar to desflurane), it has low potency as an anesthetic agent with a minimum alveolar concentration (MAC) of 104% at standard temperature and pressure, but it does have documented analgesic properties. The precise mechanisms and sites of nitrous oxide's analgesia are unknown; however, it has been postulated that release of endogenous opioids in the brainstem, dopamine modulation, and N-methyl-D-aspartate (NMDA) antagonism may all be involved. Nitrous oxide does

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not cause significant skeletal muscle relaxation when compared to the volatile inhalational anesthetics.

Nitrous oxide is easily administered to parturients using a facemask or mouthpiece and a tank or wall supply of $N_2O/O_2$ mixture.

- The most commonly used mixture is 50% nitrous oxide and 50% oxygen, which if supplied in a pre-mixed cylinder is known as Entonox (first used in 1961) and if mixed by a blender from pipeline wall supply is termed Nitronox.

Most nitrous oxide/oxygen delivery systems are equipped with a demand valve and scavenging system to minimize environmental contamination during use. Nitrous oxide undergoes scant metabolism in humans and as such is exhaled essentially unchanged. This exhaled gas is another potential source of environmental contamination.

The peak analgesic effect of inhaled nitrous oxide occurs approximately 50 seconds after inhalation, and therefore timing of administration of the drug during contractions is important to maximize benefit. Delivering continuous nitrous oxide during labor avoids this problem but has side effects, including dysphoria, drowsiness, and dizziness, which are considered unacceptable by most. Due to its hemodynamic stability, ease of administration, lack of effect on uterine contractility, and inability to trigger malignant hyperthermia, nitrous oxide is an option for labor analgesia that has at times enjoyed significant popularity.

## Contemporary use

- Nitrous oxide is currently used for labor analgesia infrequently in the US but much more commonly in other jurisdictions. A 2005 survey in the US observed nitrous oxide being used in 1% of births, while surveys during the same time period in Finland and New South Wales, Australia noted usage rates of 48% and 46%, respectively. The most recent data in the UK are from 2000, where 62% of births employed nitrous oxide analgesia [1].
- The incongruity in worldwide usage of nitrous oxide during childbirth, in seemingly comparable countries, can likely be attributed to multiple factors. Such reasons may include availability, patient preference, potential for healthcare worker exposure, and clinician bias toward analgesic methods that are perceived to be more effective, such as parenteral opioids and neuraxial anesthesia. Even in countries where nitrous oxide use is common, it is infrequently employed as the sole analgesic technique.
- Data on its overall use in general anesthesia are also sparse but it is generally believed that its use is declining. According to a major manufacturer its use is North America has declined 5% per year during the last decade [2]. Use in Europe varies between different countries with, for example, relatively common usage in the UK and low usage in Germany [3].
- It is still relatively common practice to use nitrous oxide during general anesthesia for cesarean section (though general anesthesia itself is an uncommon mode of anesthesia for cesarean section in most centers). The potential benefits of nitrous oxide in this setting include reduced requirement for volatile agents with their potential for uterine relaxation and the second gas effect for rapid uptake of volatile agent. It has been suggested [4] that the inclusion of nitrous oxide in the gas mix during general anesthesia for cesarean section will probably reduce the incidence of maternal awareness but this has not been conclusively proven. However, this obviously limits the potential to administer high inspired oxygen concentrations during the cesarean section. There are no differences in

one- or five-minute Apgar scores or fetal neurobehavioral scores between patients undergoing cesarean section inhaling either zero or 50% nitrous oxide with 50% or 100% oxygen [5]. Inhalation of 40% nitrous oxide in oxygen provides useful anxiolysis in highly anxious women undergoing cesarean section [6].

## Current controversies

- The primary controversies surrounding the use of nitrous oxide in labor analgesia consider efficacy, side effects, and safety.
- Much of the evidence for the use of nitrous oxide in labor analgesia is from the 1960s and 1970s – the most comprehensive recent review of nitrous oxide use and side effects is by Rosen in 2002, which provides an excellent overview of the literature (see Further reading).

## Efficacy

Perhaps the most important question for an anesthesiologist considering the use of nitrous oxide in labor analgesia is that of efficacy. It makes little sense to use a drug that has several potential side effects if one is uncertain of whether it will have the desired effect for the patient. Several studies were conducted to investigate the efficacy of nitrous oxide for labor analgesia late in the last century, and most compared nitrous oxide to low-dose inhaled volatile anesthetics. Some comparison has been made in placebo-controlled studies and recently nitrous oxide has been compared to IV patient-controlled analgesia.

### Compared to placebo

- Nitrous oxide has been compared to both compressed air and 100% oxygen for labor analgesia. In a study primarily concerned with side effects, visual analogue scale (VAS) scores were compared for continuous 40%, intermittent 70% nitrous oxide, and 100% oxygen in a post-hoc analysis [7]. Continuous administration of 40% nitrous oxide resulted in the lowest VAS scores; however, no statistical analysis was performed on the data and not all subjects were included. Nitrous oxide may provide more effective analgesia than oxygen but the data in this trial are of poor quality.
- In a randomized, double-blinded trial in Canada, 50% nitrous oxide was compared with medical compressed air for analgesia in the first stage of labor [8]. Interestingly, there was no significant difference in the VAS scores between nitrous oxide and oxygen mix and air, but most women chose to continue with nitrous oxide administration after the study period was concluded.
- A larger study of over 500 patients compared entonox with 50% oxygen – both inhaled via a facemask fitted with a unidirectional valve in a blinded, randomized trial. They found clinically and statistically significant improvements in pain relief in the women breathing the entonox [9].

The data from these studies that compared nitrous oxide to placebo for labor analgesia provide no conclusive evidence that nitrous oxide provides better pain control than air or oxygen.

### Compared to inhaled anesthetics

Most literature examining the efficacy of nitrous oxide in labor analgesia compares it to either a low concentration of volatile anesthetic agent alone, or to a combination of nitrous oxide and a volatile agent. Early studies examined the differences between methoxyflurane and nitrous

oxide and as the volatile anesthetic agents became more sophisticated, the obstetric anesthesia literature moved to studies using enflurane, isoflurane and later sevoflurane and desflurane.

- Work in 1969 comparing nitrous oxide to methoxyflurane in the UK found that methoxyflurane resulted in complete relief more often than nitrous oxide (29% vs. 18% and 28% vs. 16%), considerable pain relief less often, and was consistently better than previous deliveries regardless of the previous technique used [10, 11].
- Comparisons of nitrous oxide with enflurane and isoflurane further substantiated these findings that superior analgesia is obtained with low concentrations of inhaled anesthetics over nitrous oxide.
- One study using desflurane failed to detect a significant difference in maternal satisfaction over nitrous oxide [12].
- Recently inhalation of 0.8% sevoflurane was found to provide improved analgesia, fewer side effects (including nausea and vomiting), and improved maternal satisfaction compared with inhaled entonox [13]. An accompanying editorial [14] concludes that sevoflurane may be a useful alternative to the more widely available entonox while acknowledging the advantages of epidural or intravenous (IV) analgesics.

The use of inhaled volatile anesthetic agents for labor analgesia is fraught with problems, including effects on uterine tone, oversedation, amnesia, and environmental contamination. In terms of pain control and maternal satisfaction, however, the performance of nitrous oxide is inferior to the volatile anesthetics.

### Compared to intravenous patient-controlled analgesia

- In a small randomized controlled trial in Finland in 2004, nitrous oxide was compared to IV remifentanil patient-controlled analgesia (PCA) in the first stage of labor [15]. Boluses of 0.4 μg/kg PCA were compared with 50% inhaled nitrous oxide and contraction pain, satisfaction, and side effects were studied. Remifentanil PCA was found to be more efficacious and with no increased incidence in maternal or fetal side effects.
- Although significantly more laborious for nursing staff and requiring closer physician supervision than nitrous oxide, remifentanil PCA provides better analgesia and should be considered a reasonable alternative.
- In some institutions, remifentanil PCA is used with considerable success for labor analgesia when epidural techniques are contraindicated.

### Conclusions regarding efficacy

- The evidence available to date does not convincingly support nitrous oxide as an effective analgesic agent in labor, although a substantial proportion of women report obtaining at least some relief.
- Whether compared to placebo, inhaled anesthesia, or IV PCA analgesia, nitrous oxide is either no better, or less effective at providing pain control for parturients.
- Many of the available studies were conducted with agents no longer used in clinical practice or were of poor methodological quality.
- There is a need to perform well designed, randomized controlled trials with contemporary anesthetic and analgesic drugs in laboring women to definitively establish whether nitrous oxide is of clinical benefit for this population.

# Side effects

When making the decision whether to introduce nitrous oxide for a laboring patient, the potential side effects must be considered by the practitioner and should be discussed with the patient. Possible side effects of nitrous oxide range from the unpleasant (nausea) to the potentially catastrophic (uterine atony). Most studies that have examined the efficacy of nitrous oxide in obstetric anesthesia practice have also documented side effects.

## Nausea and vomiting

An incidence of nausea and vomiting ranging from 1 in 20 to 1 in 3 parturients using nitrous oxide has been described in several studies; however, none of the published literature used an unmedicated control group. Several of the studies describing nausea and vomiting side effects also failed to control for prior or concurrent use of opioids, which are commonly known to induce nausea.

- A 1969 study in the UK found that whether nitrous oxide, trichloroethylene, or methoxyflurane was used for labor analgesia, the incidence of nausea was approximately 20% [16].
- Another study published in the same year reported significantly more nausea and vomiting with nitrous oxide compared to methoxyflurane, with incidences of 32% and 0%, respectively [11].

Given the high incidence of nausea and vomiting in unmedicated labor and the lack of studies with an unmedicated control group, it is unknown whether nitrous oxide use exacerbates the problem. Nitrous oxide is associated with postoperative nausea and vomiting when used as a component of inhalational general anesthesia. However, in that setting the gas is administered continuously and often for a longer duration, resulting in a larger dose than in obstetric use, and in conjunction with other emetogenic anesthetic drugs.

## Uterine tone and progress of labor

Studies in this area are so old as to be considered largely of historical interest!

- In a study that examined the effect of 75% nitrous oxide, spinal anesthesia, epidural anesthesia, and general anesthesia on uterine contraction pressure, no changes in uterine contractions occurred with administration of 75% nitrous oxide to laboring women [17]. Conversely, general anesthesia with other anesthetic agents including ether, cyclopropane, and halothane significantly decreased the frequency and force of uterine contractions.
- Nitrous oxide has been observed to have no effect on the progress of labor when used for analgesia [18].

## Sedation, amnesia, and dreams

- Evidence does not support a common perception that nitrous oxide causes drowsiness during its intermittent use in labor [19]. Patients do, however, commonly experience drowsiness if continuous nitrous oxide is administered or if a volatile anesthetic agent is added. Proper patient instruction and attentive nursing care minimize the sedative effects of nitrous oxide.

- Parturients are often worried about amnesia if they utilize analgesic drugs in labor, as being an active participant in childbirth and having a clear recollection of the events is important to most women and their families. Up to one third of women may have a hazy memory of labor and/or delivery using intermittent 50% nitrous oxide [8, 10, 18], and the incidence increases with higher concentrations. It is important to make patients aware of the possibility of amnesia and hazy recall of labor before initiating nitrous oxide analgesia.
- Patients may report dreaming when using nitrous oxide and the literature supports an incidence of approximately 25% of this phenomenon. Although not necessarily unpleasant, patients may be dissatisfied with the feeling of dysphoria and the sensation of dreaming.

The practitioner supervising the use of nitrous oxide needs to be aware of these potential side effects and discontinue use if the patient finds them troubling.

# Safety

Controversies surrounding the efficacy and potential side effects of nitrous oxide have been examined. No discussion of applied pharmacology is complete without an exploration of the safety profile of the drug. There are several controversial safety issues surrounding the use of nitrous oxide in the labor and delivery suite.

## Neonatal outcomes

There is concern among practitioners that nitrous oxide use during labor may cause neonatal depression as it readily crosses the placenta. However, concerns regarding neonatal depression and neurobehavioral deficits have not been borne out in clinical research.

- An observational study in 1970 in the UK found no differences in the Apgar scores or neonatal survival of babies born to mothers using 50% or 70% nitrous oxide [20], consistent with an earlier study that detected no effect of nitrous oxide administration on one-minute Apgar scores [18].
- Further work assessed Apgar scores, Neurologic and Adaptive Capacity Scores, and Early Neonatal Neurobehavioral Scale outcomes at intervals up to 24 hours of life in infants born to mothers who did and did not use inhalational analgesia in the second stage of labor. No significant difference was detected between the two groups [21].

Thus, the literature reasonably supports the contention that nitrous oxide use has no detectable effect on neonatal neurobehavioral outcomes in the first day of life. More recent concerns relate to animal studies suggesting detrimental effects of nitrous oxide (and other anesthetic agents) on brain development in the fetus or neonate. This is fully discussed in another chapter.

## Oxygen desaturation

There are several mechanisms whereby nitrous oxide inhalation could result in maternal hypoxemia:

1. Reductions in inspired oxygen concentration. Nitrous oxide is most commonly administered in a 50% mixture with oxygen resulting in an inspired oxygen concentration of 50%. However, more highly concentrated nitrous oxide mixtures can be delivered particularly if an anesthetic machine is used.

2. Diffusion hypoxia. The concept of diffusion hypoxia postulates that the low solubility in blood of nitrous oxide can flood the alveoli with the gas after the inspired source is stopped, resulting in a hypoxic gas mixture in the lungs if the patient is not given supplementary oxygen. Such could be the case between contractions when a parturient is breathing room air if sufficient blood concentration of nitrous oxide are achieved. A study performed in Sweden found no evidence to support the occurrence of diffusion hypoxia in paturients inhaling either 50% or 70% during labor [22].
3. Sedative effects especially when nitrous oxide is given concurrently with opiates. An Australian study assigned patients to one of five analgesia regimens: no analgesia; intramuscular meperidine; epidural block; intermittent 50% nitrous oxide; and intermittent 50% nitrous oxide and meperidine. Only the group receiving nitrous oxide and meperidine had oxygen saturations different from the control group [23]. One should clearly be cautious when nitrous oxide is given concurrently with opiates.
4. Maternal hyperventilation during contractions (secondary to pain) while inhaling nitrous oxide and oxygen resulting in hypocapnia, hypoventilation, and hypoxemia between contractions [24].
5. Pipeline supply failures resulting in delivery of a hypoxic gas mixture. It is a matter of concern that there were six deaths reported in Germany, Austria, and Switzerland between 2004 and 2006 due to technical supply problems with nitrous oxide [25]. Four were in patients undergoing cesarean section.
6. The two gases will separate at low temperatures (<4°C), which would permit administration of hypoxic mixtures. Therefore, it is not given from a cold cylinder without being shaken (usually by cylinder inversion) to remix the gases. This should rarely be a problem in clinical practice!

## Occupational health and safety

- The exact clinical significance and risk of long-term exposure by healthcare workers to nitrous oxide is still unclear – duration of exposure, amount of trace gas in the environment, presence or absence of active scavenging air systems, and frequency of air changes will all be of relevance. A full discussion of the health effects of long-term exposure to anesthetic gases is beyond the scope of this text. A recent review is included in the suggestions for further reading. They concluded that adverse effects are unlikely and unproven in scavenged environments where time-weighted average (TWA) exposures are below the legislated limits. This reassurance may obviously not apply to environments where gases are not scavenged.
- Different countries have established different limits to occupational exposure to nitrous oxide in terms of an eight-hour TWA – e.g. a 25 ppm TWA in the USA and 100 ppm in the UK.
- Operating rooms in industrially advanced countries will almost certainly be scavenged. Concern may be expressed in environments where gases are either exhaled (e.g. postanesthesia care units) or inhaled and exhaled (e.g. labor rooms).
- Exposure levels in postanesthesia care units are so low as to be considered negligible [26].
- In the 1970s and 1980s, room contamination by nitrous oxide was common and routinely exposed nurses and midwives to TWA concentrations of nitrous oxide in excess of occupational health guidelines.

- A recent Swedish study in obstetric units found that approximately 25% of all eight-hour TWAs measured in the study exceeded occupational health limits. Use of a scavenging system connected to the delivery mask significantly reduced exposure to delivery room personnel, and forced-air ventilation systems as well as conscientious work routines also reduced exposure to acceptable limits [27].
- A study performed on midwives in the UK [28] found similarly alarming exposures to nitrous oxide with 23% demonstrating exposure levels greater than 100 ppm – with 3% greater than 500 ppm. Clearly this should be a concern.
- Scavenging systems suitable for use in obstetric practice have been developed [29].

In hospitals where nitrous oxide is used, hospital administrators and clinical managers must be aware of the occupational exposure limits in their jurisdiction and make efforts to minimize staff exposure. The use of sufficient ventilation and scavenging systems is known to mitigate exposure risk.

## Environmental effects

Nitrous oxide is both a "greenhouse gas" and an agent that depletes the ozone layer in the atmosphere.

- Greenhouse gases are those that absorb and emit infrared radiation (i.e. heat). The main greenhouse gases in the atmosphere are water vapor, carbon dioxide, methane, nitrous oxide, and ozone. Greenhouse gases cause the greenhouse effect, which is a process in which heat radiated from the Earth's surface is absorbed by greenhouse gases in the atmosphere and reflected back towards the surface – increasing its temperature. This process is believed to contribute toward global warming.
- Ozone in the atmosphere absorbs the majority of the ultraviolet radiation from the sun. A reduction in ozone thus is potentially very harmful to life on Earth. The predominant man-made substances that depleted the ozone layer in the twentieth century were chlorofluorocarbons (CFCs) – used in refrigeration and aerosol propellants. These were phased out between 1987 and 1996 by the "Montreal Protocol" international treaty.
- Nitrous oxide is now considered to be the dominant man-made ozone depleting substance emitted in the twenty-first century [30] (and is *not* covered by the Montreal Protocol).

### Sources of nitrous oxide in the atmosphere

- Human-related sources of $N_2O$ are fertilizers, animal manure, sewage treatment, fossil fuel combustion, adipic acid production (used in nylon production), and nitric acid production.
- $N_2O$ is also produced naturally from a wide variety of biological sources in soil and water especially in wet tropical forests.
- Only approximately 1% is thought to arise from anesthetic sources.
- Fertilizers are the major source of $N_2O$ as a greenhouse gas. This makes control very difficult – one may be able to get energy from sources other than carbon but it is difficult to see how one can get food without the use of nitrogen.

Although the above is a concern, the contribution from anesthesia is minor. Eliminating nitrous oxide in all healthcare would have little or no effect on the amount of nitrous oxide in

the atmosphere. More information on this aspect of anesthesia is included in the suggestions for further reading.

## Abuse potential

Abuse of nitrous oxide is apparently on the increase. This includes abuse by healthcare workers (whose source is presumably within the hospital) and non-healthcare workers.

- Non-medical sources are readily available. Nitrous oxide is approved for use as a food additive (also known as E942), specifically as an aerosol spray propellant, e.g. in aerosol whipped cream canisters and cooking sprays; and as an inert gas used to displace oxygen and to inhibit bacterial growth when filling packages of potato chips and other similar snack foods. Nitrous oxide is also used in motor racing to improve engine performance.
- Although considered relatively innocuous by users there are reports of toxicity following abuse, e.g. posterior column myelopathy due to prolonged abuse of nitrous oxide obtained from whipped cream cartridges [31].
- Medical staff have been disciplined for abusing entonox within the hospital [32]. It would be naive not to assume there is the potential for abuse in the labor ward.

# Conclusions

- Nitrous oxide is an inhaled anesthetic gas with low potency (MAC 104%), which in some countries is commonly used for labor analgesia.
- Nitrous oxide is most often administered using a demand facemask with one-way valve, in a 50% nitrous oxide, 50% oxygen mixture, with the patient inhaling 20 seconds before the onset of a contraction for maximum analgesic benefit.
- Although many women report receiving some benefit from nitrous oxide during labor, the evidence does not strongly support clear efficacy. Most studies to date have been small, often non-randomized, comparing out-of-date alternatives, and without an unmedicated control group. Significant opportunity exists for further research.
- Patients may experience side effects including nausea, amnesia, dreams, and dysphoria. Clinically important adverse events such as neonatal depression, uterine atony, and maternal desaturation may occasionally occur, but not to such an extent that usually precludes the use of nitrous oxide.
- The potential exists for environmental contamination with resultant occupational exposure by healthcare workers and others. Detrimental effects of this exposure in scavenged environments are unclear.
- There are significant concerns regarding the environmental effects of nitrous oxide.

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Chapter 17

# Fasting and aspiration prophylaxis in labor and for cesarean section

Dr K Teague and Dr S Dhir

## Introduction: acid aspiration syndrome

- In studies initially published in 1946, Mendelson described the pathophysiology of acid aspiration syndrome (AAS) in 61 obstetric patients having a general anesthetic for vaginal delivery [1].
- The ensuing chemical pneumonia, also known as Mendelson's syndrome, is due primarily to the inflammatory reaction of the lung parenchyma to the insult of inhalation of gastric contents.

The initial chemical "burn" associated with inhalation of gastric contents with a pH <2.5 leads to additional lung damage brought on by the activation of the inflammatory cascade and its potent chemical mediators and cytokines. Clinical findings associated with Mendelson's syndrome include, but are not limited to, respiratory distress, audible wheezing, and cough with pink or frothy sputum. Development of these symptoms is abrupt, often occurring acutely within two hours of the aspiration event. Interestingly, none of the patients in Mendelson's original series died following their aspiration.

Studies of AAS have highlighted the importance of the volume of gastric contents aspirated in addition to the pH of the aspirate.

- James *et al.* found that as the pH of the aspirate decreased the subsequent incidence of mortality increased.
- They found that late deaths, accounting for 22% of all fatalities, occurred exclusively in animals aspirating solutions with a pH <2.5. These late deaths indicated progressive lung damage as opposed to acute cardiorespiratory failure, which early deaths suggested.
- Their findings also showed that aspiration volumes of up to 1.0 ml/kg resulted in no deaths as long as the pH of the aspirate was >2.5, thus demonstrating that the critical volume of aspirate is primarily influenced by its pH and not the volume of the aspirate per se [2].

Treatment of AAS is mainly supportive and includes initial suctioning of the upper airway after a witnessed aspiration of gastric contents, with intubation and protection of airway as dictated by the patient's ability to adequately protect their airway. Often treatment is conservative, and in the intubated patient management includes PEEP and judicious suctioning of endotracheal tube secretions. Marik's review of aspiration pneumonia and pneumonitis also discusses the controversial roles of early use of antibiotic and corticosteroid therapy in this syndrome, with suggestions to withhold both therapies until clinically indicated by patient status [3].

*Controversies in Obstetric Anesthesia and Analgesia*, ed. Ian McConachie. Published by Cambridge University Press.  

## Aspiration and the obstetric patient

It is difficult to accurately estimate the incidence of aspiration in the obstetric patient undergoing a cesarean section under general anesthesia with tracheal intubation.

- Using historical data from assorted sources, Schneck and Scheller estimated the incidence of aspiration was 1 in 1,600 (0.0625%) in patients undergoing any type of cesarean section, and extrapolated that the incidence of fatal AAS is approximately 1 in 80,000 cesarean sections, or 0.00125% [4].
- What is known for certain is that the incidence of aspiration leading to AAS in the obstetric patient is declining. In a continuing analysis of maternal deaths in England and Wales, the Department of Health and Social Security found that the incidence of maternal deaths from pulmonary aspiration decreased from 18 deaths between 1964 and 1966 to one death between 2000 and 2002 [5].

Many authors are now questioning whether the risk of aspiration in the obstetric patient may be overestimated.

- A large retrospective analysis of patients requiring general anesthetics for peripartum obstetric procedures showed that of 1,870 patients anaesthetized without tracheal intubation, only one patient showed signs of mild aspiration [6].

The laryngeal mask airway (LMA) has also been shown to be a safe and effective airway management device in elective cesarean sections.

- A study of 1,067 patients showed that only seven patients required subsequent tracheal intubation, and none of the patients demonstrated any signs or symptoms of pulmonary aspiration [7]. This study excluded patients who had pharyngeal reflux, a pre-pregnancy body mass index >30, or had a known/predicted difficult airway, and ensured that the patients had fasted for six hours and were pretreated with aspiration prophylaxis.

Obstetric patients are considered at increased risk of aspiration due to numerous factors.

- The stomach is displaced upwardly by the gravid uterus resulting in a decrease in lower esophageal sphincter tone.
- Combined with an increase in intragastric pressure, also attributed to the gravid uterus, the parturient is at an increased risk of regurgitation and aspiration compared to the non-pregnant patient.
- In addition to this, parturients presenting for cesarean section under general anesthetic are more prone to difficult airway management (both bag mask ventilation and intubation) and also rapid oxygen desaturation – situations that increase the likelihood of regurgitation and aspiration.

It has long been believed that pregnancy also results in a decrease in gastric emptying, thus also predisposing to increased potential for aspiration.

- Wong *et al.* disproved this assumption in term, non-laboring pregnant women by studying gastric emptying after ingestion of 300 ml of water [8]. They found that gastric emptying was significantly shorter in patients who had ingested 300 ml of water when compared to a control group that had ingested 50 ml of water.

- These findings were limited to the non-laboring patient so the results cannot be assumed to pertain to the laboring patient. Additionally, the laboring patient has often been given epidural or intrathecal opioids for labor analgesia, with a proven decrease in gastric emptying associated with the administration of either 15 μg intrathecal fentanyl or 100 μg epidural fentanyl [9]. This study did find that the administration of 50 μg of epidural fentanyl caused no decrease in gastric emptying time.
- In addition to opioid administration, the pain associated with labor also leads to a decrease in gastric emptying.

# Aspiration prophylaxis

## Sodium citrate

- Sodium citrate is a commonly used non-particulate antacid, which when administered orally 15 to 20 minutes preoperatively, effectively raises the pH of gastric contents to above 2.5.
- Non-particulate antacids are preferred in the setting of aspiration prophylaxis because they mix more readily with gastric contents than particulate antacids, thus leading to a more rapid onset of clinically appreciable effect.
- Additionally, the risk of development of aspiration pneumonitis from aspiration of non-particulate antacids is lower than that of particulate antacids.
- Advantages of sodium citrate administration include lack of significant side effects and interaction with other drugs, speed of effect in raising gastric pH, in addition to being relatively inexpensive.
- The major criticism of sodium citrate is its very unpleasant taste due to its relative pH of 8.4 – thus it is not very palatable to both the laboring and non-laboring parturient.
- Kjaer *et al.* studied the association of sodium citrate administration and intraoperative nausea, and in a study of 125 patients found that there was an increase in intraoperative nausea when compared to patients who were administered famotidine instead of sodium citrate [10].

## H2-antagonists

- The H2-antagonists are a class of medications that block the effect of histamine on the parietal cells of the stomach. Examples of this class of medication include cimetidine, ranitidine, and famotidine.
- Their effect is to reduce the production of acid in these cells thus leading to a subsequent increase in pH.
- The use of cimetidine is somewhat limited due to side effects such as sedation, confusion, and the possible inhibition of certain hepatic enzymes.
- Ranitidine is a newer, more potent H2-antagonist that has fewer appreciable side effects and is as effective as cimetidine in increasing gastric pH. An additional advantage of ranitidine over cimetidine is the fact that cimetidine therapeutic plasma levels decline within four hours, whereas therapeutic concentrations of ranitidine are sustained for approximately eight hours.

## Proton pump inhibitors

- Proton pump inhibitors (PPIs) are a newer class of drug that act by irreversibly blocking the $H^+K^+$ATPase enzyme system in the gastric parietal cells. This proton pump is the terminal stage in gastric acid secretion, which results in the secretion of $H^+$ ions into the gastric lumen.
- These drugs can result in a reduction of gastric acid secretion by up to 99%, which is significantly more effective than H-2 antagonists.
- In addition to this demonstrated increase in efficacy over H-2 antagonists, the duration of effect of the PPIs is also considerably longer than that of the other classes of drugs.
- Examples of PPIs include omeprazole, pantoprazole, and lansoprazole.
- The efficacy of the PPIs certainly seems to be supported by clinical studies.
- A recent study by Pisegna *et al.* found that in elective-surgery patients IV pantoprazole (both 40 mg and 80 mg doses) decreased gastric acid output, lowered gastric volume production below 25 ml/hr, and raised gastric pH above 2.5 [11].
- In a study that looked at reduction of risk of acid aspiration at emergency cesarean section, Rocke *et al.* compared omeprazole to placebo. They found that the 40 mg IV omeprazole group had significantly higher mean gastric pH and significantly lower gastric volumes [12]. The major stipulation to these findings was that the administration of the omeprazole had to be at least 30 minutes before the start of the surgery for a statistically significant effect to be appreciated. That said, regardless of how soon before the start of a cesarean section a PPI is administered, it would be beneficial to reduce the acidity of gastric contents in the event of aspiration during emergence and extubation.

## Metoclopramide

- Metoclopramide is a procainamide derivative that increases lower esophageal sphincter tone and stimulates upper gastrointestinal motility, thus effectively accelerating gastric clearance of both solids and fluids.
- The onset of clinical effect of metoclopramide is rapid, with decreases in gastric volume in cesarean patients being realized with 15 minutes of administration [13].
- These same authors speculate that metoclopramide may be most beneficial in patients undergoing emergency cesarean section. This is because in addition to the benefit of increasing lower esophageal tone, the clinical effect on increasing gastric motility may be more pronounced in patients who have altered gastric emptying such as laboring parturients.
- Metoclopramide is a dopamine antagonist that has numerous adverse side effects and significant drug interactions. Side effects following IV administration may include abdominal cramping, bradycardia or tachycardia, cardiac dysrhythmias, and potentially dystonic extrapyramidal reactions (oculogyric crises, trismus, torticollis).

# Fasting and labor

Historically a major concern with fasting of the laboring mother has been that the physical exertion of labor requires a large expenditure of calories.

- In the primiparous patient, who may have a prolonged labor, fasting can potentially be harmful to both mother and fetus.
- Fasting laboring patients have a relative depletion of carbohydrates, which forces their bodies to metabolize fat to meet their energy demands. This situation is tolerated well for the short term, but in the situation of prolonged labor fat metabolism results in an accumulation of fatty acids and ketones in both the mother and fetus.
- If left unmanaged this ketosis can lead to ketoacidosis, and has been found to be related to prolonged labor, increased need for induction and augmentation in nulliparous women, increased need for forceps delivery, and increased peripartum blood loss [14].
- Scrutton *et al.* performed a randomized controlled trial that compared outcomes between two groups of laboring mothers – those who were given a low-residue diet versus those who had only water for the duration of their labor. They found that there were no differences between the groups with respect to the duration of first or second stage of labor, oxytocin requirements, mode of delivery, Apgar scores, and umbilical artery and venous blood samples [15]. They found that the liberal diet group had a statistically significant increase in the volume of gastric contents in patients who vomited during labor. In addition there were undigested solid food particles in the vomitus, a finding concerning when considering this could potentially increase the severity of postaspiration pulmonary sequelae.
- These results were replicated in a recent large, randomized trial [16], which confirmed that there are no additional benefits from eating during labor compared to drinking water. In particular, the mode of delivery, neonatal status, and incidence of vomiting were no different.
- A recent study has shown that the substitution of an isotonic "sport drink" results in similar benefits to the water-only labor diet, but also leads to a statistically significant reduction in maternal ketone production, thus potentially reducing ketoacidosis in parturients experiencing prolonged labor [17].

### Recommendations

- The most recent version of the ASA practice guidelines for obstetric anesthesia recommends that oral intake of modest amounts of clear liquids may be allowed for uncomplicated laboring patients.
- With regards to ingestion of solid foods during labor, the recommendation is to avoid this practice due to the fact that oral intake of solids during labor increases maternal complications.
- The corollary to these recommendations is that fasting guidelines should be individualized to each patient on a case-by-case basis because certain patient factors that may put the patient at an increased risk of aspiration may require more stringent fasting guidelines [18].

## Aspiration prophylaxis for cesarean section

The most recent Cochrane review guidelines on drug therapy for prevention of aspiration during cesarean section and for routine prophylaxis use during labor are cited in the section on Further reading.

It is widely accepted that the safest and most effective means of aspiration prophylaxis for cesarean section is the use of neuraxial anesthesia. Practice guidelines state that neuraxial techniques are preferred to general anesthesia for most cesarean deliveries. However, the decision to use a particular anesthetic technique should be individualized based on anesthetic, obstetric or fetal risk factors, the preferences of the patient, and the judgment of the anesthesiologist.

## ASA guideline recommendations

- The patient undergoing an elective cesarean section may have modest amounts of clear liquids up to two hours before induction but should undergo a fasting period for solids of six to eight hours.
- The ASA practice guidelines make no suggestions for routine aspiration prophylaxis for elective cesarean section, likely because there is no solid evidence that routine prophylaxis is beneficial in this patient population.

In fact routine aspiration prophylaxis may seem like an unnecessary use of resources considering the very low rate of conversion to general anesthesia in routine elective cesarean sections started under spinal anesthesia. For example, in an audit of regional anesthesia failure in 5,080 cesarean sections, Kinsella found that in patients having non-urgent elective cesarean sections his institution had a spinal anesthesia to general anesthesia conversion rate of 0.5% [19].

## NICE guideline recommendations

The National Institute for Health and Clinical Excellence (NICE) is part of the National Health Service in the UK. It is an independent organization whose primary objective is promotion of clinical excellence via best available evidence.

- The most recent NICE guidelines for cesarean sections, published in 2004, suggest that women who are having an elective cesarean section should be offered regional anesthesia because it is safer and results in less maternal and neonatal morbidity than general anesthesia [20].
- In addition to this they suggest that, to reduce the risk of aspiration pneumonitis, women should be offered drugs to reduce gastric volume and acidity before cesarean section.

In light of the very low rate of conversion to general anesthesia in these patients, this suggestion for routine prophylaxis seems unwarranted considering that non-emergent conversion to a general anesthetic usually affords time for appropriate prophylaxis to be given.

Aspiration prophylaxis for emergency cesarean section is often dictated by the need for rapid induction of anesthesia to facilitate emergency surgical delivery. If possible all patients requiring general anesthesia for cesarean section should be administered aspiration prophylaxis.

- H-2 blockers can be safely used in conjunction with sodium citrate to further decrease acidity of gastric contents in patients requiring emergency cesarean section.
- Ormezzano *et al.* studied gastric pH at both the time of tracheal intubation and also at tracheal extubation in patients who received sodium citrate alone, or the combination of sodium citrate and an H-2 blocker. They found that the combination of the two drugs led to an increase in mean pH of approximately 0.5, in addition to decreasing the percentage of patients with gastric pH <2.5 from 10% or greater to 1.6% [21].

Considering the full-stomach status of these patients, in addition to pharmacologic aspiration prophylaxis these patients may warrant a rapid sequence induction to secure the airway in a safe and timely manner but this is fully discussed in the airway chapter.

## Further reading

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Chapter 18

# Controversies surrounding airway management and cesarean delivery

Dr P Kuszewski and Dr P Armstrong

## Introduction

In the industrialized nations of the world, cesarean section (CS) rates are at an all-time high.

- Statistics from 2008 [1] show the following rates:

  24% in the UK
  26% in Canada
  30% in the USA
  in excess of 45% in Brazil.
- This compares to rates of less than 5% in the 1960s.
- In the USA, approximately one million CSs are being carried out annually making it the most common surgical procedure performed.

This chapter aims to:

- review the data on maternal mortality with an emphasis on the deaths related to failed intubation
- explore the role of video laryngoscope and supraglottic airways in managing the parturient's airway
- debate induction agents and muscle relaxants used in anesthesia for CS
- discuss the role simulation plays in resident education related to airway management, as clinical exposure to general anesthesia for CS remains limited.

## Maternal morbidity and mortality

The first Confidential Enquiries into Maternal Deaths covered maternal deaths in England and Wales for the triennium commencing in 1952. In 1985, it was expanded to cover all of the UK [2].

- In the first triennium there were 49 deaths due to anesthesia, the majority secondary to aspiration.
- In the subsequent three triennia, deaths due to anesthesia declined to approximately 30.
- This number peaked in the late 1960s at approximately 50 deaths per triennium. The majority of these deaths occurred at CS.

*Controversies in Obstetric Anesthesia and Analgesia*, ed. Ian McConachie. Published by Cambridge University Press.  

- Since that time there has been a steady decline in anesthetic-related deaths and deaths at CS secondary to failed intubation.
- In the most recent report covering the period from 2006 to 2008 there were still several airway deaths – including one that occurred in the intensive care unit. Overall there has been an average of five airway-related deaths per triennium over the last 15 years worth of reports [3].

Hawkins *et al.* recently published data on anesthesia-related maternal mortality in the US between the years 1979 and 2002 [4].

- Between 1991 and 2002 there were 56 deaths following live birth or still birth. Of these deaths, 86% occurred in women having a CS under general anesthesia.
- Approximately two-thirds of the deaths associated with general anesthesia were caused by failed intubation or problems during induction at CS.
- Comparing the years 1991 to 2002 with 1979 to 1990, anesthesia-related maternal mortality has decreased 59% from 2.9 deaths per million live births, to 1.2 deaths per million live births.
- Estimated case fatality rates for general anesthesia during CS decreased from 16.8 per million CSs in 1991 to 1996, to 6.5 per million CSs in the years 1997 to 2002.
- The relative risk ratio comparing general anesthesia to regional anesthesia for the past three six-year periods has declined dramatically. The ratio was 16.7 between 1985 and 1991, 6.7 between 1991 and 1996, and only 1.7 for the years 1997 to 2002.

Overall, in the USA and UK the pregnancy-related mortality ratios due to anesthesia are similar.

The large number of maternal deaths seen when general anesthesia was the primary anaesthetic employed for CS caused anesthesiologists to change practice patterns.

- During the 1980s in the UK, rates of general anesthesia for CS were greater than 75%. The rate today is less than 10% [5].
- At Brigham and Women's hospital in the USA, CS rates under general anesthesia in 1990 were 7.2% [6]. In 2005, they performed approximately 2,700 CS, only 22 (<1%) were performed under general anesthesia [7].

Nevertheless, it is of concern that deaths related to airway management during general anesthesia continue to occur. All anesthesiologists involved in management of obstetric patients should develop strategies to effectively and safely manage patients with difficult airways.

## The maternal airway

- Marked physiological changes occur during pregnancy, which can make the maternal airway difficult to manage in terms of mask ventilation and intubation.
- Pregnancy, in general, is a state of fluid retention. This fluid retention can lead to edema of the upper airway and the tongue may become swollen. Edema can be exacerbated by IV fluid administration and conditions such as pre-eclampsia.
- Maternal weight gain can lead to fat deposition in the upper airway. This along with airway edema can result in decreased soft tissue mobility.

- The airway mucosa due to edema may be friable. Minimal trauma can lead to airway bleeding that can further impair visualization of the vocal cords at direct laryngoscopy (DL).
- It has been shown that the Mallampati score for predicting ease of intubation can increase during pregnancy [8] – and even during labor [9] – and should prompt careful airway examination at the start of labor and prior to any airway manipulation.
- Breast enlargement during pregnancy can also lead to difficulties manipulating the laryngoscope during DL.

### Patient factors

- A documented challenging or difficult intubation can be made worse due to the changes associated with pregnancy.
- In our society obesity has become more prevalent and it affects the airway directly. Obesity has also been associated with obstetrical pathologies such as pre-eclampsia, gestational diabetes, gestational hypertension, and the need for planned or emergency CS.
- Both pregnancy and obesity are conditions that decrease the FRC, increase the metabolic rate, and therefore shorten the time available to secure the airway before development of hypoxemia [10].
- The gastrointestinal system also undergoes significant changes. Lower esophageal sphincter tone is decreased, gastric emptying is delayed during labor, and the gravid uterus exerts increased pressure on the stomach. Inability to secure the airway with an endotracheal tube puts the parturient at risk of aspiration.

### Surgical factors

- Optimal patient positioning ramped with left uterine displacement, can often be overlooked due to the stressful nature of an emergency CS. Limited patient mobility may also make positioning difficult. The "sniffing position" can be achieved by stacking folded blankets under the chest and head [11]. This technique has been shown to improve laryngoscopic view in morbidly obese patients undergoing elective bariatric surgery. This manoeuver can play a vital role in securing the airway and improving maternal respiratory function.
- As a result of the limited exposure to general anesthesia that nurses and operating room assistants receive, experienced help may be an issue in the obstetrical suite. This may result in inadequate patient positioning, improper use of cricoid pressure, and unfamiliarity with different airway adjuncts in the case of failed DL. Therefore proper preparation is of utmost importance along with reviewing the induction plan with everyone involved and clarifying any concerns prior to induction.

## Predicting difficult intubation

- The combination of Mallampati score, thyromental distance, and inter-incisor gap appears to be the best predictor of difficult laryngoscopic intubation [12]. These predictors relate only to DL and they do not seem to reliably predict difficulty when using alternate techniques for tracheal intubation [12].
- Rocke suggests that a combination of Mallampati class, short neck, receding mandible, and protruding maxillary incisors are the best predictors of difficulty [13].

- A meta-analysis in 2005 suggested that a combination of Mallampati classification and thyromental distance were the most useful bedside tests. They further commented that bedside screening tests are of limited value [14].
- Iranian researchers prospectively evaluated 400 parturients scheduled for elective CS in an attempt to predict difficult intubation by DL. There were no failed intubations and 35 patients had grade 3 Cormack–Lehane (CL) views at the time of DL. It was suggested that the ratio of height to thyromental distance (RHTMD) may be a useful predictor of difficult intubation [16].
- In a three-year period, a single anesthesiologist recruited 239 parturients undergoing emergency CS. Five bedside predictors of potentially difficult intubation (Mallampati score, sternomental distance, thyromental distance, inter-incisor gap, and atlanto-occipital extension) were measured. It was found that 225 women had CL grade 1 or 2 views, and 14 had CL grade 3 view. There were no failures. The author concluded that these tests are of limited value in predicting difficult intubation (grade 3 CL view) by DL [19].
- Intubation is more difficult in the obese parturient. A case control study showed that the incidence of difficult intubation among pregnant women over 136 kg was 35% (6 of 17) compared with 0% (0 of 8) of controls [10].

In summary, predicting difficult intubation is an imprecise science and no single clinical sign or combination of signs has been demonstrated to reliably predict difficulty. The low incidence of difficult intubation will always lead to tests that result in low positive predictive values [17]. This reinforces the requirement for anesthesiologists to develop strategies to deal with the unexpectedly difficult intubation.

## Failed intubation

The reported incidence of failed intubation at the time of CS varies.

- Two surveys [18][19] from a single health region in the UK reported an incidence of 1 in 249 and 1 in 238.
- Hawthorne reported an incidence of 1 in 300 in 1984, and 1 in 250 in 1994 [20].
- Rocke reported from South Africa an incidence of 1 in 750. In 1,500 obstetrical patients scheduled for CS, intubation failed in only two. In that same group there were 30 parturients that were described as very difficult [13].
- A review from a tertiary care teaching hospital in the US had one failed intubation in 536 CSs under general anesthesia in a six-year period from 1990 to 1995 [6]. A follow-up report from the same institution for the years 2000 to 2005 had one failed intubation in 98 CSs [7].
- A retrospective audit of 3,430 obstetric general anesthetics over an eight-year period reported no failed intubations. However, three patients had awake fiberoptic intubation, and 20 parturients (5.8%) were described as difficult [21].

It appears that there is a greater incidence (around ten times) of failed intubation in parturients (~1 in 250) than in the general population (~1 in 2,250). When failed intubation occurs, the estimated mortality is 13 times higher than that in the general surgical population [22].

## Alternatives to direct laryngoscopy

The first generation of video laryngoscopes (Bullard and WuScope) came into clinical practice in the early 1990s. Although they were effective they did not become widely accepted for a variety of reasons (difficult to use and cost). The new generation video laryngoscopes (VL), the first being the GlideScope® (GVL), arrived into clinical practice in 2001. Since 2003 there have been several other video laryngoscopes that have been introduced, some examples are AirTraq® (AQ-L), McGrath®, Pentax-AWS®, and most recently the C-MAC®. These VLs do not require alignment of the oral, pharyngeal, and laryngeal axes to allow glottic visualization.

- The GVL and the AQ-L have the most scientific evidence in the literature supporting their use.
- Cooper reported the first GVL use in a patient who could not be intubated by DL at a previous anesthetic because of a grade 3 CL view. A CL grade 1 view was achieved and the patient was easily intubated with the GVL [23].
- Cooper *et al.* reported a high rate (96.3%) of successful intubations with the GVL in a series of 728 patients. In a subset of 35 patients with grade 3 and 4 CL views by DL, the GVL converted 27 of these to either a CL grade 1 or 2 view [24].
- Two large randomized controlled trials demonstrated high rates of success for intubation with the GVL (100% and 97.9%) in patients who were not expected to be challenging. As well, 294 of the 296 patients in the studies had a grade 1 or 2 CL view [25][26].
- In a woman who required general anesthesia immediately postpartum for the repair of a fourth-degree tear, the GVL was reported to have converted a failed intubation, grade 4 CL view, into a straightforward intubation [27].
- A recent review of GVL use in 2,004 patients showed a 95% success rate. In a group of 239 patients that failed DL the success rate was 94%. Interestingly there was a statistical difference between the two institutions involved in the report. The authors suggested that success rate improves with practice and experience [28].
- In 2005, the AQ-L came into clinical practice and it has been shown to be effective in both routine and difficult cases of tracheal intubation [29].
- In a randomized controlled trial in morbidly obese patients all 53 patients in the AQ-L group, had a grade 1 CL view and were successfully intubated. In addition, six patients of the 53 who were assigned to DL were intubated with the AQ-L after having failed that technique [30].
- Two morbidly obese parturients undergoing CS were intubated with the AQ-L after having failed DL secondary to CL grade 3 and 4 views [31].
- A group from France reported on an institutional algorithm for the management of the difficult airway in non-obstetric patients. In a two-year period, 29 patients failed intubation by DL, 27 of them were intubated with the AQ-L [32].
- A case series published as an abstract commented on video laryngoscopic (video MAC) intubation in 27 obstetric patients at CS. The view by VL in all patients was CL grade 1. In comparison, the views obtained by DL were 14 CL grade1, 12 CL grade 2, and 1 CL grade 3. All intubations were reported to be easy [33].

Thus, it seems clear that the use of VLs is of value in the obstetric patient population and may improve the ease of intubation and reduce the rate of failed intubations. It is unclear if any of

the available VLs are superior in this role to any other. A different (but related) debate centers around whether a VL should be our normal tool for intubation as opposed to being used in difficult or failed intubations. This has yet to be resolved but future anesthesiologists may find our reliance on conventional laryngoscopes quaint.

## The use of larnygeal mask airway in the obstetric population

The larnygeal mask airway (LMA) was introduced into clinical practice in the UK in 1988 and North America in 1992. It is widely believed that the LMA has revolutionized airway management. Within a short time it was seen to be of value in obstetric patients. In addition, the LMA has become an extremely important airway rescue device. It was incorporated into the ASA difficult airway algorithm in 1996 after being available for only four years in North America.

- In 1989 and 1990 there were reports of its use following failed intubation in the parturient [34][35].
- Verghese and Brimacombe reported a success rate of 99.8% for the LMA in 11,910 patients undergoing general anesthesia over a two-year period. In addition there were three failed intubations that were managed with the LMA [36].
- Palanisamy *et al.* described a failed intubation at the time of CS in which the LMA was unable to provide rescue ventilation most likely secondary to severe laryngospasm [7].
- In 2001, Han *et al.* [37] reported on the use of the LMA for elective CS. 1,067 consecutive ASA 1 and 2 parturients who preferred general anesthesia were recruited. They were excluded if they had a known or predicted difficult airway, symptoms of reflux, or BMI > 30. Patients were fasted and received ranitidine and sodium citrate prior to induction. The LMA provided an effective airway in 99% of patients with 98% first-pass success. Seven patients required endotracheal intubation. There were no episodes of hypoxia, aspiration, regurgitation, or laryngospasm.
- In 2004, a case report was published describing the use of the LMA ProSeal$^{TM}$ (LMA-PS) in a parturient undergoing urgent CS. The patient failed DL and bag mask ventilation (BMV) at which time an LMA-PS was easily inserted on the first attempt. A gastric tube was inserted and gastric fluid was drained from the stomach. The procedure was completed and the patient was ventilated for eight hours in the intensive care unit until stable [38].
- In 2010, a group from Jordan [39] reported on their use of the LMA-PS in 3,000 ASA 1 and 2 patients who presented for elective CS. Patients were fasted and received ranitidine. Patients with a known or suspected difficult airway, BMI > 30, and symptoms of reflux were excluded. A total of 2,992 patients had successful placement of the size-4 LMA-PS on the first attempt. Eight patients required a size-5 LMA-PS and no patient required intubation. All patients had gastric tubes inserted and gastric fluid was allowed to drain. Patients were paralyzed for the duration of the surgical procedure. There was one case of regurgitation, which did not result in aspiration. There were no cases of hypoxia and laryngospasm.

The LMA has gone through many modifications since its first introduction, and currently there are several types offered on the market. The LMAs are available as both reusable and single-use devices. There are standard LMAs, LMAs that have gastric drains and larger cuffs

generating seals of up to 30 cm $H_2O$ (which allows for the option of positive pressure ventilation (Proseal/ Supreme)), and intubating LMAs (Fastrach). The role of other supraglottic airways, for example I-gel and King Laryngeal tube, in the parturient is undetermined. These devices have performed comparably to the LMA in non-obstetric patients.

## Unanticipated difficult airway algorithm

Although central neuraxial blockade has become the preferred anaesthetic technique for CS there will always be situations maternal, fetal, or both where general anesthesia will be necessary. The unanticipated difficult airway will occur and it must be handled calmly and efficiently if disaster is to be averted.

- Tunstall's failed intubation drill was first published in 1976 giving the obstetric anesthesiologist a straightforward approach to the issue [40].
- In 1991, the comprehensive ASA difficult airway algorithm was published. The parturient was not specifically dealt with.
- Harmer, in 1997, improved on Tunstall's original drill incorporating the LMA [41].
- The Canadian Airway Focus Group in 1998 discussed the obstetric airway, and although they alluded to alternatives for difficult intubation they did not explicitly advocate their use [42].
- There have been tremendous technological advances in equipment for airway management. Since 2001 there have been numerous video laryngoscopes (VLs) come to the market (Glidescope, AQ-L and AWS).
- The VLs have been demonstrated to be highly effective in the non-obstetric population and their successful use in the parturient has been reported. It is our opinion and that of others [5], that the body of evidence demonstrating their effectiveness in non-obstetrical patients is sufficient to incorporate these devices into a difficult airway algorithm for the parturient. The LMA Classic and LMA-PS have proven themselves to be invaluable in situations of failed intubation and ventilation. The LMA-S has been shown to behave comparably to the LMA-PS. We believe the LMA-S, which is very easy to place and separates the alimentary and respiratory tracts, is the ideal supraglottic device for the parturient [43].
- The last resort is access to the trachea by the cricothyroid membrane via percutaneous cricothyrotomy or (less commonly) tracheostomy.
- The algorithm (Figure 18.1) that we have presented for failed intubation at the time of CS incorporates the equipment most commonly employed at our institution. Other institutions will incorporate equipment and tools appropriate for their own use. Algorithms that allow clinicians to use equipment that they are most proficient with will be more effective than adopting guidelines from another institution [44]. The low number of CSs being performed under general anesthesia means that failed intubation is a rare occurrence. Anesthesiologists must ensure competency with novel devices by first employing these in the non-emergency setting.
- Algorithms are designed to give practitioners a framework from which to work. However, clinical judgment is always an important aspect of providing anesthetic care for the parturient. Maternal condition and the status of the fetus will dictate the clinician's course of action.

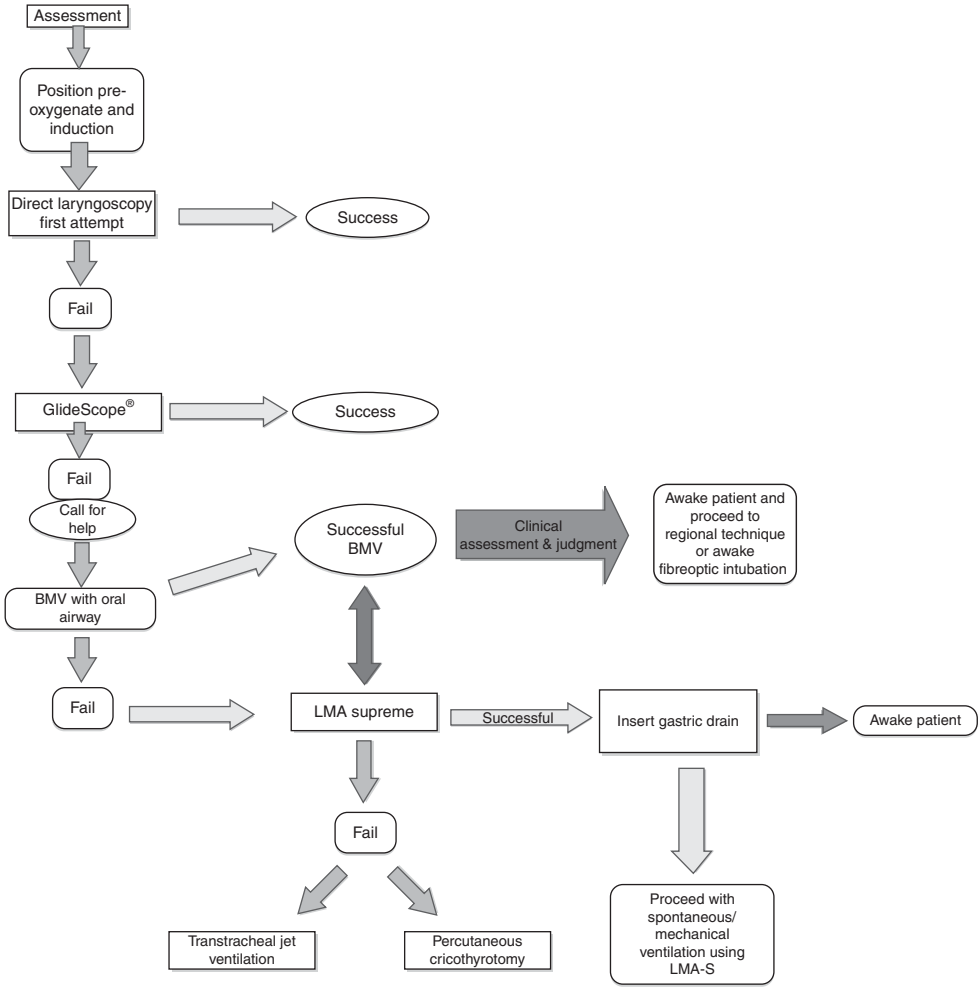


**Figure 18.1** Unanticipated difficult airway algorithm.

- Having a standardized protocol for managing a difficult airway in the parturient where oxygenation not intubation is paramount will no doubt reduce morbidity and mortality.
- Another important, but often overlooked, component in managing the difficult airway is the plan for extubating the patient following a surgical procedure and their disposition.
- The section on further reading includes online links to practice guidelines produced by specialist societies.

## Cricoid pressure in obstetrical anesthesia

Rapid sequence induction (RSI) is the standard of practice during induction of general anesthesia for CS. Along with preoxygenation and denitrogenation, cricoid pressure (CP) is applied prior to the induction agent being administered.

- The use of CP was first described in 1961 by Sellick, who proposed that the lumen of the esophagus could be compressed against the cervical vertebrae by applying a posterior force to the cricoid cartilage. He described these following manoeuvers: an assistant should apply 10 newtons (N) of force on the cricoid cartilage, which is increased to 30 N after loss of consciousness; application of the full amount of force while the patient is awake can actually cause reflux. This higher force should be continued until correct endotracheal placement has been confirmed.
- The evidence base for this standard practice is weak.
- This is difficult to translate into clinical practice due to the inability of the assistant to know the exact pressure that he or she is exerting on the cricoid cartilage. Also, most assistants are unaware that two different forces should be used.
- The idea that a force applied to the cricoid occludes the esophagus and thus prevents reflux of stomach contents into the oropharynx in every patient is still being debated. Smith *et al.*, using magnetic resonance images in [22] healthy volunteers, showed that the esophagus was displaced laterally in 50% of patients without cricoid pressure (CP) and this increased to 90% when CP was applied [45].
- Incorrect application of cricoid pressure can make the view at laryngoscopy more difficult in up to 45% of cases. It can also negatively affect facemask ventilation and LMA insertion, both important rescue strategies if intubation fails [46].
- This may lead one to question whether CP should be performed on every parturient at the time of RSI, especially when confronted with a difficult or challenging airway.

This issue is still being debated but, at present, the use of CP, though controversial, remains standard practice. Respected authorities have called for its routine use to be abandoned [47].

## Induction agents in the parturient

The induction agent of choice for the parturient requiring general anesthesia is still being debated. The two main agents in use are propofol and to a lesser extent thiopental. Both drugs are reliable induction agents. They both have a rapid onset/elimination time, negative inotropic effects, and cross the placenta.

### Propofol

- In the industrialized nations, propofol is the most commonly used induction agent.
- Anesthesiologists have developed a great deal of confidence in its dosing and side effect profile.
- It has antiemetic properties.
- Surprisingly it is a cheaper induction agent than thiopental in many centers.
- Propofol (2.4 mg/kg) compared to thiopental (5mg/kg) may carry a higher risk of awareness. Celleno *et al.* showed that electroencephalographic patterns consistent with light anesthesia and verified with clinical signs were present in 50% of patients [48]. This risk of awareness may, in part, be due to the shorter duration of action of propofol – essentially wearing off before the volatile agent concentrations have sufficiently built up yet after the skin incision.

### Thiopental

- Thiopental (known as thiopentone in some countries) is an extensively studied drug with a reassuring track record of being safe for both mother and fetus.
- There is a low fetal brain concentration with maternal induction dose of 4 mg/kg due to the preferential uptake by fetal liver and rapid redistribution of the drug into maternal tissues. However, large doses, greater than 8 mg/kg can produce significant neonatal depression.
- New residents and staff anesthesiologists that have been primarily exposed to propofol during their training may have limited experience with thiopental and thus may not feel as comfortable using it in an emergency situation.
- Thiopental is being infrequently used in daily anesthetic practice. Recently, our center has been unable to restock the drug further limiting the residents exposure to it.

Both drugs have been safely used in the parturient, though arguably thiopental has a slight advantage over propofol. In many centers propofol has become the exclusive intravenous agent available to use for the parturient.

## Choice of muscle relaxant in obstetric anesthesia practice

Succinlycholine has classically been the drug of choice for RSI. It has the advantage of having a rapid onset, short duration of action, and the disadvantage of being contraindicated in select patients (hyperkalemia, spinal cord transection, malignant hyperthermia, etc.). Postoperative myalgia (POM) is the main side effect that is associated with its use. A meta-analysis in 2005 (52 randomized trials with a total of 5,318 patients) reported the following outcomes in their discussion [49]:

- The incidence of POM is high and symptoms sometimes last for a few days.
- A small dose of non-depolarizing muscle relaxant (10 to 30% of ED 95) prevents fasciculation and POM to some extent, but the risk of potential serious side effects is not negligible.
- Higher doses of succinylcholine (1.5 mg vs. 1 mg) decrease the risk of POM compared with lower doses.
- There is no clear relation between succinylcholine-related fasciculation and POM.
- Pretreatment with a sodium channel blocker (lidocaine) or non-steroidal anti-inflammatory drugs (diclofenac and aspirin) may prevent POM.
- Rocuronium at high doses (1.2 mg/kg) is an alternative to succinycholine for RSI and has been shown to be as effective in providing optimal intubating conditions [50].
- If a "cannot intubate/cannot ventilate" situation is encountered with rocuronium, the ability to return a patient to spontaneous ventilation may be life saving.
- Sugammadex [51] reverses the effect of rocuronium by fully binding the molecule and inhibiting its action on the motor endplate. Sugammadex is now available in Canadian operating rooms as an emergency reversal drug. As a result of its high cost, approximately Canadian $93 for a 200 mg dose, its use will be restricted. We would argue that all anesthesia providers should have access to this drug.

- When the cost of sugammadex comes down substantially, the use of succinylcholine may become obsolete. The ability to reverse the effects of rocuronium at any point is an exciting proposition.

## Training in airway management of the parturient

In many countries CS management has shifted almost entirely to regional techniques over the last two decades. The use of endotracheal intubation for CS has been reserved for situations where a regional technique has failed, is contraindicated, or when maternal condition or fetal status requires an emergent course of action.

- As a result of this shift to regional anesthesia, trainees' exposure to general anesthesia in the parturient has become limited.
- Last year at our teaching institution we carrried out approximately 1,300 CSs of which 130 were performed under general anesthesia.
- We informally surveyed the senior residents at our institution at the end of their training (five-year residency) and found on average residents had performed six to eight intubations in parturients. The greatest number of intubations by a resident was 13 and the fewest number 4.
- The group from Liverpool published their experience with general anesthesia and CS over an eight-year period. They reported that in 2007, each resident on average was involved with two general anesthetics for CS each month [21].
- This is quite different from our experience, and of that reported by the group from Boston (approximately 20 CSs under GA per year) where resident exposure is even more limited [7].
- It has been shown that the use of the GVL facilitates learning of intubation skills by novices compared to a standard Macintosh laryngoscope [52]. Perhaps in the future all intubations in obstetric patients will be performed using a video laryngoscope?

With the management of CS continuing to favor neuraxial blockade, it is our responsibility to adequately train residents to deal with the obstetric airway. The introduction of simulation to many anesthesia training programs may help by exposing trainees to various infrequently encountered scenarios involving the obstetrical patient. It is believed that this may improve patient care especially for infrequent scenarios such as GA for CS. Research is ongoing to test this hypothesis.

## Summary and conclusions

- Airway-related problems and related maternal deaths still occur.
- The maternal airway is more difficult to manage.
- Prediction of difficult airways in the parturient is unreliable.
- Video laryngoscopes show promise in improving management of the maternal airway.
- The LMA has been a significant advance in airway management in parturients.
- Institutions and individual anesthesiologists should develop strategies for dealing with difficult airways in the parturient.
- Cricoid pressure during intubation in the parturient remains controversial.

- Propofol is likely to become the main induction agent in parturients – if only by default.
- Rocuronium may supplant succinylcholine in the future.
- Through practical exposure, simulation, and didactic teaching, trainees should gain the skills to comfortably manage the parturient's airway.

## Further reading


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Chapter 19

# Oxygen supplementation for cesarean section

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## Introduction

- It seems plausible that maternal oxygen supplementation during a cesarean section would be beneficial, even when a neuraxial technique is used.
- Oxygen is a vital precursor for oxidative metabolism; without an adequate supply, anaerobic metabolism and acidosis can ensue. Maternal hypoxemia can also lead to fetal hypoxemia and acidosis, fetal distress, and poorer neonatal outcomes.
- Unlike in postnatal life, where the lungs are responsible for oxygen uptake, and where the functional residual capacity acts as an oxygen reservoir, the fetus has very little oxygen reserve, and thus relies on a constant oxygen supply from the mother. This oxygen is required for the fetus to provide the energy it needs to maintain life, via oxidative metabolism.
- Oxygen supplementation during general anesthesia for cesarean section has been shown to improve fetal oxygen delivery as well as neonatal outcomes [1], and has been standard practice since the 1960s.
- Some advocate for its use even in elective cesarean sections done under neuraxial anesthesia; during the past few decades, it has been common practice to apply oxygen via nasal prongs or a facemask to a patient undergoing elective cesarean section under neuraxial anesthesia. This widespread use was justified mainly by a presumed fetal benefit [2].
- More recently, the literature has questioned this beneficial effect in the uncompromised fetus. Some research proposes that there may even be detrimental effects of maternal oxygen supplementation in this situation [3].
- For this reason, there exists ongoing controversy as to whether or not maternal supplemental oxygen should be applied when a neuraxial anesthetic technique is used for an elective lower-segment cesarean section delivery of an uncompromised fetus.

## Physiology of fetal oxygen uptake, transport, and use

Uterine blood flow at term is approximately fifty times that of the non-pregnant state due to increased maternal cardiac output and blood volume and also due to estrogen-related uterine vessel vasodilation (mediated by nitric oxide). The placenta at term receives 90% of total uterine blood flow leading, one might assume, to a luxury perfusion of the fetus. However;

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- Uterine blood flow is not autoregulated and is, therefore, unable to be increased in times of maternal or fetal stress.
- There are no placental autoregulation mechanisms that can adjust placental blood flow in response to decreases in maternal $PaO_2$.
- Fetal oxygenation occurs via transplacental passive diffusion of oxygen from the uterine circulation to the umbilical circulation. One umbilical vein provides the fetus with oxygenated blood, while two umbilical arteries carry deoxygenated fetal blood back to the placenta. The transfer of oxygen in the placenta is flow limited. Placenta to fetal oxygen transfer is likely a result of a concurrent exchange mechanism (as opposed to a countercurrent exchange mechanism as occurs in the nephron). This exchange mechanism is less efficient explaining why increases in maternal inspired oxygen may increase uterine artery oxygenation without major increases in umbilical vein $pO_2$.

The placenta is much less efficient than the adult lung at oxygen transfer. There are multiple reasons for the large gradient that exists between maternal $PaO_2$ and umbilical vein $pO_2$ [4]:

- The uterus itself consumes oxygen.
- The uterine system also supplies the placenta with oxygen, which (when studied in sheep) accounts for about 20 to 30% of transferred oxygen [5].
- The placenta acts as a venous equilibrator rather than an arterial one.
- There exists some degree of shunting on both the uterine and umbilical sides of the placental circulation.

As a result, under isobaric conditions, fetal arterial $pO_2$ does not increase above 50 to 60 mmHg, regardless of maternal $FiO_2$ [4].

The oxygen content of blood delivered to the fetal heart (and pumped to the tissues of the fetus) is less than that leaving the placenta. This is due to mixture in the fetal inferior vena cava of relatively oxygenated blood from the ductus venosus (the major branch of the umbilical vein) and the relatively deoxygenated blood from the fetal portal sinus and the blood from the fetal lower body. This fetal perfusion of relatively deoxygenated blood is compensated in part by:

- the increased fetal CO
- the left-sided shift of the fetal hemoglobin (Hb) oxygen dissociation curve leading to increased placental uptake of oxygen
- increased fetal Hb concentrations.

Despite the low $pO_2$ of fetal blood, this does not translate into fetal tissue hypoxia under normal conditions.

- Oxygen delivery to fetal organs is determined by the blood flow multiplied by the oxygen content of fetal blood, which is much higher than that of adult blood.
- Oxygen content is primarily dependent on hemoglobin concentration and saturation; this is especially true in a fetus, where the amount of dissolved oxygen is very low, and the hemoglobin concentration is high compared to that of an adult (approximately 180 g/L).
- In addition to having an increased hematocrit, the fetus also has a high concentration of fetal hemoglobin (75 to 84% of total hemoglobin at term) [6]. Fetal haemoglobin (HbF) has a greater affinity for oxygen (secondary to a decreased interaction with 2,3

diphosphoglycerate), which results in a left shift of the oxyhemoglobin saturation curve, and a P50 of approximately 19 to 21 mmHg (compared to the P50 of 27 mmHg in adult blood).

- The greater oxygen affinity of HbF, compared to that of HbA, not only increases the carrying capacity of fetal blood, but also augments the transfer of oxygen from mother to fetus within the intervillous space.
- In addition to these measures of increasing supply, the fetus also prevents tissue hypoxia by altering demand. Growth and activity of the fetus account for a significant portion of the fetal $VO_2$ [7, 8]. Thus, during times of stress, fetal $VO_2$ can be greatly diminished, further decreasing the likelihood of tissue ischemia.

## Supplementary oxygen – maternal benefit?

Since the 1960s, it has been a well established practice to provide oxygen supplementation during general anesthesia.

- The requirement for supplemental oxygen in order to maintain an adequate saturation is attributed to the physiologic changes to the respiratory system that occur during general anesthesia and mechanical ventilation [9].
- Neuraxial anesthesia to a level of T4 (which is required for adequate pain control during a lower-segment cesarean section) also has a number of effects on respiratory function, including paralysis of the intercostal muscles, leading to decreased peak expiratory flow, expiratory reserve volume, and forced vital capacity.
- Despite the combined effects of pregnancy and of neuraxial anesthesia on respiratory function, maternal oxygen saturation is maintained at adequate levels even when the patient continues to breathe room air [10].

Given this information, it becomes less likely that there is any true maternal benefit to providing supplementary oxygen to healthy patients during elective lower-segment cesarean section deliveries done under neuraxial anesthesia, although some theoretical indications do exist.

- Those who support the routine use of oxygen during elective cesarean sections argue that some degree of hypotension is inevitable during spinal anesthesia, and that by providing the parturient with supplemental oxygen, we are increasing their oxygen delivery during this time [3, 11].
- However, others advocate that it is better practice to treat the hypotension with vasopressors as necessary, and that oxygen supplementation is only required in the face of refractory hypotension [11].

It has also been suggested that supplementary oxygen may decrease the incidence of nausea and vomiting. Although the mechanism of this effect is not well understood, increased $FiO_2$ levels during gynecological surgery have been shown to significantly decrease the incidence and severity of postoperative nausea and vomiting [12].

- A more recent study, however, showed that the administration of supplemental oxygen during elective and semi-urgent cesarean sections done under neuraxial anesthesia, did not reduce the incidence or the severity of postoperative nausea and vomiting [13].

Another possible maternal advantage of oxygen supplementation during elective cesarean section that has been proposed is a decreased incidence of surgical wound infections.

- This suggestion stems from recent studies that showed a reduced incidence of surgical wound infection after colorectal resections when supplemental oxygen was administered intraoperatively and in the immediate postoperative period [14].

This may be the first true maternal benefit for oxygen supplementation during routine elective cesarean section. However, at this point, there is insufficient evidence to extrapolate this possible benefit to the patient population of interest.

To summarize, there has been no well established *maternal* benefit to providing supplementary oxygen to healthy patients during elective lower-segment cesarean section deliveries done under neuraxial anesthesia.

## Supplementary oxygen – fetal benefit?

In 1984, the fifth edition of *Principles and Practice of Obstetric Anesthesia* by Crawford was published and therein suggested that it was advisable, for *fetal* reasons, to provide maternal oxygen supplementation for cesarean section under regional anesthesia, until the time of delivery [15]. This became a widely accepted practice, and is still advocated by some, although the numbers have decreased greatly over the last several years given more recent evidence that does not support its use.

- In 1982, Ramanathan and colleagues showed that increasing $FiO_2$ from 21% to 47%–100% (via a facemask and the anesthesia circuit) in healthy parturients during elective cesarean section under epidural anesthesia resulted in a significantly higher umbilical vein $pO_2$ (UV $pO_2$) and umbilical artery $pO_2$ (UA $pO_2$). Despite these increases in $pO_2$, they found no significant change in umbilical artery pH or Apgar score. They did, however, find that hyperoxic fetuses were less acidotic as measured by base deficit. With these results, they concluded that maternal supplemental oxygen should be applied during an elective cesarean section under neuraxial anesthesia, even when baseline maternal oxygen saturation is normal. Their rationale was that by increasing UV $pO_2$ (and presumably fetal oxygen content given the steep slope of the hemoglobin saturation curve at typical fetal $pO_2$ levels), fetal oxygen stores would be increased, which may subsequently aid the neonate in being able to withstand episodes of unexpected intrapartum or postpartum oxygen deprivation [16].
- Several years later, Kelly *et al.* found that supplying mothers with 35% oxygen by facemask did not significantly improve UV $pO_2$ or umbilical vein pH values [10].
- Cogliano's randomized controlled trial in 2002 agreed with Kelly's findings; they randomized healthy parturients undergoing elective cesarean section under spinal anesthesia to oxygen at 2L/min via nasal prongs, and 21% or 40% oxygen by facemask. They found no significant changes in any of the measured biochemical outcomes (UV $pO_2$, UV pH, UV $pCO_2$, UA $pO_2$, UA pH, UA $pCO_2$), between any of the three groups. Furthermore, they found no differences in clinical outcome as measured by Apgar scores. They concluded that supplemental oxygen was not warranted for elective cesarean sections under spinal anesthesia in healthy parturients with an uncompromised fetus [17].
- Also in 2002, Khaw *et al.* performed a randomized controlled trial of healthy parturients undergoing cesarean section under spinal anesthesia. They randomized patients to an $FiO_2$ of either 21% or 60%, and found a modest increase in UV $pO_2$ (36.1 mmHg vs. 30.1 mmHg, $p = 0.04$) in the group receiving $FiO_2$ of 60%. All other measured outcomes

showed no significant change. These included: UA $pO_2$, UA $pCO_2$, UA pH, and base excess, as well as UV $pCO_2$, UV pH, and base excess, in addition to Apgar scores. This group concluded that providing a high $FiO_2$ (60%) could modestly increase fetal oxygenation but that it also may be detrimental via the production of oxygen free radicals (discussed below) [3].

- Khaw *et al.* later conducted another randomized controlled trial looking at supplemental oxygen for elective cesarean section under spinal anesthesia in healthy parturients. This time, patients were randomized to an $FiO_2$ of 21%, 40%, or 60% by facemask. They found UV $pO_2$ was modestly increased in patients that received 60% oxygen compared to both 40% and 21%. There was no significant difference in UV $pO_2$ between the 40% and 21% groups. Furthermore, they showed no significant differences in UApH, fetal acidosis (defined as UApH < 7.2) or Apgar score between any of the three groups [18].
- In 2007, Backe and colleagues showed no significant difference in biochemical or clinical neonatal outcomes in their randomized controlled trial involving healthy parturients for elective cesarean section under spinal anesthesia. They compared an $FiO_2$ of 21% to that of 40%. UV $pO_2$ and UA pH were compared, and there was no significant difference found. Additionally, they measured Apgar score and Neurologic Adaptive Capacity Score (NACS) and, again, found no significant difference between groups. With these results, they concluded that supplemental oxygen provided no benefit over room air in the normal neonate at elective cesarean delivery, as it did not appear to improve fetal oxygen delivery, acidosis, or neonatal behavioral effects in this population [19].

Although it remains somewhat controversial, the most recent available literature does not seem to support oxygen supplementation during elective cesarean section under neuraxial anesthesia for fetal benefit. It appears that very high inspired oxygen concentrations ($\geq$60%) are required for only modest increases in fetal oxygenation (as measured by UV $pO_2$). The standard facemasks used in clinical practice do not provide an $FiO_2$ in this range; it would be impractical, both clinically and economically, to use apparatuses capable of attaining these inspired oxygen concentrations on a routine basis for all elective cesarean section deliveries. Furthermore, even when an increase in UV $pO_2$ was seen, this did not translate into a significant clinical improvement (Apgars or NACS), nor did it result in a significant difference in any other biochemical outcome measured, including pH and base excess – which is thought by some to best indicate the presence of perinatal asphyxia and predict neonatal outcome [16].

## Supplementary oxygen – detrimental effects?

Despite the fact that the majority of recent evidence indicates no maternal or neonatal benefit of oxygen supplementation for elective cesarean section under neuraxial anesthesia, there exists the argument of: "there may be no benefit, but it will do no harm." This rationale has come into question in recent years.

- In Cogliano's randomized controlled trial, although patients did not report significantly more discomfort with the facemask, they did report significantly increased impedance to communication with the facemask over that with nasal prongs [17]. One advantage of neuraxial anesthesia for cesarean section is that mothers are awake, and able to communicate and interact with their support person, as well as communicate any concerns, or symptoms to the anesthesiologist during the intraoperative period; it seems reasonable to avoid any unnecessary impedance to this communication.

- Although Ramanathan reported that hyperoxic fetuses were less acidotic in his study (noted above), there has been some conflicting data that show prolonged hyperoxia may actually result in worsening of umbilical blood gas profiles [20].
- Thorpe *et al.*, in their randomized controlled trial, found a significant increase in fetal acidosis (defined as UApH < 7.20) when mothers were administered oxygen (at 10 L/min by facemask) for greater than ten minutes during the second stage of labor. Their conclusion was that prolonged maternal oxygen treatment during the second stage of normal labor may result in deterioration, rather than an improvement, of cord blood gas values at birth. It has been suggested that this finding may be due to hyperoxia-induced vasoconstriction of placental vessels, leading to a decrease in placental blood flow [20]. It must be noted, however, that this study was performed in laboring women, and the results may not translate to patients undergoing elective cesarean section.
- Litchfield *et al.* performed a study in 2007 , which suggested that maternal hyperoxia may decrease cardiac index and increase systemic vascular resistance in healthy term parturients. Limitations of this study included small sample size, the use of thoracic electrical bioimpedance to estimate hemodynamic parameters, and the fact that neonatal oxygenation and outcome were not assessed [21].
- In 2002, Khaw *et al.* suggested that maternal hyperoxia, secondary to oxygen supplementation, may have detrimental effects on the neonate by promoting the formation of oxygen free radicals and lipid peroxidation [3]. Oxygen free radicals are molecules that contain unpaired electrons, and are therefore incredibly reactive, leading to extremely short half lives. Free radical species can react with phospholipids in cell membranes, as well as with DNA, leading to cellular damage. They are produced by a number of pathways, including those initiated by hypoxic stress with ischemia–reperfusion injury, as well as those promoted by hyperoxic environments. In Khaw's randomized controlled trial, healthy parturients were randomized to receive either 21% or 60% oxygen during elective cesarean section under spinal anesthesia. At the time of delivery, lipid hydroperoxides (the products of the reaction between free radicals and polyunsaturated fatty acids) were measured as a marker of oxygen free radical activity. They found that maternal plasma concentrations of lipid peroxides were significantly higher within ten minutes of oxygen supplementation, and that both UA and UV plasma concentrations of lipid peroxides were significantly higher in the group that received 60% $FiO_2$ than in the group that received 21%. They also found a positive correlation between maternal $PaO_2$ and umbilical concentration of lipid peroxides, which suggests a direct relationship between maternal $PaO_2$ and the amount of free radical activity in the fetus [3]. Interestingly, they found that in the setting of *emergency* cesarean section performed under regional anesthesia, there was no increase in lipid peroxidation when an $FiO_2$ of 0.6 vs. 0.21 was used [22]. In their most recent study, they found that the use of *general anesthesia* for elective cesarean section resulted in a marked increase in free radical activity, independent of the inspired oxygen concentration [23].

Unfortunately, the clinical relevance of an increase in free radical activity is not known.

- In Khaw's study, there were no significant differences seen in neonatal outcome between groups, despite the differences in lipid peroxides. However, only gross measures (Apgar scores) were used to assess neonatal outcome, and all patients were otherwise healthy, without any evidence of fetal compromise.

- An increase in oxygen free radical production results in depletion of intrinsic antioxidant systems, which may leave the neonate with a decreased ability to withstand any subsequent insult [3].
- Hyperoxia may be particularly detrimental in the setting of fetal distress, where it may increase ischemia–reperfusion injury, or to the premature neonate because of their lower levels of antioxidant enzymes; hyperoxia has been implicated in premature neonatal diseases such as retinopathy of prematurity, bronchopulmonary dysplasia, intracranial hemorrhage, and necrotizing enterocolitis [3].
- It has been shown that neonatal outcome may be better following resuscitation with air rather than with supplemental oxygen [24], and this finding has changed clinical practice.
- The association between hyperoxia and a worse outcome from resuscitation has been confimed in other populations thus supporting the potential importance of increases in oxygen free radical activity. For example, the presence of hyperoxia in survivors of cardiac arrest is associated with worse in-hospital mortality [25].

Because both hypoxia and hyperoxia can result in adverse effects, the most recent American Heart Association (AHA) recommendations state that it is reasonable to initiate neonatal resuscitation with room air rather than 100% oxygen, which was previously the standard of care. Furthermore, they state that supplemental oxygen should be decreased or discontinued once saturation has reached 95% [26].

## Summary

For decades it has been common practice to provide supplemental oxygen during elective cesarean sections, mainly for presumed fetal benefit. To date, this practice remains somewhat controversial. The majority of recent literature suggests that a very high $FiO_2$ (>60%) is required to produce even a modest improvement in fetal oxygenation, as measured by UV $pO_2$. Other biochemical endpoints (such as fetal acidosis) as well as clinical endpoints (including Apgar score and NACS) have not reliably been shown to improve when supplemental oxygen is used. In addition to the lack of evidence supporting the use of supplemental oxygen during elective cesarean section performed under neuraxial anesthesia, there has been some recent suggestion of a possible detrimental effect of hyperoxia. The clinical relevance of this increase in oxygen free radical activity remains unknown. For these reasons, it is becoming more common practice to omit the routine use of maternal supplemental oxygen when a neuraxial anesthetic technique is used for an elective lower-segment cesarean section delivery of an uncompromised fetus [3, 17–19, 27, 28].

Of note, it remains standard practice to provide maternal oxygen supplementation during a cesarean section when there is any sign of fetal distress, or if a general anesthetic is used [28].

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Chapter

20

# Oxytocin use and dosage during cesarean section

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## Introduction

The use and dosage of oxytocin during cesarean section has been increasingly controversial in recent years and traditional practice has been challenged. Oxytocin is given for prophylaxis of uterine atony and, less commonly, as treatment for established uterine atony and during postpartum hemorrhage. This chapter makes no comment on the usage of oxytocin for augmentation of labor or for prevention of postpartum hemorrhage following vaginal delivery.

## Physiology of oxytocin

Oxytocin is the major hormone stimulating uterine contractions during parturition.

- Oxytocin is a nine-amino acid peptide produced in the hypothalamus and released into the systemic circulation from the posterior lobe of the pituitary gland in response to multiple physiological stimuli.
- During parturition, oxytocin is involved in a positive feedback loop, i.e. oxytocin causes uterine contractions leading to more oxytocin release. Oxytocin is also released from the pituitary gland during breastfeeding to promote ongoing breastmilk production.
- Increases in estrogen levels during pregnancy produce an increase in oxytocin receptors in the uterus resulting in increasing sensitivity of the uterus to oxytocin.
- Oxytocin stimulates the release of nitric oxide in the vascular endothelium to produce vasodilation.
- A synthetic form of oxytocin is widely used to augment labor, to prevent uterine atony, or to treat established postpartum hemorrhage.

## Historical usage and dosages

Postpartum hemorrhage (PPH) due to uterine atony is a frequently encountered complication of birth and is a leading cause of maternal death. The diagnosis may be delayed due to:

- the nature of the bleeding, which is initially concealed
- the physiological adaptations of pregnancy, which tend to accommodate hemorrhage with minimal early clinical signs.

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In the prevention and treatment of PPH, oxytocin is an essential uterotonic pharmacological intervention.

Consequently, the administration of uterotonic drugs during cesarean section has become essential to reduce the risk of, or to treat, PPH as well as to improve maternal safety. The optimal dose of oxytocin for these purposes is unknown. An oxytocin bolus of five to ten international units (IU) intravenously, has been a standard dose until recently – often with an underappreciation of any potential adverse effects. This dose and mode of administration has recently been questioned.

## Hemodynamic effects of oxytocin

- Oxytocin directly relaxes vascular smooth muscle leading to decreases in systemic vascular resistance, hypotension, and tachycardia.
- Oxytocin may also cause tachycardia by stimulating myocardial receptors affecting atrioventricular conduction and myocardial repolarization.
- Oxytocin has been shown to cause vascoconstriction in splanchnic arterioles and in coronary arteries.
- Hypotension due to oxytocin administration during cesarean section may be falsely attributed to blood loss or the sympathectomy from neuroaxial anesthesia.

Various studies have examined the hemodynamic effects of oxytocin in parturients.

- Early studies [1] on the cardiovascular effects of 5 to 10 IU of oxytocin in elective termination of pregnancy in healthy women showed that oxytocin by bolus injection caused decreases in blood pressure, tachycardia, and increases in cardiac output of 30 to 50%. In contrast, infusions of oxytocin caused minimal hemodynamic changes and were recommended by the authors.
- Similar studies [2] also in the first trimester of pregnancy found similar hemodynamic effects but with the interesting observation that there were significant increases in pulmonary artery pressure following a 10 IU bolus of oxytocin.
- Langesaeter *et al.* [3] studied hemodynamic effects of oxytocin in women with severe pre-eclampsia. Eighteen women with severe pre-eclampsia were monitored invasively during spinal anesthesia for cesarean section and given intravenous boluses of 5 IU oxytocin following delivery. Following this bolus all patients had an increase in heart rate, a decrease in systemic vascular resistance, and a decrease in blood pressure. Five patients had a decrease in cardiac output due to an inability to increase stroke volume.
- Interestingly, it seems that the expected changes in blood pressure and cardiac output are reduced when giving a second bolus of oxytocin compared to the intial dose [4].
- The hypotension associated with bolus administration of oxytocin may be mitigated by prior administration of phenylephrine immediately prior to the bolus of oxytocin [5].

Thus it is clear that even relatively small bolus doses of synthetic oxytocin cause hemodynamically significant changes in maternal heart rate and blood pressure. Caution is warranted if using oxytocin in cardiovascularly unstable patients including patients with pre-eclampsia or patients with cardiac disease.

## Maternal mortality

Oxytocin is a drug commonly associated with side effects, particularly hypotension, and has been implicated as being a factor in several known maternal deaths:

- The administration of 10 IU of oxytocin was considered to be a contributory factor in the death of two UK mothers in the period 1997 to 1999 as reported in the subsequent Confidential Enquiries into Maternal Deaths (CEMD) report [6]. The report recommended that an initial bolus dose should be reduced from 10 to 5 IU IV.
- More recently in South Africa, Dyer reports that oxytocin was implicated in a further two maternal deaths. One where the hypotension was thought to worsen hemodynamic instability associated with spinal anesthesia, and the other where the administration of a bolus of 10 IU IV during emergency cesarean section resulted in cardiac arrest [7].
- In 2007, oxytocin was added to the Institute for Safe Medication Practices (ISMP) list of medications requiring special attention to reduce the risk of error and harm [8].

## Safety of a 10 IU bolus

Further concerns have been raised regarding the safety of a 10 IU bolus dose of oxytocin – traditional practice for many anesthesiologists in the past.

- Pinder *et al.* [9] studied the effects of 5 or 10 IU of IV oxytocin in healthy parturients at term having cesarean section under spinal anesthesia. There were significant and greater reductions in blood pressure and increases in heart rate and cardiac output after a 10 IU bolus compared to a 5 IU bolus.
- This is of importance in that women with hypovolaemia or cardiac disease may be unable to mount the appropriate compensatory responses and are therefore at greater risk of hemodynamic compromise after boluses of oxytocin.
- Chilvers *et al.* [10] describe a patient who suffered myocardial ischemia during cesarean section after the administration of a bolus dose of 5 IU oxytocin. Measurements of serum troponins confirmed myocardial damage despite subsequent demonstration of normal coronary artery anatomy. Two mechanisms were postulated. Coronary artery vasospasm has been observed following in vitro intracoronary administration of oxytocin in dogs. In addition, intravenous oxytocin produces vasodilatation of vascular smooth muscle resulting in a reduction in both systolic and diastolic blood pressures. The diastolic hypotension may reduce coronary perfusion. This, in combination with tachycardia and the physiological anemia of pregnancy, may result in myocardial ischemia.
- A randomized controlled trial [11] also studied dose-related cardiovascular side effects of oxytocin. Interim analysis showed that 24% of patients receiving 10 IU intravenously of oxytocin by bolus injection had signs of myocardial ischemia. This supports the possibility of precipitating myocardial ischemia after administering large bolus doses of oxytocin.
- In an interesting study Svanstrom *et al.* [12] compared women undergoing cesarean section under spinal anesthesia with healthy, non-pregnant, non-anesthetized controls. The control patients and half the cesarean section women were given 10 IU of intravenous oxytocin while the other half of the cesarean section women received 0.2 mg methylergometrine. In both groups oxytocin caused increases in heart rate and decreases

in blood pressure. In addition ST changes and symptoms associated with ischemia were noted. Methylergometrine caused slight increases in blood pressure but no EKG changes. It seemed that 10 IU of oxytocin intravenously can produce changes strongly suggestive of myocardial ischemia. The similar changes seen in the control patients suggest that this was due to the oxytocin as opposed to the effects of pregnancy, surgery, or the spinal block.

## Bolus vs. infusion

As discussed, there may be concerns related to the administration of oxytocin by IV bolus. Intravenous oxytocin has a very short half life (10 to 15 minutes). Thus, the potential advantages of an oxytocin infusion at cesarean section are that it maintains uterine contractility throughout the surgical procedure and immediate postpartum period when most primary hemorrhages occur.

- Thomas *et al.* [13] showed that infusions of oxytocin produce lesser increases in heart rate and less sudden changes in heart rate compared with oxytocin administered by IV bolus.
- George *et al.* [14] studied women undergoing elective cesarean section and using an up–down sequential allocation technique determined that the ED90 of an oxytocin infusion required to produce appropriate increases in uterine tone within three minutes of fetal delivery was 0.29 IU/min. This is approximately equivalent to 15 IU in a one liter bag of IV fluid infused over one hour. However, almost 20% of patients required additional uterotonics.
- King [15] compared oxytocin IV infusions with or without 5 IU of oxytocin by IV bolus in elective cesarean section patients under regional anesthesia. Although the bolus group patients showed increased uterine tone after placental delivery, there were no differences in measured blood loss or need for transfusion in either group. Thus, they found no benefit when an IV bolus of oxytocin was added to an infusion of oxytocin.

## Further dose studies

In view of the adverse effects of oxytocin, it is desirable to administer the lowest effective dose. Recent studies suggest that an effective dose of oxytocin for prophylaxis against uterine atony during cesarean delivery may be lower than the 5 to 10 IU intravenous bolus dose historically used by anesthesiologists.

- Sarna *et al.* [16] studied the effect of different oxytocin infusion doses from 5 IU to 20 IU during elective cesarean section. There were no differences in the assessment of uterine tone between the different groups. Indeed, it seemed that further increases beyond 5 IU had no additional benefit.
- Carvalho *et al.* [17] performed a randomized trial in elective cesarean section patients under spinal anesthesia. The ED90 oxytocin bolus was estimated to be 0.35 IU with 97.1% response rate at 0.5 IU and 100% response at 1.0 IU. They concluded that current intravenous bolus dosing of oxytocin during elective cesarean section may be reduced.
- In a follow-up study [18], the same group showed that the ED90 was increased to 2.99 in women proceeding to cesarean section following labor arrest despite augmentation with oxytocin infusion. This suggests that administration of oxytocin during labor may produce desensitization or oxytocin receptor downregulation (see below). It should be noted that this is the only study performed in non-elective cesarean sections.

- Butwick *et al.* [19] compared the effects of zero (placebo group), 0.5, 1, 3, and 5 IU boluses on uterine tone during elective cesarean section under regional anesthesia. They concluded that an oxytocin dose of 0.5 to 3 IU is sufficient in most elective cases with no apparent benefits from 5 IU (but a trend towards more hypotension). Many patients in the placebo group achieved adequate uterine tone at two minutes after delivery!
- Sartain *et al.* [20] compared 2 or 5 IU boluses of intravenous oxytocin followed by an infusion of 10 IU/hr during elective cesarean sections performed under regional anesthesia. Blood pressure was maintained by an infusion of phenylephrine. There were no differences in uterine tone, need for additional uterotonic drugs, or estimated blood loss, but hypotension, tachycardia, and nausea were all greater in the 5 IU bolus group.

Thus, it seems that lower doses of oxytocin at cesarean section than traditionally used by anesthesiologists are effective with less potential for side effects. The effective response of the uterus to these low doses is not surprising given the increase in oxytocin receptor density in the uterus during pregnancy.

Balki and Tsen [21] have proposed a protocol for administration of oxytocin at cesarean delivery based on what they call "the rule of threes" (editorial). This includes the use of up to three, 3 IU intravenous boluses (given over 15 seconds) as required with three-minute assessments of uterine tone in between doses. They also suggest a relatively low maintenance regimen of 3 IU of oxytocin in one liter of infusate given at 100 L/hr and use of other uterotonics if this regimen fails. Although based on recent research, this protocol has yet to be prospectively validated.

NB It is worth noting that dosages appropriate for elective cesarean sections under regional anesthesia may not be appropriate in all circumstances, e.g. emergency cesarean sections under general anesthesia.

## Acute receptor downregulation

Constant exposure to high doses of oxytocin has negative effects on oxytocin receptors in the uterus, causing desensitization with prolonged administration.

- This may occur during augmentation of labor with oxytocin infusion [22].
- This desensitization occurs rapidly – within three hours of oxytocin infusion [23].
- Animal studies support this as a real phenomenon that does not seem to occur with other uterotonic agents such as ergometrine [24].
- Prior exposure to oxytocin in labor is strongly associated with the development of PPH severe enough to warrant blood transfusion [25] suggesting a reduced uterine response to oxytocin.

In addition, potential receptor desensitization has implications for the anesthesiologist.

- The lesser hemodynamic effects of a second dose of oxytocin compared to the first dose support the concept of receptor desensitization or downregulation [4].
- This, is part, explains the need to choose alternative uterotonic agents if a poor response is seen to increasing or repeated doses of oxytocin.

## International surveys

The approach to dosing and usage of oxytocin has changed in many countries in recent years, though practice may still be at variance with official recommendations.

- In 2001, 87% of respondents to a survey in the UK still administered 10 IU as a bolus during cesarean section [26].
- Following recommendations in the CEMD as mentioned above, a more recent survey found that the initial oxytocin dose used during cesarean section in the UK was substantially reduced – 100% of the respondents administered oxytocin as a bolus of at least 5 IU but only 12% administered 10 IU as a bolus [27].
- A recent survey from Germany [28] showed mixed dosing practice regarding oxytocin. Many respondents only administered oxytocin by infusion, with a variety of bolus doses also being reported including many who still administered 10 IU or more by bolus. The total dose of oxytocin being administered varied from 1 to 80 IU.
- Finally, another recent survey from Australia and New Zealand [29] reported on oxytocin dosage at elective cesarean section. The majority of respondents administered either 5 or 10 IU as a bolus with additional infusion of oxytocin. The commonest infusion regimen was 40 IU in one liter of infusion, given over four hours.

## Effect of volatile agents on oxytocin requirements

The relaxant effect of volatile anesthetics on uterine smooth muscle during cesarean section performed under general anesthesia has been known for many years. Clinical studies show significant and progressive depression of uterine contractility with all volatile anesthetics. Fortunately, the uterus still responds to oxytocin.

1. Enflurane, isoflurane, and halothane are equally depressing to isolated human uterine muscle [30].
2. With regard to the more recent agents, desflurane and sevoflurane, in vitro studies confirm the dose-dependent inhibition of oxytocin-induced uterine contractions [31]. However, desflurane at 1 MAC concentration seemed to have a lesser effect than 1 MAC of sevoflurane. They concluded that up to 0.5 MAC of sevoflurane and 1 MAC of desflurane may be used during cesarean section under GA without significantly increasing the risk of uterine atony.

## Alternatives to oxytocin

Although it has been a well established treatment to use oxytocin as a first-line agent to prevent uterine atony at cesarean section, it may not be the ideal agent for treatment of PPH, as we saw previously, in compromised patients with pre-eclampsia, cardiac disease, or prolonged labor. It is also important to have access to other agents if first-line therapy is unsuccessful. Some of these alternatives are discussed further in the chapter on obstetric hemorrhage.

## Summary

- Oxytocin boluses of 10 IU are not recommended.
- Lower bolus doses (1 to 3 IU) may be equally effective and result in lesser side effects.

- Rapid infusions of oxytocin may be preferable to bolus IV dosing.
- Receptor downregulation may occur rapidly following exposure to oxytocin. Administration of excessive doses of oxytocin may lead to increased requirements, or requirements for other agents.
- Infusions minimize hemodynamic effects and are preferred where possible.
- Bolus doses of oxytocin should be used with caution, if at all, in patients with significant cardiac disease or pre-eclampsia.
- The optimal infusion doses and rates of oxytocin to prevent or treat uterine atony have not been clearly determined.
- There may be a need for uterotonics with a different mechanism of action for patients with uterine atony.

## Further reading


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Chapter

21

# Analgesia post cesarean section

Dr T Quach, Dr S Singh and Dr G Bellingham

## Introduction

- A recent study revealed a 17% prevalence of severe pain (defined as a pain score of 6 or greater out of 10), 24 hours after cesarean section [1].
- This bears significance since uncontrolled postoperative pain can prevent the mother from optimally caring for her child during the immediate postpartum period, in addition to reducing her ability to breastfeed effectively.
- Inadequate pain control may also limit a patient's mobility, which may further increase the already higher risk of thromboembolic disease in pregnant and postpartum women.
- Finally, poorly managed acute postoperative pain is a risk factor for the development of chronic pain [2].
- Clearly, effective post cesarean section analgesia can influence many facets of a mother's recovery.
- In a study where pregnant women were surveyed to assess their preferences regarding cesarean section, effective pain control during and after cesarean section was found to be of greatest concern for these patients [3].
- Treatment of pain must be both safe and effective while not interfering with the woman's ability to care for herself and her newborn.
- In addition, breastfeeding necessitates the choice of analgesic options that are both minimally transferred in breast milk and result in little adverse effect on the neonate.

This chapter serves as a guide for the current clinical management options and discusses the controversies around analgesia post cesarean section.

## Neuraxial opioids

The addition of an opioid to intrathecally or epidurally administered local anesthetic provides an effective means to maintain prolonged analgesia after cesarean section. There are several reviews indicating that neuraxial opioid administration provides superior analgesia over the systemic route [4–6].

- Preservative-free morphine is the most commonly used opioid for neuraxial administration. However, the optimal effective dose of morphine that provides adequate duration of analgesia after cesarean section with minimal side effects continues to be debated.

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- Hydromorphone is less commonly administered neuraxially. However, it may be a reasonable alternative for patients with an intolerance to morphine.
- Meperidine is the only opioid that possesses some local anesthetic properties. Thus, when administered neuraxially it may result in motor blockade, and it has been used as a sole agent for spinal anesthesia for cesarean delivery [7].

Adverse effects of neuraxial opioids are dose dependent and include sedation, pruritus, nausea, vomiting, constipation, urinary retention, and respiratory depression.

- Consideration for prophylactic treatment of pruritus, and nausea and vomiting should be routinely made.
- Although respiratory depression has been shown to be very rare [8], it is a potentially fatal complication of neuraxial opioid usage for cesarean sections, and therefore respiratory monitoring for 24 hours is recommended.
- There is also concern that neuraxial morphine causing pruritus in the trigeminal nerve dermatomes may increase the risk of herpes simplex labialis virus type II reactivation [9].

## Intrathecal opioids

Opioids administered intrathecally act on the μ (mu) receptors in the substantia gelatinosa of the dorsal horn by suppressing excitatory neuropeptide release from C fibers [10].

The uptake of opioids into the systemic circulation after intrathecal administration is usually not significant because the typical doses used are very small. The degree of uptake from the cerebrospinal fluid is determined by the lipid solubility of the drug.

### Fentanyl

- Fentanyl, with its high lipid solubility, has a relatively rapid uptake into the dorsal horn and thus has a fast onset of action.
- Fentanyl's rapid uptake results in small cerebrospinal fluid concentrations and a decreased potential for it to diffuse to higher spinal levels.
- Thus, fentanyl's analgesic effect is mostly segmental.

### Morphine

- Morphine, with its low lipid solubility, has a relatively prolonged duration of action because it remains in the cerebrospinal fluid longer than fentanyl.
- A systematic review of intrathecal opioid studies showed that intrathecal morphine at doses of 100 to 200 μg provided optimal analgesia with a median time to request supplemental analgesia of 27 hours (range 11 to 29 hours), whereas intrathecal fentanyl provided analgesia for 4 hours (range 2 to 13 hours).
- Intrathecal morphine reduced pain scores and the amount of supplemental analgesics required in a 24-hour period after cesarean section, while the use of intrathecal fentanyl did not affect 24-hour post cesarean section pain scores or consumption of supplemental analgesics compared to controls [5].
- Intrathecal morphine has a dose ceiling effect for analgesia. A meta-analysis showed excellent efficacy of morphine at doses of 100 to 200 μg but no additional pain relief when the doses exceeded 200 μg, and minimal analgesia with doses less than 100 μg [5].

## Epidural opioids

- Epidurally administered morphine prior to removal of the catheter has been shown to provide a duration of postoperative analgesia of 18 to 26 hours, which is similar to intrathecal morphine [11].
- Morphine slowly crosses the arachnoid granulations, and thus the speed of onset of analgesia is slow. Large concentrations of ionized morphine eventually accumulate in the cerebrospinal fluid that lead to cephalad diffusion and a long duration of analgesia.
- Fentanyl diffuses rapidly into epidural veins, segmental arteries, and across the arachnoid granulations and dural cuff into the cerebrospinal fluid. Thus, in addition to diffusing to spinal receptors in the cerebrospinal fluid, fentanyl likely acts at both spinal and supraspinal (by systemic delivery) sites [12].
- Epidural morphine also has a dose ceiling effect. Palmer *et al.* evaluated the use of varying doses of epidural morphine (0 to 5 mg) and found that there was no additional pain relief with doses greater than 3.75 mg [11].
- A systematic review of epidural morphine concluded that 4 mg was the optimum dose – giving the best balance of duration of analgesia and side effect profile [13].
- Sustained-release preparations of morphine via the epidural space have been shown to provide prolonged analgesia without increased side effects compared to conventional epidural morphine preparations [14].

The use of indwelling epidural catheters post cesarean section is uncommon because although they provide good postoperative analgesia, they have a high incidence of becoming dysfunctional and the epidural infusion equipment can be cumbersome and interfere with ambulation and the mother's ability to care for her newborn.

## Adjuvant neuraxial medications

- Neuraxial neostigmine (an acetylcholinesterase inhibitor) produces analgesia through inhibition of the degradation of acetylcholine in the spinal cord, leading to increased stimulation of spinal muscarinic and nicotinic receptors. It also prolongs and intensifies analgesia through the release of nitric oxide in the spinal cord. It has been shown to increase the duration of analgesia and have no significant effect on fetal heart rate and uterine contractions. However, clinical use is limited because of concern regarding sedation, severe nausea and vomiting, and prolongation of motor block when combined with local anesthetics for intrathecal administration [15, 16].
- Neuraxial clonidine (α2 adrenergic receptor agonist) added to hyperbaric bupivacaine has been shown to prolong spinal anesthesia, and improve early post cesarean section analgesia, but does not reduce opioid consumption [17]. However, hypotension, sedation, prolonged motor blockade, and perioperative vomiting are potential severe side effects [18].

## Systemic opioids

- Systemic administration of opioids is most commonly used for post cesarean section pain management after general anesthesia.
- The ease of administration, low cost, and long history of use in postpartum women are the main advantages of systemic administration.

- Opioids can be administered as needed by nurses (intramuscular, subcutaneous, or intravenous) or through a patient-controlled analgesia (PCA) pump.
- Pain relief with PCA has been shown to be superior to intramuscular opioids in women after cesarean section [19]. However, when comparing post cesarean section pain in patients treated with PCA morphine vs. epidural morphine, 40% had moderate to severe pain in the PCA group compared to 15% in the epidural morphine group [19]. Although less efficacious than neuraxial analgesia, patient satisfaction scores are higher with PCA [4, 5, 19]. Greater autonomy with PCA may correlate with greater patient satisfaction compared to neuraxial opioid. Also, the higher incidence of pruritus, nausea and vomiting, and urinary retention likely contributes to the lower patient satisfaction scores for neuraxial opioids.

## Oral opioids

- Oral opioids are usually used as step-down analgesia after neuraxial or PCA opioids. Tylenol® #3 (acetaminophen with codeine) was previously the most common oral opioid offered. As a prodrug, the analgesic effects of codeine are almost entirely attributed to its principal metabolite, morphine.
- However, the pharmacokinetics of codeine are unpredictable. Specifically, polymorphisms in the cytochrome P450 CYP2D6 isoenzyme can enhance the rate of metabolism of codeine to morphine. This pharmacogenetic variation has been implicated in the death of a breastfed neonate, whose mother had been administered codeine postpartum [20]. The ultra-rapid metabolization of codeine resulted in greater quantities of morphine being transferred through breast milk and causing neonatal respiratory depression.
- At our center, codeine is no longer promoted for analgesia after cesarean section. Instead, we emphasize the use of multimodal analgesia, with oxycodone for breakthrough pain in the first two to three days post cesarean section. The small volumes of colostrum ingested during the first two to three days postpartum limit the neonate's exposure and thus pose minimal risk [21]. No adverse effects have been observed in breastfed neonates of mothers using oxycodone in the early postpartum period [21].
- Most of our patients do not require substantial amounts of supplemental oxycodone after receiving a neuraxial opioid, and our usual dose is 5 mg every four to six hours as needed (equating to the recommended maximum daily dosage of 20 to 30 mg). However, nurses and mothers are educated to monitor their babies for signs of opioid exposure, such as sedation, poor attachment, gastrointestinal symptoms, and respiratory depression.

NB Motherisk (The Hospital for Sick Children, Toronto, www.motherisk.org) is currently investigating the effects of oxycodone in breastfeeding mothers and their babies.

## Multimodal analgesia

Neuraxial analgesia may not completely relieve pain after cesarean section. However, intake of analgesics postpartum is often inadequate because mothers wish to avoid medication during breastfeeding. The aim of a multimodal approach is to gain synergistic or additive analgesia with fewer side effects by combining lower quantities of each drug, which have different mechanisms of action.

## Non-steroidal anti-inflammatory drugs (NSAIDs)

- NSAIDs have been shown to potentiate the quality of systemic or neuraxial opioid analgesia, while decreasing opioid consumption and side effects for post cesarean section analgesia [22, 23].
- Although they have a ceiling effect for analgesia, they have both anti-inflammatory and antipyretic properties. In addition, they are effective for treatment of uterine cramping pain.
- Potential problems with bleeding, platelet dysfunction, gastrointestinal side effects, and renal insufficiency may limit the use of NSAIDs.
- Although there is an FDA black box warning against the use of ketorolac in laboring (theoretical adverse affect on fetal circulation and risk of uterine atony) and nursing mothers (potential adverse effect of prostaglandin inhibitor drugs on the neonate), NSAIDs are generally regarded as safe in breastfeeding women by the American Academy of Pediatricians [24].

## Acetaminophen

- Acetaminophen (known as Tylenol® or paracetamol) is a common component of multimodal analgesic regimens used postoperatively.
- A Cochrane review found that acetaminophen provides effective postoperative analgesia with few adverse effects [25].
- Acetaminophen may work through central COX 2 inhibition, with a reduction in central nervous system prostaglandin E2 production and activation of descending serotonergic pathway.

Studies in the obstetric population are limited, with mixed results.

- A randomized controlled trial comparing intravenous acetaminophen 1 g with oral ibuprofen 400 mg post cesarean section found no difference in opioid consumption and concluded that intravenous acetaminophen was a reasonable alternative to oral ibuprofen as an adjunct to PCA morphine after cesarean section [26].
- Siddik *et al.* found a significant morphine-sparing effect with rectal diclofenac but not intravenous propacetamol (a precursor of acetaminophen) and no additional benefit when both were combined [27].
- In contrast, Munishankar *et al.* found that the combination of acetaminophen and diclofenac resulted in significantly less morphine consumption than acetaminophen alone [28].

Despite these mixed results, there is little risk associated with acetaminophen therapy and it is used almost routinely for postoperative pain management.

## Ilioinguinal and iliohypogastric nerve blocks

Both ilioinguinal and iliohypogastric nerves can transmit the somatic pain from a Pfannenstiel incision. Evaluation of the efficacy of these nerve blocks for managing post cesarean section pain has been limited since the original study published in 1988 [29].

- In a double-blind, randomized, and placebo-controlled trial bilateral nerve blocks were carried out after cesarean section using anatomical landmarks and the loss of resistance technique [30]. The primary outcome measure was the total intravenous morphine consumption at 24 hours after surgery. Those patients receiving nerve blockade with bupivacaine had a significant decrease in morphine consumption compared to the placebo group. However, there was no significant decrease in opioid-related side effects such as nausea and pruritus.
- The variation of the locations of the ilioinguinal and iliohypogastric nerves reduces the success of blind techniques, and clinical studies have quoted success rates ranging between 55 and 95% [30].

The use of ultrasound has been advocated to ensure consistent successful nerve blockade.

- A recent case series reported three patients who received ultrasound-guided ilioinguinal and iliohypogastric continuous nerve blockade via catheters using ropivacaine 0.2% for 72 hours postoperatively [31]. Patients were reported to have had low pain scores for the duration of the blocks with minimal opioid consumption and side effects. Despite the small sample size, these results are encouraging and warrant further investigation in formal trials using ultrasound guidance.

## Transversus abdominis plane (TAP) blocks

An important component of the pain experienced by women after cesarean delivery originates from the surgical incision in the lower anterior abdominal wall. This area is innervated by the ventral rami of the lower six thoracic spinal nerves (T7 to T12) and the first lumbar nerve. Branches of these nerves travel in the neurofascial plane between the internal oblique and transversus abdominis muscles of the abdomen, in the transversus abdominis plane (TAP). Injection of local anesthetic in this plane blocks these sensory nerves and can provide analgesia to the skin, muscles, and parietal peritoneum of the anterior abdominal wall from T7 to L1 [32].

Randomized, controlled trials examining the efficacy of TAP blocks in the obstetric population are few and have reported conflicting results. The mixed results are likely due to differences in technique, drugs, and outcome measures.

- The first study by McDonnell was performed using the anatomical landmark of the lumbar triangle of Petit and a loss of resistance technique to access the TAP [33]. In this study, patients were randomized to receive ropivacaine 0.75% or a saline placebo block.
- The other two studies by Belavy and Costello were performed with ultrasound guidance and lower concentrations of ropivacaine, 0.5% and 0.375% respectively [34, 35].
- In the studies by McDonnell and Belavy, patients were given spinal anesthetic without morphine for the cesarean section. Both these studies found that TAP blocks significantly decreased opioid requirements for patients. However, visual analogue scale (VAS) pain scores were not significantly different between groups after 24 hours.
- The randomized, controlled trial by Costello *et al.* examined the efficacy of TAP blocks after cesarean section when used as part of a multimodal regimen inclusive of spinal morphine [35]. This study failed to show any difference in VAS pain scores between groups at 24 hours, which was the primary outcome measure. As well, supplemental opioid consumption was no different. In this particular study, there has been concern

raised that the block was performed in such a manner that there may be inconsistent block of the targeted nerves [36, 37]. Local anesthetic was deposited some distance from the iliac crest and above the fascial layer overlying the transversus abdominus muscle. This would result in a failed block since nerves that supply the lower abdominal wall travel close to the anterior iliac crest below this layer.

- A recent randomized, controlled trial by Kanazi *et al.* compared the efficacy of ultrasound-guided TAP blocks with bupivacaine 0.375%, 20 ml each side, to spinal morphine for pain after cesarean delivery [38]. The time to first analgesic request, which was the primary outcome, was longer in the spinal morphine group compared to the TAP group (8 hr vs. 4 hr). However, there were more side effects in the spinal morphine group. Of note, the dose of spinal morphine used in this study was 200 μg, which is twice the dose many recommend.

Presently, the role of TAP blockade for cesarean section pain seems limited to reducing the use of supplemental opioid consumption. Early postoperative pain scores tend to be significantly reduced but this effect may be limited to the first 24 hours postoperatively. Further studies should be conducted to more thoroughly evaluate the role of the TAP block but particular attention must be paid to the correct anatomical deposition of local anesthetic. In addition, the use of TAP catheters to extend the duration of analgesia would be of interest since benefits of single-shot injections seem limited to the duration of action of the local anesthetic.

## Wound infiltration

Infiltration of cesarean section wounds for pain control has been investigated in several trials. The placement of catheters for infusions or one-time injections of local anesthetic at wound closure have been studied. Such techniques are simple, safe, and can reduce postoperative pain and the need for supplemental opioids.

- Study outcomes for infusion catheters have been variable, possibly owing to differences in methodology and catheter placement. Several randomized, double-blind, controlled trials placing catheters above muscular fascia have shown that local anesthetic infusions can reduce opioid consumption from 25 to 73%. Pain score reduction seems to be modest with most studies showing that control and placebo groups experience equivalent pain scores after the first postoperative day [39–41]. In contrast, three studies have failed to show benefit from wound infusion catheters when compared to epidural catheters or intravenous NSAIDs [42–44].
- Infusion of NSAIDs instead of local anesthetics through wound catheters has also been investigated. A local infusion of diclofenac (300 mg over 48 hours) had a greater opioid-sparing effect and better postoperative analgesia than the same dose administered as an intermittent intravenous bolus. Furthermore, analgesia produced by local diclofenac infusion was as effective as local ropivacaine infusion with systemic diclofenac [45].

One of the criticisms of past studies is that wound catheter placement should be between the parietal peritoneum and transversalis fascia. This may have better analgesic efficacy owing in part to improved blockade of parietal nociceptors.

- A randomized, controlled trial comparing above-fascia to below-fascia catheter placement showed a robust decrease in 48 hour, postoperative opioid consumption for below-fascia catheter placement [46].

Single-shot injections of local anesthetic to the wound have also been evaluated.

- For women undergoing cesarean section under general anesthesia, wound infiltration and peritoneal spraying with 0.75% ropivacaine has been found to reduce the incidence of severe/unbearable pain as well as the need for opioids in the immediate postoperative period [47].
- A similar trial was performed with similar results for women undergoing cesarean section with spinal anesthesia, using 0.75% ropivacaine infiltration to the wound only [48].

Overall, wound infiltration techniques have produced modest results for postoperative pain control.

- A recent Cochrane analysis has revealed that women with wound infiltration benefit through reducing opioid consumption. A standard mean difference of –1.70 mg morphine (95% CI –2.75 to –0.94) at 24 hours postoperatively was reported [49].

## Conservative therapies

The use of acupuncture and transcutaneous electrical nerve stimulation (TENS) to reduce postoperative pain has been evaluated in randomized, controlled trials [50–52]. However, trials have been limited by unblinding or a lack of detail surrounding the intraoperative anesthetic care (e.g. describing if patients received spinal vs. general anesthesia).

- Use of acupuncture has been evaluated in a randomized, controlled trial in which patients were assigned to a control group or a session of acupuncture or electro-acupuncture in the post anesthetic care unit. Spinal anesthesia was provided to all patients but details of intrathecal drug administration were not reported. Patients were provided with PCA morphine postoperatively. Both acupuncture groups had reductions in the total dose of PCA morphine used within the first 24 hours by 30 to 35% compared to the control group. Pain scores in the acupuncture groups were lower than those in the control group but this effect was only significant for the first two postoperative hours [52].
- A randomized, placebo controlled trial has provided an unblinded evaluation of the use of postoperative TENS unit therapy. Participants were provided with spinal anesthetics without the use of opioids in the intraoperative peroid. In the immediate postoperative period, patients were provided with a standard acetaminophen dose, patient-controlled analgesia with morphine, and those in the treatment arm received TENS unit therapy continuously for at least 24 hours. Total morphine consumption after the first 24 hours was significantly less with the use of TENS unit therapy by approximately 50%, with no differences in VAS scores [51].

Evidence for the use of acupuncture and TENS unit therapy in the postoperative period for pain control is limited. However, there is a suggestion that these conservative therapies can serve as useful adjuvants. Ultimately, trials evaluating these modalities are limited given that patients and investigators are not easily blinded to treatment allocations.

## Development of chronic pain following cesarean section

The Pfannenstiel incision is a favorable approach for cesarean deliveries and other gynecologic surgeries due to its low rate of incisional hernias and discrete scar line [53]. However, studies have shown that development of chronic postoperative pain is a common occurrence.

- A survey of women who had Pfannenstiel incisions for cesarean sections revealed that 18.6% of patients had pain at three months and 12.3% of patients still had pain at a mean follow-up of 10.2 months. Of those 12.3%, 5.9% had pain present daily or almost daily [54].
- A commonly proposed etiology of chronic pain following Pfannenstiel incisions is injury to the ilioinguinal, iliohypogastric, or genitofemoral nerves. These nerves originate from the lumbar plexus, which has a large degree of anatomic variability. Consequently, these nerves are vulnerable to injury during surgical procedures since anatomic landmarks may not be reliable. Injury may include nerve transection, trauma, or entrapment in surrounding scar tissue resulting in neuroma formation. It is estimated that 15 to 53% of patients complaining of chronic pain from these incisions have neuropathic pain caused by entrapment of these nerves [53, 55].

Several risk factors have been identified that correlate with the development of chronic pain after Pfannenstiel incisions [53–55]:

- length of incision
- use of general anesthetic
- severe, acute postoperative pain
- numbness surrounding the incision
- recurrent Pfannenstiel incision
- emergency cesarean delivery.

If chronic pain is suspected to be secondary to a neuroma, patients may be treated conservatively with neuropathic pain medications (such as tricylic antidepressants or gabapentenoids). Invasive therapies can include the injection of local anesthetics, with or without steroids, around the injured nerves. Further intervention can include referral to a peripheral nerve surgeon either for resection of a neuroma or nerve decompression from fibrous scar tissue [56].

## Our practice

- Currently at our center, intrathecal morphine (100 to 300 μg) or epidural morphine (2 to 4 mg) is used with regional anesthesia for cesarean section.
- If a general anesthetic is provided, patients are prescribed opioid-based patient-controlled analgesia for post cesarean section pain.
- TAP blocks may also be offered.
- Multimodal analgesia including NSAIDs and acetaminophen dosed around the clock, with oxycodone for breakthrough pain, is usually prescribed. In addition, prophylactic antiemetics and antipruritics are usually given.

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