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Non-obstetric surgery for the obstetric patient

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INTRODUCTION

Diagnosis of non-obstetric surgical conditions in an obstetric patient can be challenging. Clinicians may be misled by the “natural” symptoms of pregnancy which often results in the delay of treatment(1).

The incidence of surgical intervention in pregnant patients’ worldwide range from 0.75-2% (2). Surgery in pregnant patients is associated with a higher risk for post-operative complications including pneumonia, sepsis, urinary tract infection and in hospital mortality (3–5). With pregnant patients, the goal is to ensure maternal safety and maintain the pregnancy in order to achieve the best possible foetal outcome. Coleman and colleagues showed surgical mortality was not significantly greater in pregnant women compared non-pregnant women (6).

All available data are obtained from retrospective case series and meta-analyses with no randomized control trials available (7). Norwitz and co-workers established guidelines for the optimal management of pregnancy patients undergoing non-obstetric surgery.

TYPES AND TIMING OF SURGERY

Upadya et al., found the most common non-obstetric indications for surgery being; appendicitis, ovarian disorders and trauma (8).

Reitman and colleagues quote acute abdominal infections (acute appendicitis incidence 1:2000 pregnancies and cholecystitis 6:1000 pregnancies), maternal trauma and surgery for maternal malignancy as being the most common indications for non-obstetric surgery (9).

During a 16 year retrospective, case controlled cohort study, Devroe and colleagues looked at 171 pregnant women and also found intra-abdominal surgeries to be the most commonly performed, followed by trauma and urological procedures (10).

Mezze and colleagues conducted a large study focusing on anaesthesia and surgery during pregnancy, and found that 42% of surgery occurred during the first trimester, 35% during the second trimester & 23% during the third trimester (11).

DECISION MAKING FOR NON-OBSTETRIC SURGERY

The American College of Obstetricians and Gynaecologists' Committee (ACOG) passed an opinion which stated that a pregnant woman should not be denied indicated surgery or have her surgery delayed, regardless of trimester(12). It is also advised that a multi-disciplinary team involving obstetricians, anaesthesiologists and surgeons should be involved in the decision making process and the primary obstetric care provider should be notified (12).

Timing of surgery appears to be critical to foetal outcome with an overall miscarriage rate of 5.8% after surgery, and rising to 10.5% during the first trimester (13). The decision for surgery is dictated by the maternal indication.

Elective surgery should be delayed until after delivery, as late as 6 weeks postpartum (8,12), which allows for the return of maternal physiology to its non-pregnant state. The second trimester appears to be the ideal time for semi-elective surgery, with the latter part being more favourable to ensure the foetus is viable in the event of a precipitous delivery (1,8). The advanced stages of pregnancy are associated with greater risk of uterine irritability and preterm labour as a result of the direct handling of the uterus or disease process with no evidence found to suggest a correlation between anaesthetic technique, agent or dose used (8). Urgent surgery should not be delayed (8).

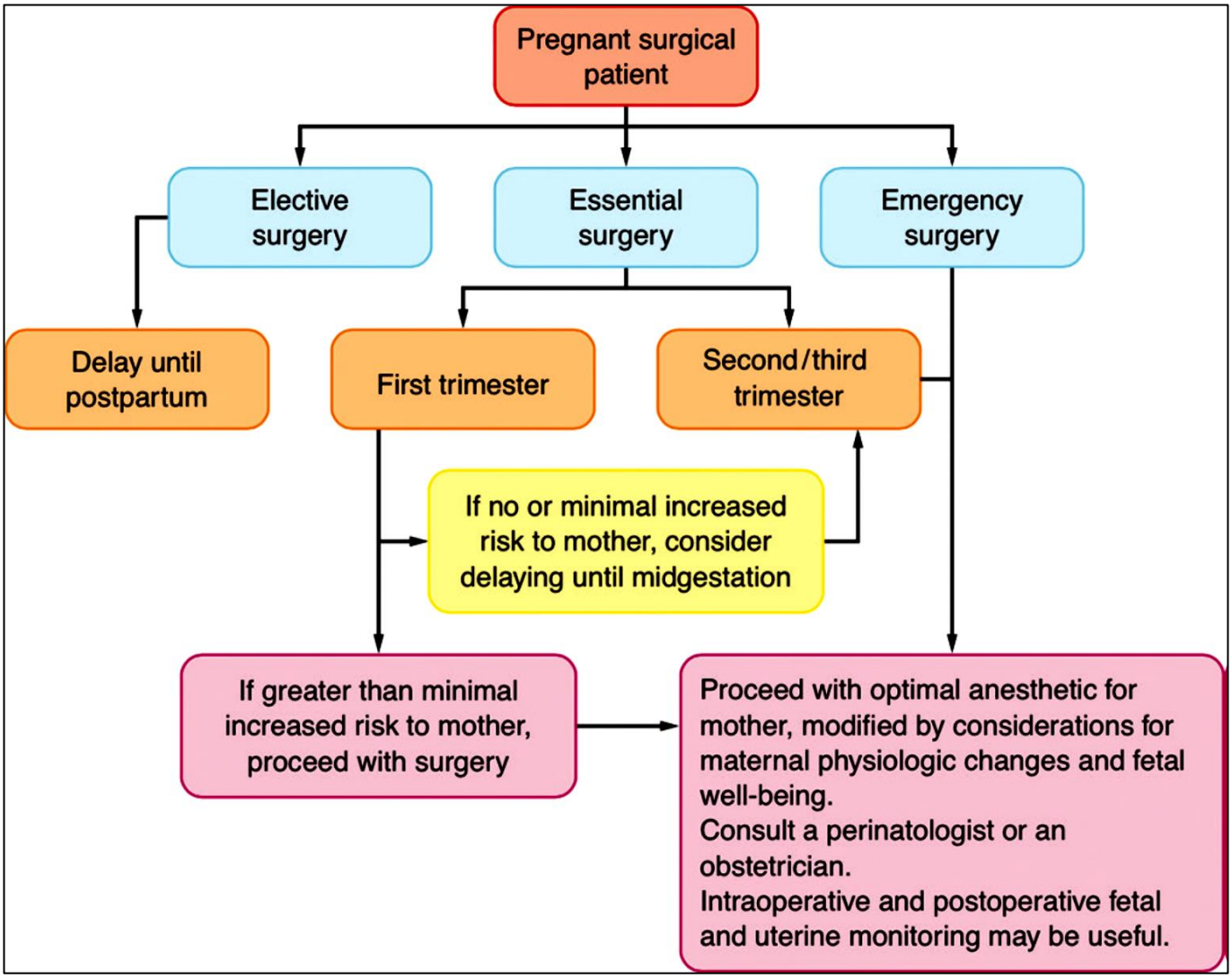

***Figure 1**. Decision making algorithm (8)*

PHYSIOLOGICAL CHANGES OF PREGNANCY

Changes that occur later in pregnancy are associated with mechanical effects of the enlarging uterus, increased metabolic demands of the foetus and the low resistance placental circulation (2).

HAEMATOLOGY	Plasma volume increases: this increases preload and VD of polar drugs. It increases up to 50% by term. RBC mass increases: plasma increases more than RBC, causing physiological anaemia. WBC increase: to 12 × 10^9/L by term, with a further increase to 30 × 10^9/L during labour. Platelets reduce due to consumption. Albumin decreases: this increases the free active proportion of protein-bound drugs. Plasma oncotic pressure reduces, increases the risk of oedema. Plasma cholinesterase reduces: the effect of suxamethonium is offset by the increased VD.

	Hypercoagulable: all clotting factors increase except XI and XIII. BT, PT and APTT shortened. High risk of thromboembolic complications. CRP and ESR increase.
CARDIOVASCULAR	Stroke volume and heart rate increase: cardiac output increases by up to 60% by term (8 L/min). Systemic vascular resistance reduction: reduction in DBP greater than SBP leading to an increased pulse pressure. This is due to oestrogen and progesterone. Maintenance of SVR is governed by sympathetic drive, which is diminished by central neuraxial blockade. Left ventricular mass increases: ECG shows left axis deviation, ST depression and even a flat or inverted T-wave. Systolic murmur almost universal at term but note that a diastolic murmur is not normal. Vena caval compression reduces venous return and preload, decreased cardiac output, decreased BP and engorged vertebral veins. Aortic compression: occurs from 20 weeks gestation. Increases afterload, decreases cardiac output and utero-placental blood flow. This is decreased by avoiding supine position and using at least 15° lateral tilt.
RESPIRATORY	**Anatomy:** Capillary enlargement and mucosal congestion can lead to voice changes and difficulty breathing in some women. The diaphragm is elevated by 4cm, thoracic circumference increases as the ribs 'splay' out and breathing becomes largely diaphragmatic by term. **Volumes:** FRC reduces by up to 20% and closing volume encroaches on FRC, leading to airway closure and increasing the risk of hypoxia. This is made worse when supine, obese or with multiple pregnancy. TLC and VC remains unchanged. Ventilation: respiratory rate and minute ventilation increase. Dead space increases due to bronchodilation. Mechanics: chest wall compliance reduces but lung compliance remains unchanged. Oxygen consumption increases: by up to 60%, increasing the risk of developing hypoxia during induction of anaesthesia. ABG: pH increases (to ~7.5), PO_2 increases (to ~14kPa), PCO_2 reduces due to hyperventilation (to ~3.5kPa) and HCO_3^- reduces (to ~18mmol/L).
GASTRO-INTESTINAL	Barrier pressure reduces due to increased intragastric pressure. Gastric emptying is reduced: this occurs during labour due to the effects of pain and opiates. Risk of aspiration increases: this returns to normal levels 48 hours post-partum.
RENAL	Renal blood flow and GFR increase by up to 50%. Urea and creatinine levels reduce, meaning that a 'normal' creative level in pregnancy is abnormal. Glycosuria and proteinuria: common.

CENTRAL NERVOUS SYSTEM	Epidural space reduces due to the engorged extradural venous plexus. Cerebrospinal fluid volume is also reduced. Hence reduced volumes of local anaesthetic agents are required during central neuraxial blockade (reduce dose by one-third). There is also an increased risk of inadvertent intravascular catheter placement. Anaesthesia: MAC decreased. Inhalational induction is faster (as raised MV is more significant factor that raised CO in this case). Following labour, a woman has reduced strength in respiratory muscles for around 4 hours. Anaesthesia compounds this effect and reduces ability to cough.
ENDOCRINE	Thyroid: increases in T3 and T4, may suppress TSH. Insulin: increased secretion from hypertrophied beta cells, but increased production of 'anti-insulin' hormones, e.g., cortisol. Gestational diabetes can result. Glucose crosses placenta by facilitated diffusion to protect foetus from fluctuating maternal levels.

Table 1. *Physiological changes of pregnancy (14)*

VD=volume of distribution; RBC=red blood cell; WBC= white blood cells; BT= bleeding time; PT= prothrombin time; aPTT= activated partial thromboplastin time; CRP= c reactive protein; ESR= erythrocyte sedimentation rate; SBP= systolic blood pressure; DBP= diastolic blood pressure; FRC= functional residual capacity; TLC= total lung capacity; VC= vital capacity; GFR= glomerular filtration rate; MAC= minimal alveolar concentration; MV=minute ventilation; CO= cardiac output; T3= tri-iodothyronine; T4= thyroxine ; TSH= thyroid stimulating hormone

PERI-OPERATIVE CONSIDERATIONS

ANAESTHETIC CONSIDERATIONS

Maternal safety (8)	1. Physiological changes of pregnancy 2. Conditions compelling surgery during pregnancy
Foetal safety	1. Placental transfer of drugs 2. Issue of teratogenicity: -Timing of exposure -Duration/dosage of exposure -FDA pregnancy category -Individual anaesthetic drugs 3. Maternal factors leading to foetal compromise: -Maternal hypoxia -Maternal hyper/hypocarbia -Changes in uterine blood flow
Avoidance and/or treatment of preterm labour and delivery	1. Identification 2. Management

Table 2. *Anaesthetic considerations for a pregnant patient (1)*

MATERNAL

PHYSIOLOGICAL CHANGES (1)	ANAESTHETIC IMPLICATIONS
Airway:	
Increased soft tissue in the neck, weight gain and breast engorgement. Increase in Mallampati Grading as pregnancy progresses.	Difficult mask ventilation, laryngoscopy and intubation
Increased oedema of the airway and vocal cord	Difficult intubation. Smaller sized endotracheal tubes should be used
Increased vascularity of mucous membranes	Epistaxis with nasal intubation
Respiratory:	
Respiratory alkalosis (PaCO2 28-32 mmHg)	Maintain PaCO2 at normal pregnancy levels
Reduced FRC (20%) and increased oxygen demand (20%)	Tendency for early desaturation. Careful preoxygenation is a must.
Increased minute ventilation	Faster inhalational induction
Cardiovascular:	
Decreased BP, SVR	Increased incidence of hypotension after general and spinal anaesthesia
Lack of autoregulation of uterine vasculature	Foetal blood supply depends on maternal BP. Maintain normotension.
Aortocaval compression after 20 weeks of gestation	Supine hypotension syndrome is common. Left lateral tilt (15°) to reduce compression
Gallop rhythm, left axis deviation, systolic murmur, minor ST-T changes	Misleads the clinician to a cardiac disease
Increased blood volume and cardiac output	Decompensation of cardiac valvular lesions
Blood and coagulation:	
Haemodilution with resting tachycardia	Delay in onset of classical signs of hypovolemia and increased risk of bleeding.
Hypercoagulability	Perioperative DVT prophylaxis in high-risk patients
Gastrointestinal:	
Reduced lower oesophageal sphincter tone	Consider all pregnant patients as full stomach. Mandates Rapid sequence induction
Distorted gastric and pyloric anatomy	Anti-aspiration prophylaxis and antacids as part of pre-operative preparation (after 16 weeks)
Increased gastric volume and acidity	
Pharmacological	
Non-depolarising muscle relaxants have a prolonged duration of action.	
Decrease in plasma cholinesterase levels.	Prolongs neuromuscular blockade with depolarising muscle relaxants, however, this is not common due to increased blood volume causing an increased volume of distribution
Increase in neural tissue sensitivity and free fraction.	Therapeutic and toxic doses of local anaesthetics are decreased.

Table 3*. Anaesthetic consideration for a pregnant patient: maternal* (13,15)

Airway

In a study of 1500 pregnant women undergoing caesarean under general anaesthesia, Rocke and colleagues calculated the relative risk of difficult intubation in women with Mallampati grade III and IV to be 7.5 and 11.3 compared to those with grade I airways (16). They also concluded that the Mallampati classification of airways is more predictive of difficult intubation in pregnancy than in non-pregnant women. Pilkington et al. photographed oral airway examinations in 242 pregnant women and found that from 12 to 38 weeks gestational age; the incidence of grade IV airways increased by 34% (17).

The higher incidence of failed intubation during general anaesthesia in pregnant patients has been debated in the literature. Whilst not all pregnant women are difficult to intubate, there is an increase in the incidence of failed intubation as we have moved away from routine general anaesthesia in pregnancy (2).

Cheek and colleagues described interventions to decrease the risk of maternal airway loss which included improved clinical training with the use of simulations and emergency airway algorithm drills, availability of advanced airway devices, experienced anaesthetic clinicians readily available and the use of regional anaesthesia (18).

Respiratory

Due to the demands of the growing foetus, there is an increase in oxygen demand (up to 60% at term) which is met by an increase in minute ventilation and cardiac output (19). This increase in minute ventilation by up to 45% at term is due to an increase in both respiratory rate and tidal volumes and causes a subsequent respiratory alkalosis ($PaCO_2$ decreases by 1kPa) which is limited by increased excretion of bicarbonate by the kidneys (19). Mild hyperventilation is mediated by progesterone-enhanced brainstem sensitivity to $PaCO_2$. During ventilation, relative hypocapnia targeting a $PaCO_2$ of 3.7-4.3kPa should be maintained, as rise in maternal $PaCO_2$ causes acidosis in the foetus by limiting the gradient for CO_2 diffusion (15).

Positioning

The gravid uterus causes aortocaval compression and impedes venous return to the heart. Vena caval compression has been reported as early as 13-16 weeks (20). The gestational age for which one should institute 15 degree left uterine displacement (LUD) is inconsistent (15). Haggerty recommends using LUD starting at 18 weeks (15) with Nejdlova and colleagues suggesting 20 weeks (13). LUD is indicated earlier in pregnant patients who have a raised BMI, multiple gestion or polyhydramnios (13,15). This can be achieved by placing a wedge under the right hip.

ANAESTHETIC CONSIDERATIONS: FOETAL

The effect of drugs delivered to the foetus depends on numerous factors including the timing of foetal exposure; with respect to its development, dosage and route of administration etc. To date, no anaesthetic drug has been proven to be clearly hazardous to the human foetus (8). There are no animal models available that perfectly simulates human gestation and randomised trials on pregnant women would be unethical.

Placental transfer of drugs

Mechanisms of transfer of drugs across the placenta include:

1. Simple diffusion: oxygen and carbon dioxide.
2. Active transport: calcium and iron
3. Secondary active transport: amino acids
4. Facilitated transport: glucose
5. Pinocytosis: immunoglobulin G

Whilst all substances in the maternal circulation are potentially available to the foetus, the transfer of drugs depends on a variety of factors including:

1. Lipid solubility: The more lipid-soluble a substance is, the more rapidly it will be transferred across the placental membrane.
2. Degree of protein binding: A highly protein bound substance will not cross the placenta readily. The unbound fraction of substances will cross through the placenta and become available in the foetal circulation. A higher fraction of “free” drug is found in pregnant women as they have a low total protein content.
3. Degree of ionisation: The more ionised a drug is, the less easily it is able to diffuse across the placenta.
4. pH: This affects the degree of ionisation of the drug, as dictated by its pKa.
5. Molecular weight: Substances with a molecular weight of less than 600 Daltons cross the placenta easily.
6. Concentration gradient across the placenta: This affects speed of transfer.

Drug	Properties	Placental transfer	Remarks
Induction agents:			
Thiopental	Highly lipid soluble, weak acid	+++	Quickly cleared by neonate after delivery
Propofol	Lipid soluble	+++	Transient depression of Apgar score and neurobehavioral effects in neonate
Ketamine	Weak base	++++	F/M ratio 1.26 occurs within 2 min of intravenous bolus Inhalation agents
Inhalational agents:			
Volatiles	Highly lipid soluble; low molecular weight	+++	Greater sedative effect on neonate if dose-delivery interval is prolonged
Nitrous oxide		++	Possible diffusion hypoxia in neonate
Opioids:			
Morphine	Less lipid soluble; but low protein-binding	++	
Fentanyl	Lipid soluble	+++	
Pethidine	Only 50% plasma protein bound	++	Prolonged neonatal depression due to increased half-life of meperidine and its metabolite - normeperidine
Remifentanil		+	No adverse foetal effects as rapidly metabolised by foetus
Naloxone		+++	Though short-term safety of naloxone is well documented, it should be used only in cases of absolute or relative maternal opioid overdose.
Benzodiazepine	Highly lipid soluble	++	More neonatal depression; midazolam - less placental transfer than diazepam
Neuromuscular blockade agents	Large molecules; poorly lipid soluble; highly ionised	-	No significant clinical effects on foetus
Anticholinergics			
Atropine	Lipid soluble; tertiary amine	++	
Glycopyrrolate	Fully ionised; quaternary ammonium compound	-	
Neostigmine	Quaternary ammonium compound; but a small molecule	+++	May cause foetal bradycardia; hence it is better to add atropine to neostigmine in incidental surgery during pregnancy
Local anaesthetics:			
Lignocaine	Less lipid soluble; low protein binding	++	Can accumulate in the foetus due to 'ion trapping' if the foetus becomes acidotic
Bupivacaine, Ropivacaine	Highly lipid soluble; but high protein binding	++	

Table 4. *The placental transfer of commonly used drugs (8)*

TERATOGENECITY

Drugs affect cell signalling, cell division and DNA synthesis all of which are integral components of organogenesis (21). A teratogen is defined as a substance that causes an increase in the incidence of a specific defect in a foetus that cannot be attributed to chance occurrence (8).

For a substance to exert its teratogenic effects on a foetus, it must be administered in a sufficient dose for a substantial time period and at critical development point (8).
During the first 2 weeks of human gestation, the foetus displays an all or none phenomenon when exposed to a teratogen (19). During organogenesis (week 3 to 8), the foetus is most sensitive to the disruption of cellular processes (1). Following this period, organ growth occurs and exposure here, may lead to growth restriction or organ dysfunction (1).

Despite many studies in the animal population and observational studies in humans; no anaesthetic drug has been shown to be clearly hazardous to the human foetus (1,2,8). It is important to use the lowest effective concentrations for the minimum possible time, so as to avoid changes in maternal physiology (8). A key point to also consider is the incidence of congenital anomalies which is noted to be approximately 3% (8). In addition physiological derangements during anaesthesia and surgery such as hypoxaemia, hypercarbia and hypotension may be teratogenic as well (8).

Benzodiazepines (FDA Class D) have been associated with a cleft palate and cardiac anomalies in animal studies but its association in humans remains controversial with more recent studies refuting the association (2,19). A single dose of midazolam has not been associated with teratogenicity (1).

Nitrous oxide has been found to inhibit methionine synthetase which affects the synthesis of the developing foetus and thus should be avoided (22). It has shown to be teratogenic during peak organogenesis in rodents, but there is no evidence in humans (19). Studies have showed a convincing association between exposure to unscavanged nitrous oxide and reduced fertility in medical personnel (2), with a secondary analysis of the data analysed by Rowland and colleagues finding an increased risk of spontaneous abortion with exposure to unscavanged nitrous oxide in the dental setting (23). Studies carried out in hospital settings with scavenging systems in place have failed to show an association between nitrous oxide use and adverse pregnancy outcome (2).

Ketamine increases uterine tone and is found to cause foetal asphyxia (1). It is best avoided during the first 2 trimesters with no effect found in the third trimester (19).

Most other anaesthetic drugs, including barbiturates, propofol, opioids, neuromuscular blockade drugs and local anaesthetics have a good safety record for use during pregnancy, however, subtle associations cannot be ruled out (2).

- ACE inhibitors	- Valproic Acid
- Alcohol	- Lithium
- Androgens	- Phenytoin
- Antithyroid drugs	- Streptomycin
- Carbamazepine	- Tetracycline
- Chemotherapy agents	- Thalidomide
- Cocaine	- Trimethadione
- Warfarin	- Diethylstilbesterol

Table 5. *Drugs associated with teratogenicity (2)*

Maternal factors linked to foetal asphyxia

During surgery, uterine asphyxia poses a serious risk to the foetus. This is avoided by maintaining haemodynamic stability and maternal oxygenation (19). The utero-placental circulation lacks autoregulation with changes in maternal blood pressure and cardiac output leading to foetal affectation (8). The foetus is sensitive to a reduction in utero-placental blood flow as this facilitates the maintenance of its high metabolic rate and can lead to foetal ischaemia (1,8). It is therefore integral to ensure adequate utero-placental perfusion during the surgery (1).

The gravid uterus leads to aorto-caval compression which reduces uterine blood flow (1). Hypotension is also caused by neuraxial blockade, anaesthetic agents and hypovolaemia (19). It is important to maintain adequate blood pressure and avoid hypovolemia with the aid of left uterine displacement and liberal fluid administration (1,8). Care should be taken with fluid administration in maternal renal or cardiac disease (8). Vasopressors including ephedrine and phenylephrine are considered safe and effective for the management of maternal hypotension (8). Multiple trials demonstrated that α-agonists (e.g. phenylephrine or metaraminol) are generally more effective than ephedrine alone to prevent maternal hypotension and its complications (e.g. nausea and vomiting) (2). Alpha agonists such as phenylephrine produce a better foetal acid balance than indirect sympathomimetic agents such as ephedrine (19). Ephedrine has a slow onset and long duration of action relatively (19). Additionally it is associated with a higher incidence of acidosis in the neonate (2). Tachyphylaxis can also pose a challenge to titrating its effect.

Foetal haemoglobin has a high affinity for oxygen (8). A decrease in maternal oxygenation briefly, is usually well tolerated by the foetus (24). Prolonged maternal hypoxaemia leads to vasoconstriction of the placental vessels and subsequently foetal hypoxaemia, acidosis and death (25).

There is a direct relationship between maternal and foetal PaCO2, however, maternal hypercarbia limits the gradient for fetomaternal diffusion of carbon dioxide (19). Maternal hypercarbia causes uterine artery vasoconstriction and foetal respiratory acidosis (2). Hypocarbia also causes a reduction in uterine blood flow which results in foetal acidosis (2), although the mild physiological hypocapnia during pregnancy should be maintained (19).

Risk of preterm labour

Various studies have observed an increased incidence of spontaneous abortion and preterm labour after non-obstetric surgery during pregnancy with an increased incidence of preterm labour during abdominal surgery (19). Visser and colleagues showed the incidence of preterm labour occurring during the second and third trimester was 26% and 82% respectively, and more common in patients with appendicitis and after adnexal surgery. Delivery of preterm infants occurred in 16% of the patients and appeared to be directly related to the abdominal surgery in only 5% of cases (26). They concluded that surgery during the first and second trimester was not associated with significant preterm labour or foetal loss (26).

In the latter stages of pregnancy; haemodynamic changes occurring as a result of the anaesthetic, can cause the uterus to contract prematurely and lead to preterm labour. Uterine irritability can be triggered by surgery, manipulation of the uterus and the underlying condition of the patient i.e. sepsis and hypoxemia (1). The lowest risk for preterm labour is during the second trimester and includes surgeries that do not manipulate the uterus (8). If preterm labour is suspected, then tocolysis may be administered. However, prophylactic tocolysis is controversial and not recommended due to the risk of maternal side effects and a lack of proven efficacy (19,26).

Drugs that are known to increase uterine tone (e.g., ketamine) should be avoided. Minimize uterine manipulation and monitor uterine activity after surgery. Volatile anaesthetic agents results in the relaxation of the uterus, however, high concentrations can cause undesirable hypotension (8).

Foetal loss

It is difficult to determine the exact incidence of foetal loss during non-obstetric surgery as losses can be attributed to anaesthesia and/or surgery. Foetal loss after surgery is found to be 5.8% in all trimesters with the incidence being higher (10.5%) in those patients in their first semester of pregnancy (1).

FOETAL MONITORING

Monitoring the foetus during the peri-operative period is controversial. From 18-22 weeks foetal heart rate (FHR) monitoring is practical with heart rate variability observed from 25 weeks (2). Nejdlova et. al advises the consideration of continuous CTG monitoring after 24 weeks where feasible and the availability of obstetric services in the event of delivery (13). There is no data supporting the continuous monitoring of foetal heart rate which can be technically difficult during intra-abdominal surgeries or obesity (2,19).

During general anaesthesia, anaesthetic agents (i.e. magnesium sulphate, B blockers, opioids and atropine) reduces both baseline FHR and variability leading to challenges in interpretation and premature interventions (19). In this context, foetal distress is evidenced by decelerations or persistent foetal bradycardia. Bradycardia indicates foetal hypoxaemia and acidosis, however, it also could indicate maternal hypothermia, respiratory acidosis, drug effects (2).

Monitoring allows for swift intervention, such as the optimisation of maternal haemodynamics, oxygenation and ventilation (19). Perioperative foetal monitoring has not shown improvements in foetal outcome (19). During the decision-making process, the obstetricians and neonatologists should be consulted, and appropriately trained personnel should be available to interpret the CTG and a prior action plan discussed in the event foetal delivery is necessary. If the foetus is not viable or peri-operative CTG monitoring is not possible, FHR monitoring should occur pre and post-operatively (19).

The *American College of Obstetrics and Gynaecology* have advised the following:

- The decision to utilize foetal monitoring should be individualized. Consider the gestational age, type of surgery and facilities available (12). Each case should include a multi-disciplinary approach for optimal safety of both the woman and foetus.

General guidelines for foetal monitoring include (12):

- If the foetus is considered pre-viable, it is sufficient to ascertain the foetal heart rate by Doppler before and after the procedure. In certain circumstances, intraoperative foetal monitoring may be performed to facilitate positioning or oxygenation interventions.
- If the foetus is considered to be viable, simultaneous electronic foetal heart rate and contraction monitoring should be performed before and after the procedure to assess foetal well-being and the absence of contractions.
- Intraoperative electronic foetal monitoring may be appropriate when the following are met:

- The foetus is considered to be viable.
  There is no statutory definition, regarding viability. Viability was defined in the repealed Birth, Marriages, and Deaths Registration Act 81 of 1963 “in relation to a child means that it had at least six months of intrauterine existence” (27). The Birth and Deaths Registration Act defines a stillbirth as the birth of a fetus that has completed 26 weeks of intrauterine life (27). The assumption is therefore that the legal definition of gestational age should be noted from conception and be in keeping with time of intrauterine life (27). This is medically regarded as 2 weeks after the first day of the last normal menstrual period, thus a foetus of 28 weeks’ gestational age has spent 26 weeks intra-uterine (27). The 6 months of intrauterine existence is in keeping with 26 weeks of gestational age as in the Births and Deaths Registration Act.
  The definition outlined in The Guidelines for Maternity Care in South Africa according to the Births and Deaths Registration Act, No. 51 of 1992, defines a non-viable foetus as a foetus less than 28 weeks of gestation or a weight of less than 1000g where the gestational age is unknown (28).
- It is physically possible to perform intraoperative electronic foetal monitoring.
- An obstetric health care provider is readily available.
- When possible, the pregnant woman has consented to an emergency caesarean delivery for foetal indications.
- The nature of the planned surgery will allow for the safe interruption or alteration of the procedure to provide access to perform emergency delivery.

If the foetus is monitored, consider the following recommendations (12):

- Surgery should be done at an institution with neonatal and paediatric services.
- A qualified individual should be readily available to interpret foetal heart rate patterns.
- An obstetric care provider should be available to perform a caesarean section if deemed necessary.

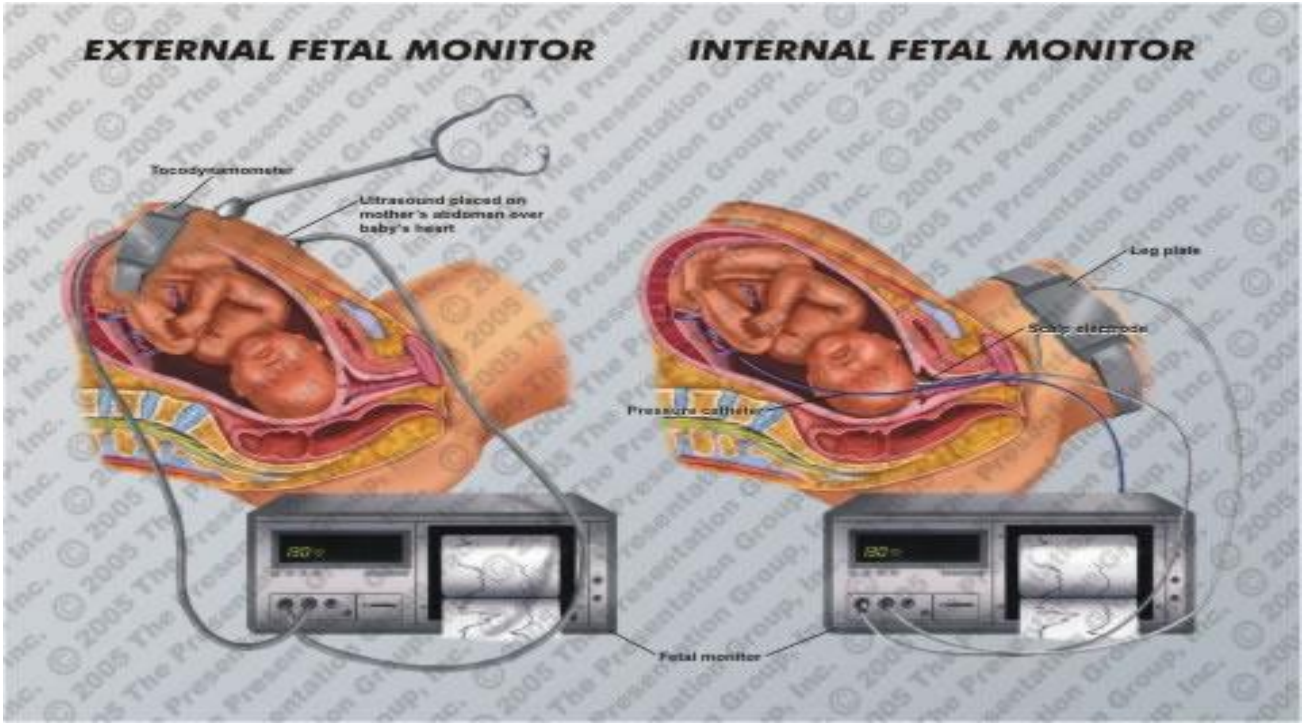

Figure 2. *Sourced from embarazo10.com*

ANAESTHETIC MANAGEMENT

Pre-operative management

The evaluation of a pregnant patient is similar to that of a non-pregnant patient with special focus on the following:

- Careful assessment of the airway
- Aspiration prophylaxis: Whilst standard fasting guidelines are applied for pregnant patients, the risk of aspiration of gastric contents is higher than the non-pregnant population (8). Explore additional risk factors for gastric regurgitation including active acid reflux and obesity.
  Prophylaxis against aspiration should be administered from 16 weeks of pregnancy with non-particulate acids (30 ml sodium citrate) and H2 -receptor antagonists (ranitidine 150 mg orally or 50mg intravenously). (8)
- Antibiotic prophylaxis: Prophylaxis is procedure dependant with more careful selection of antibiotics with a good safety profile in pregnancy.
- Prophylactic glucocorticoids: Between 24 and 34 weeks of gestation, the administration of glucocorticoids 24 – 48 hours before surgery can reduce perinatal morbidity and mortality if preterm delivery (8). Avoid the antenatal administration of steroids in the setting of systemic infection as this may cause immunosuppression.
- Prophylactic tocolytics: Tocolytics are indicated for the treatment of preterm labour until resolution of the underlying, self-limited condition that may have caused the contractions.
- Pregnant women should be screened for venous thromboemboli. Those who are deemed eligible would receive prophylactic low-molecular weight heparin (8,12).
- Counselling: In addition to the surgical and anaesthetic procedures, counselling should be extended to the risks of preterm labour, miscarriage and teratogenic drugs.

FHR Monitoring

Discussed above

Type of anaesthesia

The choice of anaesthetic technique and drug selection should be guided by the surgical indication, nature, and site of procedure. No anaesthetic drug has shown to be disadvantageous to a foetus (1). The aim of anaesthetic should be to provide safe and appropriate anaesthetic with mild perturbation of maternal haemodynamic and physiology.

Regional anaesthesia

Regional anaesthesia including both neuraxial and peripheral nerve blocks is preferred as this allows for patient to maintain her airway thus mitigating the risk of a failed intubation (13). This technique also decreases the exposure of teratogenic agents to the foetus and provides postoperative analgesia (13). Despite the aforementioned advantages there is no evidence demonstrating superior safety for a regional technique over a general anaesthetic technique (8,13).

Neuraxial anaesthesia often causes maternal hypotension which impairs placental perfusion (8). The following need to be considered:

- Oedema and obesity can pose a challenge to locating anatomical landmarks. With regards to neuraxial techniques, the interspinal ligaments are softened as a result of hormonal influences and this can impair the appreciation of a loss of resistance technique (13).

- Lower doses of local anaesthetic are required as the cranial spread of local anaesthetic is favoured and an increased sensitivity to local anaesthetic agents (13).
- The risk of local anaesthetic toxicity is higher as there is an increased concentration of the free fraction of drugs as a result of decreased albumin levels (13).
- Neuraxial blockade causes significant maternal hypotension in the presence of hypovolaemia due to the increased sympathetic activity during pregnancy. Hypotension needs to be managed aggressively with intra-vascular volume replacement and vasopressors (13).

General anaesthesia

Induction

The airway of a pregnant patient is noted to be 8 times more difficult than a non-pregnant female with the oropharyngeal airway becoming more narrow as gestational age progresses (29). Mask ventilation, laryngoscopy and intubation are thus all challenging due to multifactorial reasons (13). Difficult airway equipment should be prepared and readily available (13,29). The aim should be for a first pass successful intubation.

Position is often challenging in these patients as they often necessitate reverse Trendelenburg position or a ramp which aids in alleviating the risk of regurgitation and aspiration and reduce the interference of enlarged breasts during intubation (13).

Pregnant patients tolerate apnoea poorly with hypoxia developing up to 3 times faster in pregnancy (13,28). Head-up tilt helps in improving functional residual capacity by optimizing respiratory mechanics (13). Careful preoxygenation with an appropriately size mask for at least 3 min is recommended (29) whilst aiming for an end tidal oxygen fraction of >0.9.

Induction should be a rapid sequence technique with cricoid pressure and a rapid acting muscle relaxant with a cuffed endotracheal tube. There is no consensus regarding tracheal intubation for a specific gestational age (15). Optimal intubating conditions are achieved with intravenous induction with pregnant patients being more sensitive to intravenous and inhalational hypnotics (28).

Propofol seems to be the preferred induction agent in healthy pregnant patients with studies suggesting an 8% reduction in the adult dose (30). During late pregnancy, thiopentone has no significant effect on intra-uterine pressure (8). During early pregnancy, ketamine was found to cause uterine contractions but was found to exert no effect in late pregnancy (31).

Patients have an increased sensitivity to neuromuscular blockers, however, the dose of succinylcholine is not reduced (29). This produces a clinically insignificant prolongation of neuromuscular block as a result of a decrease in pseudocholinesterase levels (29). Studies have shown an increase onset of action with non-depolarizing muscle relaxants i.e. vecuronium and rocuronium (32).

Maintain

The aim during maintenance of anaesthesia should be to avoid hypoventilation, hypotension and over sedation whilst carefully maintaining stable maternal haemodynamic parameters and oxygenation. This requires careful titration of drugs. Positive pressure ventilation should be used to maintain the partial pressure of carbon dioxide in the normal range for pregnancy (13). End tidal CO_2 should be used to guide $PaCO_2$; there is a good correlation between end-tidal CO_2 ($ETCO_2$) and $PaCO_2$ in pregnancy (8).

There are conflicting studies regarding the sensitivity of pregnant patients to volatile agents (29). Nejdlova and colleagues discuss an increased sensitivity to volatile agents, resulting in a slightly reduced minimum alveolar concentration value (13). Studies suggest that there is up to a 30% reduction in the MAC for isoflurane (33,34), with other studies reporting that the effect is not clear (29). Up to a MAC of 1.5; all volatile agents dilate uterine arteries resulting in an increase in uterine blood flow, however, at higher concentrations cause a reduction arterial blood pressure and cardiac output which offsets the therapeutic effect on the uterine blood flow (13). Additionally volatile agents have shown to cause uterine relaxation, although it should be used cautiously as increased concentrations can cause hypotension with other agents including calcium channel blockers, magnesium sulphate and prostaglandin synthetase inhibitors (e.g. indomethacin) are not recommended (13). Nitrous oxide is avoided during the first trimester as it has been found to affect DNA synthesis (22) .

Maintenance of adequate uteroplacental perfusion with the avoidance of sympathetic release of catecholamines as a result of pain and light planes of anaesthesia (29).

Where external tocodynamometers can be placed without interfering with the surgical field, uterine contractions may be monitored during surgery (8). In the event of the detection of uterine contractions, attempts should be made to improve maternal haemodynamics and consideration should be given to the use of tocolytic agents (8).

Reversal of neuromuscular blockade: Neuromuscular blockade can be reversed using neostigmine and atropine (15).
The use of Sugammadex is controversial. It is indicated for the reversal of rocuronium and vecuronium bromide (35). Pharmacological stimulation studies have shown that sugammadex reduce progesterone levels with a resultant effect on uterine growth in early pregnancy and myometrial quiescence and cervical integrity in the latter stages of pregnancy (29). Whilst animal studies have reported mixed conclusions of miscarriage and teratogenicity of this drug; the potential effects on the foetus are unknown (29,36). It has been postulated that its large molecular size and polarization in an aqueous solution limits its placental transfer(36). Torres and colleagues reported on six cases of urgent non-obstetric surgery during pregnancy and concluded that sugammadex seemed to be safe for both mother and baby (36).
The 2019 Society for Obstetric Anaesthesia and Perinatology consensus on sugammadex recommends against its use during pregnancy unless confronted with a ‘cannot intubate, cannot ventilate’ scenario (15).

Emergence

Emergence from anaesthesia requires close monitoring with special attention to the airway and respiratory system (8). Patients tend to experience the most severe anaesthetic complications as a result of airway obstruction or hypoventilation which occurs during emergence or extubation (8).

Recovery should be performed with the maintenance of LUD (8,29). The pregnant patient should be extubated fully awake (13).

In addition to the aforementioned complications, patients can experience depression of the airway reflexes resulting in aspiration and cardiovascular complications including hypotension, arrhythmias and cardiac arrest (29).

Tocometry is considered where surgical technique involved uterine manipulation as this exacerbates the risk for premature labour (8,29). Post-operative analgesia may obscure awareness of mild contractions (8).

POST OPERATIVE CARE

The assessment of the foetus via uterine contraction and foetal heart rate monitoring is important to ensure the vitality of the foetus. It also allows us to assess the risk of preterm labour.

Patients should be kept in the left lateral position to promote uterine displacement and prevent aortocaval compression.

Beyond the first week after surgery, patients who have a continued pregnancy are at no higher risk for preterm labour and do not require further tocometry or foetal heart rate monitoring (11).

Pregnancy is a hypercoagulable state with the risk of thromboembolic disease increased by postoperative venous stasis. Patients should be encouraged to maintain adequate hydration, ambulate early, use calf compression devices and pharmacological prophylaxis.

Analgesia

It is integral to ensure patients receive adequately analgesia as pain results in increased circulating catecholamines which impairs uteroplacental perfusion. In addition pain can predispose to preterm labour (19).

Regional or neuraxial techniques provide excellent analgesia and reduce the risk of opioid-induced hypoventilation when compared with intravenous administration of opioids (8).

For mild to moderate pain, the analgesic agent of choice is paracetamol (8). NSAIDs should be avoided, especially after 32 weeks of gestation, as they may cause premature closure of the ductus arteriosus (8,29). Additionally, the use of NSAIDs are associated with oligohydramnios and reduced renal function of the foetus (8).

The FDA developed a classification system which uses evidence to categorize the risk of drugs to the foetus. Below is the FDA classification and common analgesics.

CATEGORY A	Adequate and well controlled studies have failed to demonstrate a risk to the foetus in the first trimester of pregnancy (and there is no evidence of risk in later pregnancies).
CATEGORY B	Animal reproduction studies have failed to demonstrate a foetal risk but there are no controlled studies in pregnant women, OR animal reproduction studies have shown an adverse effect, but adequate well controlled studies in pregnant women have failed to demonstrate a risk to the foetus in any trimester.
CATEGORY C	Animal reproduction studies have shown an adverse effect on the foetus and there are no adequate well controlled studies in humans, or studies in animals and humans are not available. Potential benefits of drugs may warrant use of drug in pregnant women despite potential risks.

CATEGORY D	There is positive evidence of human foetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., life threatening situation or serious disease for which safer drugs are not available).
CATEGORY X	Studies in animals or humans have demonstrated foetal abnormalities, or evidence based on human experience, and the risk of use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Table 6. *FDA classification of foetal harm risk from drugs (19).*

DRUG	FDA Risk	FOETAL RISK
Paracetamol	B	Crosses placenta. Safe for short term use. No well controlled human data.
Ibuprofen	C	No adequate human data. Studies in animals show adverse foetal effects. Use in 3rd trimester can cause constriction of ductus arteriosus.
Diclofenac	B	No adequate human data but studies in animals do not indicate risk to foetus. Can cause constriction of ductus arteriosus in 3rd trimester.
Codeine	C	No adequate human data. High doses at term can cause neonatal withdrawal / respiratory depression.
Morphine	C	Chronic maternal use causes neonatal withdrawal and respiratory depression.
Tramadol	C	Human data is lacking. When used in labour may cause fewer maternal side effects and lower neonatal respiratory depression than other opioids.

Table 7. *Common analgesics used in pregnancy (19).*

LAPAROSCOPIC SURGERY

During laparoscopic surgery, there are many potential mechanisms of injury which include direct trauma to the foetus or uterus and foetal acidosis resulting from the absorption of carbon dioxide (9). Hypotension occurs as a result of decreased cardiac output due to a rise in intra-abdominal pressures(9). Hypercarbia, hypoxaemia and hypotension can lead to vasoconstriction and reduce uteroplacental perfusion (15).

Laparoscopic surgery, however, has shown to result in reduced morbidity compared with open procedures and confer a number of advantages to both the mother and the foetus (19). These include a reduced need for analgesics due to a decrease in pain post-operatively, improved recovery times and a lower risk of thromboembolic events (19).

The following guidelines were issued by the *Society of American Gastrointestinal Endoscopic Surgeons* regarding laparoscopic surgery during pregnancy:(2)

- Surgery should be deferred to the second trimester, where possible
- Monitor foetal and uterine status.
- An open technique should be used to enter the abdomen.
- Monitor maternal end-tidal PCO2 (4–4.6 kPa range) to avoid foetal hypercarbia and acidosis.
- Maintain low pneumoperitoneum pressure (1.1 –1.6 kPa) or use gasless technique.
- Limit the extent of Trendelenburg or reverse Trendelenburg positions and initiate any position slowly.

A Swedish study compared laparotomy and laparoscopy surgery in over 2 million pregnant women and found that whilst preterm delivery, growth restriction and low birth weight were more common in both groups compared to the general population, there were no differences between the two techniques (9,19).

OUTCOMES POST SURGERY

The Duncan study carried out amongst Canadian women attempted to define the foetal risk associated with anaesthesia and surgery (37). The study included 2,565 pregnant women and found no significant difference in the rate of congenital abnormalities but found a statistically significant increase in the risk of spontaneous abortion in both the first and second trimesters (from 6.5 to 7.1%), notably in undergoing gynaecological procedures (37).

Mazze and Kallen studied adverse outcomes in pregnant patients undergoing non-obstetric surgery. Among the 720 000 obstetric patients, 5405 underwent non-obstetric surgery (0.75%) with 2252 women undergoing procedures in the first trimester of pregnancy (11). Of those undergoing surgery, 55% underwent a general anaesthetic which included the use of nitrous oxide in 97% of cases (11). There was no increase in the incidence of congenital anomalies or stillbirths (11). The study did however find an increased incidence of foetal mortality within 168 hours of surgery and very low birth weight infants (11). These findings were attributed to prematurity and intra-uterine growth restriction (11). The authors found no correlation between a specific type of anaesthesia or surgery and the increased incidences of adverse reproductive outcomes (11).

A retrospective study from 2017 reviewed 6,486,280 pregnancies and found that 47,628 parturient who underwent non-obstetric surgery had a higher risk of adverse birth outcomes (38). This study estimated that every 287 surgical operations was associated with 1 additional stillbirth, every 31 operations was associated with 1 additional preterm delivery, every 39 operations was associated with 1 additional low birth weight baby, every 25 operations was associated with 1

additional caesarean section, and every 50 operations was associated with 1 additional prolonged inpatient stay (38).

A meta-analysis evaluated 54 of 4052 publications which observed 12 452 pregnant women undergoing non-obstetric surgery (39). Cohen et al., found the maternal mortality was less than 1 in 10 000 (40). The rate of spontaneous abortion was 5.8%, however there were no matched controls present (40). Non-obstetric surgery did not increase the risk of major birth defects with incidence in the first trimester found to be 3.9% (40). Foetal loss was the result of 2.5% of pregnancies (40). The rate of preterm labour was found to be 3.5% and this was noted specifically following appendectomy versus other types of interventions ($P < .001$). Further analysis of patient's undergoing appendicectomies, revealed, acute appendicitis with peritonitis posed a risk for foetal loss.

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A pregnant woman should never be denied or delayed of medically needed surgery regardless of the trimester as this can affect the pregnant women or foetus adversely. Elective surgery should be postponed until after delivery.

Given the potential for preterm delivery with some non-obstetric procedures during pregnancy, corticosteroid administration for foetal benefit should be considered for patients with foetuses at viable premature gestational ages, and patients should be monitored in the perioperative period for signs or symptoms of preterm labour.

Pregnant women undergoing non-obstetric surgery should be screened for venous thromboembolism risk and should have the appropriate perioperative prophylaxis administered.

If that health care provider is not at the institution where surgery is to be performed, another obstetric care provider with privileges at that institution should be involved.

The following generalizations may be helpful to guide decision making:

- No currently used anaesthetic agents have been shown to have any teratogenic effects in humans when using standard concentrations at any gestational age.
- There is no evidence that *in utero* human exposure to anaesthetic or sedative drugs has any effect on the developing foetal brain; and there are no animal data to support an effect with limited exposures less than 3 hours in duration.
- Foetal heart rate monitoring may assist in maternal positioning and cardiorespiratory management and may influence a decision to deliver the foetus.

CONCLUSION

Management of any pregnant patient should be multi-disciplinary in nature using evidence-based practices. This involves a myriad of factors with special consultation of a neonatology team and obstetric surgeon.

Timing of surgery is imperative, with the second trimester suggested for elective surgery.

Patients should be thoroughly evaluated and counselled with specific emphasis on the physiological changes and pregnancy related complications of a parturient. Consideration should be given to the choice of anaesthetic and the pharmacokinetic and pharmacodynamics changes of anaesthetic drugs in the pregnant patient. Regional technique allows for the maintenance of hemodynamic stability, perfusion of the utero-placental circulation and uterine relaxation.

Anaesthetic management includes the provision of adequate postoperative analgesia with regional, plane and peripheral nerve blocks encouraged. This should be carefully planned to preserve the pregnancy and to ensure the safety of both the mom and foetus.

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