



Society for Obstetric Anesthesia and Perinatology

Statement on Sugammadex during pregnancy and lactation

Ad Hoc task force: Willett, Butwick, Togioka, Bensadigh, Hofer, Zakowski

April 22, 2019

Statement Purpose:

Use of sugammadex has steadily increased in the United States since FDA approval in 2015. Concerns for hormonal binding, given its potential effect on serum progesterone assays, interaction with hormonal contraceptives, and its relatively high affinity for Toremifene, a selective estrogen receptor modulator.¹ The Society for Obstetric Anesthesia and Perinatology (SOAP) receives questions regarding sugammadex use in women of reproductive age, as well as during pregnancy and lactation. The purpose of this statement is to inform anesthesiology providers regarding the most appropriate use of sugammadex in pregnant women, breastfeeding women, and women of childbearing age.* While the approach to any therapy should always be individualized, taking into account surgical and anesthetic needs, as well as patient preference, we provide recommendations based on the unique and specific needs of each of the following patient populations:

**This information is based on the current state of evidence from both the medical literature as well as from pharmaceutical data. It is solely intended to serve as an educational tool when weighing potential benefits against risks in these populations and should not substitute as clinical decision making.*

**PATIENTS IN EARLY
PREGNANCY**

AVOID

While the literature is insufficient to evaluate the safety of sugammadex during early gestation and fetal development, in vitro studies indicate that sugammadex binds to and encapsulates progesterone. Progesterone is critical for the maintenance of pregnancy, and until the clinical implications of this is known, we advise against the use of sugammadex in this population (see Section II—Use of sugammadex during pregnancy: current state of evidence).

**PATIENTS AT TERM
OR NEAR TERM PREGNANCY**

AVOID OR USE WITH CAUTION

For patients who are at term or near-term pregnancy requiring general anesthesia for Cesarean delivery, sugammadex appears to be safe and effective from a maternal perspective. However, the literature is insufficient to evaluate the effect on lactation success and the extent of drug exposure through breast milk. When considering sugammadex for reversing neuromuscular blockade in pregnant women undergoing general anesthesia for cesarean delivery, providers should presume infants will be breastfed soon after delivery. Because the early postpartum period is critical for establishing breastfeeding, the task force recommends the judicious use of sugammadex in this patient population until more is known regarding its effects on lactation (see Section IIIa. Use of sugammadex in breastfeeding women: early postpartum versus established lactation). If sugammadex is given, the patient should be informed that effects on lactation are unknown.

**PATIENTS WITH
ESTABLISHED LACTATION**

SAFE TO USE

After receiving sugammadex, it is likely safe to resume a normal breastfeeding routine once the patient has recovered from general anesthesia. However, the patient should be informed that the effects on lactation are unknown (see Section IIIa. Use of sugammadex in breastfeeding women: early postpartum versus established lactation).

**PATIENTS OF
REPRODUCTIVE AGE**

SAFE TO USE PROVIDED PATIENT IS COUNSELED

All women of childbearing age who have received sugammadex should be provided with counseling to use additional non-hormonal contraception, such as condoms, for 7 days. The task force encourages institutions to create standard wording for these conversations. In cases where sugammadex has been administered intraoperatively, the task force strongly recommends providing post-procedure education (see Section IV. Use of sugammadex in women of childbearing age on hormonal contraception).

**PATIENTS FOR WHOM BENEFIT MAY OUTWEIGH THEORETICAL OR UNKNOWN
RISKS TO FERTILITY, PREGNANCY, OR LACTATION**

1. Patients with an unanticipated difficult airway (cannot intubate, cannot ventilate), where a dose of 16 mg/kg (actual body weight) of sugammadex can be administered to rapidly reverse neuromuscular blockade.
2. Patients in whom the administration of cholinesterase inhibitors has reached a ceiling effect but who remain at an elevated risk for inadequate reversal,ⁱⁱ i.e. postoperative residual neuromuscular blockade due to high-dose magnesium therapy, or presence of disorders of impaired neuromuscular transmission such as myasthenia gravis.ⁱⁱⁱ

Section I. Background sugammadex pharmacology:

The sugammadex molecule is a γ -cyclodextrin with a hydrophilic oligosaccharide exterior and a lipophilic core. Sugammadex inactivates aminosteroid non-depolarizing neuromuscular blocking agents (which we will henceforth refer to as ANDMB) by encapsulating free molecules to form a water-soluble complex that is renally excreted. Binding of plasma ANDMB creates a gradient of higher concentration at the neuromuscular junction and a lower concentration in plasma of free (non-bound) sugammadex. As free ANDMB moves from muscle to plasma the percentage of nicotinic receptors bound by ANDMB drops, resulting in rapid restoration of muscle function^{iv}. Sugammadex exhibits first-order kinetics in the dosage range of 1-14 mg/kg, undergoes no metabolism, and is almost exclusively excreted through the kidneys. With a normal glomerular filtration rate (GFR), elimination half-life of sugammadex is approximately 2 hours.ⁱ Decreased renal function would delay total body elimination. Half-life of sugammadex bound to rat bone is 172 days. Note that invitro studies with similar structure to ANDMB may also be bound by sugammadex including but not limited to some hormones, hormonal contraceptives and pheromones. During normal pregnancy, renal function (glomerular filtration rate, GFR) is increased 50% from baseline by the end of first trimester.^v Note that renal function may be decreased during preeclampsia or other medical conditions. Incidence of anaphylaxis to sugammadex ranges from 0.0025-0.03%.^{vi}

Section II. Use of sugammadex during pregnancy: current state of evidence

Because of the increased risk for aspiration and desaturation, rapid sequence induction is advocated for almost all pregnant patients after the second trimester.^v Therefore, quick restoration of neuromuscular function is critical should a situation arise where ventilation and intubation cannot be established. Immediate reversal of dense rocuronium blockade with sugammadex (14 mg/kg dosing) may be quicker than spontaneous recovery from succinylcholine.^{vii} In addition, pregnancy and the immediate postpartum period is associated with a near 25% reduction in plasma cholinesterase levels, theoretically exposing the patient to a prolonged succinylcholine blockade.^v

It is understandable then why a handful of small studies have attempted to establish the utility of sugammadex in the obstetric population. Early results suggest that in women requiring general anesthesia for cesarean delivery, it is non-inferior in preventing return of muscle weakness,^{vi,vii} may be effective in reversing rocuronium blockade when cholinesterase inhibitors are unable to do so,ⁱⁱ and poses minimal risk with regards to maternal safety or side effect profile.^{viii}

However, the impact of sugammadex administration on human fetal development remains unknown as there are no clinical data on exposure during early pregnancy. Pharmacological simulation studies by Merck indicate that a 4 mg/kg dose of sugammadex is predicted to reduce unbound progesterone levels by 34%^{ix} which is theoretically consequential given that progesterone secretion by the corpus luteum supports endometrial growth and is required for the success of early human pregnancy.^x Results from animal models are mixed: a single dose of sugammadex 30 mg/kg, where the maximum recommended human dose (MRHD) is 16 mg/kg, in early rat gestation did not affect the duration of pregnancy or rate of stillbirths or miscarriages.^{xi} Treatment of daily sugammadex during organogenesis at six times the MRHD had no teratogenic effects on rat pups.ⁱ However, pregnant rabbits that received daily doses of 2- and 8-times MRHD during organogenesis produced offspring with 10 and 14% reduction in birth weight, respectively. Rabbit offspring that received the higher dose had incomplete ossification at the sternum and first metacarpophalangeal joint. It is conceivable that these bony effects may be due to sugammadex as it has been shown to remain in areas of active mineralization (with a mean half-life of 172 days in bone versus 2 hours in plasma).

The literature is insufficient to evaluate the safety of sugammadex with regards to effects on plasma hormone levels as well as teratogenicity. Therefore, the task force recommends traditional neuromuscular blockade reversal during pregnancy.

Section IIIa. Use of sugammadex in breastfeeding women: early postpartum versus established lactation

At the time of this statement publication, a search of the scientific literature did not yield any studies regarding excretion of sugammadex into human breast milk, or its effect on lactation or the breastfed infant. We take this opportunity to review the optimal pharmacokinetic factors and physical characteristics of a drug to estimate its probability in entering human milk.^{xii, xiii} Medications that are characterized by high lipid solubility, small molecular size (less than 300 g/mol), and long half-life, will tend to penetrate milk in higher concentrations. Furthermore, drugs with a pKa higher than that of breastmilk (7.2) will become sequestered in milk as a result of ion-trapping. The sugammadex molecule is large (2198 g/mol) and hydrophilic, forming tight water soluble complexes with ANDMB in a 1:1 ratio, has a half-life of 2 hours, and a pKa of 2.82.^{xiv} Taken all together, this would favor limited excretion into breast milk. It is likely for these reasons, that both the Drugs and Lactation Database (LactMed)^{xv} and the European Medicine Agency (EMA)^{xii} state that sugammadex can be safely used during breastfeeding.

However, it is important to note that several important pharmacokinetic features of sugammadex may pose challenges during breastfeeding initiation. First, the sugammadex molecule exhibits absolutely no protein binding.^{xvii} High degrees of protein-binding tend to give low concentrations of drug in milk because only the free fraction of the drug is available for transfer;^{xix} according to Hale, this is the single most important parameter that predicts how readily a drug penetrates milk. Furthermore, during the early postpartum period, i.e. first 4-10 days of life, there are large gaps between the maternal alveolar cells lining the lactating ducts, permitting enhanced access for maternal proteins to enter the milk. After this time period, the intracellular gaps close, thereby limiting access to milk. Therefore, it is generally agreed upon that medications are more likely to penetrate milk during the neonatal period than in mature milk.^{xvi} This is extremely important given another pharmacokinetic feature of sugammadex—peak onset time, a major determinant of when the most amount of drug is expected be transferred from plasma to milk. After receiving a single dose of 1.25 MRHD on postnatal day 9, rat dams demonstrated a peak drug concentration occurring 30 minutes after administration with an approximate milk:plasma ratio (M/P) of 1.ⁱ For patients

who have received general anesthesia for Cesarean section, this peak onset time would correspond with when many hospitals initiate skin-to-skin bonding, and is often the first opportunity a newborn has to attempt suckling. Because the M/P ratio does not provide exact concentrations, it is usually not helpful in this context. Furthermore, there is known variability of the M/P ratio in colostrum.^{xvi} And while the oral absorption of cyclodextrins is thought to be low, it is unclear how the immature metabolism and clearance of the neonate may affect this. When considering sugammadex for ANDMB reversal in postpartum women undergoing general anesthesia for cesarean delivery, providers should presume that the newborn will be fed breastmilk after delivery and thus, we recommend traditional reversal agent therapy (see Section IIIb).

If a postpartum patient with established lactation receives sugammadex, the task force recommends that providers inform patients that the effects on lactation or the breastfed infant is currently unknown. However, moms can be reassured that based on the drug pharmacokinetic profile, both Lactmed and EMA consider sugammadex safe during breastfeeding. The conventional advice of pumping and discarding for breastfeeding moms who have undergone a general anesthetic is likely outdated/not applicable. This advice is generally reserved for drugs which may accumulate and theoretically increase the risk for neonatal sedation or respiratory depression or drugs which pose serious hazardous effects such as those with radioactive compounds.^{xvi, xx} However, if a patient desires to do so, breastmilk can be expressed and discarded for the first 12-14 hours after surgery (the equivalent to 5.5 half-lives to achieve < 2.5% peak concentration).

Section IIIb. Use of routine reversal (Neostigmine and Glycopyrrolate) in breastfeeding women

In order to provide the clinician with comprehensive information necessary when selecting an appropriate ANDMB reversal regimen, we present what is known regarding the safety of the traditional reversal agents, neostigmine and glycopyrrolate on breastfeeding.

Neostigmine is a quaternary ammonium compound with a half-life of 15-30 minutes, thus it is largely ionized in maternal plasma and therefore unlikely to pass into breast milk in clinically significant quantities.^{xxi, xxii} The literature on neostigmine is derived from a case series following lactating mothers with myasthenia gravis on maintenance anticholinesterase therapy. There have been reports of neonatal abdominal cramping though no detectable drug levels were found in breast milk.^{xxiii} Glycopyrrolate is a quaternary ammonium structure also with a short half-life of about 30 minutes. Long-term anticholinergic therapy can reduce lactation in animals by way of reducing oxytocin secretion.^{xxiv, xxv} Unlike anticholinergic drugs which decrease oxytocin, cholinergic drugs have shown to evoke release of oxytocin.^{xxvi} It is conceivable then that the simultaneous administration of neostigmine with atropine in nursing mothers has a “neutralizing effect” on lactation. More likely, it is that the average patient is not on chronic cholinergic/anticholinergic therapy, and therefore, a single dose of neostigmine and glycopyrrolate during GA for C/S is likely not to be associated with adverse effects on breastfeeding. Furthermore, unlike sugammadex, which is not FDA approved in the pediatric population, neostigmine and glycopyrrolate have established recommended pediatric doses.

Section IV. Use of sugammadex in women of childbearing age on hormonal contraception

A dose of 4 mg/kg sugammadex has been predicted to decrease progesterone exposure by 34% which is similar to the decrease that occurs when a daily dose of an oral contraceptive is taken 12 hours too late. If sugammadex is given to a patient who is on hormonal contraception (oral or non-oral, combined estrogen with progesterone, or progesterone only), it is recommended that an additional, non-hormonal contraceptive method (such as condoms and spermicides) be used for the next 7 days.

When considering sugammadex use in female patients of reproductive age, caution should be applied and when possible, traditional neuromuscular blockade reversal administered. If sugammadex administration is anticipated, every effort should be made by the anesthetic provider to either consent the patient a priori and/or provide post-procedure mandatory counseling to those who have been exposed. A standardized informational item can be especially helpful in achieving this (see Appendix A).

The task force takes the firm stance that the use of sugammadex in women of childbearing age should always include discussion and post-procedure educational information. This should take place regardless of provider knowledge of a patient's contraception status. This is particularly consequential given 1) the potential risk for unintended pregnancy and 2) that certain patient populations may be vulnerable when disclosing information regarding fertility, i.e. underage individuals, those in abusive relationships, and may not be able to safely disclose their use of hormonal contraception in the preoperative setting.

Appendix A

Suggested Patient Information to be provided for women of childbearing age who received sugammadex:

You were given a medication called sugammadex during surgery. This medication was given to improve your muscle strength and help you wake-up from anesthesia. Sugammadex is known to affect the activity of hormone contraceptives such as the pill, vaginal ring, implants, and intrauterine devices (IUDs). The effect of sugammadex on hormone contraceptives is thought to be the equivalent of missing one oral contraceptive pill. If you use hormone-based contraceptives it is recommended that you use an **additional** form of barrier method/non-hormone contraceptive, such as a condom, for the next 7 days.

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