Acta Anaesth. Bel., 2024, 75 (1): *57-66*

Review

General anesthesia for maternal surgery during pregnancy: dogmas, myths and evidence, a narrative review

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Abstract

Up to 1% of pregnant women require general anesthesia and maternal non-obstetric surgery during pregnancy, of which urgent abdominal procedures are most commonly indicated. This narrative review summarizes several dogmas and myths on the management of general anesthesia during pregnancy and the corresponding evidence. While historical studies found delayed gastric emptying during pregnancy, recent evidence concluded that gastric emptying remains nearly normal during the entire pregnancy until the onset of labor. To correctly estimate the aspiration risk, gastric ultrasound should be increasingly performed. Based on the available evidence, the application of cricoid pressure should be discouraged during rapid sequence induction of pregnant women. A cuffed endotracheal tube is traditionally recommended, but laryngeal masks have been used in > 9000 patients undergoing cesarean section without observation of aspiration. All material to manage a difficult airway should be available as difficult intubation remains an ongoing concern in obstetrics. Risk factors for difficult intubation are nonobstetric in nature. Due to the lack of evidence for hemodynamic management, it is not possible to make an evidence-based recommendation. We recommend to adhere to the expert opinion of maintaining maternal blood pressure close to the normal physiologic value by using (15°-)30° left lateral tilt position, intravenous fluids and noradrenaline or phenylephrine. Most recent clinical observational studies suggested to consider laparoscopic over open surgery as a standard treatment for abdominal surgery. While animal studies observed impaired fetal brain development after prenatal anesthesia exposure, this could not be confirmed by an observational clinical study.

Keywords: **Anesthesia, pregnancy, surgery.**

Introduction

It is not very uncommon for pregnant women to receive general anesthesia. One reason for general anesthesia during pregnancy is when the mother has a medical condition that requires surgical treatment, with the fetus being an "innocent bystander". This can be indicated for non-obstetric procedures (for example a laparoscopic appendectomy), which is required in approximately 0.39-0.96% of all pregnancies[1-4]. Additionally, obstetric surgery (for example cerclage), may require general anesthesia[5]. Lastly, general anesthesia may be required for fetal surgery during pregnancy, such as in the case of prenatal spina bifida repair[5].

This review focuses on the use of general anesthesia in maternal non-obstetric surgeries. Intra-abdominal procedures are most often performed (35-81%), followed by trauma surgery (8-24%), urological procedures (8-16%), dental procedures (11%), surgery on nail and skin (10%), and oncologic surgery (2-8%)[1-4,6,7]. The most common indications requiring surgery are appendicitis (6-39%) and adnexal pathology (6-36%)[1,3,4,8-10]. The majority of these procedures (68-91%) are emergency cases[4,7,10]. Generally, surgery is performed more frequently in the first (20-50%) and second (35-58%) trimesters of pregnancy compared to the third trimester (10-24%)[1,3,4,7,10,11]. Laparoscopic surgery is the most frequently employed technique for intra-abdominal

procedures (63-79%)[1,2] and general anesthesia (70-81%) is used more often than locoregional anesthesia (19%)[1,6,7].

Overall, pregnant women have the same odds to undergo surgical interventions as non-pregnant women, with the exception of cholecystectomies (due to increased bile lithogenicity and decreased gallbladder motility) and adnexal pathology, which occur more frequently secondary to pregnancy[8,12-14]. Although, the incidence of appendicitis is similar in pregnant and non-pregnant women, with postoperative complications like peritonitis and sepsis more likely to occur during pregnancy due to a more challenging diagnosis and delayed treatment[14-17].

Dogmas and myths on the management of general anesthesia for non-obstetric maternal surgery during pregnancy often prevail in clinical recommendations. These are mainly based on historical studies, theoretical assumptions, and beliefs. The aim of this narrative review is to summarize the most common dogmas and myths and to provide the evidence supporting or rejecting these. After this critical analysis, practical recommendations are provided for each item, which can also be found in Table I.

Gastric emptying

Dogma/myth: Gastric emptying is delayed during pregnancy with an increased risk for aspiration as a consequence[8,13,18-34].

Evidence: pregnant women with a gestational age of 8-20 weeks showed that intragastric pressure increases from early pregnancy while the tone of the lower esophageal sphincter decreases[31]. In 1991, gastric emptying of pregnant women was compared for the first time with that of non-pregnant women by measuring the (time to) peak plasma concentration of paracetamol after oral paracetamol intake[36]. In 1992, gastric ultrasound was introduced to investigate gastric emptying in pregnant women[19]. Using both techniques, multiple studies concluded consistently that gastric emptying remains close to normal during the entire pregnancy until the onset of labor[18,19,27,36-38]. Even in non-laboring term pregnant women scheduled for elective cesarean, a normal gastric emptying was observed[36-38]. Bedside gastric ultrasound is a feasible and reliable tool to estimate the gastric volume in individual patients[27].

Recommendation/conclusion: Gastric emptying remains close to normal during the entire pregnancy until the onset of labor. In doubtful situations (e.g., emergency surgery, trauma, diabetic gastroparesis, ileus or labor), gastric ultrasound should be performed[27].

Cricoid pressure during rapid sequence induction

Dogma/myth: Starting from 15-18 weeks of gestation, it is recommended to perform a rapid-

Table I. — Overview of the recommendations/conclusions.

- Gastric emptying remains close to normal during the entire pregnancy until the onset of labor. In doubtful situations (e.g., emergency surgery, trauma, diabetic gastroparesis, ileus or labor), gastric ultrasound should be performed.
- Based on the available evidence, the application of cricoid pressure should be discouraged.
- There is evidence suggesting that a laryngeal mask may be used as an alternative for a cuffed endotracheal tube during cesarean section, at least in non-laboring parturients provided that non-obstetric risk factors for aspiration are absent.
- All material to manage a difficult airway should be instantly available as difficult intubation in obstetrics remains an ongoing concern.
- Due to the lack of evidence, it is not possible to make evidence-based recommendations. We recommend to adhere to the expert opinion of maintaining maternal blood pressure close to the normal physiologic value by using (15°-)30° left lateral tilt position, intravenous fluids and noradrenaline or phenylephrine.
- Neostigmine has been used in pregnant women since several decades. In contrast, evidence on the maternal and foetal safety of sugammadex is limited to clinical case reports, and preclinical data on its safety are not unequivocally positive.
- Clinical observational studies suggest that laparoscopic surgery should be considered as standard treatment.
- Animal studies have repeatedly observed impaired fetal brain development after prenatal anesthesia exposure, but a clinical observational study failed to confirm this finding and concluded that the effect size of prenatal anesthesia exposure is comparable to that of rather innocent risk factors.

sequence induction with cricoid pressure[13,20-24,26,34,39,40].

Evidence: In 1961, Sellick introduced, based on a small (n=26) non-randomized uncontrolled observational study, the application of cricoid pressure aiming to occlude the esophagus to decrease the risk of aspiration[41]. Even with performing cricoid pressure, there was still an incidence of 11.5% of regurgitation in this historical study[41]. Recent randomized controlled studies failed to demonstrate a reduced risk of pulmonary aspiration when cricoid pressure was compared with no cricoid pressure during rapid sequence induction[42,43]. Magnetic resonance imaging during cricoid pressure showed a lateral displacement instead of an occlusion of the esophagus[44,45]. Moreover several important disadvantages of cricoid pressure were observed: a higher incidence of Cormack-Lehane grade 3-4, a more difficult mask ventilation, a more difficult laryngeal mask insertion, a decreased lower esophageal sphincter tone and a more frequent gag reflex and higher incidence of vomiting[43]. Additionally, teaching the right practice of cricoid pressure remains impossible: neither anesthesiologists nor nurses can be trained to apply a pressure of 10 + 5 N and 30 + 5 N in a training model[46]. Furthermore, in clinical practice, even with the feedback of real-time measurements, it is biomechanically impossible to achieve 30 N cricoid pressure during the counter force of laryngoscopy[47].

Recommendation/conclusion: Based on the available evidence, the application of cricoid pressure should be discouraged.

Airway device

Dogma/myth: A cuffed endotracheal tube is recommended[13,20-24,26,34,39,40].

Evidence: At least 12 studies including 9113 women investigated the use of a laryngeal mask in elective and urgent cesarean sections and no increased risk of aspiration was observed[48-59]. The laryngeal mask was placed using a rapid-sequence induction in most of these studies. Three studies[48,52,53] performed bag-mask ventilation, lasting less than one minute[48,52], with[52] or without[48,53] cricoid pressure. It is important to note that pregnant women with gastro-oesophageal reflux and obese patients were excluded from above-mentioned studies.

Recommendation/conclusion: There is evidence suggesting that a laryngeal mask may be used as an alternative for a cuffed endotracheal tube during cesarean section, at least in non-laboring parturients provided that non-obstetric risk factors for aspiration are absent.

Airway

Dogma/myth: Pregnant as compared to non-pregnant women desaturate earlier during apnea[8,13,14,20,24,26,28-30,32-34,60-62]. Mucosal edema, enlarged breasts and more fragile mucosa complicate intubation during pregnancy[8,13,14,20,23-25,28-30,32,34,39,60-62]. Pregnant women have higher Mallampatti scores, and an eight times higher risk of failed intubation (1 in 224 cases) than non-pregnant women[8,12-14,23-25,29,33,34,61,62].

Evidence: In pregnancy, there is a 20% reduction in functional residual capacity standing upright and a 50-70% reduction in the recumbent position. Additionally, there is an increased oxygen consumption of 35-70%, which leads to rapid desaturation during apnea[8,13,14,20,24,26,28-30,32-34,60-62]. A recent retrospective cohort study investigated 14 748 women undergoing general anesthetics for cesarean section 63. A risk of 1/49 was found for difficult intubation, and 1/808 for failed intubation. Nevertheless, all these cases of failed intubation could be managed with a laryngeal mask[63]. Risk factors for difficult intubation were mainly nonobstetric in nature[63].

Recommendation/conclusion: All material to manage a difficult airway should be instantly available as difficult intubation in obstetrics remains an ongoing concern[63].

Hemodynamics

Dogma/myth:The pregnant uterus lacks autoregulation, meaning that the uterine blood flow is pressure dependent. To maintain the uterine perfusion pressure, and thereby the uterine blood flow, maternal blood pressures must be maintained around normal physiologic values[8,13,20,22,23,26,28,30,33,40,61,62,64]. Most recommendations only state to “treat hypotension” or to “maintain normotension”, but do not provide target ranges. A limited number of recommendations provide concrete blood pressure target values: 70%[65], 80%[5], 90%[39] of baseline or a mean arterial pressure >65mmHg[66]. These targets should be achieved by using phenylephrine, intravenous fluids and avoiding excessive levels of anesthesia. In addition, a left lateral tilt position (≥ 15°) is recommended from 10-18 weeks of gestation, to avoid aortocaval compression by leftward displacement of the uterus[5, 8,13,14,21-23,25,28-30,32-34,39,40,60,62,65].

Evidence: During the first trimester, cardiac output increases gradually and reaches its peak (140-150% of baseline value) during the second trimester[8,13,14,23,25,26,33,34,62]. The blood pressure

decreases in the first trimester, attains its lowest point during the second trimester, and then increases again in the third trimester[8,33,67].

In the non-pregnant population, anesthesia-induced hypotension is increasingly recognized to be associated with postoperative morbidity and mortality68. In observational studies even brief episodes of mean arterial pressures < 60-70 mmHg were associated with acute kidney injury, myocardial injury and mortality and it has become clinical standard to maintain mean arterial pressures (MAP) at 65 mmHg or higher using vasoactive medication and/or fluids during the perioperative phase[69]. However, evidence on the efficacy of this strategy is limited to only four randomized-controlled trials performed in high-risk patients undergoing major surgery[70-73]. Two of these studies showed a decreased risk for organ injury after stricter blood pressure management[70, 71], whereas the two other studies failed to demonstrate this effect[72,74].

Studies in pregnant sheep and rabbit models have effectively shown that the perfusion of the pregnant uterus lacks autoregulation and that therefore every reduction in maternal blood pressure will result in a decreased uterine blood flow[75,76]. Yet, sheep studies have demonstrated that healthy fetuses tolerate decreases in uterine blood flow of up to 50%[77]. This illustrates a luxury perfusion of uterine blood flow that may protect the fetus in case of a decreased uterine perfusion pressure.

For decades, ephedrine has been the gold-standard treatment of hypotension during neuraxial anesthesia for cesarean section as ephedrine did not decrease uterine blood flow in sheep[78,79] in contrast to phenylephrine[80,81] and (nor)adrenaline[80-84]. Also in non-human primates[85] and humans[86,87], uterine blood flow was reduced by the use of phenylephrine, in contrast to ephedrine. Yet in 2002, a meta-analysis of clinical studies examined neuraxial anesthesia for cesarean section and found that fetal pH was significantly higher with the use of phenylephrine versus ephedrine (mean difference: 0.03 [95% confidence interval: 0.02-0.04]), while no difference in Apgar scores was observed[88]. Whilst this difference was statistically significant, it is important to note that for both, ephedrine and phenylephrine, the fetal pH and Apgar scores were within the normal range[88-91], even when high doses were used[90]. In 2015, Ngan Kee et al. showed that fetal outcomes with noradrenaline were comparable to phenylephrine[92]. Noradrenaline has some advantages over phenylephrine: less maternal bradycardia is seen, it preserves maternal cardiac output, and there are lower levels of catecholamines found in the fetus[92]. A recent network meta-analysis determined the following rank for highest fetal pH and lowest maternal nausea and vomiting incidence: noradrenaline > phenylephrine > ephedrine[91].

In contrast to the extensive evidence in the setting of neuraxial anesthesia for cesarean section, evidence on the hemodynamic management during general anesthesia for non-obstetric surgery is nearly absent. The hypothesis that maintaining the maternal blood pressure around the awake value would improve fetal outcome during general anesthesia for maternal surgery was recently tested in a preclinical study[93]. In rabbits, several parameters of fetal brain development were impaired and fetal mortality was higher when maternal blood pressure was maintained at ≥ 80% of the awake value using noradrenaline when compared to untreated maternal hypotension[93]. The most likely explanation for this observation is that noradrenaline reduces uterine blood flow in rabbits[93,94]. Clinical relevance of these observations remains to be investigated[93].

In 1970-1974, it was demonstrated that 15° left lateral tilt during cesarean section improved fetal pH[95-97]. However, recent studies using magnetic resonance imaging showed that the inferior vena cava was completely compressed in both the supine and 15° left lateral tilt position, while 30° left lateral tilt position partially relieved the compression[98,99]. A study randomizing pregnant women for elective cesarean section to the supine position or 15° left lateral tilt position failed to demonstrate differences in fetal pH, but phenylephrine consumption was lower and maternal cardiac output was higher in the 15° left lateral tilt position as compared to the supine position[100]. Moreover, in a more recent study it was shown that most patients can compensate for the decreased flow in the vena cava inferior in the supine position by increasing the blood flow through the azygos system[101].

Recommendation/conclusion: Due to the lack of evidence, it is not possible to make evidence-based recommendations. We recommend to adhere to the expert opinion of maintaining maternal blood pressure close to the normal physiologic value by using (15°-)30° left lateral tilt position, intravenous fluids and noradrenaline or phenylephrine.

Antagonisation of neurmuscular blocking drugs

Dogma/myth: The use of neostigmine is preferred over sugammadex in pregnant women, as there is insufficient evidence in the literature to ensure the safety of sugammadex[102].

Evidence: Neostigmine crosses the placenta

and can result in fetal bradycardia[13,22,30,32,40,62,103]. Therefore, atropine needs to be co-administered with neostigmine, because atropine crosses the placenta and can prevent fetal bradycardia. In contrast, glycopyrrolate does not cross the placenta[13,22,30,32,40,62,103]. There is clinical experience with the use of neostigmine in pregnant women during several decades[103].

The data on the fetal effects of reversal of the maternal neuromuscular block using sugammadex are limited to the following. First, the placental transfer of sugammadex has never been measured[103]. Theoretical predictions suggest a very limited placental transfer as sugammadex is a large polarised molecule. This theory was also suggested in a case report in which the maternal neuromuscular block was reversed by sugammadex, followed by fetal administration of rocuronium resulting in an effective fetal immobilisation[104]. Second, sugammadex can encapsulate progesterone components of hormonal contraceptives in vitro[105]. Therefore, concerns regarding the effects of sugammadex on the maintenance of an early pregnancy can be raised[103]. However, suggamadex given to pregnant rats during the first trimester, neither decreased progesterone concentrations nor increased the incidence of spontaneous abortions[106]. Third, sugammadex results in neuronal apoptosis in cell cultures, by depleting neuronal cholesterol, which triggers oxidative stress[107]. Exposure of neonatal mice to the combination of sevoflurane and sugammadex showed increased neuronal apoptosis when compared to sevoflurane exposure only[108]. Of note, sevoflurane was associated with the disruption of the blood brain barrier in these mice[108]. Fourth, in rabbits, a decreased birth weight and ossification impairments were observed in the fetuses daily exposed to maternal supraclinical doses of sugammadex (65 and 200 mg/kg) during organogesis, but no impairments were observed with lower supraclinical doses (daily 20 mg/kg)[105]. No teratogenic malformations were observed at any dose in these fetal rabbits105. In rats, no fetal impairments were observed after daily maternal administration of supraclinical doses (20, 100, and 500 mg/kg)[105]. Fifth, clinical evidence is limited to case reports suggesting that sugammadex can safely be used regarding maternal and fetal outcomes[109].

Recommendation/conclusion: Neostigmine has been used in pregnant women since several decades. In contrast, evidence on the maternal and foetal safety of sugammadex is limited to clinical case reports, and preclinical data on its safety are not unequivocally positive.

Laprascopy versus laparotomy

Dogma/myth: Laparoscopy is contra-indicated during pregnancy.

Evidence: In 1995-2004, the effects of laparoscopic surgery during pregnancy were investigated in a pregnant sheep model[110-114]. As a 40% decrease in the uterine blood flow and fetal acidosis were observed[110-114], initially laparoscopy was contra-indicated during pregnancy. However, in most of these studies, there was also a maternal respiratory acidosis during the CO_2 pneumoperitoneum[110-114], reflecting an inappropriate adjustment of maternal ventilation during insufflation, clearly in contrast to clinical practice.

In clinical practice, there has been an upward trend in the utilization of laparoscopic techniques in pregnancy during the last decades. Clinical observational studies showed no significant differences between laparoscopy and laparotomy in fetal outcomes (birth weight and Apgar scores) and obstetric outcomes (fetal loss rates, preterm labor, cesarean section rates)[9,15,64,65,115]. Notably, laparoscopy offers several advantages: reduced postoperative pain, quicker return of bowel function and oral intake, shorter recovery periods, and a decreased risk of thromboembolic events[8,9,12,14,15,65,115,116]. Additionally, it is suggested that pneumoperitoneum, compared to manual retraction of the uterus during open surgery, may confer greater safety[14,16,116]. Fetal blood gas values and uterine blood flow (which were measured in the studies performed in sheep), were not measured in the clinical studies[9,15,64,65,115].

Recommendation/conclusion: Clinical observational studies suggest that laparoscopic surgery should be considered as standard treatment[1,4,9,10,12,14-16,34,65,115,117].

Obstetric and fetal outcomes

Dogma/myth: General anesthesia and surgery during pregnancy may impair fetal outcome.

Evidence: Retrospective observational studies have examined the occurrence of unfavorable pregnancy outcomes following non-obstetric surgeries[1-4,6,7,10]. These investigations revealed a significantly increased risk of preterm labor[1-3], particularly among patients in the third trimester who underwent lower abdominal procedures[1-5,32,64]. Additionally, a higher incidence of low birth weights was observed[1,2,7]. Although two studies reported a significantly elevated risk of cesarean section[2,3], one study did not find this difference[1]. Miscarriages[2,3], pregnancy terminations[3], and stillbirths[2] were more prevalent following surgery.

No teratogenic effects have been associated with clinical use of anesthetics (both intravenous and volatile anesthetic drugs), opioids and neuromuscular blocking drug agents[5,8,24-26,32,34,116,118,119].

In the late 1990s and early 2000s, Ikonomidou and Jevtovic-Todorovic conducted experiments exposing fetal and neonatal rats to general anesthesia. They observed widespread brain cell death (apoptosis) in these animals, leading to persistent learning and memory deficits[120, 121]. Subsequently, a growing body of preclinical research emerged, spanning various animal species, which demonstrated that exposure to all commonly used general anesthetics could cause neuronal damage and impaired neurobehavioral function[122-130]. In response to these findings, in 2016, the Food and Drug Administration (FDA) issued a warning, cautioning that repeated or prolonged exposure to general anesthesia during the third trimester of pregnancy could adversely affect fetal brain development[131].

A recent meta-analysis of preclinical research has corroborated that administering general anesthesia to pregnant animals hampers learning and memory abilities and leads to neuronal damage in their offspring[132]. These effects were observed across various animal species, all commonly used anesthetic drugs, and various stages of pregnancy. However, the systematic review identified several methodological concerns that limit the direct translation of these findings to the clinical context. Firstly, the duration, frequency, and doses of anesthesia exposure often exceeded what is typically used clinically. Secondly, the animals were exposed to anesthesia without accompanying surgical procedures. Lastly, the monitoring and maintenance of physiological homeostasis in these studies were far below clinical standards.

A recent clinical ambidirectional cohort study compared 129 children which were antenatally exposed to general anesthesia for maternal surgery with 453 unexposed children[133]. Ninety percent of exposed children underwent a single episode of anesthesia with an average duration of 91 minutes for a broad spectrum of maternal indications of non-obstetric surgery, with abdominal surgery being most frequent[133]. Propensity scores were used to reduce bias by confounding, e.g. for the education and income of the parents[133]. In conclusion, the study did not find evidence in the general population for an association between antenatal exposure to anesthesia and impairment of neurodevelopmental outcomes in childhood[133]. A systematic review comparing this effect size with the effect sizes of other factors potentially affecting neurodevelopment, concluded that the effect size of antenatal anaesthesia exposure is comparable to the effect of a child spending ≥ 2 h per day in front of a screen (i.e., computer, television etc.), or of > 2 hours weekend catchup sleep of a child or of more than 15 times paracetamol intake by the mother during pregnancy[134].

Conclusion: Animal studies have repeatedly observed impaired fetal brain development after prenatal anesthesia exposure, but a clinical observational study failed to confirm this finding and concluded that the effect size of prenatal anesthesia exposure is comparable to that of rather innocent risk factors.

Conclusion

Exposure of pregnant women to general anesthesia is not rare and often unavoidable. Evidence could not always confirm the dogmas/myths on the management of general anesthesia in pregnant women. Recent evidence concluded that gastric emptying remains nearly normal during the entire pregnancy until the onset of labor. For the correct estimation of the aspiration risk (especially in doubtful situations), gastric ultrasound should be performed. Based on the available evidence, the application of cricoid pressure should be discouraged during rapid sequence induction. Laryngeal masks have been safely used in > 9000 lean and healthy pregnant patients undergoing cesarean section without observation of aspiration. All material to manage a difficult airway should be available as difficult intubation remains an ongoing concern in obstetrics. Risk factors for difficult intubation are nonobstetric in nature. Due to the lack of evidence, it is not possible to make evidence-based recommendations on hemodynamic management. We recommend to adhere to the expert opinion of maintaining maternal blood pressure close to the normal physiologic value by using (15°-)30° left lateral tilt position, intravenous fluids and noradrenaline or phenylephrine. While animal studies observed impaired fetal brain development after prenatal anesthesia exposure, several factors limit the translation of these results to the clinical setting. Additionally, a clinical observational study failed to confirm this finding and concluded that the effect size of prenatal anesthesia exposure is comparable to that of rather innocent risk factors.

Acknowledgments:
Assistance with this article: None.
Declaration of artificial intelligence technologies in the writing process: During the preparation of this work the authors used ChatGPT (OpenAI, San Francisco, California, USA, https://chat.openai.com/)

in order to improve the readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Funding: The authors are funded by the European Society of Anesthesiology and Intensive Care (ESAIC) Young Investigator Start-up Grant 2021, the Society for Anesthesia and Resuscitation of Belgium (SARB) research grant 2019 and the Obstetric Anesthetists' Association (OAA) International Grant 2019. None of these funding sources played a role in the study design, data collection, analysis, interpretation or writing of the article.

Conflicts of Interest: None.

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doi.org/10.56126/75.1.08