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Review

What we need to know and do on sugammadex usage in pregnant and lactating women and those on hormonal contraceptives

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Sugammadex is a chemically modified γ-cyclodextrin that is used as a selective reversal agent for steroidal neuromuscular blockade. The use of sugammadex has greatly increased globally; however, little is known about its potential adverse effects in pregnant and lactating women or those using hormonal contraceptives. There are three important theoretical assumptions. Firstly, pregnancy-related physiological changes involve most organs and affect the pharmacokinetic profiles of medications. Considering the physiological changes in pregnant women and the pharmacokinetic properties of sugammadex, alterations in the dosage and safety profiles of sugammadex may occur during pregnancy. Secondly, very large and polarized sugammadex molecules are expected to have limited placental transfer to the fetus and excretion into breast milk. Finally, sugammadex can bind to steroidal neuromuscular blocking agents as well as other substances with similar structures, such as progesterone. As a result of using sugammadex, progesterone levels can be reduced, causing adverse effects such as early pregnancy cessation and failure of hormonal contraceptives. This narrative review aims to demonstrate the correlations between sugammadex and pregnancy, lactation, and reproductive potential based on previously published preclinical and clinical studies. This will bridge the gap between theoretical assumptions and currently unknown clinical facts. Moreover, this review highlights what anesthesia providers should be aware of and what actions to take while administering sugammadex to such patients.

Keywords: Contraceptive agents, hormonal; Lactation; Pregnancy; Sugammadex.

INTRODUCTION

Sugammadex is a chemically modified cyclodextrin, that is used as a selective reversal agent for steroidal neuromuscular blocking agents (NMBA). Before the development of sugammadex, NMBA reversal relied on acetylcholinesterase inhibitors, which could only be safely used to reverse shallow blocks [1,2]. In contrast, sugammadex can rapidly and completely reverse even intense blocks by encapsulating steroidal NMBA, which cannot be achieved using acetylcholinesterase inhibitors [2]. According to a recent worldwide survey exploring sugammadex usage (5,510 of 11,863 respondents in 183 countries reported on the availability of sugammadex), most respondents (72%) reported selective use, whereas only a few (27.8%) reported routine use [3]. Anesthesia providers limit the administration of sugammadex primarily because of cost concerns, even in the absence of restrictive usage policies. Very few anesthesia providers were

concerned about adverse events (7.8%). Sugammadex use is estimated to increase substantially globally, alleviating economic concerns as sugammadex patents have already expired or are about to expire soon [4,5].

Can sugammadex replace acetylcholinesterase inhibitors in patients undergoing surgery and receiving rocuronium? Pregnant and lactating women are generally excluded from most clinical trials; therefore, no efficacy or safety studies have been conducted on these patients. It is not surprising that there are insufficient data on the Pregnancy and Lactation Labeling Rule for sugammadex. Only theoretical assumptions are made (Table 1). Pregnancy-related physiological changes involve most organs and affect the pharmacokinetic profiles of medications. Considering the physiological changes in pregnant women and pharmacokinetic properties of sugammadex, there may be alterations in its dosage and safety profile during pregnancy. Very large polarized sugammadex molecules are expected to have limited placental transfer to the fetus and excretion into breast milk [6]. Finally, sugammadex binds to steroidal NMBA and other substances with similar structures, such as progesterone [7,8]. The use of sugammadex can reduce progesterone levels, which may cause adverse effects such as early cessation of pregnancy and failure of hormonal contraceptives. However, there is no clinical evidence supporting this assumption.

The purpose of this narrative review is twofold. The first is the scientific aspect, including preclinical and clinical studies of previously published correlations between sugammadex and pregnancy, lactation, and reproductive potential, thereby bridging the gap between theoretical assumptions and currently unknown clinical facts. The second is the practical clinical aspect, which discusses what anesthesia providers and patients should be aware of, and what hospitals need to be institutionalized to use sugammadex for these patients.

THEORETICAL ASSUMPTIONS AND PRECLINICAL EVIDENCE

Pregnancy-related physiologic and pharmacokinetic changes

During pregnancy, significant physiological changes occur owing to increased estrogen and progesterone levels, beginning in the first trimester, peaking at term and labor,

Table 1. Gaps Between Theoretical Assumptions/preclinical Studies and Clinical Evidence

Clinical situations	Theoretical assumptions/preclinical studies	Clinical evidences
Cesarean section	Increased volume of distribution and clearance: different dosing may be needed.	May be effective and safe with adult dosing. 16 mg/kg administration has never been reported but Difficult Airway Society guideline recommend to use high-dose of sugammadex when CICV occurred.
Non-obstetric surgery		
Fetal development	Large and polarized molecule: limited placental transfer Conflicting results in preclinical studies:incomplete ossification, neuronal apoptosis.	Small clinical studies: no evidence of fetal developmental abnormalities.
Maintenance of pregnancy	Capturing and eliminating progesterone: failure to maintain pregnancy	Small clinical studies: no evidence of preterm labor, miscarriage or stillbirth.
Hormonal contraceptives	Capturing and eliminating progesterone: failure of hormonal contraceptives conflicting results in preclinical studies.	Small clinical studies: steroidal hormonal changes in human are insignificant and temporal. No clinical studies to confirm the causal relationship between unintended pregnancy and sugammadex.
Lactation	Large and polarized molecule: limited breast milk transfer Preclinical study showed peak concentration in breast milk 30 min after sugammadex administration. Early in the postpartum period, gaps between the mammary alveolar cells increased and peak concentration of sugammadex may pass through breast milk.	No clinical studies of the presence of sugammadex in human breast milk. Drug and Lactation Database says it may be safe. SOAP statement recommends to avoid it at term or near term pregnancy.

CICV: cannot intubate and cannot ventilate, SOAP: Society of Obstetric Anesthesia, and Perinatology.

and gradually reversing a few weeks postpartum [9]. Pregnancy-related physiological changes involve most organs and affect the pharmacokinetic profile of medications [10,11]. Decreased gastrointestinal motility and increased gastric pH affect drug absorption. Increased total body water, plasma volume, and capillary hydrostatic pressure lead to a significantly increased volume of distribution. Decreased concentrations of drug-binding proteins increase the bioactivity of certain drugs. Increased cardiac output induces greater hepatic and renal blood flow, resulting in the increased clearance of some medications.

However, information regarding pharmacokinetic changes or dosage requirements is lacking for most drugs used during pregnancy [12]. Moreover, it is often unclear whether altered pharmacokinetics lead to changes in drug efficacy or to adverse effects. Unfortunately, the use of sugammadex during pregnancy is not exempt. As sugammadex has no affinity for plasma proteins when administered intravenously, it immediately encapsulates rocuronium in a 1:1 molar ratio [13,14]. This leads to a concentration gradient that shifts rocuronium from the peripheral compartment (neuromuscular junction) to the central compartment (plasma), where it is encapsulated by sugammadex [15]. The sugammadex-rocuronium complex is highly soluble, and urinary excretion is the major route for its elimination without being metabolized by the liver [13].

Considering the physiological changes in pregnant women and pharmacokinetic properties of sugammadex, several analogies can be made. First, an increase in total body water increases the volume of distribution of the hydrophilic drug, which lowers the plasma concentration. The glomerular filtration rate (GFR) increases during pregnancy, and for drugs excreted by glomerular filtration, renal clearance parallels the changes in GFR during pregnancy [16]. However, the extent to which volume distribution increases and whether the dose of hydrophilic drugs should be increased remain unclear. Unlike the uniform increase in the GFR during pregnancy, the effect of renal tubular transport on renal clearance varies among drugs. Therefore, there are limitations in theoretically estimating the efficacy and safety of sugammadex during pregnancy.

Maternal-fetal transfer and fetal development

Sugammadex is a modified γ-cyclodextrin with a lipophilic core and hydrophilic periphery and a molecular weight of 2,178 daltons. The addition of eight side chains extended the cavity size to achieve a better fit for steroidal NMBA [17]. In addition, negatively charged carboxyl groups were added at the ends of the eight side chains to maintain structural integrity and enhance electrostatic binding to the positively charged quaternary nitrogen of rocuronium [6]. Theoretically, it is difficult for sugammadex to pass through the placenta owing to its large molecular size and negatively charged characteristics [18].

Preclinical studies by Merck have reported conflicting results [19]. In an embryo-fetal development study, pregnant rats received daily intravenous administration of sugammadex up to six times the maximum recommended human dose (MRHD). No treatment-related maternal or embryo-fetal changes were observed. In another embryo-fetal development study, pregnant New Zealand white rabbits received daily intravenous administration of sugammadex up to eight times the MRHD. A decrease in fetal body weight was observed in the offspring at maternal doses of 65 and 200 mg/kg. Moreover, incomplete ossification of the sternum and an unossified first metacarpal were found in the offspring at a maternal dose of 200 mg/kg/day. Furthermore, maternal toxicity was observed at 200 mg/kg. Considering that bone retention of sugammadex occurred in rats after intravenous injection with a mean half-life of 172 days, these findings may be attributed to the drug [19]. No evidence of malformation was observed at any dose. In a prenatal and postnatal development study, pregnant rats were intravenously administered sugammadex at concentrations up to six times the MRHD dose. There were no drug-related effects on rat parturition during prenatal or postnatal development. However, there was postnatal loss due to pup cannibalization. Therefore, effects of sugammadex on steroidal hormones and pheromones should not be excluded.

The effect of drugs on fetal neuronal development is an emerging issue. Palanca et al. [20] reported that sugammadex alone promoted neural apoptosis in primary cultures. Neural apoptosis was further promoted when sugammadex was used alone rather than in combination with steroidal NMBA in primary cultures [21]. It was concluded that sugammadex caused depletion of neuronal cell cholesterol, resulting in oxidative stress and neuronal apoptosis. However, this does not occur in vivo because the mature blood-brain barrier (BBB) prevents the passage of sugammadex. Thus, sugammadex may pass through a compromised BBB, such as an immature or damaged one. The potential of anesthetics to cause neuroapoptosis and other neurodegenerative changes in the developing brain has become evident in

animal studies over the past 20 years [22,23]. One study postulated that the co-administration of sugammadex with neonatal sevoflurane may exacerbate neuronal apoptosis due to changes in BBB integrity [24]. Neonatal mice exposed to 2% sevoflurane for 6 h developed BBB ultrastructural abnormalities. The co-administration of sugammadex with sevoflurane in neonatal mice further increased neuroapoptosis in the brain compared to 2% sevoflurane alone, whereas sugammadex alone did not induce apoptosis. This possibility should be considered when administering sugammadex with inhaled anesthetics in pregnant women. However, further studies are required to confirm these findings.

Interaction with progesterone

As sugammadex encapsulates steroidal NMBA, it may also bind to other appropriately sized steroidal substances. Progesterone is such a substance and in vitro binding studies suggest that progesterone levels may decrease by approximately 34% when exposed to sugammadex [19]. Decreased progesterone levels can lead to two serious adverse effects. One is failure to maintain early pregnancy, and the other is hormonal contraceptive failure.

Two animal studies that investigated the effect of sugammadex on progesterone levels in pregnant animals have been conducted [25,26]. Pregnant rats were randomly assigned to three groups and injected under sedation on the 7th day of gestation: control, sugammadex 30 mg/kg, and rocuronium 3.5 mg/kg + sugammadex 30 mg/kg [25]. Blood samples were obtained 35 min after injection to determine progesterone levels. Progesterone levels were not significantly different between the groups, and successful completion of pregnancy and absence of stillbirths or miscarriages were reported.

Pregnant rabbits were randomly divided into three groups: control, rocuronium administered at the onset of general anesthesia (GI group), and rocuronium + sugammadex administered 60 min after general anesthesia (GII group) [26]. In the GII group, progesterone levels at 60 and 90 min after general anesthesia were significantly lower than the baseline progesterone levels. In addition, the progesterone levels at 60 and 90 min after general anesthesia were significantly lower in the GII group than those in the GI group. However, all pregnancies were successful without early birth or stillbirth. Because studies are still lacking and the results are inconclusive, it cannot definitely be concluded that sugammadex affects pregnancy by lowering progesterone levels.

Lactation

Generally, low plasma protein binding, low molecular weight, and highly lipophilic and cationic drugs favor increased drug excretion into breast milk [27]. In contrast, sugammadex is large, hydrophilic, and has a half-life of 2 h and pKa of 2.82 [6]. Therefore, it is appropriate to predict minimal excretion of sugammadex into breast milk. Moreover, the oral absorption of sugammadex is thought to be low; therefore, it can be assumed that the amount of sugammadex delivered to breastfed infants is negligible. In a milk excretion study in rats, 20 mg/kg sugammadex was injected intravenously on postnatal day 9 and the maximum drug level was achieved at approximately 30 min [19]. The oral administration of sugammadex via milk did not induce adverse effects on survival, body weight, or physical or behavioral development in rats. However, there is no published evidence to support this.

CLINICAL EVIDENCE

Cesarean section

In cesarean sections, neuraxial anesthesia is preferred over general anesthesia; however, general anesthesia is still administered under some conditions [28]. Because pregnancy-related physiological changes peak at term and delivery, the efficacy and safety profiles are of primary concern when using sugammadex after fetus delivery. A randomized controlled noninferiority trial was conducted to show that a high-dose of rocuronium can achieve intubation conditions comparable to those of succinylcholine for cesarean delivery [29]. In the rocuronium group, 2 mg/kg sugammadex was administered if the train of four (TOF) count was ≥ 1 and 4 mg/kg sugammadex was used if the post-tetanic count was ≥ 1. Among the 120 patients, the time from neuromuscular blockade reversal to TOF ratio > 0.9 was 104 ± 63 (mean ± SD) s. In addition, no signs of residual blockade or side effects were observed. These findings are similar to those reported in other clinical studies [30,31].

The sugammadex doses required for the routine reversal of moderate or deep blocks during cesarean section appear to be sufficiently effective and safe at doses equivalent to adult doses (2–4 mg/kg). In emergencies, such as cannot intubate and cannot ventilate (CICV), a high-dose of sugammadex (16 mg/kg) must be administered for immediate reversal before fetal birth; however, these cases have not yet

been reported. Recent large multicenter studies showed difficult intubation rates of 2.0–5.4% which is similar to the general surgical population (4.4%) [32-34]. In contrast, failed intubation rate is higher in pregnant women (0.12–0.53%) compared with that in the general surgical population (0.06%) [32,33,35]. In 2015, the Obstetric Anesthetists' Association and Difficult Airway Society developed the first national obstetric guidelines for difficult airway management [36]. The guidelines recommend considering high-dose sugammadex administration for immediate reversal of CICV. Although there is no evidence for the efficacy and safety of high-dose sugammadex in pregnant women and fetuses, it is reasonable to consider sugammadex administration because the risks of exposure to severe hypoxia could be more harmful than the potential risk of using high doses of sugammadex.

Non-obstetric surgery

Unlike cesarean sections, pregnant women undergoing non-obstetric surgery do not deliver a fetus and must continue their pregnancy. Therefore, few clinical studies have reported the use of sugammadex in such cases, and these have only recently been published in the form of case series [18,37-40]. Theoretically, the passage through the placenta or BBB is limited; however, animal experiments have shown worrisome results [19,24]. In 2019, an interesting case of sugammadex placental transfer was reported [37]. A woman at 29 weeks of gestation required an intrauterine transfusion for Rh (D) alloimmunization. During the intrauterine transfusion procedure, maternal respiratory distress occurred because of the intramyometrial injection of rocuronium, which was intended to be administered intramuscularly to the fetus. After the administration of sugammadex (100 mg), the patient's respiratory distress resolved. After the patient had stabilized, additional rocuronium was administered to the fetal buttocks. Interestingly, adequate paralysis was achieved in the fetus without sustained paralysis induced by the maternal sugammadex injection, suggesting limited maternal-fetal placental transfer of sugammadex.

Recently, several case series and a multicenter retrospective study on maternal and fetal outcomes after sugammadex use in pregnant women have been published [18,38-40] (Table 2). In two case series, patients were at 4–26 gestational age and received 0.7–4.3 mg/kg sugammadex. Although preterm premature rupture of membranes (N = 8/25) and preterm labor (N = 12/25) occurred, none of these episodes

Table 2. Summary of Obstetric and Fetal Outcomes after Sugammadex Administration in Non-obstetric Procedure

Study	Study design	Number of patients	GA at SGX administration (wk)	Dose of SGX	GA at delivery (wk)	Unplanned CD/total CD	Preterm labor	PPROM or placental abruption	Abortion or stillbirth	Neonatal	Congenital anomaly	Others
Singh et al. [18]	Single center, case series	25	4^{+5}–27^{+5}	120–460 mg	27^{+5}–40^{+6}	14/19*	12*	8* (PPROM)	0	1 (pre-maturity)	1 (ASD)	3 (developmental delay)
Torres et al. [38]	Single center, case series	6	8–24	0.6–1.1 mg/kg	35^{+6}–41^{+1}	3/4†	1†	0	0	0	0	-
Noguchi et al. [39]	Multi centers, retrospective data review	73 (with SGX)	15.0 ± 5.1, 4–34	200 mg	10–41‡	-	-	-	3 (2 induced, 1 congenital anomaly)	0	1 (constricted umbilical cord)	-
Karahan et al. [40]	Single center, case series	15	14.06 ± 6.65, 6–28	8 mg/kg	-	-/5	0	1† (placental abruption)	4 (3 induced, 1 spontaneous)	-	-	1 (neonatal respiratory distress)

Values are presented as number only, median (range), or mean ± SD. GA: gestational age, SGX: sugammadex, CD: cesarean delivery, PPROM: preterm premature rupture of membranes, ASD: atrial septal defect. *None < 2 weeks after sugammadex administration, †None < 12 weeks after sugammadex administration, ‡Data available only for women who received sugammadex in the first trimester.

occurred within 2 weeks of receiving sugammadex [18]. In another case series, only one patient experienced preterm labor; however, it was induced by severe preeclampsia and developed 12 weeks after sugammadex administration [38]. In a multicenter retrospective observational study with 73 patients who received sugammadex and 51 patients who did not [39], the gestational age was 15.0 ± 5.1 (mean ± SD) weeks and the median total dose of sugammadex was 200 mg. Miscarriages and preterm births within 4 weeks of sugammadex administration were not significantly different between the patients with and those without sugammadex exposure. In one study, a larger dose of sugammadex (8 mg/kg) was administered to 15 patients who underwent electroconvulsive therapy [40]. Spontaneous abortion occurred in one patient and one infant developed neonatal respiratory distress. Moreover, no patients experienced preterm delivery or labor induced by sugammadex administration. Although these studies did not show obvious detrimental effects of sugammadex on maternal and fetal outcomes, their retrospective nature and small sample size cannot confirm the safety concerns.

Levels of progesterone and unintended pregnancy

Few clinical studies have examined steroidal hormone levels after sugammadex injection [41,42]. One study investigated the hormonal profiles of 50 young male patients randomly divided into N (neostigmine) and S (sugammadex 4 mg/kg) groups [42]. Sugammadex showed no adverse effects on progesterone and cortisol levels, while it was associated with a temporary increase in aldosterone and testosterone levels. They explained that sugammadex has no effect on progesterone levels because of its relatively low affinity (120 to 700 times lower than that of rocuronium) and tight binding to plasma proteins. A more recent prospective observational study was conducted to investigate the effects of sugammadex on perioperative estrogen and progesterone levels in premenopausal women aged 18–50 years [41]. After 240 min of sugammadex administration, progesterone in patients taking oral contraceptives tended to decrease; however, it was non-significantly decreased within 20% below baseline, far less than the 34% expected pharmacokinetically. Nonetheless, they did not consider the menstrual cycle or surgical stress, which significantly affect hormonal levels. In addition, because endogenous progesterone is suppressed by oral contraceptives (exogenous progesterone), a small change in progesterone exaggerates the percentage change. Both authors suggested that statistically significant changes in hormonal levels were borderline or temporary and would be clinically insignificant.

However, investigating the association between unexpected pregnancies and sugammadex use is difficult. Lazorwitz et al. [43] reported a single case (0.7%; 95% confidence intervals: 0–4.1%) of unexpected pregnancy after sugammadex administration in 134 patients using hormonal contraceptives. Based on the ultrasound measurements, the estimated date of conception was 19 days after sugammadex administration. Although there are no clinical reports of unintended pregnancy due to sugammadex-progesterone interaction, the manufacturer advises seriously considering this interaction. They recommended that if an oral contraceptive is taken on the same day that sugammadex is administered or non-oral hormonal contraceptives are used, the patient must use an additional non-hormonal contraceptive method or a backup method of contraception for the next 7 days [19]. Unintended pregnancy can be personally, socially, and economically burdensome; therefore, patients should be informed and educated even if there is a slight possibility. However, several studies show that 78–94% of anesthesia providers are aware of the risk of oral contraceptive failure with sugammadex, whereas only 20 to 33% of anesthesia providers discuss this with their patients [44,45]. Appropriate education and policies are required to overcome discrepancies between knowledge and practice. Anesthesia providers must assess the risk of oral contraceptive failure induced by sugammadex preoperatively and screen women of childbearing age for oral contraceptive administration. If women are at risk of oral contraceptive failure, anesthesia providers should counsel about sugammadex and its alternatives (acetylcholinesterase inhibitors) and make decisions regarding the choice of NMB antagonists. After surgery, information should be provided through a take-home leaflet or letter to improve postoperative recall [46,47]. Along with these perioperative processes, education of relevant medical staff and feedback from audits are necessary.

Lactation

Currently, there is no clinical evidence regarding the use of sugammadex during breastfeeding [48]. However, owing to the biochemical and pharmacokinetic characteristics of sugammadex and preclinical evidence, sugammadex is acceptable for use during breastfeeding [49]. In contrast, a

statement published by the Society for Obstetric Anesthesia and Perinatology (SOAP) disagrees with immediate breastfeeding [8]. According to the World Health Organization recommendations, breastfeeding should be initiated within the first hour of birth [50]. If a mother who received sugammadex after cesarean section began breastfeeding within 1 h after delivery, she may have breastfed at the peak concentration of sugammadex. Moreover, in the early postpartum period, large gaps between mammary alveolar cells enhance the delivery of maternal proteins to breast milk and may allow sugammadex to pass through breast milk [51]. Immature metabolism and renal function delay sugammadex clearance in infants. Therefore, SOAP recommends the use of acetylcholine esterase inhibitors and, if not, pumping and discarding breast milk for the first 12–14 h after surgery [8].

CONCLUSION

The use of sugammadex in pregnant and lactating women and in those of childbearing age taking oral contraceptives shows a large gap between theoretical estimation and clinical practice. Scientific and clinical evidence is increasingly being published to fill this gap; however, it remains insufficient. Therefore, it seems that now is the time to practice "Do not harm" rather than practicing "Doing good". Premature birth and miscarriage owing to failure to maintain pregnancy, fetal deformities, developmental disorders, and unexpected pregnancies are completely different from the acute and temporary side effects of drugs. These are permanent afflictions and catastrophes for both individuals and the society. Therefore, it should be approached with more caution than other issues. However, although there is a lack of clear evidence, it is most likely that sugammadex is already playing the role of "Doing good" in some clinical situations such as cesarean section and CICV. Thus, what we need to know are theoretical knowledge and accumulated scientific data. What we have to do is establish a perioperative process of sugammadex use in pregnant and lactating patients and those on oral contraceptives. In addition, we must conduct related research and share our data worldwide. If we accomplish what we need to know and do, we will be able to move forward from "Do not harm" to "Doing good".

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

AUTHOR CONTRIBUTIONS

Conceptualization: Ah-Reum Cho. Data curation: Wangseok Do, Ah-Reum Cho. Methodology: Wangseok Do, Ah-Reum Cho. Writing - original draft: Wangseok Do, Ah-Reum Cho. Writing - review & editing: Wangseok Do, Ah-Reum Cho. Supervision: Ah-Reum Cho.

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REFERENCES

1. Hristovska AM, Duch P, Allingstrup M, Afshari A. Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. Cochrane Database Syst Rev 2017; 8: CD012763.
2. Abad-Gurumeta A, Ripollés-Melchor J, Casans-Francés R, Espinosa A, Martínez-Hurtado E, Fernández-Pérez C, et al. Evidence Anaesthesia Review Group. A systematic review of sugammadex vs neostigmine for reversal of neuromuscular blockade. Anaesthesia 2015; 70: 1441-52.
3. O'Reilly-Shah VN, Wolf FA, Jabaley CS, Lynde GC. Using a worldwide in-app survey to explore sugammadex usage patterns: a prospective observational study. Br J Anaesth 2017; 119: 333-5.
4. Mylan Ireland. Sugammadex Mylan. European Medicines Agency [Internet]. 2021 Nov 22 [updated 2022 Oct 3; cited 2023 Mar 23]. Available from https://www.ema.europa.eu/en/medicines/human/EPAR/sugammadex-mylan.
5. Sugammadex. PharmaCompass [Internet]. 2023 [cited 2023 Mar 23]. Available from https://www.pharmacompass.com/patent-expiry-expiration/sugammadex.
6. Nag K, Singh DR, Shetti AN, Kumar H, Sivashanmugam T, Parthasarathy S. Sugammadex: a revolutionary drug in neuromus-

cular pharmacology. Anesth Essays Res 2013; 7: 302-6.
7. Richardson MG, Raymond BL. Sugammadex administration in pregnant women and in women of reproductive potential: a narrative review. Anesth Analg 2020; 130: 1628-37.
8. Society for Obstetric Anesthesia and Perinatology. Statement on Sugammadex during pregnancy and lactation. Society for Obstetric Anesthesia and Perinatology [Internet]. 2019 Apr 22 [cited 2023 Mar 23]. Available from https:// www.soap.org/assets/docs/SOAP_Statement_Sugammadex_During_Pregnancy_Lactation_APPROVED.pdf.
9. Bhatia P, Chhabra S. Physiological and anatomical changes of pregnancy: implications for anaesthesia. Indian J Anaesth 2018; 62: 651-7.
10. Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. Front Pharmacol 2014; 5: 65.
11. Pariente G, Leibson T, Carls A, Adams-Webber T, Ito S, Koren G. Pregnancy-associated changes in pharmacokinetics: a systematic review. PLoS Med 2016; 13: e1002160.
12. McCormack SA, Best BM. Obstetric pharmacokinetic dosing studies are urgently needed. Front Pediatr 2014; 2: 9.
13. Gijsenbergh F, Ramael S, Houwing N, van Iersel T. First human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. Anesthesiology 2005; 103: 695-703.
14. Sorgenfrei IF, Norrild K, Larsen PB, Stensballe J, Ostergaard D, Prins ME, et al. Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: a dose-finding and safety study. Anesthesiology 2006; 104: 667-74.
15. Akha AS, Rosa J 3rd, Jahr JS, Li A, Kiai K. Sugammadex: cyclodextrins, development of selective binding agents, pharmacology, clinical development, and future directions. Anesthesiol Clin 2010 28: 691-708. Erratum in: Anesthesiol Clin 2011; 29: 1.
16. Feghali M, Venkataramanan R, Caritis S. Pharmacokinetics of drugs in pregnancy. Semin Perinatol 2015; 39: 512-9.
17. Kovac AL. Sugammadex: the first selective binding reversal agent for neuromuscular block. J Clin Anesth 2009; 21: 444-53.
18. Singh S, Klumpner TT, Pancaro C, Rajala B, Kountanis JA. Sugammadex administration in pregnant women: a case series of maternal and fetal outcomes. A A Pract 2021; 15: e01407.
19. Merck & Co., Inc. BRIDION®. Merck & Co., Inc. [Internet]. 2015 [updated 2022 Nov; cited 2023 Mar 22]. Available from https://www.merck.com/product/usa/pi_circulars/b/bridion/bridion_pi.pdf.
20. Palanca JM, Aguirre-Rueda D, Granell MV, Aldasoro M, Garcia A, Iradi A, et al. Sugammadex, a neuromuscular blockade reversal agent, causes neuronal apoptosis in primary cultures. Int J Med Sci 2013; 10: 1278-85.
21. Aldasoro M, Jorda A, Aldasoro C, Marchio P, Guerra-Ojeda S, Gimeno-Raga M, et al. Neuronal effects of Sugammadex in combination with Rocuronium or Vecuronium. Int J Med Sci 2017; 14: 224-30.
22. Creeley CE, Dikranian KT, Dissen GA, Back SA, Olney JW, Brambrink AM. Isoflurane-induced apoptosis of neurons and oligodendrocytes in the fetal rhesus macaque brain. Anesthesiology 2014; 120: 626-38.
23. Rappaport BA, Suresh S, Hertz S, Evers AS, Orser BA. Anesthetic neurotoxicity--clinical implications of animal models. N Engl J Med 2015; 372: 796-7.
24. Satomoto M, Sun Z, Adachi YU, Makita K. Sugammadex-enhanced neuronal apoptosis following neonatal sevoflurane exposure in mice. Anesthesiol Res Pract 2016 2016: 9682703. Erratum in: Anesthesiol Res Pract. 2017; 2017: 1368514.
25. Et T, Topal A, Erol A, Tavlan A, Kılıçaslan A, Uzun ST. The effects of Sugammadex on progesterone levels in pregnant rats. Balkan Med J 2015; 32: 203-7.
26. Türk R, Kaya S, Dönmeİ, Özaydiİ, Merhan O, Yayla S, et al. The effect of Rocuronium and Sugammadex on progesterone levels in pregnant rabbits under general anesthesia. Kafkas Univ Vet Fak Derg 2019; 25: 179-84.
27. Ito S, Lee A. Drug excretion into breast milk--overview. Adv Drug Deliv Rev 2003; 55: 617-27.
28. Watson SE, Richardson AL, Lucas DN. Neuraxial and general anaesthesia for caesarean section. Best Pract Res Clin Anaesthesiol 2022; 36: 53-68.
29. Stourac P, Adamus M, Seidlova D, Pavlik T, Janku P, Krikava I, et al. Low-dose or high-dose Rocuronium reversed with Neostigmine or Sugammadex for cesarean delivery anesthesia: a randomized controlled noninferiority trial of time to tracheal intubation and extubation. Anesth Analg 2016; 122: 1536-45.
30. Williamson RM, Mallaiah S, Barclay P. Rocuronium and Sugammadex for rapid sequence induction of obstetric general anaesthesia. Acta Anaesthesiol Scand 2011; 55: 694-9.
31. Pühringer FK, Kristen P, Rex C. Sugammadex reversal of rocuronium-induced neuromuscular block in caesarean section patients: a series of seven cases. Br J Anaesth 2010; 105: 657-60.
32. Reale SC, Bauer ME, Klumpner TT, Aziz MF, Fields KG, Hurwitz R, et al. Multicenter Perioperative Outcomes Group Collaborators. Frequency and risk factors for difficult intubation in women undergoing general anesthesia for cesarean delivery: a multicenter retrospective cohort analysis. Anesthesiology 2022; 136: 697-708.
33. Odor PM, Bampoe S, Moonesinghe SR, Andrade J, Pandit JJ, Lucas DN. General anaesthetic and airway management practice for obstetric surgery in England: a prospective, multicentre ob-

servational study. Anaesthesia 2021; 76: 460-71.
34. Kheterpal S, Healy D, Aziz MF, Shanks AM, Freundlich RE, Linton F, et al. Multicenter Perioperative Outcomes Group (MPOG) Perioperative Clinical Research Committee. Incidence, predictors, and outcome of difficult mask ventilation combined with difficult laryngoscopy: a report from the multicenter perioperative outcomes group. Anesthesiology 2013; 119: 1360-9.
35. Schroeder RA, Pollard R, Dhakal I, Cooter M, Aronson S, Grichnik K, et al. Temporal trends in difficult and failed tracheal intubation in a regional community anesthetic practice. Anesthesiology 2018; 128: 502-10.
36. Mushambi MC, Kinsella SM, Popat M, Swales H, Ramaswamy KK, Winton AL, et al. Obstetric Anaesthetists' Association and Difficult Airway Society guidelines for the management of difficult and failed tracheal intubation in obstetrics. Anaesthesia 2015; 70: 1286-306.
37. Munro A, McKeen D, Coolen J. Maternal respiratory distress and successful reversal with Sugammadex during intrauterine transfusion with fetal paralysis. Int J Obstet Anesth 2019; 39: 129-31.
38. Torres SM, Duarte DF, Glória AS, Reis C, Moreira JF, Cunha S, et al. Sugammadex administration in pregnant patients undergoing non-obstetric surgery: a case series. Braz J Anesthesiol 2022; 72: 525-8.
39. Noguchi S, Iwasaki H, Shiko Y, Kawasaki Y, Ishida Y, Shinomiya S, et al. Fetal outcomes with and without the use of Sugammadex in pregnant patients undergoing non-obstetric surgery: a multicenter retrospective study. Int J Obstet Anesth 2023; 53: 103620.
40. Karahan MA, Büyükfırat E, Binici O, Uyanıkoğlu H, Incebıyık A, Asoğlu M, et al. The effects of Rocuronium-sugammadex on fetomaternal outcomes in pregnancy undergoing electroconvulsive therapy: a retrospective case series and literature review. Cureus 2019; 11: e4820.
41. Devoy T, Hunter M, Smith NA. A prospective observational study of the effects of Sugammadex on peri-operative oestrogen and progesterone levels in women who take hormonal contraception. Anaesthesia 2023; 78: 180-7.
42. Gunduz Gul G, Ozer AB, Demirel I, Aksu A, Erhan OL. The effect of sugammadex on steroid hormones: a randomized clinical study. J Clin Anesth 2016; 34: 62-7.
43. Lazorwitz A, Dindinger E, Aguirre N, Sheeder J. Pre- and post-operative counseling for women on hormonal contraceptives receiving Sugammadex at an academic hospital. J Anesth 2020; 34: 294-7.
44. Dwan RL, Raymond BL, Richardson MG. Unanticipated consequences of switching to Sugammadex: anesthesia provider survey on the hormone contraceptive drug interaction. Anesth Analg 2021; 133: 958-66.
45. Passi NN, Mutebi M, Tan M, Oliver CM. Contraceptive failure and Sugammadex administration: a single centre survey and audit of professional knowledge and practice. Br J Anaesth 2023; 130: e412-4.
46. Liverpool Women's National Health Service (NHS) Foundation Trust. Anaesthetics leaflets. Liverpool Women's NHS Foundation Trust [Internet]. 2020 [cited 2023 Mar 29]. Available from https://www.liverpoolwomens.nhs.uk/patients/ patient-information-leaflets/anaesthetics/.
47. University College London Hospitals. University college hospital: Contraceptive advice for patients who have received Sugammeadex. National Health Service [Internet]. 2022 Jul [cited 2023 Mar 29]. Available from https://www.uclh.nhs.uk/ application/files/9716/5815/8160/Sugammeadex_Contraceptive_advice.pdf.
48. Sugammadex. In: Drugs and lactation database (LactMed®). Bethesda (MD), National Institute of Child Health and Human Development. 2020.
49. Mitchell J, Jones W, Winkley E, Kinsella SM. Guideline on anaesthesia and sedation in breastfeeding women 2020: guideline from the Association of Anaesthetists. Anaesthesia 2020; 75: 1482-93.
50. World Health Organization (WHO). Breastfeeding. WHO [Internet]. [cited 2023 Mar 23]. Available from https://www.who.int/health-topics/breastfeeding.
51. Newton ER, Hale TW. Drugs in breast milk. Clin Obstet Gynecol 2015; 58: 868-84.