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Megan Berens
megan.berens@otterbein.edu

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Breastfeeding After Maternal Anesthesia: A Guideline Development

Megan Berens, BSN, RN

Doctor of Nursing Practice Final Scholarly Project

In Partial Fulfillment of the Requirements for the Degree

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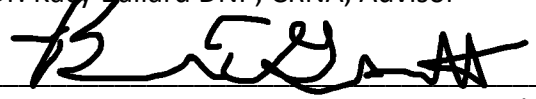
DNP Final Scholarly Project Team:

Dr. Kacy Ballard DNP, CRNA, Advisor



Dr. Brian Garrett DNP, CRNA, Team Member

Abstract

Postoperative breastfeeding recommendations for lactating mothers by anesthesia providers are inconsistent and often inaccurate. Inappropriate recommendations have led to withholding of breastmilk to the infant, unnecessary disposal of breastmilk, surgical delay, exposure of an infant to high levels of drugs in breastmilk, and early cessation of breastfeeding. The purpose of the scholarly project was to develop a set of evidenced-based practice guideline recommendations and a proposed implementation plan for anesthesia providers to use in support of breastfeeding mothers who recover from surgery. Many studies in the literature indicate that there are inconsistencies in postoperative breastfeeding recommendations by anesthesia providers. When postoperative breastfeeding guidelines were implemented, anesthesia staff were more likely to recommend breastfeeding in the immediate postoperative period and feel more confident in their recommendation. In addition, there were fewer preventable delays in breastfeeding resumption and fewer neonatal safety events. Tools from the Johns Hopkins Nursing Evidence-Based Practice model were used to guide a systematic literature review, synthesize evidence, and develop an implementation plan. The literature review included the safety of commonly used perioperative medications in the lactating mother. Overall, almost all medications used in the perioperative period are safe to use in lactating mothers, except for codeine, meperidine, tramadol, diazepam, and hydromorphone. As part of this project, a guideline implementation plan for future use by anesthesia providers was developed and proposed to occur over 11 months. Additionally, a ten-question knowledge and confidence assessment regarding breastfeeding recommendations was proposed to be distributed to all anesthesia providers (e.g., Anesthesiologists and Certified Registered Nurse

Anesthetist [CRNAs]) prior to guideline implementation, one month after implementation, and six months after implementation. The anticipated statistical analysis plan for knowledge and confidence outcome data is recommended to utilize the one-way analysis of variance (ANOVA) test. The clinical importance of this scholarly project is that the project's proposed clinical practice guidelines may help to increase anesthesia provider knowledge and confidence in providing effective postoperative education concerning the safety and compatibility of certain anesthesia medications and continued practices of breastfeeding patients following surgery.

Keywords: lactation, anesthesia, guidelines, safety, breastfeeding, post-surgical

Final Scholarly Project

Problem Identification

The number of breastfeeding women who require anesthesia, both during labor and for non-childbirth related procedures, has increased throughout the United States (Martin et al., 2018). Anesthesia providers need to be aware of the implications of administered medications in the infant of the lactating mother however, many studies indicate that some patients and surgical staff have an inaccurate understanding of the safety of breastfeeding after anesthesia (Moore et al., 2021; Reith et al., 2018). Staff recommendations given to nursing mothers are often inconsistent and can lead to unnecessary and prolonged interruptions in breastfeeding, disposal of breastmilk, and early breastfeeding cessation (Mitchell et al., 2020). In addition, lax recommendations may expose the infant to dangerous levels of medications in the breastmilk (Gilder et al, 2021).

The facility of interest, a large urban hospital with a busy labor and delivery department, does not have a policy or practice guideline regarding breastfeeding after maternal anesthesia. Therefore, anesthesia providers' recommendations for breastfeeding may be inconsistent or might not be aligned to up to date and best evidence. Lack of standardized breastfeeding protocols can lead to withholding of breastmilk to the infant, unnecessary disposal of breastmilk, surgical delay, exposure of an infant to high levels of drugs in breastmilk, and early cessation of breastfeeding (Gilder et al., 2021; Mitchell et al., 2020). This facility of interest may benefit from the implementation of an evidence-based guideline for breastfeeding after anesthesia.

Literature reviewing the implementation of a protocol for breastfeeding after anesthesia is rare. Moore et al. (2021), describes the implementation of a post anesthesia breastfeeding protocol at a mid-sized military hospital. A literature review was performed to determine best practice for common medications used in anesthesia. Information was obtained from peer reviewed articles and LactMed, a database that contains information on the transfer and safety of medications in breastmilk (LactMed, 2018). This knowledge was presented to staff in a lecture and developed into a unit policy. Results from this study indicate that personnel were more likely to recommend immediate breastfeeding after anesthesia and feel more confident in their recommendation (Moore et al., 2021). Another article by Folh and Stephens (2019) describes the implementation of a post-anesthesia breastfeeding program at a large, academic level 1 trauma center. Educational materials were created and distributed to all perioperative staff and lactation support procedures were implemented. After the implementation of this program, findings indicated that there were no preventable delays in the resumption of breastfeeding and there were fewer neonatal safety events (Folh & Stephens, 2019).

Professional anesthesia organizations, such as the American Society of Anesthesiologists (ASA)(2019), have released statements on the importance of safely resuming breastfeeding after anesthesia. Drug safety of commonly used medications in the perioperative period was described using the relative infant dose (RID), the infant's weight based daily dose through breastmilk divided by the mother's weight based daily dose. RID less than 10% is generally considered safe (Hendrickson & McKeown, 2012). The American Association of Nurse Anesthesiology (AANA) presents general concepts regarding breastfeeding after maternal

anesthesia including “A nursing mother should be allowed to breastfeed as soon as she is awake and aware after general anesthesia” (AANA, n.d.).

Background/Significance

Over 75% of laboring women receive some form of anesthesia including epidural, spinal, and general anesthesia (Butwick et al., 2018; Ring et al., 2021). In addition, many women who are breastfeeding require anesthesia for non-pregnancy related operations. Most medications used in anesthesia will cross into the breastmilk but are harmless to the infant (Oliveira et al., 2019). Generally, breastfeeding may resume after maternal anesthesia once a mother is alert and able to breastfeed independently (Mitchell et al., 2020). However, some medications can cause neonatal respiratory depression or sedation. Depending on anesthesia medications administered, mothers may resume breastfeeding immediately after surgery or may have to dispose of their breastmilk.

Exclusive breastfeeding for six months after birth is considered the gold standard for infant nutrition by all major health organizations (WHO, 2018a; CDC, 2021; AAP, 2012). Breastfeeding provides complete and inexpensive nutrition to infant. Breastfeeding offers many benefits to infant including decreased risk of infection, obesity, and sudden infant death syndrome. Breastfeeding also benefits the mother by increasing postpartum weight loss and decreasing the risk of type 2 diabetes mellitus, ovarian cancer, and breast cancer (Kelsey, 2016).

Inappropriate recommendations for breastfeeding mothers after anesthesia can lead to withholding of breastfeeding, “pumping and dumping “, or adverse neonatal affects. Withholding breastfeeding may cause the mother to develop mastitis, breast engorgement, and decreased milk supply. Disposal of breastmilk after anesthesia is mostly unneeded, can be

costly, and can contribute to unneeded maternal stress. If medications are utilized that are not safe for the lactating woman and breastfeeding is resumed immediately postoperatively, infants may suffer sedation, CNS depression, or even death.

The current literature indicates a need for postoperative breastfeeding protocols and education in perioperative units. Implementation of these protocols may increase breastfeeding outcomes and decrease adverse events for both the mother and infant.

PICO Question

In anesthesia providers who provide care to lactating mothers (P), how does using an established postoperative breastfeeding guideline (I) in comparison to current practice (C) affect provider knowledge and confidence in providing postoperative breastfeeding recommendations (O)?

Project Objectives

- Perform a systematic literature review to create evidence-based practice guidelines for anesthesia providers to make recommendations for breastfeeding after maternal anesthesia.
- Use the Johns Hopkins Nursing Evidence-Based Practice (JHNEBP) Model to develop a guideline implementation plan
- Determine how to measure outcomes from the postoperative breastfeeding guideline implementation.
- Increase anesthesia provider knowledge of the implications of commonly used medications in anesthesia on breastfeeding.

- Increase anesthesia provider confidence in providing postoperative breastfeeding recommendations.
- Use the continuous cycle of the JHNEBP model for guideline adjustment if initial outcomes are poor.

Purpose

The purpose of the scholarly project was to develop a set of evidenced-based practice guideline recommendations and a proposed implementation plan for anesthesia providers to use in support of breastfeeding mothers who recover from surgery. Anesthesia providers will use this guideline to direct safe breastfeeding practices before and after anesthesia administration.

Literature Review

To establish current practices and knowledge of breastfeeding after anesthesia, a systematic literature review was performed using the Cumulative Index to Nursing and Allied Health Literature (CINAHL), MEDLINE, PubMed, and Cochrane Library. Search terms used included “breastfeeding or breast-feeding or lactation or lactating or breast milk or mother’s milk or colostrum or suckling” and the generic and brand name, if applicable, of commonly used perioperative medications including propofol, etomidate, ketamine, thiopental, dexmedetomidine, fentanyl, sufentanil, alfentanil, remifentanil, morphine, meperidine, codeine, hydromorphone, tramadol, diazepam, midazolam, lorazepam, ketorolac, and acetaminophen. Search expanders were applied to search for related words and equivalent subjects. Articles were limited to the English language. Articles were analyzed using the Research Evidence Appraisal and Non-Research Evidence Appraisal tool from the Johns Hopkins

Nurse Evidence-Based Practice Model. The level of evidence (I-V) was determined by research design and the evidence quality (A, B, or C) was determined by sample size, consistency of results, thorough research process, and strong results. Descriptions of the articles selected for this literature review can be found in Appendix A. As no human subjects participated in this portion of this scholarly project, this project was exempt for Institutional Review Board (Appendix B).

In total, 45 articles were used for the literature review. Because literature detailing anesthesia and breastfeeding is rare, articles from as early as 1972 were included for review. Articles obtained from the four research databases were reviewed and their sources were also analyzed for relevance. There were two level I articles, four level II articles, 25 level III articles, four level IV articles, and 10 level V articles. There were 21 articles with "A" evidence quality, 22 articles with "B" evidence quality, and two articles with "C" evidence quality.

In addition to utilizing research databases, Lactmed, a free and open access online drug and lactation database, was used for medications without resulting articles. Lactmed is operated by the National Institute of Health and uses a peer review panel to assess data validity and currency (Lactmed, n.d.).

Lactation and Infant Pharmacokinetics

Most medications utilized in the perioperative period are safe to use for breastfeeding mothers. However, each drug's pharmacokinetic profile must be investigated before administration. The safety of a medication in a nursing mother is determined by a multitude of factors including the half-life of a medication, presence of active metabolites, dose, frequency of administration, and the likelihood of drug transfer into breastmilk. Medications that are

unionized, have short half-lives, low molecular weight, low protein binding, and increased lipid solubility are more likely to cross from the maternal circulation into breast milk (Lobkova & Wolf, 2014). Drugs with high oral bioavailability are more likely to cause side effects in the infant (Mitchell et al., 2020). In addition, large amounts and frequent doses of medications increase the risk of an adverse reaction (Dalal et al., 2014).

Various characteristics of the infant may alter their susceptibility to maternal anesthesia including gestational age at birth, chronological age, weight, and presence of physiological derangements. Premature and newborn infants have decreased hepatic and renal metabolism, thus prolonging the action of any drugs consumed. Infants with a history of apnea may be more sensitive to drugs that decrease respiratory drive, such as benzodiazepines and opiates (Reece-Stremtan et al., 2017). Infants with physiologic derangements may be more sensitive to maternal medications (Moore et al., 2020).

The effect of maternal medications on infants is also determined by the volume of breastmilk consumed by the infant and the infant's weight. Breast milk may always be expressed and used when the infant is older or diluted with breastmilk pumped prior to surgery (Reece-Stremtan et al., 2017).

Drugs

Sedatives and Hypnotics.

Propofol (Diprivan).

Propofol is a gamma-aminobutyric acid (GABA)-A receptor agonist used often in the perioperative period for induction and maintenance of anesthesia. In addition, propofol is used for procedural sedation, nausea prevention and treatment, and medically induced comas. Many

of the beneficial qualities of propofol, such as a low oral bioavailability and high protein binding, make propofol less likely to enter breastmilk.

In the review of the literature, three sources indicated that propofol levels in breastmilk are negligible. In a study by Nitsun et al. (2006), five lactating women who presented for scheduled procedures requiring general anesthesia received 2.5 mg/kg of intravenous (IV) propofol for induction. All breastmilk was expressed by pump and collected for 24 hours after drug administration. An average total of 0.027% of the maternal propofol dose was collected in the participants' breastmilk over 24 hours. Because of the minimal amount of drug transfer into milk and the low likelihood that the infant would have consumed the total volume expressed, the authors recommend that the mother may resume breastfeeding as soon as she recovers from general anesthesia. Struttman et al. (2010), recorded the amount of propofol in the breastmilk of lactating mothers 90 and 300 minutes after an IV induction dose. Although the values were increased in comparison to Nitsun et al., at 0.09% and 0.028% respectively, theoretical amounts of propofol that would be consumed were still considered negligible. Dailland et al. (1989) found that the levels of propofol in colostrum after use for both IV induction and infusion doses during a general anesthetic for cesarean section were negligible in comparison to the placental exposure that occurred during birth. After birth and breastfeeding, propofol had minimal effects on the healthy newborn. Due to the low levels of propofol excreted in the breastmilk after both induction and infusion doses and the low bioavailability of propofol, there is a low risk of adverse effects from the use of IV propofol in the nursing mother.

Etomidate (Amidate).

Etomidate is a GABA-A receptor agonist used commonly for induction of general anesthesia. Etomidate is commonly used in patients who require hemodynamic and respiratory stability. Etomidate is a weak base that is moderately protein bound and rapidly metabolized.

The systematic review of the literature resulted in one study detailing etomidate concentration in breastmilk. Esener et al. (1992), found that after an IV induction dose of 0.3 mg/kg of etomidate used for women undergoing cesarean section, levels of etomidate in the colostrum were 79 ng/ml at 30 minutes and 16 ng/ml at two hours. Four hours after use, etomidate was undetectable in colostrum. Because of the extremely low levels of IV etomidate excreted into breastmilk, there is a low risk of adverse effects in the infant of a lactating woman.

Ketamine (Ketalar).

Ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist used for induction of general anesthesia, perioperative and postoperative analgesia, sedation of mechanically ventilated patients in critical care areas, and treatment of psychiatric disorders. Ketamine also has effects on opiate, monoamine, and GABA receptors (Wallach & Brandt, 2018). Ketamine has high lipid solubility, low protein binding, low oral bioavailability, and produces a metabolite, norketamine, that has 25% potency of ketamine.

This literature review resulted in two articles describing ketamine use in the lactating mother. In the study by Gilder et al. (2021), patients in a resource received an average of 1.16 mg/kg of IV ketamine for induction and maintenance of general anesthesia. Although the amount of ketamine in the breastmilk of these patients was not quantified, infants did not

show increased weight loss, jaundice, poor breastfeeding, sleepiness, seizures, mortality or long-term neurological damage when compared to a control group. The second study, recently released results from a US clinical trial, is the first study to quantify ketamine and norketamine in breastmilk. Wolfson et al. (2021) administered 0.5 mg/kg or 1 mg/kg of intramuscular (IM) ketamine to four lactating women who presented for ketamine therapy for postpartum depression. Bioavailability of IV and IM ketamine is similar, 100% and 95% respectively (Clements et al., 1982). Expressed breast milk was obtained from participants at 0, 3, 6, 9, and 12 hours after administration. The highest accumulation in the participants' breastmilk over 12 hours was 24 mcg of ketamine and 21 mcg of norketamine, leading to a relative infant dose of 0.8%. The findings from the above studies indicate that it is unlikely that IV ketamine will cause adverse effects in the nursing infant however, the study by Wolfson et al. only included four participants and has yet to be peer reviewed. There is further need of investigating the use of IV ketamine in lactating woman in a study with a larger sample size.

Dexmedetomidine (Precedex).

Dexmedetomidine is a highly selective Alpha 2 adrenergic agonist used for the prevention of emergence delirium and sedation of mechanically ventilated patients. Patients who receive dexmedetomidine also maintain spontaneous respiration even at high doses (Ramsay & Luterman, 2004). Dexmedetomidine is a highly protein bound drug with low bioavailability.

The literature review resulted in three articles describing dexmedetomidine in breastmilk. In a study by Dodd et al. (2021), a patient presented for an open craniotomy four weeks postpartum. A dose of 45 micrograms (mcg) of IV Precedex was used for sedation,

followed by an infusion at 0.7-1 mcg/kg/hr. Breastmilk was expressed twice during the procedure and one and four hours postoperatively. The highest concentration of 89 pg/mL, an extremely small dose, was found one hour after conclusion of the procedure. Yoshimura et al. (2017) and Nakanishi et al. (2017) measured dexmedetomidine concentrations in the blood and colostrum of women who presented for scheduled cesarean sections. The participants received 6 mcg/kg/hour of IV Precedex for ten minutes after cord clamping followed by a dose of 0.2-0.7 mcg/kg/hour until peritoneal closure. Six hours after Precedex administration, Yoshimura found that the median plasma level was 19.7 pg/mL and the median colostrum level was 12.3 pg/mL, leading to a M:P ratio of 0.76 and a relative infant dose of 0.034%. Nakanishi found that after six hours, the mean plasma level was 18.2 pg/mL and the mean colostrum level was 15.1 pg/mL, leading to a M:P ratio of 0.62 and a relative infant dose of 0.05%. Due to the pharmacokinetic characteristics of dexmedetomidine and the evidence found above, single doses and short infusion of IV dexmedetomidine has a low risk of use in the lactating mother. Further evidence is required for patients receiving dexmedetomidine as a long-acting transfusion.

Opioids.

Fentanyl.

Fentanyl is a short acting synthetic opioid agonist that is commonly used for pain control, sedation, and induction of general anesthesia. In terms of analgesic potency, Fentanyl is about 100 times stronger than morphine. Fentanyl is a highly lipophilic drug with a short duration of action and moderately high protein binding.

Three articles were found regarding the safety of both epidural and intravenous fentanyl in the breastfeeding mother. In a study performed by Nitsun et al. (2006), five lactating women received 100 mcg of IV fentanyl for induction of general anesthesia for tubal ligation or laparoscopic cholecystectomy. All breastmilk was collected for 24 hours and analyzed for fentanyl concentration. The median amount of fentanyl found in the total breastmilk volume was 0.024 mcg, 0.024% of the maternal dose. Steer et al. (1992) used 2 mcg/kg of IV fentanyl for induction of general anesthesia for patients receiving a cesarean section or tubal ligation. Serum and breastmilk were collected for 10 hours after administration. The highest fentanyl concentration found in breastmilk, 0.45 ng/mL, was 45 minutes after administration. Lastly, Goma et al. (2008), assessed fentanyl levels in breastmilk of patients who received 100-150 mcg of epidural fentanyl or 50 mcg of IV fentanyl. The average concentration of fentanyl in the breastmilk was 40 ng/mL for women who received epidurals and 19 ng/mL for women who received IV fentanyl. All three studies obtained in this literature review indicate that there is a low risk in using fentanyl as an IV induction dose or an epidural additive for nursing mothers. Further investigation into the safety of fentanyl infusions in the nursing mother is warranted.

Morphine.

Morphine is a naturally occurring opioid agonist commonly used for pain control in the perioperative period as well as an adjunct in neuraxial anesthesia. Morphine has low protein binding, is hydrophilic, has low oral bioavailability, and has a moderate duration of action. Ten percent of morphine is broken down into an active metabolite, morphine-6-glucuronide (M6G), a hydrophilic substance. There is conflict in the scientific community regarding the safety of morphine in the lactating mother.

The literature review resulted in three articles, one randomized control trial and two nonexperimental studies. Wittels et al. (1990), measured breastmilk concentrations of women who received meperidine or morphine for postoperative analgesia through a patient-controlled analgesic (PCA) pump. The highest average breastmilk concentration of morphine, 60 ng/mL, was found 4 hours after morphine administration, however, M6G levels were not measured. Wittels et al. (1997) assessed the alertness and orientation of infants of mothers who received morphine or meperidine PCAs. Nursing infants of mothers who received morphine PCAs were more alert and oriented than nursing infants of mothers who received meperidine PCAs and bottle fed infants. Lastly, Boka et al. (2002) assessed the plasma and breastmilk concentrations of both morphine and M6G of women who were on morphine PCAs. The highest mean morphine concentration in the breastmilk was 34 ng/mL and the highest mean concentration of M6G was 672 ng/mL. These studies indicate that using IV morphine for a short period of time poses a low risk of harm to the nursing infant. However, because morphine does have an active metabolite, using prolonged morphine infusion may result in a buildup of M6G, which has both analgesic and ventilatory depressant effects (Stoelting, 2015).

Meperidine (Pethidine).

Meperidine is a synthetic opioid agonist that shares structural features with local anesthetics and anticholinergics. Meperidine has about 1/10 of the analgesic potency of morphine, has a moderate duration of action, and has an active metabolite, normeperidine. Normeperidine is about half as potent as meperidine, has proconvulsant properties, and has a prolonged elimination half- time of 15 hours (Stoelting, 2015).

The review of literature resulted in four articles. Wittels et al. (1990) studied women who used a meperidine or morphine PCA after cesarean section. The authors found that women who received 1 mg/kg dose of meperidine followed by a 12.5 mg meperidine PCA with a 6 minute lockout had an average peak breastmilk meperidine concentration of 1100 ng/mL at 2 hours after administration. Additionally, participants also had an average peak breastmilk normeperidine concentration of 500 ng/mL at 3 hours after administration. Wittels et al. (1990), also used a neonatal behavioral assessment scale (NBAS) to assess infants for alertness and orientation. Neonates that were in the meperidine group consistently scored lower than the neonates in the morphine group. In an additional study similar in design with a larger pool of participants, Wittels et al. (1997) again found that patients of mothers receiving meperidine scored lower on the NBAS. Al-Tamimi et al. (2011) investigated the concentration of both meperidine and normeperidine in the breastmilk of women with meperidine PCAs after cesarean section. The highest calculated mean infant dose of meperidine via breastmilk was 20 mcg/kg/day. The highest calculated mean infant dose of normeperidine via breastmilk was 22 mcg/kg/day. Participants in a study by Borgatta et al. (1997) received 25 mg of meperidine as part of a general anesthetic for tubal sterilization. The peak average meperidine level was 176 ng/mL at one hour after administration.

There is disagreement throughout the literature of the use of meperidine in the lactating mother. Although the mean levels of Pethidine in breastmilk in the above studies are far below the maximum therapeutic dose of 1.5 mg/kg/day, levels of norpethidine were not measured in all studies. Additionally, there was a statistically significant depression in behavior in infants of mothers on meperidine PCAs. There is likely a low risk of a single dose of IV

meperidine in the nursing mother, but more evidence is needed to determine the safety of multiple doses.

Codeine.

Codeine is a weak opioid agonist once used commonly for postpartum mothers. Codeine has low protein binding and high oral bioavailability. Most importantly, codeine is a prodrug that is metabolized to morphine in the body by the enzyme CYP2D6. Morphine is responsible for almost all the analgesic and central nervous depression (CNS) depressant effects of codeine. Because mothers can have varying levels of CYP2D6, resulting and unpredictable morphine levels may result. The review of the literature resulted in seven articles discussing the safety of codeine in the nursing mother.

Much of the hesitance in the medical community to use codeine in the nursing mother resulted from the "Toronto Case", a case study by Madadi et al. (2007) that describes morphine overdose in an infant of a woman taking codeine. Postmortem blood levels in the infant were five times higher than a therapeutic concentration. The authors concluded that the mother was an ultrarapid metabolizer of codeine, resulting in high morphine levels in her breastmilk and consequently in her child. CYP2D6 ultrarapid metabolism can occur in up to 29% of the population, leading the authors to recommend the avoidance of codeine in the nursing mother (Madadi et al., 2007). Due to this occurrence, the U.S. Food and Drug Administration (FDA) and American College of Obstetrics and Gynecology (ACOG) released statements of caution in the use of codeine in the nursing mother.

Madadi et al. (2008) compared genetic and nongenetic characteristics of infants who exhibited or did not exhibit CNS depression while nursing from mothers taking codeine. Almost

25% of mothers reported CNS depression in their infants that resolved with the cessation of breastfeeding or maternal codeine use. When infants exhibited CNS depression, mothers were likely to exhibit CNS depression. Additionally, mothers of symptomatic infants consumed a 60% higher dose than mothers of asymptomatic infants. Mothers of infants who exhibited CNS depression were six times more likely to be ultrarapid metabolizers of CYP2D6.

Using data and characteristics from the Toronto case, Willmann et al. (2009) developed a pharmacokinetic model to determine the exposure and clearance of morphine and codeine by the infant of a nursing mother who is taking codeine. The authors determined that morphine clearance was the most important determinant of morphine accumulation in neonates. Toxic blood morphine levels in the neonate can be attained within four days of repeated maternal codeine administration. The authors were unable to obtain infant blood levels equal to the Toronto case while running a worst-case scenario on the pharmacokinetic model, an ultrarapid metabolizer mother with an infant with minimal morphine clearance. However, infant blood levels obtained were considered lethal.

In a retrospective cohort study of over 7,800 nursing women who used codeine after birth, Juurlink et al. (2012) found that there were no more adverse events, hospitalizations, or injuries when compared to a matched control group of women who did not use codeine after birth.

Lam et al (2012) studied CNS depression in infants of mothers who used codeine, oxycodone, or Tylenol. Infants of mothers who used oxycodone or codeine were much more likely to have CNS depression, 21% and 16% of participants respectively, in comparison to infants of mothers using Tylenol (0.5% of participants).

In 2020, Zipursky and Juurlink published a review article arguing the implausibility of the Toronto case due to the small volume of opioids passed in the breastmilk, the need for severely impaired kidney function to allow morphine accumulation, and the elevated level of codeine in the postmortem analysis. Zipursky and Juurlink argued that the use of short-term codeine should not be considered hazardous (2020). After the release of these results, the *Canadian Pharmacists Journal* and the *Canadian Family Physician* printed a joint statement of retraction for the original article that described the Toronto case. (Tsuyuki & Pimlott, 2020).

Due to the invariability of neonatal response to maternal codeine consumption, the anesthetist should avoid codeine use in the lactating woman, instead using acetaminophen or nonsteroidal anti-inflammatory drugs, shown to be as equally effective as codeine in the treatment of postoperative pain (Choi et al., 2021). In the event that codeine use is initiated in the lactating patient, Kelly et al. (2013), found a decrease in adverse neonatal effects after implementing a breastfeeding guideline. This guideline advises codeine use no longer than four days and to seek medical attention for neonatal or maternal CNS depression.

Hydromorphone (Dilaudid).

Hydromorphone is a longer acting opioid analgesic commonly used for perioperative and postoperative pain control. Hydromorphone has low protein binding and moderate oral bioavailability. The review of the literature resulted in one nonexperimental study describing the use of intranasal hydromorphone in lactating mothers. Edwards et al. (2003) administered 2 mg of intranasal hydromorphone to eight lactating mothers between the ages of 24-32 years. Plasma and milk samples were obtained from the participants at 2, 4, 6, 8, 12, and 24 hours after hydromorphone administration. The calculated average relative infant dose of

hydromorphone was 0.67%. The authors concluded that the risk for adverse effects for the infant of a lactating mother receiving intranasal hydromorphone were low because of negligible drug crossover into the breastmilk. Because intravenous and intranasal hydromorphone have different bioavailabilities, 100% or 55%, these recommendations should not be generalized for IV hydromorphone (Coda et al., 2003). Until more evidence is developed that determines the safety of IV hydromorphone in lactating women, anesthetists should opt to use an alternative agent.

Tramadol (Ultram).

Tramadol is a longer acting weak opioid analgesic that also inhibits norepinephrine and serotonin reuptake. Tramadol is low protein binding and high oral bioavailability. Like codeine, tramadol is a prodrug metabolized by the enzyme CYP2D6. Tramadol's active metabolite, O-desmethyltramadol (M1), has a higher affinity for the opioid receptor than tramadol and is responsible for the drug's analgesic properties (WHO, 2018b).

This literature review resulted in two articles regarding the use of tramadol in breastfeeding mothers. Both Ilett et al. (2008) and Salman et al. (2011) used the same dataset, 75 lactating women who received 50-100 mg of IV tramadol every four to six hours for postoperative analgesia after cesarean section. Breastmilk and plasma samples were obtained after 4 doses of medication, so as both tramadol and M1 would be at steady state concentrations. Ilett et al. (2008) found that the relative infant dose of tramadol was 2.24% and the relative infant dose of M1 was 0.64%, leading to a combined relative infant dose of 2.88%. Salman et al. (2011) developed a pharmacokinetic model to estimate the relative infant dose for infants of ultra-slow and ultra-fast maternal metabolizers. The authors found that the

infants of ultra-slow metabolizers received an average relative dose of 3.07% and the infants of ultra-fast metabolizers received an average relative dose of 3.09%. Although IV tramadol appears to be safe in the participants in the above study, caution still should be exercised in the administration of this medication due to the action of its metabolites.

Benzodiazepines.

Diazepam, lorazepam, and midazolam are GABA-A receptor agonists that increase the binding affinity of the GABA-A receptor. Benzodiazepines are used in the perioperative period for their sedative, anxiolytic, and amnestic properties.

Diazepam (Valium).

Diazepam is a long-acting benzodiazepine with extremely high protein binding, high lipid solubility, high oral bioavailability, and an active metabolite, nordiazepam. The literature review resulted in four articles describing the safety of diazepam in the nursing mother. Gilder et al. (2021) administered low dose, less than 1 mg/10 kg, and high dose, greater than 1 mg/10 kg, of IV diazepam to participants presenting for a postpartum tubal ligation. As the dose of diazepam increased, infants of nursing mothers were more likely to result in hyperbilirubinemia and weight loss. In a study by Borgatta et al. (1997), 9 participants received between 0-10 mg of IV diazepam before a general anesthetic for tubal ligation. Participant's breastmilk was obtained three times within 24 hours after surgery. Diazepam and nordiazepam levels did not exceed the lower limit of reportable range at all three sampling periods. Dusci et al. (1990) measured levels of diazepam and metabolites in the plasma and breast milk of a woman who was on a taper withdrawing from chronic benzodiazepine use. Diazepam and metabolite levels were also measured in her one-year-old infant. The highest milk concentration of diazepam or

metabolites found was 300 mcg/L of diazepam. Diazepam was undetectable in the infant plasma, but low levels of metabolites were found. In addition, the infant did not present with any signs of benzodiazepine intoxication. Erkkola and Kanto (1972) sampled the maternal plasma, breastmilk, and infant plasma after mothers received 10 mg of diazepam three times a day for six days. The highest infant plasma concentrations found were 172 ng/mL of diazepam and 283 ng/mL of nordiazepam during day four of the study. Due to the high level of diazepam and nordiazepam found in the infant plasma, the authors concluded that lactating mothers should not take diazepam. Because of these results, diazepam's pharmocokinetic characteristics, and the decreased ability of infants to breakdown active metabolites, diazepam should be avoided in the nursing mother until more consistent results are found.

Midazolam (Versed).

Midazolam is a short acting benzodiazepine with high protein binding, moderate oral bioavailability, and water solubility. Midazolam breaks down into hydroxymidazolam, an active metabolite with 10% of the potency of midazolam (Stoelting, 2015). This literature review resulted in three articles describing midazolam use in the lactating mother. In a case study by Koitabashi et al. (1997), a 20-year-old postpartum mother presented for a general anesthetic for laparoscopic cholecystectomy with 6 mg of IV midazolam used for induction. Plasma and breastmilk levels were obtained 1, 2, 4, 6, and 24 hours after administration. The highest concentration, 9 ng/mL, was found one hour after administration. Nitsun et al. (2006) administered 2 mg of IV midazolam to five lactating woman who presented for surgery. Breastmilk was collected for 24 hours after surgery; the highest amount of midazolam collected in the breastmilk was 0.08 mcg, or less than 1% of the relative infant dose. Matheson et al.

(1990) studied the use of 15 mg of oral midazolam in 12 postpartum breastfeeding mothers. Breastmilk concentrations were obtained 7 hours after administration. The average concentration of midazolam was 3.3 ng/mL and the average concentration of hydroxymidazolam was 3.4 ng/mL. Because of midazolam's pharmacokinetics and extremely low breastmilk concentrations in the above studies, IV and oral midazolam have a low likelihood of causing adverse effects in the nursing infant.

Lorazepam (Ativan).

Lorazepam is a moderate acting benzodiazepine with high protein binding, high oral bioavailability, low lipid solubility, and inactive metabolites. The literature review resulted in three studies researching the safety of lorazepam in the lactating woman. Summerfield and Nielsen (1985) administered 3.5 mg of oral lorazepam to lactating women presenting for surgery. Four hours after administration, mean breastmilk levels of lorazepam were 8.5 ng/mL, around 21% of mean plasma levels. A participant of a larger study by Whitelaw et al. (1981) received 2.5 mg of lorazepam twice a day for five days after birth. On day five, her breastmilk contained 12 ng/mL of lorazepam. Because of lorazepam lack of active metabolite and minimal excretion into breastmilk, the likelihood of adverse events in the nursing infant are low.

Non-opioid analgesics.

Ketorolac (Toradol).

Ketorolac is a commonly used non-steroidal anti-inflammatory drug (NSAID) that is commonly used in mothers in the postpartum period. Ketorolac has high protein binding and oral bioavailability. The literature review resulted in one article describing the use of oral Toradol in lactating mothers. Wischnik et al. (1989) administered 10 mg of oral Toradol four

times a day for three days to postpartum women who were abstaining from breastfeeding. Breastmilk and plasma samples were obtained every day during the intervention. The highest ketorolac concentration detected in breastmilk was 7.9 ng/mL with a M:P ratio of 0.037. The minimum amount of ketorolac excreted into breastmilk in this study indicates that nursing infants of mothers who take Toradol are unlikely to suffer from any adverse effects.

Acetaminophen (Tylenol).

Acetaminophen is one of the most common medications advised for use in lactating mothers. Tylenol is an antipyretic analgesic that has low protein binding, is lipid soluble, and is mostly unionized at physiologic pH. The literature review resulted in three articles describing the use of acetaminophen in lactating women. Berlin et al. (1980) administered one dose of 650 mg of oral Tylenol to 12 nursing mothers. Plasma and breastmilk concentrations were obtained at 0, 0.25, 0.5, 0.75, 1, 2, 3, 5, 8, 12, and 24 hours after maternal dosing. The peak concentration of Tylenol in breastmilk was 15 mcg/mL, found between 1-2 hours after dose administration. Bitzen et al. (1981) administered one dose of 500 mg of oral Tylenol to postpartum women who were abstaining from breastfeeding. Plasma and breastmilk levels of Tylenol were obtained every 2, 4, 6, 8, 10, and 12 hours after administration. The highest breastmilk concentration of Tylenol, 4.4 mcg/mL, was found 2 hours after administration. Notarianni et al. (1987) administered 1 gram of acetaminophen to 4 nursing women. Plasma and breastmilk Tylenol concentrations were obtained every 30 minutes for 3.5 hours. The average peak Tylenol concentration in breastmilk was 10.1 mcg/mL. The average Tylenol concentration in breastmilk was 6.1 mcg/mL. Because the amount of acetaminophen that neonates would consume is negligible in comparison to an appropriate infant dose of Tylenol,

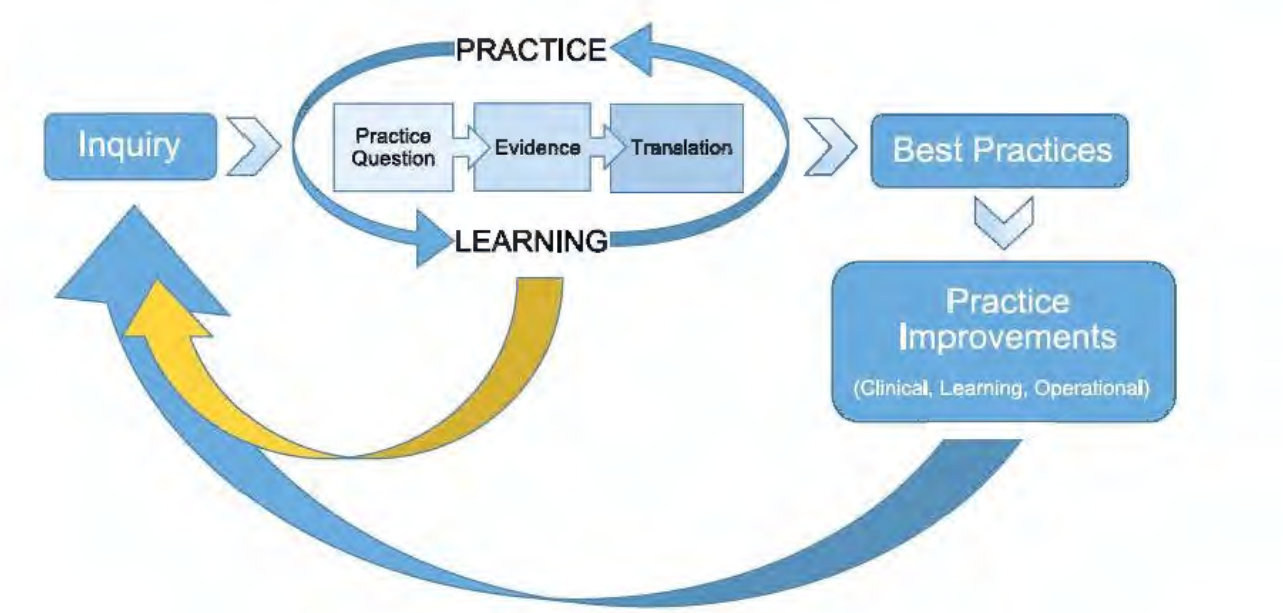
maternal use of acetaminophen while nursing is highly unlikely to cause adverse effects in the neonate.

Theoretical Framework

The Johns Hopkins Nursing Evidence-Based Practice (JHNEBP) Model was utilized for this scholarly project. The JHNEBP Model uses a 19-step process that is based on inquiry, practice, and learning (Dang & Dearholt, 2018). The JHNEBP includes various tools that guide the literature review, evidence synthesis, guideline development, and implementation plan for this scholarly project. This author obtained permission from the Johns Hopkins Nursing Center for Evidence-Based Practice to use the JHNEBP model and tools (Appendix C).

Clinical inquiry was the trigger for this process. Throughout the literature a need for a postoperative breastfeeding protocol was indicated, as many anesthesia providers gave incorrect postoperative recommendations to breastfeeding mothers (Moore et al., 2021; Reith et al., 2018). This clinical inquiry began the PET process, which was divided into three phases: practice question, evidence, and translation. The use of the PET process helps to develop best practices and practice improvements. This JHNEBP model is a dynamic process that promotes both learning and practice improvement, where new questions that arise trigger a new EBP cycle (Melnyk & Fineout-Overholt, 2019). The JHNEBP model can be found in figure 1.

Figure 1



Johns Hopkins Nurse Evidence-Based Practice Model. (Dang and Dearholt, 2018)

The first phase of the PET process, practice question, included recruiting an interprofessional team, developing and defining the scope of the EBP question, identifying stakeholders, determining responsibility for project leadership, and scheduling team meetings (Dang & Dearholt, 2018). The interprofessional team comprised of this graduate student and a nurse anesthesia program director. The EBP question was as follows: In anesthesia providers who provide care to lactating mothers (P), how does using an established postoperative breastfeeding guideline (I) in comparison to current practice (C) affect provider knowledge and confidence in providing postoperative breastfeeding recommendations (O)? The key stakeholders include the anesthesia providers, anesthesia management, and patients at the proposed facility of implementation. This graduate student was the primary investigator for this

project. Their responsibilities included performing the literature review, developing the postoperative breastfeeding guidelines, and developing a proposed implementation and statistical analysis plan. The nurse anesthesia program director served as an advisor to the graduate student. Meetings between the graduate student and the nurse anesthesia program director occurred at least once a semester until project completion.

The next phase of the PET process, evidence, included an external evidence search, appraisal of evidence, synthesis of evidence, and recommendation development based on evidence synthesis (Dang & Dearholt, 2018). The graduate student performed a systematic literature review of each commonly used anesthetic medication and "anesthesia" in multiple research databases. The Research Evidence Appraisal Tool and the Non-research Evidence Appraisal Tool, question-based guides that aid the reader in determining the strength of the evidence gathered in the literature review, were used (Dang & Dearholt, 2018). The five levels of evidence (I-V) in these tools were determined by research design. Evidence also received a quality rating of good (A), fair (B), or poor (C), which was determined by the validity and reliability of study methods (Dang & Dearholt, 2018). After the evidence was appraised and selected, the Individual Evidence Summary Tool was used. This chart provided summary of each source used for evidence synthesis. Information on this chart included the year of publication, level of evidence, quality of evidence, and study findings (Dang & Dearholt, 2018). The Synthesis Process and Recommendation Tool was used to compile the evidence gathered from individual resources to answer the initial practice question. Findings were categorized by evidence level. The Synthesis Process and Recommendation Tool also emphasizes the importance of practice change that is compatible with organizational culture, practices, and

funding (Dang & Dearholt, 2018). This tool was used to summarize information from the literature review and to develop the clinical guideline.

Lastly, the translation phase included creating a proposed guideline implementation and assessment plan. The Action Planning Tool was utilized to develop a proposed plan for the clinical implementation of the breastfeeding after anesthesia guideline. This tool aided the project team in identifying milestones, barriers, and tasks needed for successful implementation. The Action Planning Tool also required the identification of pre-intervention and post-intervention measures.

Breastfeeding After Maternal Anesthesia Guideline

The following guideline is designed for use by anesthesia providers in the perioperative period. Prolonged or excessive administration of these medications may alter their safety profile. The guideline was developed to present implications of commonly used medications in anesthesia on breastfeeding using a stop light appearance. Green indicates medications that have little risk to the nursing infant. Yellow indicates medications that require vigilant supervision, but benefits may outweigh the risks of medication use. Red indicates medications that should be avoided in the nursing mother. Purple indicates medication with little human research to affirm its use for lactating women, so avoidance is advised until further data is developed. The developed guideline can be found in table 1.

Table 1

Guideline for Administering Perioperative Medications to Lactating Women

Drug	Review
Sedatives/Hypnotics	
Propofol	**Low risk**
Etomidate	**Low risk**
Ketamine	**Low risk**
Dexmedetomidine	**Low risk**
Opioids	
Fentanyl	**Low risk**
Morphine	**Low risk**
Meperidine	**With Caution**
Codeine	**Avoid**
Hydromorphone	**Insufficent Data - Avoid**
Tramadol	**With Caution**
Benzodiazepines	
Diazepam	**With Caution**
Midazolam	**Low risk**
Lorazepam	**Low risk**
Non-Opioid Analgesics	
Ketorolac	**Low risk**
Acetaminophen	**Low risk**

Comprehensive Plan

Setting

The setting of proposed project implementation will be a large urban hospital with an active labor and delivery unit in the Midwest United States. The population for this scholarly project will comprise of anesthesia providers at the facility of implementation. All anesthesia providers will be included in the breastfeeding after anesthesia education and will receive the breastfeeding after anesthesia guideline. Anesthesia providers at the hospital used for this project will include anesthesiologists and CRNAs.

Methods

Design.

The chief CRNA will use the PET Management Guide and the Action Planning Tool from the JHNEBP model to establish the project timeline and plan of implementation with the lactation specialist at the proposed facility of implementation. The chief CRNA and lactation specialist for the facility of implementation will recruit an interprofessional team, identify stakeholders, and schedule team meetings. Next, the team will obtain IRB approval. The chief CRNA will draft an educational email with the postoperative breastfeeding guidelines and print off the laminated QR codes that provide an electronic link to the guideline at this time.

Implementation.

The chief CRNA will email the pre-implementation survey to anesthesia providers. Two weeks later, the guideline will be emailed to all anesthesia providers and the QR codes will be affixed to dedicated areas. Post implementation data will be collected one month and six months after implementation by email surveys. Data analysis will occur after the six-month post-implementation data is collected.

Integration into Practice.

To continue anesthesia provider knowledge and confidence in providing postoperative breastfeeding recommendations, the guideline will be updated yearly by the hospital lactation specialist and chief CRNA with new evidence and given to anesthesia providers.

Timeline and Budget

Timeline.

The duration estimate for the proposed implementation of postoperative breastfeeding guideline is eleven months.

-Month One: Establish timeline and plan of implementation with chief CRNA and lactation specialist. Submit and obtain IRB approval or exemption. Print off guidelines and QR codes.

-Month Two: Send pre-implementation survey.

-Month Three: Guideline emailed to staff and QR codes affixed to dedicated areas.

-Month Four: Collect one month post implementation data.

-Month Nine: Post implementation data collected six months after implementation.

-Month Ten: Data analysis and final report.

-Month Eleven: Poster presentation.

Budget.

The budget expectations for this proposed guideline implementation are minimal. The chief CRNA and the lactation specialist will be salaried through the proposed hospital of implementation, and no other compensation will occur. Distribution of the guideline will occur electronically by facility email. The participants of the multidisciplinary team will be recruited on a volunteer basis and will be uncompensated for their time. A laminated QR code that leads to the postoperative breastfeeding guidelines and additional information will be fixed to each Pyxis machine in the pre-operative, intraoperative, post-operative, labor and delivery, and post-partum units. The cost of 50 QR codes will be about $100. To encourage anesthesia providers to complete surveys to obtain project data, all participants will be entered into a raffle for one $50 gift card. Lastly, at the conclusion of the project, a poster will be printed for presentation. This

cost of printing will be between $50-$100. Overall, the maximum estimated budget for this scholarly project will be between $200-$250.

Outcome Analysis Plan

Data Collection.

Anesthesia providers at the proposed facility of implementation will complete a ten-question assessment about breastfeeding after anesthesia. Providers will also rate their confidence in providing recommendations regarding breastfeeding in the perioperative period. Data collection will occur three times: before guideline implementation, one month after guideline implementation to assess for initial knowledge and confidence change, and six months after guideline implementation to assess for knowledge and confidence retention. All data collection will occur by electronic correspondence.

Data Analysis.

Knowledge and confidence data collected from pre-implementation, one month after implementation, and six months after implementation will be compared using the one-way analysis of variance (ANOVA) test. Knowledge questions answered will be scored as “correct” or “incorrect”. The knowledge assessment will be scored from one to ten. Provider confidence questions will be answered on a five-point Likert scale, where one is “not confident at all” and five is “completely confident”. The knowledge and confidence assessment can be found in Appendix D.

Facilitators

At the proposed institution of implementation, the chief CRNA and a lactation consultant will serve on the multidisciplinary team to guide facility specific implementation.

Anesthesia providers including CRNAs and anesthesiologists at the institution of implementation will be the final facilitators of this guideline.

Project Evaluation

The success of this scholarly project will be based on meeting the objectives established using the PET management guide, maintaining the project timeline, and a statistically significant increase in knowledge and confidence in providers regarding breastfeeding in the perioperative setting.

Conclusion

The purpose of the scholarly project was to develop a set of evidenced-based practice guideline recommendations and a proposed implementation plan for anesthesia providers to use in support of breastfeeding mothers who recover from surgery. Using these guidelines and implementation plan, the CRNA can assess current provider knowledge regarding breastfeeding, implement evidence-based postoperative breastfeeding guidelines, assess effectiveness of the implementation, and ensure lasting change. Further investigation in the safety of anesthetic medications in the lactating mother is warranted. Gaps in the literature indicate the need for up to date and large cohort studies in the use of anesthetic medications in all lactating mothers and additionally in lactating mothers of children with comorbid disease.

Limitations and Barriers

Literature regarding breastfeeding safety for some medications used in the perioperative area is limited (Oliveira et al., 2018; Verstegen & Ito, 2019; Cobb et al., 2015). In addition, some lactation safety references may be older than ten years. If high quality evidence was unable to be found, LactMed, an online drug and lactation database, was utilized (LactMed,

n.d.). Though limited, there are some anticipated barriers to the implementation of this scholarly project. Provider hesitancy to adopt new guidelines may also occur (Alatawi et al., 2020). Lastly, provider knowledge and confidence may decrease after implementation, as improvements can be difficult to sustain without further intervention.

References

AANA. (n.d.). Does Anesthesia Affect a New Mom's Ability to Breastfeed? Aana.com. Retrieved March 1, 2022, from https://www.aana.com/patients/does-anesthesia-affect-a-new-mom-s-ability-to-breastfeed

Alatawi, M., Aljuhani, E., Alsufiany, F., Aleid, K., Rawah, R., Aljanabi, S., & Banakhar, M. (2020). Barriers of implementing evidence-based practice in Nursing Profession: A literature review. American Journal of Nursing Science, 9(1), 35. https://doi.org/10.11648/j.ajns.20200901.16

Al-Tamimi, Y., Ilett, K. F., Paech, M. J., O'Halloran, S. J., & Hartmann, P. E. (2011). Estimation of infant dose and exposure to pethidine and norpethidine via breast milk following patient-controlled epidural pethidine for analgesia post caesarean delivery. *International Journal of Obstetric Anesthesia*, *20*(2), 128–134. https://doi.org/10.1016/j.ijoa.2010.12.004

American Academy of Pediatrics (AAP). (2012). Breastfeeding and the use of human milk. *Pediatrics, 129(3)*, e827–e841. Retrieved from https://pediatrics.aappublications.org/content/129/3/e827

ASA. (2019). Statement on Resuming Breastfeeding after Anesthesia. Statement on Resuming Breastfeeding after Anesthesia | American Society of Anesthesiologists (ASA). https://www.asahq.org/standards-and-guidelines/statement-on-resuming-breastfeeding-after-anesthesia.

Baka, N.-E., Bayoumeu, F., Boutroy, M.-J., & Laxenaire, M.-C. (2002). Colostrum morphine concentrations during Postcesarean intravenous patient-controlled analgesia. Anesthesia & Analgesia, 94(1), 184–187. https://doi.org/10.1213/00000539-200201000-00035

Berlin, C. M., Jr, Yaffe, S. J., & Ragni, M. (1980). Disposition of acetaminophen in milk, saliva, and plasma of lactating women. Pediatric pharmacology (New York, N.Y.), 1(2), 135–141.

Bitzen, P.O., Gustafsson, B., Jostell, K. G., Melander, A., & Wahlin-Boll, E. (1981). Excretion of paracetamol in human breast milk. European Journal of Clinical Pharmacology, 20(2), 123–125. https://doi.org/10.1007/bf00607148

Butwick, A. J., Wong, C. A., & Guo, N. (2018). Maternal Body Mass Index and Use of Labor Neuraxial Analgesia. *Anesthesiology*, *129*(3), 448–458. https://doi.org/10.1097/aln.0000000000002322

Centers for Disease Control and Prevention (CDC). (2021). *Facts*. Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/breastfeeding/data/facts.html

Choi, M., Wang, L., Coroneos, C. J., Voineskos, S. H., & Paul, J. (2021). Managing postoperative pain in adult outpatients: A systematic review and meta-analysis comparing codeine with NSAIDs. *Canadian Medical Association Journal*, *193*(24). https://doi.org/10.1503/cmaj.201915

Cobb, B., Liu, R., Valentine, E., & Onyi, O. (2015). Breastfeeding after Anesthesia: A Review for Anesthesia Providers Regarding the Transfer of Medications into Breast Milk.

Translational Perioperative and Pain Medicine, 2(2). https://doi.org/10.31480/2330-4871/023

Coda, B. A., Rudy, A. C., Archer, S. M., & Wermeling, D. P. (2003). Pharmacokinetics and bioavailability of single-dose intranasal hydromorphone hydrochloride in Healthy Volunteers. Anesthesia & Analgesia, 117–123. https://doi.org/10.1213/01.ane.0000066311.40978.4f

Clements, J., Nimmo, W., Grant, I. (1982). Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. J Pharm Sci 71(5):539–542

Dalal, P. G., Bosak, J., & Berlin, C. (2014). Safety of the breast-feeding infant after maternal anesthesia. Pediatric Anesthesia, 24(4), 359–371. https://doi.org/10.1111/pan.12331

Dang, D., & Dearholt, S. (2018). *Johns Hopkins nursing evidence-based practice: Model and guidelines*. Sigma Theta Tau International.

Dailland, P., Cockshott, I. D., Lirzin, J. D., Jacquinot, P., Jorrot, J. C., Devery, J., Harmey, J. L., & Conseiller, C. (1989). Intravenous propofol during cesarean section. *Obstetric Anesthesia Digest*, *10*(2), 84. https://doi.org/10.1097/00132582-199007000-00035

Dodd, S. E., Hunter Guevara, L. R., Datta, P., Rewers-Felkins, K., Baker, T., & Hale, T. W. (2021). Dexmedetomidine levels in breast milk: Analysis of breast milk expressed during and after awake craniotomy. *Breastfeeding Medicine*, *16*(11), 919–921. https://doi.org/10.1089/bfm.2021.0138

Edwards, J. E., Rudy, A. C., Wermeling, D. P., Desai, N., & McNamara, P. J. (2003). Hydromorphone transfer into breast milk after intranasal administration. Pharmacotherapy, 23(2), 153–158. https://doi.org/10.1592/phco.23.2.153.32081

Erkkola, R., & Kanto, J. (1972). Diazepam and breast-feeding. The Lancet, 299(7762), 1235–1236. https://doi.org/10.1016/s0140-6736(72)90954-3

Esener, Z., Sarihasan, B., Güven, H., & Ustün, E. (1992). Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum. *British journal of anaesthesia*, *69*(6), 586–588. https://doi.org/10.1093/bja/69.6.586

Folh, K., & Stephens, K. (2019). Implementation of a Post-Anesthesia Care Breastfeeding Program. *Journal of Obstetric, Gynecologic & Neonatal Nursing*, *48*(3). https://doi.org/10.1016/j.jogn.2019.04.015

Gilder, M. E., Tun, N. W., Carter, A., Tan, F. F., Min, A. M., Eh, H., Aye, P., Carrara, V. I., Angkurawaranon, C., & McGready, R. (2021). Outcomes for 298 breastfed neonates whose mothers received ketamine and diazepam for postpartum tubal ligation in a resource-limited setting. BMC Pregnancy and Childbirth, 21(1). https://doi.org/10.1186/s12884-021-03610-1

Goma, H. M., Said, R. N., & El-Ela, A. M. (2008). Study of the newborn feeding behaviors and fentanyl concentration in colostrum after an analgesic dose of epidural and intravenous fentanyl in cesarean section. *Saudi medical journal*, *29*(5), 678–682.

Gilder, M. E., Tun, N. W., Carter, A., Tan, F. F., Min, A. M., Eh, H., … McGready, R. (2021). Outcomes for 298 breastfed neonates whose mothers received ketamine and diazepam for postpartum tubal ligation in a resource-limited setting. *BMC Pregnancy and Childbirth*, *21*(1). https://doi.org/10.1186/s12884-021-03610-1

Ilett, K. F., Paech, M. J., Page-Sharp, M., Sy, S. K., Kristensen, J. H., Goy, R., Chua, S., Christmas, T., & Scott, K. L. (2008). Use of a sparse sampling study design to assess transfer of Tramadol and its O-desmethyl metabolite into transitional breast milk. British Journal of Clinical Pharmacology, 65(5), 661–666. https://doi.org/10.1111/j.1365-2125.2008.03117.x

Juurlink, D. N., Gomes, T., Guttmann, A., Hellings, C., Sivilotti, M. L., Harvey, M.-A., & Mamdani, M. M. (2012). Postpartum maternal codeine therapy and the risk of adverse neonatal outcomes: A retrospective cohort study. Clinical Toxicology, 50(5), 390–395. https://doi.org/10.3109/15563650.2012.681052

Kelly, L. E., Chaudhry, S. A., Rieder, M. J., 't Jong, G., Moretti, M. E., Lausman, A., Ross, C., Berger, H., Carleton, B., Hayden, M. R., Madadi, P., & Koren, G. (2013). A clinical tool for reducing central nervous system depression among neonates exposed to codeine through breast milk. PLoS ONE, 8(7). https://doi.org/10.1371/journal.pone.0070073

Koitabashi, T., Satoh, N., & Takino, Y. (1997). Intravenous midazolam passage into breast milk. Journal of Anesthesia, 11(3). https://doi.org/10.1007/s0054070110242

LactMed. (2018). *Drugs and lactation database*. National Library of Medicine.

Lam, J., Kelly, L., Ciszkowski, C., Landsmeer, M. L. A., Nauta, M., Carleton, B. C., Hayden, M. R., Madadi, P., & Koren, G. (2012). Central Nervous System Depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. The Journal of Pediatrics, 160(1). https://doi.org/10.1016/j.jpeds.2011.06.050

Lobkova, N., & Wolf, E. W. (2014). Performing Elective Surgery on the Breastfeeding Patient. *Foot & Ankle Specialist*, *7*(3), 225–230. https://doi.org/10.1177/1938640014532132

Madadi, P., Koren, G., Cairns, J., Chitayat, D., Gaedigk, A., Leeder, J. S., Teitelbaum, R., Karaskov, T., & Aleksa, K. (2007). Safety of codeine during breastfeeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. Canadian Family Physician Medecin de Famille Canadien, 53(1), 33–35.

Madadi, P., Ross, C. J. D., Hayden, M. R., Carleton, B. C., Gaedigk, A., Leeder, J. S., & Koren, G. (2008). Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: A case–control study. Clinical Pharmacology & Therapeutics, 85(1), 31–35. https://doi.org/10.1038/clpt.2008.157

Martin, E., Vickers, B., Landau, R., & Reece-Stremtan, S. (2018). ABM Clinical Protocol #28, Peripartum Analgesia and Anesthesia for the Breastfeeding Mother. *Breastfeeding Medicine*, *13*(3), 164–171. https://doi.org/10.1089/bfm.2018.29087.ejm

Matheson, I., Lunde, P. K., & Bredesen, J. E. (1990). Midazolam and nitrazepam in the Maternity Ward: Milk concentrations and clinical effects. British Journal of Clinical Pharmacology, 30(6), 787–793. https://doi.org/10.1111/j.1365-2125.1990.tb05443.x

Melnyk, B. M., & Fineout-Overholt, E. (2019). *Evidence-based practice in Nursing & Healthcare: A guide to best practice*. Wolters Kluwer.

Mitchell, J., Jones, W., Winkley, E., & Kinsella, S. M. (2020). Guideline on anaesthesia and sedation in breastfeeding women 2020. *Anaesthesia*, *75*(11), 1482–1493. https://doi.org/10.1111/anae.15179

Moore, C. B., Bond, J. D., Bundoc, E. G., Hefley, J. B., Wofford, K. A., & Bonds, R. L. (2021). Resuming Breastfeeding After Surgery: Influencing Practice Recommendations. *Journal of PeriAnesthesia Nursing*. https://doi.org/10.1016/j.jopan.2020.12.010

Nakanishi, R., Yoshimura, M., Suno, M., Yamamoto, K., Ito, H., Uchimine, Y., Toriumi, T., Kurosawa, A., Sugawara, A., & Kunisawa, T. (2017). Detection of dexmedetomidine in human breast milk using liquid chromatography–tandem mass spectrometry: Application to a study of drug safety in breastfeeding after cesarean section. *Journal of Chromatography B*, *1040*, 208–213. https://doi.org/10.1016/j.jchromb.2016.11.015

Nitsun, M., Szokol, J., Saleh, H., Murphy, G., Vender, J., Luong, L., Raikoff, K., & Avram, M. (2006). Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clinical Pharmacology & Therapeutics*, *79*(6), 549–557. https://doi.org/10.1016/j.clpt.2006.02.010

Notarianni, L. J., Oldham, H. G., & Bennett, P. N. (1987). Passage of paracetamol into breast milk and its subsequent metabolism by the neonate. British journal of clinical pharmacology, 24(1), 63–67. https://doi.org/10.1111/j.1365-2125.1987.tb03137.x

Oliveira, M. R., Santos, M. G., Aude, D. A., Lima, R. M., Módolo, N. S., & Navarro, L. H. (2019). Should maternal anesthesia delay breastfeeding? A systematic review of the literature. *Brazilian Journal of Anesthesiology (English Edition)*, *69*(2), 184–196. https://doi.org/10.1016/j.bjane.2018.12.006

Ramsay, M. A., & Luterman, D. L. (2004). Dexmedetomidine as a total intravenous anesthetic agent. *Anesthesiology*, *101*(3), 787–790. https://doi.org/10.1097/00000542-200409000-00028

Reece-Stremtan, S., Campos, M., Kokajko, L., Brodribb, W., Noble, L., Brent, N., Bunik, M., Harrel, C., Lawrence, R. A., LeFort, Y., Marinelli, K. A., Rosen-Carole, C., Rothenberg, S., Seo, T., St. Fleur, R., & Young, M. (2017). ABM Clinical Protocol #15: Analgesia and Anesthesia for the Breastfeeding Mother, Revised 2017. *Breastfeeding Medicine*, *12*(9), 500–506. https://doi.org/10.1089/bfm.2017.29054.srt

Reith, E. F., Barnett, K. M., & Simon, J. A. (2018). Implementation and Organization of a Perioperative Lactation Program: A Descriptive Study. *Breastfeeding Medicine*, *13*(2), 97–105. https://doi.org/10.1089/bfm.2017.0193

Ring, L., Landau, R., & Delgado, C. (2021). The Current Role of General Anesthesia for Cesarean Delivery. *Current Anesthesiology Reports*, *11*(1), 18–27. https://doi.org/10.1007/s40140-021-00437-6

Salman, S., Sy, S. K., Ilett, K. F., Page-Sharp, M., & Paech, M. J. (2011). Population pharmacokinetic modeling of Tramadol and its O-desmethyl metabolite in plasma and breast milk. European Journal of Clinical Pharmacology, 67(9), 899–908. https://doi.org/10.1007/s00228-011-1023-6

Steer, P. L., Biddle, C. J., Marley, W. S., Lantz, R. K., & Sulik, P. L. (1992). Concentration of fentanyl in colostrum after an analgesic dose. *Canadian Journal of Anaesthesia*, *39*(3), 231–235. https://doi.org/10.1007/bf03008782

Stuttmann, R., Schäfer, C., Hilbert, P., Meyer, M. R., & Maurer, H. H. (2010). The breast feeding mother and xenon anaesthesia: Four case reports. breast feeding and xenon anaesthesia. *BMC Anesthesiology*, *10*(1). https://doi.org/10.1186/1471-2253-10-1

Summerfield, R. J., & Nielsen, M. S. (1985). Excretion of Lorazepam into breast milk. British Journal of Anaesthesia, 57(10), 1042–1043. https://doi.org/10.1093/bja/57.10.1042-a

Tsuyuki, R. T., & Pimlott, N. (2020). Risks of maternal codeine intake in breast-fed infants: A joint statement of retraction from the Canadian Pharmacists Journal and Canadian family physician. *Canadian Pharmacists Journal / Revue Des Pharmaciens Du Canada*, *154*(1), 7–8. https://doi.org/10.1177/1715163520970443

Wallach, J., Brandt, S. D. (2018). 1,2-diarylethylamine- and ketamine-based new psychoactive substances. New Psychoactive Substances, 305–352. https://doi.org/10.1007/164_2018_148

Westerfield, K. L., Koenig, K., & Oh, R. C. (2018). *Breastfeeding: Common Questions and Answers*. American Family Physician. https://www.aafp.org/afp/2018/0915/p368.html.

Whitelaw, A., Mcfadyen, I., & Cummings, A. (1981). Effect of maternal lorazepam on the Neonate. *BMJ*, *282*(6280), 1973–1974. https://doi.org/10.1136/bmj.282.6280.1973-c

Willmann, S., Edginton, A. N., Coboeken, K., Ahr, G., & Lippert, J. (2009). Risk to the breast-fed neonate from codeine treatment to the mother: A quantitative mechanistic modeling study. Clinical Pharmacology & Therapeutics, 86(6), 634–643. https://doi.org/10.1038/clpt.2009.151

Wischnik, A., Manth, S. M., Lloyd, J., Bullingham, R., & Thompson, J. S. (1989). The excretion of Ketorolac tromethamine into breast milk after multiple oral dosing. *European Journal of Clinical Pharmacology*, *36*(5), 521–524. https://doi.org/10.1007/bf00558080

Wittels, B., Scot, D. T., & Sinatra, R. S. (1990). Exogenous opioids in human breast milk and acute neonatal neurobehavior. *Anesthesiology*, *73*(5), 864–869. https://doi.org/10.1097/00000542-199011000-00012

Wittels, B., Glosten, B., Faure, E. A., Moawad, A. H., Ismail, M., Hibbard, J., Senal, J. A., Cox, S. M., Blackman, S. C., Karl, L., & Thisted, R. A. (1997). Postcesarean analgesia with both

epidural morphine and intravenous patient-controlled analgesia. *Anesthesia & Analgesia*, *85*(3), 600–606. https://doi.org/10.1097/00000539-199709000-00021

Wolfson, P., Cole, R., Lynch, K., Yun, C., Wallach, J., Andries, J., & Whippo, M. (2021). The pharmacokinetics of ketamine in the breast milk of lactating women: Quantification of ketamine and metabolites. https://doi.org/10.22541/au.161325028.80476344/v1

World Health Organization (WHO). (2018a). *Breastfeeding*. World Health Organization. Retrieved from https://apps.who.int/nutrition/topics/exclusive_breastfeeding/en/index.html

World Health Organization (WHO). (2018b). Critical review report: Tramadol - World Health Organization. Critical Review Report: Tramadol . Retrieved March 7, 2022, from https://www.who.int/medicines/access/controlled-substances/Tramadol.pdf?ua=1

Yoshimura, M., Kunisawa, T., Suno, M., Sugawara, A., Kurosawa, A., Nakanishi, R., Aoki, K., & Toriumi, T. (2017). Intravenous dexmedetomidine for cesarean delivery and its concentration in colostrum. *International Journal of Obstetric Anesthesia*, *32*, 28–32. https://doi.org/10.1016/j.ijoa.2017.05.002

Zipursky, J., & Juurlink, D. N. (2020). The implausibility of neonatal opioid toxicity from breastfeeding. Clinical Pharmacology & Therapeutics, 108(5), 964–970. https://doi.org/10.1002/cpt.1882

Appendix A

Citation (Author, Year, Title, etc...)	Conceptual Framework (Theoretical basis for study)	Design/ Method	Sample/Setting (Number, Characteristics, Exclusions, Criteria, Attrition, etc...)	Major Variables; definitions (Independent variables; Dependent variables)	Outcome Measurement (What scales used – reliability information – alphas)	Data Analysis (What stats used?)	Findings (Statistical findings or qualitative findings)	Level of evidence	Quality of evidence
Mitchell, J., Jones, W., Winkley, E., & Kinsella, S. M. (2020). Guideline on anaesthesia and sedation in breastfeeding Women 2020. Anaesthesia, 75(11), 1482–1493. https://doi.org/10.1111/anae.15179	Performed literature review to provide evidence based information about the pharmacokinetics and passage into breastmilk of drugs commonly used in anesthesia.	Clinical Guideline	Used lactation databases, current guidelines, and breastfeeding expert journals and websites.	NA	NA	NA	Almost all medications used in the perioperative setting do increase the risk of harm to the infant. Opioids have caused respiratory depression in infants, and their use should be monitored closely.	V	A
Gilder, M. E., Tun, N. W., Carter, A., Tan, F. F., Min, A. M., Eh, H., … McGready, R. (2021). Outcomes for 298 breastfed neonates whose mothers received ketamine and diazepam for postpartum tubal ligation in a resource-limited setting. BMC Pregnancy and Childbirth, 21(1). https://doi.org/10.1186/s12884-021-03610-1	Identified adverse neonatal outcomes associated with varying levels of ketamine and diazepam in breastfeeding mothers.	Retrospective Cohort Study	298 breastfeeding mothers who were undergoing a tubal ligation	Low Ketamine Administration (<1.16 mg/kg of maternal body weight) High Ketamine Administration (≥ 1.16 mg kg of maternal body weight) Low Diazepam Administration (< 1 mg/10kg maternal body weight) High Diazepam Administration (≥1 mg/10kg maternal body weight)	Clinically significant weight loss Hyperbilirubinemia Neurodevelopment at 1 year	STATA-15 Chi^2 test Non-parametric tests of association Mann-Whitney Test Spears correlation coefficient	Weight loss and jaundice were unaffected by the amount of maternal ketamine received. As doses of diazepam were increased, there were increased risk of weight loss and jaundice.	III	A

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Cobb, B., Liu, R., Valentine, E., & Onyi, O. (2015). Breastfeeding after Anesthesia: A Review for Anesthesia Providers Regarding the Transfer of Medications into Breast Milk. Translational Perioperative and Pain Medicine, 2(2). https://doi.org/10.31480/2330-4871/023	Review of the literature to determine common anesthesia medications' passage into breast milk and implications for breastfed infants.	Systematic Review	Reviewed medications used for neuraxial, general, and regional anesthesia to assess the affect on neonatal outcomes.	NA	NA	NA	Most medications used in typical anesthesia practice are safe for use in women who are breastfeeding. Codeine and meperidine should be avoided, and hydromorphone should be used with caution in this patient population.	V	A
Oliveira, M. R., Santos, M. G., Aude, D. A., Lima, R. M., Módolo, N. S., & Navarro, L. H. (2019). Should maternal anesthesia delay breastfeeding? A systematic review of the literature. Brazilian Journal of Anesthesiology (English Edition), 69(2), 184–196. https://doi.org/10.1016/j.bjane.2018.12.006	A systematic literature review used to develop recommendations regarding breastfeeding after anesthesia.	Systematic Review	50 studies (16 reviews, 13 prospective trials, 4 retrospective observational studies, 6 case reports, 9 RCTs, 1 case-control study, and 1 website access)	NA	NA	NA	The transfer of medications to breastmilk from single dosages of medication is very small and the effects are negligible. Large and repeated doses of medications increase the risk of adverse effects in the neonate. Diazepam and meperidine should be avoided in nursing women.	V	A
Dalal, P. G., Bosak, J., & Berlin, C. (2014). Safety of the breast-feeding infant after maternal anesthesia. Pediatric Anesthesia, 24(4), 359–371. https://doi.org/10.1111/pan.12331	Reviewed the pharmacological implications for breastmilk of common medications used by anesthetists	Systematic Review	Searched available literature in the Pubmed database.	NA	NA	NA	The anesthetist should avoid using narcotics, benzodiazepines, and medications with active metabolites.	V	A
ASA. (2019). Statement on Resuming Breastfeeding after Anesthesia. Statement on Resuming Breastfeeding after Anesthesia | American Society of Anesthesiologists (ASA). https://www.asahq.org/standards-and-guidelines/statement-on-resuming-breastfeeding-after-anesthesia.	Clinical guideline established by the American Society of Anesthesiologists to provide anesthetists with information regarding adverse neonatal effects from maternal anesthetics.	Clinical Guideline	NA	NA	NA	NA	Narcotics and medications with active metabolites should be avoided in nursing mothers. Patients should not be encouraged to pump and dump.	IV	B

Citation (Author, Year, Title, etc...)	Conceptual Framework (Theoretical basis for study)	Design/ Method	Sample/Setting (Number, Characteristics, Exclusions, Criteria, Attrition, etc...)	Major Variables; definitions (Independent variables; Dependent variables)	Outcome Measurement (What scales used – reliability information – alphas)	Data Analysis (What stats used?)	Findings (Statistical findings or qualitative findings)	Level of evidence	Quality of evidence
Martin, E., Vickers, B., Landau, R., & Reece-Stremtan, S. (2018). ABM Clinical Protocol #28, Peripartum Analgesia and Anesthesia for the Breastfeeding Mother. *Breastfeeding Medicine*, *13*(3), 164–171. https://doi.org/10.1089/bfm.2018.29087.ejm	Clinical protocol developed by the Association of Breastfeeding Medicine to direct anesthetic practice for the peripartum patient.	Clinical Guideline	NA	NA	NA	NA		IV	A
Lobkova, N., & Wolf, E. W. (2014). Performing Elective Surgery on the Breastfeeding Patient. *Foot & Ankle Specialist*, *7*(3), 225–230. https://doi.org/10.1177/1938640014532132	Reviewed the pharmacokinetic implications of anesthesia in the mother- baby dyad.	Systematic Review	NA	NA	NA	NA	Provided an overview of the safety of common medications in anesthesia. It is essential to reference a reliable lactation medication database before administering medications to breastfeeding mothers.	V	A
Reece-Stremtan, S., Campos, M., Kokajko, L., Brodribb, W., Noble, L., Brent, N., Bunik, M., Harrel, C., Lawrence, R. A., LeFort, Y., Marinelli, K. A., Rosen-Carole, C., Rothenberg, S., Seo, T., St. Fleur, R., & Young, M. (2017). ABM Clinical Protocol #15: Analgesia and Anesthesia for the Breastfeeding Mother, Revised 2017. *Breastfeeding Medicine*, *12*(9), 500–506. https://doi.org/10.1089/bfm.2017.29054.srt	Clinical protocol developed by the Association of Breastfeeding Medicine to direct anesthetic practice for the lactating patient who presents for non-obstetric surgery.	Clinical Guideline	NA	NA	NA	NA	Provides anesthesia recommendations for lactating mothers including common medications used in surgery and their effects on the nursing infant.	IV	A
Moore, C. B., Bond, J. D., Bundoc, E. G., Hefley, J. B., Wofford, K. A., & Bonds, R. L. (2021). Resuming Breastfeeding After Surgery: Influencing Practice Recommendations. *Journal of PeriAnesthesia Nursing*. https://doi.org/10.1016/j.jopan.2020.12.010	Reviewed the literature for best practice regarding breastfeeding after anesthesia. Used findings to educate OR staff and develop unit policy.	Evidence Based Practice project	OR staff at a mid-sized military hospital N=10	Provided education on breastfeeding safety after anesthesia. Developed departmental policy.	Change in practice habits Change in confidence when making recommendations Change in knowledge	Chi^2 test McNemar test Wilcoxon test Mann-Whitney Test	OR staff who received training reported increased confidence when recommending breastfeeding after anesthesia, increased knowledge, and an increase in staff who would recommend	IV	B

Citation (Author, Year, Title, etc...)	Conceptual Framework (Theoretical basis for study)	Design/ Method	Sample/Setting (Number, Characteristics, Exclusions, Criteria, Attrition, etc...)	Major Variables; definitions (Independent variables; Dependent variables)	Outcome Measurement (What scales used – reliability information – alphas)	Data Analysis (What stats used?)	Findings (Statistical findings or qualitative findings)	Level of evidence	Quality of evidence
						Kruskal-Wallis test	breastfeeding after anesthesia.		
Nitsun, M., Szokol, J., Saleh, H., Murphy, G., Vender, J., Luong, L., Raikoff, K., & Avram, M. (2006). Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clinical Pharmacology & Therapeutics*, *79*(6), 549–557. https://doi.org/10.1016/j.clpt.2006.02.010	Collected and analyzed breastmilk drug levels of women who received midazolam, propofol, and fentanyl for a general anesthetic.	Quasi-experimental study	Five lactating women who had scheduled procedures requiring general anesthesia.	Administered 2 mg of midazolam, 100 mcg of fentanyl, and 2.5 mg/kg of propofol for induction of general anesthesia.	Drug levels in blood were measured up to 7 hours after drug administration. All breastmilk was collected for 24 hours after fentanyl administration and assessed for drug levels.	The median volume of breastmilk pumped over 24 hours was 250 mL. The median amount of drug in the breast milk was 0.08 mcg of midazolam, 26 mcg of propofol, and 0.024 mcg of fentanyl.	The fraction of maternal dose transferred to breastmilk for all drugs was less than 0.001% for all drugs.	III	B
Stuttmann, R., Schäfer, C., Hilbert, P., Meyer, M. R., & Maurer, H. H. (2010). The breast feeding mother and xenon anaesthesia: Four case reports. breast feeding and xenon anaesthesia. *BMC Anesthesiology*, *10*(1). https://doi.org/10.1186/1471-2253-10-1	Collected and analyzed breastmilk drug levels of women who received propofol, remifentanil, and inhaled xenon for a general anesthetic.	Nonexperimental study	Four lactating women who presented for urgent surgery on the condition that their ability to breastfeed would not be impaired.	Used a propofol bolus and infusion for induction and maintenance of general anesthesia before beginning inhaled xenon.	Propofol levels in breastmilk were measured 90 and 300 minutes after propofol administration.	The percentage of drug in 150 mL of breastmilk was calculated.	The percentage of the maternal dose was 0.09% at 90 minutes and 0.017%.	III	B
Dailland, P., Cockshott, I. D., Lirzin, J. D., Jacquinot, P., Jorrot, J. C., Devery, J., Harmey, J. L., & Conseiller, C. (1989). Intravenous propofol during cesarean section. *Obstetric Anesthesia Digest*, *10*(2), 84. https://doi.org/10.1097/00132582-199007000-00035	Collected and analyzed colostrum and blood from mothers who required general anesthesia for cesarean section.	Nonexperimental study	21 ASA status 1 patients 37-40 weeks' gestation, however, colostrum samples were only collected from 7 patients.	Phase 1- administered a 2.5 mg/kg dose of propofol for induction followed by halothane and nitrous for maintenance of anesthesia. Phase 2- administered a 2.5 mg/kg dose of propofol for induction followed by a continuous	Propofol levels in breastmilk were assessed 4 and 8 hours after birth in phase 1 and 4, 6, and 24 hours after birth in phase 2. .	After phase 1, the concentration of propofol in the colostrum was 0.17 mcg/ml at four hours and 0.14 mcg/ml at eight hours. After phase 2, the concentration of propofol in the colostrum was 0.54 mcg/ml at 4 hours, 0.036 mcg/ml at 6 hours, and 0.048 mcg/ml at 24 hours.	Because of the low concentration of propofol in the colostrum and the low bioavailability of propofol, the authors concluded that neonatal exposure of propofol is low.	III	A

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				infusion of propofol started at 0.5 mg/kg/hr and titrated to effect.					
Esener, Z., Sarihasan, B., Güven, H., & Ustün, E. (1992). Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum. *British journal of anaesthesia*, *69*(6), 586–588. https://doi.org/10.1093/bja/69.6.586	Collected and analyzed colostrum and blood from mothers who required general anesthesia for cesarean section.	Nonexperimental study	40 healthy pregnant women at term undergoing Cesarean section	Thiopentone 5 mg/kg OR Etomidate 0.3 mg/kg	Thiopental and etomidate levels were measured in maternal plasma, umbilical venous plasma, and colostrum	Mean concentrations of thiopentone in colostrum were 2 mcg/ml at 30 minutes, 0.91 mcg/ml at 2 hours, and 0.59 mcg/ml at 9 hours. Mean concentrations of etomidate in colostrum were 79 ng/ml at 30 minutes, 16 ng/ml at 2 hours, and undetectable at 4 hours. The M:P ratio of etomidate was 1.2 at 30 minutes after administration.	Colostrum concentrations declined rapidly for thiopentone and etomidate, but etomidate was much quicker. Both thiopentone and etomidate are safe for the nursing mother.	II	A
Dodd, S. E., Hunter Guevara, L. R., Datta, P., Rewers-Felkins, K., Baker, T., & Hale, T. W. (2021). Dexmedetomidine levels in breast milk: Analysis of breast milk expressed during and after awake craniotomy. *Breastfeeding Medicine*, *16*(11), 919–921. https://doi.org/10.1089/bfm.2021.0138	Collected breastmilk perioperatively and postoperatively from a single lactating mother receiving dexmedetomidine for awake craniotomy	Nonexperimental study	29 year old lactating woman who presented for an awake craniotomy 4 weeks post partum	Patient was sedated with 45 mcg of precedex and then placed on an infusion between 0.7-1 mcg/kg/hr.	Breastmilk was expressed and analyzed twice intraoperatively and twice postoperatively.	The concentration of precedex in the breastmilk was assessed in pg/ml. The highest concentration found both intraoperatively and postoperatively was 89 pg/ml.	Because a typical pediatric dose of precedex is 0.2-0.7 mcg/kg/hr, and the bioavailability of precedex is low, the amount present in the breastmilk is negligible in terms of neonatal effect.	III	C
Yoshimura, M., Kunisawa, T., Suno, M., Sugawara, A., Kurosawa, A., Nakanishi, R., Aoki, K., & Toriumi, T. (2017). Intravenous dexmedetomidine for cesarean delivery and its concentration in colostrum. *International Journal of Obstetric Anesthesia*, *32*, 28–32. https://doi.org/10.1016/j.ijoa.2017.05.002	Collected blood and breastmilk levels of precedex in patients undergoing cesarean section	Nonexperimental study	10 healthy parturients presenting for scheduled cesarean section between 18-40 years	After cord clamping 6 mcg/kg/hr of precedex was administered followed by 0.2-	Blood and colostrum precedex levels were collected at 6, 12, and 24 hours after precedex administration.	Six hours after administration, the median precedex concentration in colostrum was 12.3 pg/m, the median RID was 0.034%, and the	Maternal sedation using precedex is unlikely to harm the nursing infant.	III	B

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				0.7 mcg/kg/hr until peritoneal closure.		median M:P ratio was less than 1.			
Nakanishi, R., Yoshimura, M., Suno, M., Yamamoto, K., Ito, H., Uchimine, Y., Toriumi, T., Kurosawa, A., Sugawara, A., & Kunisawa, T. (2017). Detection of dexmedetomidine in human breast milk using liquid chromatography–tandem mass spectrometry: Application to a study of drug safety in breastfeeding after cesarean section. *Journal of Chromatography B*, *1040*, 208–213. https://doi.org/10.1016/j.jchromb.2016.11.015	Collected blood and breastmilk levels of precedex in patients undergoing cesarean section	Nonexperimental study	4 women between the ages of 24-40 presenting for cesarean section	After cord clamping 6 mcg/kg/hr of precedex was administered followed by 0.2-0.7 mcg/kg/hr until peritoneal closure.	Blood and colostrum levels of precedex were measured at 6 and 24 hours.	Six hours after administration, the average colostrum concentration of precedex was 15.1 pg/mL. The average M/P ratio was 0.62 and the average RID was 0.05%.	These findings indicate that using intraoperative precedex during cesarean sections is unlikely to harm the nursing infant.	III	C
Goma, H. M., Said, R. N., & El-Ela, A. M. (2008). Study of the newborn feeding behaviors and fentanyl concentration in colostrum after an analgesic dose of epidural and intravenous fentanyl in cesarean section. *Saudi medical journal*, *29*(5), 678–682.	Collected breastmilk levels of fentanyl in patients who received IV and epidural fentanyl	RCT	100 multiparas between the age of 25-35 who had breastfed before	50 patients received between 150-200 mcg of fentanyl in their epidural with bupivacaine 50 patients received a spinal and were administred 50 mcg of fentanyl IV after delivery	Colostrum fentanyl levels were measured 45 minutes and 24 hours after birth	At 45 minutes, there was an average of 0.4 ng/mL in the epidural fentanyl group and an average of 0.19 ng/mL in the IV fentanyl group.	Using IV or epidural fentanyl in the nursing mother has low risk of causing adverse effects.	I	A
Steer, P. L., Biddle, C. J., Marley, W. S., Lantz, R. K., & Sulik, P. L. (1992). Concentration of fentanyl in colostrum after an analgesic dose. *Canadian Journal of Anaesthesia*, *39*(3), 231–235. https://doi.org/10.1007/bf03008782	Collected blood and colostrum from patients who received fentanyl for a general anesthetic	Nonexperimental study	13 health women undergoing cesarean section of a postpartum tubal ligation	2 mcg/kg of fentanyl was administered to patients for induction in tubal ligation patients and after cord clamping for cesarean section patients	Serum and colostrum fentanyl concentrations were obtained at 45 minutes, 2 hours, 4 hours, 6 hours, 8 hours, and 10 hours after fentanyl administration.	The highest colostrum concentration was at 45 minutse, at a mean concentration of 0.4 ng/mL with a serum concentration of 0.19 ng/mL.	The amount of fentanyl that crosses into breastmilk after a typical dose used for general anesthesia is not likely to cause infant depression.	III	B

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Wittels, B., Scot, D. T., & Sinatra, R. S. (1990). Exogenous opioids in human breast milk and acute neonatal neurobehavior. *Anesthesiology*, *73*(5), 864–869. https://doi.org/10.1097/00000542-199011000-00012	Collected breastmilk samples from mothers who received meperidine or morphine for postoperative analgesia	Nonexperimental study	10 multigravida mother who were ASA I/II undergoing elective cesarean sections	Half of participants received a loading dose of opioid (1 mg/kg of meperidine or 0.1 mg/kg of morphine), then a intravenous PCA pump with a six minute lockout with either 12.5 mg of meperidine or 1-1.5 mg of morphine	Breastmilk specimens were obtained at 12, 24, 36, 48, 72, and 96 hours post partum. The authors calculated the concentration of meperidine, morphine, normeperidine, and morphine-3-glucuronide in the breastmilk. Additionally, the authors calculated the cumulative dose of meperidine and morphine.	The highest concentration of meperidine was an average of 1100 ng/mL at 2 hours after administration. The highest concentration of morphine was an average of 60 ng/mL 4 hours after administration.	Because concentrations of morphine-6-glucuronide (M6G) were not calculated, findings from this study must be interpreted with caution.	III	B
Wittels, B., Glosten, B., Faure, E. A., Moawad, A. H., Ismail, M., Hibbard, J., Senal, J. A., Cox, S. M., Blackman, S. C., Karl, L., & Thisted, R. A. (1997). Postcesarean analgesia with both epidural morphine and intravenous patient-controlled analgesia. *Anesthesia & Analgesia*, *85*(3), 600–606. https://doi.org/10.1097/00000539-199709000-00021	Used the Neonatal Behavioral Assessment Scale (NBAS) to assess infants of nursing and bottle-feeding mothers who received meperidine or morphine PCA	RCT	102 parturients who underwent cesarean section	Mothers received a PCA pump with a 6 minute lockout and dose of 12.5-15 mg of meperidine or 1-1.5 mg of morphine. Infants were either breast or bottle fed.	NBAS was used to assess infants for alertness and orientation to human cues	Nursing infants exposed to morphine were significantly more alert and oriented than infants who were exposed to meperidine and the bottle feeding group.	PCA morphine is superior to PCA meperidine in treatment of the nursing parturient	I	A
Baka, N.-E., Bayoumeu, F., Boutroy, M.-J., & Laxenaire, M.-C. (2002). Colostrum morphine concentrations during Postcesarean intravenous patient-controlled analgesia. Anesthesia & Analgesia, 94(1), 184–187. https://doi.org/10.1213/00000539-200201000-00035	Collected plasma and breastmilk samples from mothers who were on a morphine PCA after cesarean section	Nonexperimental study	7 ASA status I or II patients scheduled for cesarean section	Mothers received a 4 mg of morphine after delivery and 1 mg of morphine every 10 minutes until their visual analog scale score was less than 3. Then, a morphine PCA with a 10	Plasma and breastmilk concentrations of morphine and morphine-6-glucuronide were obtained.	The highest milk to plasma ratio for morphine was 0.62 and M6G was 2.73 at 12 hours. The highest mean morphine concentration in the breastmilk was 34 ng/mL at 0 hr. the highest mean	The amount of morphine and M6G in the breastmilk was minute.	III	B

Citation (Author, Year, Title, etc...)	Conceptual Framework (Theoretical basis for study)	Design/ Method	Sample/Setting (Number, Characteristics, Exclusions, Criteria, Attrition, etc...)	Major Variables; definitions (Independent variables; Dependent variables)	Outcome Measurement (What scales used – reliability information – alphas)	Data Analysis (What stats used?)	Findings (Statistical findings or qualitative findings)	Level of evidence	Quality of evidence
				minute lockout with a dose of 1 mg and max dose of 20 mg/4 hours		concentration of M6G was 672 ng/mL at 12 hours.			
Al-Tamimi, Y., Ilett, K. F., Paech, M. J., O'Halloran, S. J., & Hartmann, P. E. (2011). Estimation of infant dose and exposure to pethidine and norpethidine via breast milk following patient-controlled epidural pethidine for analgesia post caesarean delivery. International Journal of Obstetric Anesthesia, 20(2), 128–134. https://doi.org/10.1016/j.ijoa.2010.12.004	Collected plasma and breastmilk levels of pethidine and norpethidine from mothers who were on a meperidine PCA after cesarean section	Nonexperimental study	20 ASA status I or II patients scheduled for cesarean section at 37 weeks gestation or greater	Mothers had a pethidine PCA with a dose of 20 mg and lockout of 20 minutes	Plasma and breastmilk concentrations of pethidine and norpethidine were measured	The highest mean absolute dose of meperidine was 21 mcg/kg/day and of normeperidine was 22 mcg/kg/day.	As relative infant doses of meperidine are very low, this drug appears to be safe to administer to the lactating mother.	III	B
Borgatta, L., Jenny, R. W., Gruss, L., Ong, C., & Barad, D. (1997). Clinical significance of methohexital, meperidine, and diazepam in breast milk. The Journal of Clinical Pharmacology, 37(3), 186–192. https://doi.org/10.1002/j.1552-4604.1997.tb04780.x	Collected plasma and breastmilk levels of pethidine, methohexital, and diazepam of mothers who presented for a general anesthetic	Nonexperimental study	9 women who presented for tubal sterilization at least one month after birth	Mothers received 120-150 mg of methohexital, a dose of 25 mg of meperidine, and a dose of 0-10 mg of diazepam	Three sets of blood and milk samples were obtained from each woman	The highest methohexital concentration was 1 one hour after administration with a milk concentration of 407 ng/mL, with a calculated infant exposure index of 1-2%. The highest mean value of meperidine was 176 ng/mL, with a calculated infant exposure index between 0.5-1.7%. Diazepam levels did not exceed the lower limit of the reportable range at any time point in the study.	The amount of drug excreted in the breastmilk is not of clinical importance and does not warrant an interruption in breastfeeding.	III	B
Ilett, K. F., Paech, M. J., Page-Sharp, M., Sy, S. K., Kristensen, J. H., Goy, R., Chua, S., Christmas, T., & Scott, K. L. (2008). Use of a sparse sampling study	Collected plasma and breastmilk levels of tramadol and M1 of	Nonexperimental study	75 breastfeeding mothers who received oral	Mothers received 50-100 mg of	Plasma and breastmilk samples were obtained after	The relative infant dose of tramadol was 2.24% and M1 was	Administration of tramadol in the lactating mother is	III	A

Citation (Author, Year, Title, etc...)	Conceptual Framework (Theoretical basis for study)	Design/ Method	Sample/Setting (Number, Characteristics, Exclusions, Criteria, Attrition, etc...)	Major Variables; definitions (Independent variables; Dependent variables)	Outcome Measurement (What scales used – reliability information – alphas)	Data Analysis (What stats used?)	Findings (Statistical findings or qualitative findings)	Level of evidence	Quality of evidence
design to assess transfer of Tramadol and its O-desmethyl metabolite into transitional breast milk. British Journal of Clinical Pharmacology, 65(5), 661–666. https://doi.org/10.1111/j.1365-2125.2008.03117.x	mothers who received tramadol for analgesia after cesarean section		tramadol on days 2-4 after cesarean section	tramadol every 4-6 hours	the fourth administration of tramadol	0.64%, for a total relative infant dose of 2.88%.	unlikely to cause adverse effects in the infant.		
Salman, S., Sy, S. K., Ilett, K. F., Page-Sharp, M., & Paech, M. J. (2011). Population pharmacokinetic modeling of Tramadol and its O-desmethyl metabolite in plasma and breast milk. European Journal of Clinical Pharmacology, 67(9), 899–908. https://doi.org/10.1007/s00228-011-1023-6	Used Ilett et al.'s data set to create a pharmacokinetic model of tramadol and M1 in plasma and breastmilk	Nonexperimental study	75 breastfeeding mothers who received oral tramadol on days 2-4 after cesarean section	Mothers received 50-100 mg of tramadol every 4-6 hours	Plasma and breastmilk samples were obtained after the fourth administration of tramadol	Infants of ultra-slow metabolizers received an average relative dose of 3.07% and the infants of ultra-fast metabolizers received an average relative dose of 3.09%.	Administration of tramadol in the lactating mother is unlikely to cause adverse effects in the infant even if metabolism is altered.	III	A
Edwards, J. E., Rudy, A. C., Wermeling, D. P., Desai, N., & McNamara, P. J. (2003). Hydromorphone transfer into breast milk after intranasal administration. Pharmacotherapy, 23(2), 153–158. https://doi.org/10.1592/phco.23.2.153.32081	Collected plasma and breastmilk levels from lactating women who received intranasal dilaudid	Nonexperimental study	5 healthy, nonsmoking, lactating women between the ages of 24-32	Mothers received 2 mg of intranasal versed	Plasma and breastmilk samples were obtained 2, 4, 6, 8, 12, and 24 hours after administration.	The relative infant dose is 0.67%.	Administration of intranasal dilaudid is unlikely to cause adverse events in the infant.	III	B
Wolfson, P., Cole, R., Lynch, K., Yun, C., Wallach, J., Andries, J., & Whippo, M. (2021). The pharmacokinetics of ketamine in the breast milk of lactating women: Quantification of ketamine and metabolites. https://doi.org/10.22541/au.161325028.80476344/v1	Collected breastmilk from lactating women who received intramuscular ketamine	Nonexperimental study	4 healthy lactating women between the ages of 21-45	Mothers received 0.5 mg/kg and 1 mg/kg of IM ketamine separated by 5 days to 2 weeks	Breastmilk samples were obtained 0, 3, 6, 9, and 12 hours after administration.	The maximum amount transferred into breastmilk over 12 hours was 24 mcg of kertamime and 21 mcg of norketamine.	The relative infant dose of ketamine was less than 1%, indicating there is low likelihood of adverse effects in the nursing infant.	III	B
Dusci, L. J., Good, S. M., Hall, R. W., & Ilett, K. F. (1990). Excretion of diazepam and its metabolites in human milk during withdrawal from combination high dose diazepam and oxazepam. British Journal of Clinical Pharmacology, 29(1), 123–126. https://doi.org/10.1111/j.1365-2125.1990.tb03612.x	Collected breastmilk and plasma samples from a lactating woman going through withdrawal of diazepam and oxazepam. Infant plasma drug levels were also collected	Case Study	22 year old polydrug abuser with a 12 month old son	The mother was detoxed over 30 days with a taper of diazepam and oxazepam	Plasma and breastmilk samples were obtained from the mother on days 14, 15, 23, 25, 28, and 39. Plasma samples were obtained from the infant on days 14, 28, and 38.	The highest concentration of diazepam or metabolite throughout the study was 300 mcg/L of diazepam in the breastmilk on day 15. Diazepam was undetectable in infant plasma, however there were low	The amounts of diazepam and its metaboiites detected in the blood were minimal.	V	B

Citation (Author, Year, Title, etc...)	Conceptual Framework (Theoretical basis for study)	Design/ Method	Sample/Setting (Number, Characteristics, Exclusions, Criteria, Attrition, etc...)	Major Variables; definitions (Independent variables; Dependent variables)	Outcome Measurement (What scales used – reliability information – alphas)	Data Analysis (What stats used?)	Findings (Statistical findings or qualitative findings)	Level of evidence	Quality of evidence
						concentration of metabolites in infant plasma.			
Erkkola, R., & Kanto, J. (1972). Diazepam and breast-feeding. The Lancet, 299(7762), 1235–1236. https://doi.org/10.1016/s0140-6736(72)90954-3	Collected breastmilk, maternal plasma, and infant plasma levels after nursing mothers received diazepam	Nonexperimental study	3 postpartum nursing mothers	Mothers received 10 mg of diazepam three times a day for six days	Plasma and breastmilk concentrations were obtained on days 4 and 6	The highest maternal plasma and breastmilk concentration of both diazepam and n-methyl-diazepam were found on day six at a mean of 601 ng/mL and 483 ng/mL (plasma) and 78 ng/mL and 52 ng/mL (milk). The highest infant plasma concentrations were found on day four with 172 ng/mL of diazepam and 283 ng/mL of n-methyl-diazepam.	The authors concluded that diazepam should not be consumed by the nursing mother.	III	B
Koitabashi, T., Satoh, N., & Takino, Y. (1997). Intravenous midazolam passage into breast milk. Journal of Anesthesia, 11(3). https://doi.org/10.1007/s0054070110242	Maternal plasma and blood concentrations were measured after IV midazolam administration	Case Study	A 20 year old lactating woman presenting for laparoscopic cholecystectomy	6 mg of IV midazolam was administered for induction of general anesthesia	Plasma and breastmilk concentrations were measured 1, 2, 4, 6, and 24 hours after midazolam administration	The highest concentration of midazolam, 12 ng/mL, was found 1 hour after administration.	Midazolam is unlikely to cause adverse effects in the nursing infant	V	B
Matheson, I., Lunde, P. K., & Bredesen, J. E. (1990). Midazolam and nitrazepam in the Maternity Ward: Milk concentrations and clinical effects. British Journal of Clinical Pharmacology, 30(6), 787–793. https://doi.org/10.1111/j.1365-2125.1990.tb05443.x	Collected blood and breastmilk levels of mothers who received midazolam	Nonexperimental study	12 lactating women in a postpartum unit	15 mg of oral midazolam was administered as a sleep aid	Plasma and breastmilk concentrations were obtained 7 hours after administration for 6 days after birth	Average breastmilk concentrations of midazolam were 3.3 ng/mL	Midazolam is unlikely to cause adverse effects in the nursing infant	III	A

Citation (Author, Year, Title, etc...)	Conceptual Framework (Theoretical basis for study)	Design/ Method	Sample/Setting (Number, Characteristics, Exclusions, Criteria, Attrition, etc...)	Major Variables; definitions (Independent variables; Dependent variables)	Outcome Measurement (What scales used – reliability information – alphas)	Data Analysis (What stats used?)	Findings (Statistical findings or qualitative findings)	Level of evidence	Quality of evidence
Summerfield, R. J., & Nielsen, M. S. (1985). Excretion of Lorazepam into breast milk. British Journal of Anaesthesia, 57(10), 1042–1043. https://doi.org/10.1093/bja/57.10.1042-a	Collected blood and breastmilk levels of mothers who received lorazepam	Nonexperimental study	4 lactating women presenting for post-partum sterilization	3.5 mg of oral lorazepam was administered 2 hours before surgery	Plasma and breastmilk levels of lorazepam were measured 4 hours after administration	Participants had an average breastmilk concentration of 8.5 ng/mL.	The amount of lorazepam that crosses into breastmilk is very low, leading to minimal risk for the infant.	III	B
Whitelaw, A., Mcfadyen, I., & Cummings, A. (1981). Effect of maternal lorazepam on the Neonate. *BMJ*, *282*(6280), 1973–1974. https://doi.org/10.1136/bmj.282.6280.1973-c	Collected breastmilk from a postpartum mother who received lorazepam twice daily	Case study	A postpartum woman receiving lorazepam	2.5 mg of oral lorazepam was administered twice a day for five days	Breastmilk levels of lorazepam were measured on day five of treatment	The participant's breastmilk contained 12 ng/mL/.	If the infant consumed 200 mL/kg/day, the resulting infant dose would be 2.6 mg/kg/day, a negligible dose of lorazepam.	V	B
Madadi, P., Koren, G., Cairns, J., Chitayat, D., Gaedigk, A., Leeder, J. S., Teitelbaum, R., Karaskov, T., & Aleksa, K. (2007). Safety of codeine during breastfeeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. Canadian Family Physician Medecin de Famille Canadien, 53(1), 33–35 **********RETRACTED in 2021**********.	Analyzed the maternal breastmilk and postmortem blood concentrations of a infant who died from morphine overdose after maternal codeine use.	Case study	A newborn with unremarkable birth history expires on DOL 11	The mother of the infant took Tylenol 3 (codeine and acetaminophen) for postpartum pain control	Post mortem and frozen expressed breast milk morphine levels were obtained	Frozen breast milk contained 87 ng/mL of morphine and infant blood levels were 70 ng/mL	Because a therapeutic serum concentration of morpgine in an infant is ~10 ng/mL, authors concluded the infant died from morphine overdose	V	B
Zipursky, J., & Juurlink, D. N. (2020). The implausibility of neonatal opioid toxicity from breastfeeding. Clinical Pharmacology &Therapeutics, 108(5), 964–970. https://doi.org/10.1002/cpt.1882	Discusses the infant death from maternal opioid use in the "Toronto case"	Literature review	Reviewed articles describing neonatal depression or sedation from maternal codeine use	Na	Na	na	Although the results from the Toronto case are unexplainable using appropriate pharmacokinetic models, there are still multiple instances in the literature that indication maternal codeine use and cause neonatal sedation and depression. These symptoms typically resolve with the removal of codeine or withholding of breastmilk.	V	A

Citation (Author, Year, Title, etc...)	Conceptual Framework (Theoretical basis for study)	Design/ Method	Sample/Setting (Number, Characteristics, Exclusions, Criteria, Attrition, etc...)	Major Variables; definitions (Independent variables; Dependent variables)	Outcome Measurement (What scales used – reliability information – alphas)	Data Analysis (What stats used?)	Findings (Statistical findings or qualitative findings)	Level of evidence	Quality of evidence
Willmann, S., Edginton, A. N., Coboeken, K., Ahr, G., &Lippert, J. (2009). Risk to the breast-fed neonate from codeine treatment to the mother: A quantitative mechanistic modeling study. Clinical Pharmacology & Therapeutics, 86(6), 634–643. https://doi.org/10.1038/clpt.2009.151	Describes the development of a pharmacokinetic model to estimate morphine exposure and clearance in the nursing infant of a mother who takes codeine	Nonexperimental study	Created a PBPK model of both the mother and infant to determine metabolism and excretion of codeine and morphine	Na	Na	Na	Mother's codeine and morphine clearance and infant's morphine clearance are the most important determinant of morphine accumulation in the neonate. Additionally, CYP3A4 inhibitors inhibit the breakdown of codeine, leaving more available to convert to morphine. A worst case scenario of an ultra-rapid metabolizer mother with a codeine dose of 2.5 mg/kg/day, efficient morphine crossover into the breastmilk, and lack of neonatal elimination, the infant's morphine blood level would be 54 mcg/L, almost four times higher than the therapeutic dose.	III	A
Madadi, P., Ross, C. J. D., Hayden, M. R., Carleton, B. C., Gaedigk, A., Leeder, J. S., & Koren, G. (2008). Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: A case–control study. Clinical Pharmacology & Therapeutics, 85(1), 31–35. https://doi.org/10.1038/clpt.2008.157	Compare genetic characteristics of nursing mother and baby dyads that did or did not exhibit CNS depression after maternal codeine administration	Quasi-experimental study	72 mother-child pairs who were counseled by the MotherRisk program between 2004-2007 and were reachable by telephone	Infants who experienced CNS depression Infants who did not experience CNS depression Genotype	CNS depression was defined as parental reports of sedation or abnormal breathing in the infant.	Infants exhibiting signs of CNS depression while breastfeeding from a mother who has used codeine were compared to infants who did not exhibit CNS depression. Factors compared	Mothers of infants who were CNS depressed took significantly higher doses of codeine Mothers of symptomatic infants were 6x more likely to be CYP2D6 ultrametabolizers than	II	A

Citation (Author, Year, Title, etc...)	Conceptual Framework (Theoretical basis for study)	Design/ Method	Sample/Setting (Number, Characteristics, Exclusions, Criteria, Attrition, etc...)	Major Variables; definitions (Independent variables; Dependent variables)	Outcome Measurement (What scales used – reliability information – alphas)	Data Analysis (What stats used?)	Findings (Statistical findings or qualitative findings)	Level of evidence	Quality of evidence
						include: daily maternal codeine dose per kilo- gram body weight, and CYP2D6 and UGT2B7 genotype.	mothers of asymptomatic infants Because of accumulation of active metabolites, neonatal risk is increased with prolonged codeine use		
Juurlink, D. N., Gomes, T., Guttmann, A., Hellings, C., Sivilotti, M. L., Harvey, M.-A., & Mamdani, M. M. (2012). Postpartum maternal codeine therapy and the risk of adverse neonatal outcomes: A retrospective cohort study. Clinical Toxicology, 50(5), 390–395. https://doi.org/10.3109/15563650.2012.681052	Examined if postnatal maternal codeine consumption was associated with adverse neonatal outcomes	Retrospective cohort study	15608 Women living in Ontario, Canada between the years 1998-2008 who had singleton pregnancies and were greater than 16 years old	women who received a prescription for codeine within 7 days of discharge after childbirth women who did not receive a prescription for codeine after childbirth	Admission of the neonate to a hospital within 30 days Admission of the neonate for dehydration within 30 days Admission of the neonate for injury within 30 days Admission to the hospital via ambulance Hospitalization with resuscitation or assisted ventilation Death	There were no statistical differences in readmission, dehydration, injury, arrival by ambulance, or resuscitation between the two groups.	Children of mothers prescribed codeine were at no greater risk of adverse events than children of mothers who weren't prescribed codeine	II	A
Lam, J., Kelly, L., Ciszkowski, C., Landsmeer, M. L. A., Nauta, M., Carleton, B. C., Hayden, M. R., Madadi, P., & Koren, G. (2012). Central Nervous System Depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. The	Quantified incidence of CNS depression in neonates breastfed by mothers taking codeine, oxycodone, or Tylenol	Retrospective Cohort Study	533 breastfeeding mother infant pairs	Mothers taking codeine, oxycodone, or Tylenol	CNS depression Reversibility of CNS depression on cessation of	Infants of oxycodone consuming mothers had a 21% incidence of CNS depression	Both maternal codeine and oxycodone are related to increased CNS depression in the nursing infant	II	A

Citation (Author, Year, Title, etc...)	Conceptual Framework (Theoretical basis for study)	Design/ Method	Sample/Setting (Number, Characteristics, Exclusions, Criteria, Attrition, etc...)	Major Variables; definitions (Independent variables; Dependent variables)	Outcome Measurement (What scales used – reliability information – alphas)	Data Analysis (What stats used?)	Findings (Statistical findings or qualitative findings)	Level of evidence	Quality of evidence
Journal of Pediatrics, 160(1). https://doi.org/10.1016/j.jpeds.2011.06.050					breastfeeding or opioid usage	Infants of codeine consuming mothers had a 16% incidence of CNS depression. Infants of Tylenol consuming mothers had a 0.5% incidence of CNS depression. Almost all mothers reported resolution of symptoms with cessation of breastfeeding or opioid use			
Kelly, L. E., Chaudhry, S. A., Rieder, M. J., 't Jong, G., Moretti, M. E., Lausman, A., Ross, C., Berger, H., Carleton, B., Hayden, M. R., Madadi, P., & Koren, G. (2013). A clinical tool for reducing central nervous system depression among neonates exposed to codeine through breast milk. PLoS ONE, 8(7). https://doi.org/10.1371/journal.pone.0070073	Evaluated the effectiveness of breastfeeding guidelines for mothers taking codeine at improving neonatal safety	Nonexperimental study	237 breastfeeding women taking codeine after cesarean section	Mothers received guidelines for breastfeeding while taking codeine	Duration of codeine use Occurrence of neonatal sedation occurence of maternal adverse reactions	There was a 2% incidence of neonatal sedation Women who reported neonatal CNS depression were taking codeine for > 4 days Maternal adverse response did not correlate with sedation	Implementation of breastfeeding guidelines greatly increases the safety of codeine in the nursing mother	III	A
Wischnik, A., Manth, S. M., Lloyd, J., Bullingham, R., & Thompson, J. S. (1989). The excretion of Ketorolac tromethamine into breast milk after multiple oral dosing. *European Journal of Clinical Pharmacology*, *36*(5), 521–524. https://doi.org/10.1007/bf00558080	Establish the extent in which ketorolac is excreted into breastmilk	Nonexperimental study	10 postpartum women who required an analgesic and were abstaining from breastfeeding	Patient received 10 mg of oral ketorolac 4x a day for three days	Maternal plasma and Breastmilk concentrations were collected during the two dosing days and one day after	The maximum concentration in breastmilk detected was 7.9 ng/mL.	The risk of adverse events is low in neonates of mothers taking Toradol.	III	B

Citation (Author, Year, Title, etc...)	Conceptual Framework (Theoretical basis for study)	Design/ Method	Sample/Setting (Number, Characteristics, Exclusions, Criteria, Attrition, etc...)	Major Variables; definitions (Independent variables; Dependent variables)	Outcome Measurement (What scales used – reliability information – alphas)	Data Analysis (What stats used?)	Findings (Statistical findings or qualitative findings)	Level of evidence	Quality of evidence
					completion of medication regimen	The highest M:P ratio of ketorolac detected was 0.037 the infant may receive an adjusted daily dose of 0.4%of the maternal dose			
Bitzen, P.O., Gustafsson, B., Jostell, K. G., Melander, A., & Wahlin-Boll, E. (1981). Excretion of paracetamol in human breast milk. *European Journal of Clinical Pharmacology*, *20*(2), 123–125. https://doi.org/10.1007/bf00607148	Assess the amount of Tylenol into breastmilk of mothers who took oral tylenol	Nonexperimental study	3 lactating women who stopped breastfeeding	Women received one dose of 500 mg of oral acetaminophen	Maternal plasma and Breastmilk concentrations were measuared before medication administration and 2,4,6,8,10, and 12 hours after administration.	The maximum breastmilk concentration of Tylenol was found two hours after administration. The average concentration of Tylenol in breastmilk was 4.4 mcg/mL. The milk plasma ratio was 0.76.	The amount of Tylenol that crossed over into the breastmilk was negligible, not indicating a need for breastfeeding cessation while taking Tylenol.	III	B
Berlin, C. M., Jr, Yaffe, S. J., & Ragni, M. (1980). Disposition of acetaminophen in milk, saliva, and plasma of lactating women. Pediatric pharmacology (New York, N.Y.), 1(2), 135–141.	Assessed Tylenol concentrations in saliva, breastmilk, and plasma of nursing mothers.	Nonexperimental study	12 nursing mothers	Mothers received one dose of 650 mg of oral Tylenol	Saliva and milk concentrations of Tylenol were obtained at 0, 0.25, 0.5, 0.75, 1, 2, 3, 5, 8, 12, and 24 hours after maternal dosing.	Peak breastmilk concentration of 15 mcg/mL was found between 1-2 hours.	Tylenol used in usual analgesic dosing for the mother does not appear to increase risk to the breastfeeding infant.	III	B
Notarianni, L. J., Oldham, H. G., & Bennett, P. N. (1987). Passage of paracetamol into breast milk and its subsequent metabolism by the neonate. British journal of clinical pharmacology, 24(1), 63–67. https://doi.org/10.1111/j.1365-2125.1987.tb03137.x	Assessed Tylenol and metabolite concentrations in maternal plasma, breastmilk, and infant urine.	Nonexperimental study	4 nursing mother and baby pairs	Mothers received 1 gram of Tylenol by mouth	Blood and milk samples (all from the same breast) were obtained from the mother every 30 minutes for 3.5 hours. At the end of the 3.5 hours, the	The average peak Tylenol breastmilk concentration was 10.3 mcg/mL. The average Tylenol milk concentration was 6.1 mg/mL.	The amount of Tylenol received by the infant is negligible.	III	B

Citation (Author, Year, Title, etc...)	Conceptual Framework (Theoretical basis for study)	Design/ Method	Sample/Setting (Number, Characteristics, Exclusions, Criteria, Attrition, etc...)	Major Variables; definitions (Independent variables; Dependent variables)	Outcome Measurement (What scales used – reliability information – alphas)	Data Analysis (What stats used?)	Findings (Statistical findings or qualitative findings)	Level of evidence	Quality of evidence
					other breast was emptied into a different container and breastmilk concentration was assessed.				

****still need to fix level and quality of evidence for some articles*****

Appendix B

IRB Exemption Statement

Conversation between IRB Chair, Dr. Noam Shpancer and Dr. John Chovan, Department of Nursing Chair.

From: Shpancer, Noam <nshpancer@otterbein.edu>
Sent: Wednesday, October 13, 2021 9:44 AM
To: Chovan, John <jchovan@otterbein.edu>
Subject: Re: IRB and DNP Projects

John: The way I see it, a project is not subject to IRB review unless and until it collects data from human participants. So, I agree with you that these projects will not need IRB approval until someone decides to implement them for data collection, at which point that person may apply for IRB approval.

Thanks, Noam.
From: Chovan, John <jchovan@otterbein.edu>
Sent: Wednesday, October 13, 2021 9:10 AM
To: Shpancer, Noam <nshpancer@otterbein.edu>
Subject: IRB and DNP Projects

Good morning, Noam,

I could use some advice -- maybe a conversation -- about the Doctor of Nursing Practice final scholarly projects and submitting for IRB approval. The projects parameters from our accreditors for some of the projects have changed. The list of acceptable projects now includes the option of writing a plan for a project that is not implemented. So, it can effectively stop at the proposal stage, and then these projects can be available for a future student to implement if someone has that interest. I have at least two questions.

1. The IRB Guidelines states "Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." Most of these projects are not intended to develop or contribute to generalizable knowledge. They are clinical change projects that are intended to eventually change a clinical practice of health care professionals (humans) in one identified setting. They have the possibility of contributing to generalizable knowledge in that each would be an instance of a clinical change that, if implemented in other places by others, could eventually be generalized. But that is not the primary intent of the projects. Would they be considered research? I think they would not.

2. If indeed they are considered research and should be submitted for review by the IRB, at what point in the process should IRB approval be obtained? I would think that although implementation is not part of the initial project, review by IRB would be helpful to the original team in shaping their project plan. Yet if this proposal is not going to be implemented, then the approval to move forward would be moot. But if a second team eventually reads the proposal and wants to implement it, would they be the ones seeking IRB approval?

If you would prefer that we talk in real time, I am open to that. Or perhaps you could visit one of our faculty meetings for a discussion?

Thank you.

Best,

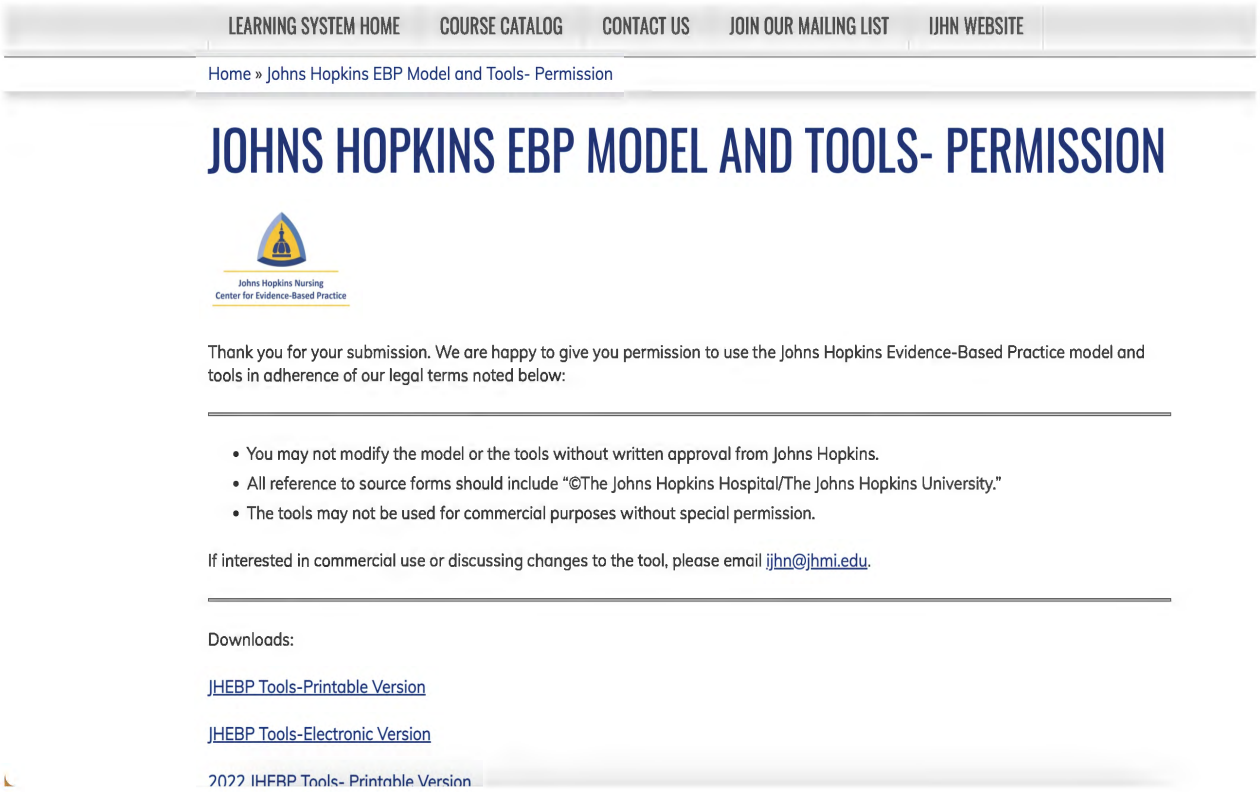
John

John D. Chovan, PhD, DNP, RN, CNP, CNS, PMHNP-BC
Associate Professor & Chair, Department of Nursing
Chief Nurse Administrator
Otterbein University

"A comprehensive institution with a strong liberal arts base"
jchovan@otterbein.edu; 614-823-1526, voice; he/him/his
"The world is starved for grace. If we are going to work at restoring fellowship and reaching people, we need grace now more than ever."
- Pastor John Swadley, Forest Park Baptist Church, Joplin, Missouri

Appendix C

JHNEBP Model Permission



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Johns Hopkins Nursing
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Downloads:

JHEBP Tools-Printable Version

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2022 JHEBP Tools- Printable Version

Appendix D

Breastfeeding After Maternal Anesthesia Knowledge and Confidence Assessment

1. In general, when is it safe for a mother to resume breastfeeding after surgery?
    a. Immediately
    b. Once she is awake and alert
    c. Four hours after extubation
    d. 24 hours after surgery
2. What induction medications are safe to use in the breastfeeding mother?
    a. Propofol
    b. Etomidate
    c. Ketamine
    d. Dexmedetomidine
    e. All of the above
3. Which medication is contraindicated for nursing mothers?
    a. Propofol
    b. Midazolam
    c. Codeine
    d. Toradol
4. What medication has inadequate evidence for the use in lactating mothers?
    a. Hydromorphone
    b. Fentanyl
    c. Acetaminophen
    d. Etomidate
5. In general, how long should breastfeeding women “pump and dump” after anesthesia?
    a. 24 hours
    b. 36 hours
    c. 12 hours
    d. Pumping and dumping is unnecessary for most anesthetics
6. Which opioid is safest for use in the lactating mother?
    a. Fentanyl
    b. Codeine
    c. Tramadol
    d. Meperidine
7. Which benzodiazepine should be administered with caution in the nursing mother?
    a. Diazepam
    b. Lorazepam
    c. Midazolam
8. What non-opioid analgesic is safe to use in the nursing mother?
    a. Acetaminophen
    b. Ketorolac
    c. All of the above
9. What types of medications are the most dangerous for the nursing mother?

    a. Pro-drugs
    b. Active drugs
10. What online resource has the most up to date resources detailing medication safety in the lactating mother?
    a. Lactmed
    b. Google
    c. UpToDate
    d. WebMD
11. How would you rate your confidence in providing postoperative breastfeeding recommendations to the lactating mother?
    a. Excellent
    b. Above Average
    c. Average
    d. Below Average
    e. Poor