Current Anesthesiology Reports (2023) 13:59–66
https://doi.org/10.1007/s40140-023-00551-7

OBSTETRIC ANESTHESIA (LR LEFFERT, SECTION EDITOR)

Sedating Pregnant Patients for Minimally Invasive Fetal Interventions

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Accepted: 19 February 2023 / Published online: 22 March 2023

Abstract

Purpose of Review This article discusses sedation in pregnant patients undergoing minimally invasive fetal interventions. It includes a review of the goals of sedation in this population, relevant existing guidelines, physiological considerations unique to pregnant patients undergoing sedation, and a brief discussion of perioperative management using pharmacologic and nonpharmacologic anxiolysis.

Recent Findings Sedation is used by most fetal therapy centers performing minimally invasive fetal interventions in combination with local or neuraxial anesthesia. Existing guidelines recommend no more than a moderate plane of sedation for pregnant patients. The impact of individual medications on the pregnant patient, fetus, and operating conditions including uterine contractility are areas of investigation relevant to fetal interventions.

Summary While most fetal centers use sedation for pregnant patients undergoing minimally invasive fetal surgery, no single regimen has been identified as optimal. Vigilance in maintaining a minimal-moderate level of sedation is essential for mitigating risks when sedating pregnant patients.

Keywords Sedation · Monitored anesthesia care · Pregnancy · Minimally invasive fetal surgery · Fetal intervention

Introduction

Recent advances in the field of fetal therapy have led to an increase in both the indications and availability of fetal interventions to address anomalies that are diagnosed prenatally [1, 2••]. A recent survey of fetal therapy centers (FTCs) registered with the North American Fetal Therapy Network (NAFTNet) revealed that while more invasive fetal procedures (e.g., neural tube defect repairs) are generally limited to larger fetal centers, minimally invasive fetal interventions (MIFIs) are performed at all FTCs [2••]. As innovations in the field continue, the list of indications for MIFIs continues to grow [3]. These cases may be performed using various modes of anesthesia including sedation, local anesthesia, neuraxial anesthesia, or a combination thereof, and occasionally general anesthesia [2••]. While anesthesiology training requirements mean that anesthesiologists are well-versed in the management of neuraxial and general anesthesia in the obstetric patient, sedation of the pregnant patient is less common, and no formal training requirements for sedation of pregnant patients exist. However, the majority of FTCs report using sedation for MIFIs either in combination with local or neuraxial anesthesia [2••]. This article will review the goals of sedation in pregnant patients, existing guidelines and evidence for the use of sedation in MIFIs, important physiologic considerations, and a brief review of pharmacologic and nonpharmacologic approaches to anxiolysis in the pregnant patient. We will use the word "maternal" to refer to the management of the pregnant patient although we acknowledge that transgender men and nonbinary individuals undergo fetal interventions, and this review pertains to their care as well.

Search Strategy

The literature search included articles from the PubMed database focused on procedure-related sedation during pregnancy. Keywords included "sedation" OR "monitored anesthesia care" AND either "pregnancy" or "pregnant" OR "fetal surgery" or "fetal intervention." A total of 28 articles

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were found in the initial search. Articles included systematic reviews, observational studies, guidelines, and case reports; editorials were excluded. We excluded articles related to long-term sedation in ICU settings as well as articles related to fertility procedures and pregnancy termination. Excluding articles in languages other than English yielded 7 articles for full-text review.

Goals of Sedation in Pregnant Patients

While all anesthetics aim to minimize risk and optimize operating conditions, the anesthetic goals during MIFIs have several unique aspects due to the presence of at least two separate patients undergoing simultaneous but distinct interventions. For example, the pregnant patient may undergo ultrasound-guided placement of an instrument through the abdomen and uterus, while the fetus is undergoing placement of a shunt through the chest wall. For the purposes of discussion, anesthetic goals can be considered for the pregnant patient and the fetus(es) separately, recognizing that their unique physiologic connection via the placenta blurs this distinction in actual practice. Topics specific to fetal anesthetic management, such as whether and what to administer directly to a fetus to blunt autonomic responses to noxious stimuli, are beyond the scope of this article.

The anesthetic goals of sedating a pregnant patient for MIFIs include optimizing both operating conditions and patient experience. While these goals are generally achieved using lower doses of sedation than are typical for other cases commonly performed using monitored anesthesia care, effective anxiolysis is critical. Untreated preoperative anxiety in pregnant patients is associated with higher reports of pain and lower maternal satisfaction, and perioperative anxiety in surgical patients in general is associated with physiologic derangements, including changes in heart rate, blood pressure, temperature, and increased nausea [4]. These priorities can only be undertaken safely by simultaneously maintaining maternal hemodynamics at baseline, minimizing the risk of aspiration, avoiding hypercarbia and its associated negative effects on both the pregnant patient and the fetus, avoiding unanticipated conversion to general anesthesia and/or airway manipulation, and minimizing unnecessary exposure of the fetus to anesthesia.

Existing Guidelines for Sedation in Pregnant Patients

Existing statements and guidelines that are relevant to the sedation of pregnant patients undergoing MIFIs include the American Society of Anesthesiologists (ASA) statement on the Continuum of Depth of Sedation and the first consensus statement on Anesthesia for Maternal–Fetal Interventions from the ASA Committees on Obstetric and Pediatric Anesthesiology and NAFTNet [5••, 6]. The term "sedation" refers to the spectrum that exists between a fully conscious, unmedicated patient and a patient under general anesthesia. The ASA statement defines minimal, moderate, and deep sedation based on response to stimulus, requirement for airway intervention, ventilation status, and cardiovascular function (Table 1) [6].

The 2021 ASA/NAFTNet Consensus Statement offers the most complete set of recommendations for optimal management of patients undergoing fetal interventions. The authors recommend limiting the depth of anesthesia to minimal-moderate sedation alone or in combination with neuraxial anesthesia, emphasizing the importance of preserving airway reflexes and ensuring that the patient is able to follow instructions during the procedure [5••]. For both minimal and moderate sedation, patients are spontaneously breathing with no interventions needed to support the airway, and patients are able to follow simple commands although they may require light tactile stimulation with verbal instruction in the case of moderate sedation. The consensus statement also recommends considering the administration of aspiration prophylaxis, such as non-particulate antacids, H2-receptor antagonists, and metoclopramide [5••]. Decisions about whether to administer aspiration prophylaxis when sedation is planned and which specific agents to use are often made based on the likelihood of conversion to general anesthesia

Table 1 Comparing levels of sedation

	Minimal sedation	Moderate sedation	Deep sedation	General anesthesia
Is the patient responsive to verbal stimulation?	+	+/−	−	−
Is patient responsive to light tactile stimulation?	+	+	−	−
Are airway reflexes intact?	+	+	−	−
Is spontaneous ventilation adequate?	+	+	−	−
Are hemodynamics typically maintained?	+	+	+	−

Adapted from the ASA Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia [6]

as well as patient-specific factors, including NPO status and the presence of symptomatic reflux.

Physiologic Considerations

Traditional teaching has limited the anesthetic options for patients undergoing surgery during pregnancy to either general anesthesia with an endotracheal tube or fully awake with regional, neuraxial, or local anesthesia, often with little mention of sedation [7]. The tenets of anesthesia for pregnant patients undergoing non-obstetric surgery hold for MIFIs as well, including maintenance of uteroplacental perfusion, avoidance and/or treatment of preterm labor, and caution surrounding airway management due to the increased risk of difficult airway in pregnancy [8]. This article will focus on the risks specific to sedation of the pregnant patient, namely aspiration and hypercarbia.

Pregnant patients, specifically those beyond 20 weeks of gestation, are impacted by anatomic and physiologic alterations including gastric displacement by a gravid uterus, hormonal changes (i.e., progesterone and motilin), and a higher incidence of gastric reflux. These changes all contribute to an increased risk of aspiration in this patient population [1, 9]. Concerns surrounding aspiration are not trivial: aspiration can result in significant morbidity and even mortality. Because risk is related to the volume and pH of gastric fluid, various techniques have been used to evaluate gastric emptying as a proxy for aspiration risk [9]. In order to avoid radiation (scintigraphy) and discomfort (orogastric tube), gastric ultrasound has become the primary modality used to evaluate gastric emptying and predict aspiration risk in pregnant patients.

Multiple studies have used gastric ultrasound in an attempt to determine whether gastric emptying is delayed in pregnancy (Table 2). These studies demonstrate that non-laboring pregnant patients do not have significantly slower gastric emptying times, but that gastric emptying is slowed in laboring patients [9–11]. The presence of gastric contents, however, does not necessarily lead to aspiration. Concerns about aspiration in pregnancy stem from Mendelson's 1946 paper reviewing 44,000 deliveries. Of 66 cases of aspiration, 2 deaths were described; however, most of the aspiration events occurred during vaginal deliveries or operative deliveries where a face mask was used to administer general anesthesia [12, 13]. The field of obstetric anesthesia has changed significantly over the past 75 years, with intubation considered the standard of care if general anesthesia is necessary. According to a retrospective review examining the causes of pregnancy-related mortality, the current incidence of gastric aspiration is approximately 1 in 1 million deliveries [12, 14]. Additionally, based on data from over 300,000 deliveries at 20 large centers across the USA, including more than 96,000 cesarean deliveries and more than 5000 cesarean deliveries under general anesthesia, SOAP's Serious Complication Repository does not include any reported cases of aspiration, illustrating the very low incidence of this complication despite delayed gastric emptying in laboring patients [12, 15].

Hypercarbia is a potential risk for any patient undergoing sedation, and the risk of hypercarbia increases with deeper levels of sedation due to decreased respiratory drive and inadequate spontaneous ventilation. Although healthy patients can generally tolerate some degree of hypercarbia without significant detrimental effects, hypercarbia should be avoided in pregnant patients due to its adverse effects on the fetus. Significant maternal hypercarbia causes uterine artery vasoconstriction. If severe, the resulting impairment in uteroplacental perfusion can lead to fetal acidosis. When this occurs in the setting of maternal acidosis, the ability of the fetus to offload acid can be impaired, impeding fetal recovery [16]. When severe, fetal acidosis can depress fetal cardiac function [8].

Avoiding hypercarbia and preventing gastric aspiration are of utmost importance when sedating pregnant patients, and the risks of both can be mitigated by maintaining an appropriate plane of sedation. Deep sedation and general anesthesia without a protected airway are associated with an increased risk of aspiration and hypercarbia due to impaired airway reflexes and inadequate spontaneous ventilation and should be avoided in pregnant patients. On the contrary, patients receiving minimal to moderate sedation are at very low risk of aspiration and hypercarbia because, by definition, these patients have intact airway reflexes and adequate spontaneous ventilation without intervention [6]. Patients under minimal to moderate sedation can also be aroused and directed to take a deep breath, if necessary, as they are responsive to verbal or gentle tactile stimulation [6]. Thus, staying vigilant to the level of sedation and limiting it to the minimal to moderate range is integral to minimizing risks for pregnant patients.

Alternatives to Sedation in Pregnant Patients

Alternatives to sedation in pregnant patients undergoing MIFIs include general anesthesia or the use of local or neuraxial anesthesia without sedation. MIFIs are generally well tolerated with neuraxial anesthesia, and the rate of conversion to general anesthesia is comparable to cases performed using sedation with local anesthesia [17•, 18•]. Because of the time required to perform a separate procedure, neuraxial anesthesia is associated with a longer time from operating room entry to incision. Not surprisingly, cases performed using neuraxial anesthesia are associated with increased

Table 2 Use of gastric ultrasound to evaluate gastric emptying in pregnant patients

	Study type	Subjects	Methods	Results
[9]	Cross-over study	Healthy, non-obese, non-laboring, pregnant volunteers between 37 and 39 weeks gestation	Gastric ultrasound used to compare gastric emptying following ingestion of 300 cc of water [clears] versus 50 cc of water [fasted controls] Time to peak plasma acetaminophen concentration used as indirect measure of gastric emptying following ingestion of 300 cc of water [clears] versus 50 cc of water [fasted controls]	Gastric emptying of patients who drank 300 cc of water *not* slower compared to the control group Time to peak plasma concentration decreased (i.e., faster) after ingestion of 300 cc water compared to the control group
[10]	Randomized control trial	Non-laboring pregnant patients at more than 36 weeks gestation	Gastric ultrasound used to compare gastric emptying after ingestion of 250 cc of tea with milk versus 250 cc of water	No significant difference between gastric antrum cross-sectional area (CSA) or total gastric fluid volume between groups after 2 h Similar rate of gastric emptying (according to gastric antrum CSA & total gastric fluid volume) at nearly all time points with return to baseline gastric antrum CSA between 60 and 90 min for both groups
[11]	Prospective cohort study	Four groups: (1) non-pregnant women, (2) non-laboring pregnant women at term, (3) parturients without labor analgesia, (4) parturients with epidural labor analgesia	Gastric ultrasound used to compare gastric emptying among 4 groups after eating standardized light meal (yogurt)	Statistically significant slower gastric emptying of a light meal in parturients with epidurals compared with those in the non-pregnant and non-laboring, pregnant control groups Statistically significant slower gastric emptying in parturients without epidurals compared to parturients with epidurals

vasopressor use compared to those performed using sedation with local anesthesia [17•]. MIFIs performed under neuraxial anesthesia have also been associated with decreased operating room efficiency and increased costs [17•, 18•].

General anesthesia is less commonly used for MIFIs, with 39% of FTCs reporting their use at least sometimes [2••]. In the case of an anterior placenta with inadequate surgical window, a laparotomy-assisted technique may necessitate the use of general anesthesia. Certain patient-specific factors, such as severe anxiety, history of trauma, or massive polyhydramnios associated with dyspnea or inability to lie flat, are all relative indications for general anesthesia as well. The drawbacks of general anesthesia include obstetric airway instrumentation and concerns about neurotoxicity related to anesthesia exposure in the developing fetal brain [8, 19, 20]. Compared to sedation, the use of general anesthesia is associated with longer operative time and administration of more medications, resulting in more anesthetic exposure for the fetus [18•].

Pharmacologic Agents

An ideal sedating agent for MIFIs would be rapidly titratable with a stable hemodynamic profile and no impact on maternal respiratory drive, would not increase myometrial contractility, and would not be associated with maternal or fetal adverse effects. No single approach has been determined to be clearly superior overall, and, in practice, multiple medications are often combined to improve operating conditions and patient experience while minimizing undesirable side effects.

Opioids

Fentanyl and remifentanil are used in 54.5 and 45.5% of FTCs performing MIFIs, respectively [2••]. The rapid titratability of remifentanil, a rapid-onset, ultra-short-acting synthetic opioid, makes its use particularly appealing in MIFIs. Similar to other medications commonly used for sedation, it readily crosses the placenta, but it is rapidly metabolized and redistributed in both the fetus and the pregnant patient [21]. Studies evaluating remifentanil at a dose of 0.1 mcg/kg/min in MIFIs demonstrated decreased fetal movement and improved operating conditions in the remifentanil group compared to diazepam [22, 23]. While remifentanil can decrease maternal heart rate, its use in fetal surgery has not been associated with clinically significant fetal bradycardia [24, 25]. A common bothersome adverse effect with its use is pruritus, which generally improves quickly by decreasing infusion rates.

Opioids are generally not considered to be teratogenic, and current evidence suggests that they would not be expected to cause myometrial contractility [26]. In fact, opioid receptors have been identified on myometrium and lead to relaxation in vitro, and remifentanil has been demonstrated to reduce the amount of volatile anesthetic needed during fetal myelomeningocele repair while maintaining adequate uterine relaxation [25, 27].

Benzodiazepines

The question of association between benzodiazepines and fetal malformations including oral clefts has been the subject of much controversy. Early concerns of teratogenicity were based on reports that included studies without control groups [28]. A 1998 meta-analysis demonstrated no increase in risk of overall malformations after exposure to benzodiazepines in the first trimester but suggested an increased risk in oral clefts [29]. The meta-analysis was updated in 2011, strengthening the evidence for safety by increasing the sample size to over one million pregnancies without demonstrating a link between benzodiazepines and fetal malformations [30]. However, the reliability of a link to oral clefts in these meta-analyses was low due to heterogeneity of the studies involved. In particular, the exposure to benzodiazepines was not consistently defined, was most often determined by interview with the pregnant patient, and included longer term prescription use. This data is therefore of limited relevance in the context of relatively small doses given over a limited time for procedures or surgeries. Furthermore, the palate is formed between the fifth and twelfth weeks of gestation, with the most critical stages being between weeks six and nine, so the relevance of this concern to fetal interventions is minimal [31]. Benzodiazepines are routinely used in these procedures, with over half of FTCs reporting their use during MIFIs [2••].

Propofol

Nearly half of FTCs report the use of propofol for maternal sedation during MIFIs. While care must be paid to avoid the adverse effects of decreased respiratory drive and hypotension, the doses of propofol needed to achieve the minimal-moderate sedation for MIFIs would not be expected to be associated with profound hypotension. Still, maternal hemodynamics and respiratory drive should be monitored closely. Propofol has not been shown to be teratogenic in animal studies [32].

Dexmedetomidine

Dexmedetomidine is another commonly used agent during MIFIs, and its use was reported by one third of FTCs surveyed by Wood et al. [2••]. Not surprisingly, pregnant patients who received dexmedetomidine during cesarean delivery were found to have lower blood pressure and heart rate compared with placebo groups [33, 34]. However, administration of dexmedetomidine to pregnant ewes did

not alter fetal physiologic status, and case reports describing the use of dexmedetomidine in pregnant patients have not demonstrated fetal bradycardia [35–38]. In comparison to most other intravenous anesthetic agents, the transplacental passage of dexmedetomidine is limited [33, 34]. A common bothersome side effect of dexmedetomidine reported by patients undergoing MIFIs is dry mouth.

Studies evaluating the impact of dexmedetomidine on myometrial contractility have shown mixed results [39–43]. Given the importance of avoiding preterm contractions during and after fetal interventions, more studies are needed to clarify whether a clinically significant relationship between dexmedetomidine administration and uterine contractility exists.

Nonpharmacologic Anxiolysis

Nonpharmacologic anxiolysis plays a significant role in patients undergoing MIFIs, particularly given the light planes of anesthesia used. Clear communication with all members of the perioperative team is important to ensure awareness that the patient is awake and may recall some or all of the procedure. Even brief educational and psychological interventions are effective for adults with procedure-related anxiety [4]. This includes setting clear expectations through education about the procedure and the operating room environment, acknowledging and normalizing anxiety, and finding opportunities to promote a sense of control, such as selection of music or aromatherapy.

Up to 44% of patients report their birth experiences as traumatic; the risk is presumably higher in patients with pregnancies complicated by fetal anomalies requiring prenatal intervention [44]. Many trauma survivors do not present with a diagnosis, so the routine use of trauma-informed care in this population is important to prevent acute traumatic stress and avoid retraumatization [45•]. These strategies include frequent "check-ins" with the patient about their emotional state and the effectiveness of anxiolysis strategies that are being used, respecting a patient's privacy by keeping her covered as much as possible, use of a calm voice and maintaining focus on the patient, and avoiding the use of arm straps and unnecessary oxygen masks [45•].

A Proposed Approach

Preoperatively, standard NPO guidelines should apply for patients undergoing MIFIs, keeping in mind that prolonged fasting times may exacerbate nausea in pregnancy [46]. Consideration should be given to avoiding unnecessarily long fasting periods and treating nausea as needed, even in the preoperative period. In the case of an urgent procedure in a patient who has not fasted, the anesthesiologist should weigh the risks and benefits of limited sedation with an emphasis on nonpharmacologic anxiolysis and local anesthesia versus general endotracheal anesthesia. We recommend incorporating a shared decision-making strategy in these situations, as patients often have preferences that will help determine the optimal anesthetic strategy when both options are reasonable.

Intraoperatively, careful attention to patient positioning is critical. Once the approach for surgical access has been determined by ultrasound, uterine displacement should be used as appropriate, and patients should be consulted to optimize their comfort. We incorporate ample pillows and padding where possible to avoid discomfort during the procedure, which can lead to patient movement at an inopportune time. Spending extra time to ensure patients are comfortable is worthwhile, as discomfort and inability to lie still may necessitate conversion to general anesthesia [18•]. Standard American Society of Anesthesiologists (ASA) monitors should be used to monitor the pregnant patient, and hemodynamics should be maintained at baseline to support uteroplacental blood flow [47]. Because minimal-moderate sedation, by definition, should not impact hemodynamics, uteroplacental perfusion should typically not be affected by the sedation used for fetal interventions. However, anesthesiologists should keep in mind that many patients may receive tocolytics that may impact the maternal blood pressure (e.g., nifedipine) prior to surgery. The ideal plane of sedation is one in which the patient is calm, spontaneously ventilating, and easily arousable to voice, with no interventions needed to support the airway. Beyond the risks of aspiration and hypercarbia, deeper planes of sedation are associated with slow deep breathing, which increases the technical difficulty of the procedure for the surgical team.

Forced air warming devices and room temperature are the primary methods of maintaining patient temperature, which is critical to avoid decreases in fetal heart rate [48, 49]. While concerns about pulmonary edema in these cases have been mitigated through irrigation fluid restrictions, a full bladder due to high volumes of intravenous fluids in a prolonged procedure can be very bothersome to a patient without a Foley catheter [47].

Because of the light planes of anesthesia, the recovery from anesthesia for these patients is typically short and uncomplicated. Unexpected issues such as severe or persistent pain or significant changes in hemodynamics should prompt rapid evaluation by both anesthesia and fetal intervention teams, as obstetric complications may require swift intervention.

Conclusions

The majority of fetal therapy centers use sedation with either local or neuraxial anesthesia as the preferred anesthetic for minimally invasive fetal surgery. Concerns

surrounding sedating a pregnant patient, such as the risks of aspiration and hypercarbia, can be mitigated by maintaining a minimal-moderate plane of sedation in line with existing guidelines, such that airway reflexes remain intact, spontaneous ventilation remains adequate, and patients remain responsive to verbal instructions or light touch. A combination of pharmacologic and nonpharmacologic approaches can be used to optimize operating conditions and patient experience while simultaneously minimizing risks during minimally invasive fetal interventions.

Compliance with Ethical Standards

Conflict of Interest Claire Naus and Caitlin Sutton declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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