Original Research

Bupivacaine Pharmacokinetics and Breast Milk Excretion of Liposomal Bupivacaine Administered After Cesarean Birth

Hiba J. Mustafa, MD, Henry L. Wong, PhD, Mahmoud Al-Kofahi, DDS, PhD, Malinda Schaefer, MD PhD, Ashwin Karanam, PharmD, and Michael M. Todd, MD

OBJECTIVE: To evaluate bupivacaine concentrations in maternal plasma and transfer into breast milk in women undergoing liposomal bupivacaine infiltration in the transversus abdominis plane after cesarean birth.

METHODS: Prospective cohort study of healthy pregnant women who underwent cesarean birth at term followed by a transversus abdominis plane block using 52 mg bupivacaine hydrochloride 0.25% (20 mL) and 266 mg liposomal bupivacaine 1.3% (20 mL). Simultaneous blood and milk samples were collected in a staggered fashion, three to four samples per patient at the following timepoints after block administration: 2, 6, 12, 24, 48, 72, and 96 hours. Quantification of bupivacaine was performed by liquid chromatography-tandem mass spectrometry. Neonatal drug exposure was modeled by calculating milk/plasma area under the curve (AUC) ratios, neonatal dosage, and relative neonatal dosage of bupivacaine at each sampling time.

RESULTS: Thirty patients were enrolled. Concentrations in breast milk peaked at 6 hours (mean 58 ng/mL), followed by constant and steady decline to low levels at 96 hours (mean 5.2 ng/mL). Maternal plasma concentrations had two peaks, first at 6 hours (mean 155.9 ng/mL) and then at 48 hours (mean 225.8 ng/mL), followed by steady decline. Milk/plasma AUC₀-₉₆ ratios ranged between AUC₀-₂ of 0.45 (80% CI 0.38–0.52) and AUC₀-₉₆ of 0.15 (80% CI 0.14–0.17). Neonatal dosage ranged between a mean of 355.9 ng/kg at 0–2 hours and a mean of 15,155.4 ng/kg at 0–96 hours. Relative neonatal dosage was less than 1% at all time intervals. No serious adverse reactions occurred in any neonate.

CONCLUSION: Bupivacaine is excreted in breast milk after local infiltration of liposomal bupivacaine and bupivacaine hydrochloride mixture into transversus abdominis plane blocks after cesarean birth. Relative neonatal dosages of less than 1% (less than 10% is considered to be unlikely to be of clinical concern) suggest minimal risks for breastfeeding healthy, term neonates after the administration of this combination of local anesthetics to mothers.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT03526419.

(REPRINTED) OBSTETRICS & GYNECOLOGY Vol. 136, No. 1, July 2020 (C) 2020 The Author(s). Published by Wolters Kluwer Health, Inc. This article is a U.S. Government Work. All rights reserved.

Effective pain management after cesarean birth promotes enhanced recovery, earlier patient mobilization, shorter time spent in postoperative care units, and reduced costs. Untreated postpartum pain is associated with a risk of greater opioid use, postpartum depression, and development of persistent pain that may lead to chronic opioid use and misuse disorder (White K, Bou Zgheib N, Mitchell B. Decreasing narcotic use after cesarean section with enhanced recovery: a quality improvement project [28D] [abstract]. Obstet Gynecol 2018;131:48S.) In
For decades bupivacaine has been used in obstetrics and nerve block procedures, but a major limitation is the relatively short duration of action (typically less than 8 hours). Analgesia with liposomal bupivacaine on the other hand may be maintained for up to 96 hours after a single intraoperative administration into the surgical wound. Liposomal bupivacaine infiltration has been shown to significantly reduce postsurgical pain and opioid consumption for up to 72–96 hours when administered through either local wound infiltration or using a transversus abdominis plane block in various procedures (Ang MJ, Silkiss RZ. The use of long-acting liposomal bupivacaine [Exparel] for postoperative pain control following enucleation or evisceration [letter]. Ophthalmic Plast Reconstr Surg 2018;34:599.). However, the clinical use of liposomal bupivacaine in patients undergoing cesarean birth has not been widespread for possible few reasons. First, efficacy has not been thoroughly investigated. Another reason could be cost, given the expense of liposomal bupivacaine. The last reason may be the lack of clinical data concerning breast milk transfer and neonatal safety. Therefore, in this study we evaluated bupivacaine concentrations in plasma and milk samples and modelled transfer to breast milk after liposomal bupivacaine transversus abdominis plane infiltration in low risk pregnant patients undergoing scheduled term cesarean birth.

**METHODS**

We conducted a prospective cohort study. Institutional review board approval for this study was obtained from the University of Minnesota (STUDY00003258), and written informed consent was obtained for all participants. Recruitment occurred at the University of Minnesota Medical Center Women’s Health Clinics and labor and delivery unit between March 2019 and October 2019. Participants were required to be American Society of Anesthesiologists physical status I or II, aged 18–40 years, with singleton uncomplicated full-term (37–42 weeks of gestation) pregnancies undergoing elective cesarean birth, planning to breastfeed, and considering postoperative transversus abdominis plane block for pain control. Exclusion criteria included obstetric complications (fetal anomaly, fetal growth restriction, hypertensive disorders of pregnancy, gestational diabetes, Rh incompatibility or congenital malformations), and maternal conditions including cardiac, renal, metabolic disorders, allergy or sensitivity to local anesthetics and use of medications known to affect the metabolism of bupivacaine. Maternal blood samples were collected at the day of the surgery before the cesarean birth procedure and considered to be time-point zero. Breast milk samples were not collected preoperatively. The study was designed in concordance with the 2019 U.S. Food and Drug Administration draft guidance.

All aspects of anesthetic and obstetric care were according to hospital routine. A spinal anesthetic was performed with 150 micrograms morphine (eg, Duramorph) combined with 1.4–1.6 mL of 0.75% hyperbaric bupivacaine hydrochloride plus 15 micrograms intrathecal fentanyl. Within 30 minutes after the completion of the cesarean birth, all patients received a bilateral transversus abdominis plane blocks under ultrasound guidance performed using 52 mg bupivacaine hydrochloride 0.25% (20 mL) and 266 mg liposomal bupivacaine 1.3% (20 mL).

Simultaneously, 1 mL of blood and breast milk samples were collected at 2, 6, 12, 24, 48, 72, and 96 hours after the transversus abdominis plane block administration. Collection was done in the hospital during hospital stay and by a home-visit nurse after discharge. Participants were instructed to express the milk through pumping or hand expression, to mix the collected milk, and to remove 1 mL for the research study after expression. Maternal blood samples were centrifuged after collection and plasma was extracted. Both plasma and milk samples were stored at −20 °C until analyses.

Sparse sampling technique was used in which participants were randomly assigned to one of two groups. In the group that received an odd code, paired blood and milk samples were obtained at 2, 12, and 48 hours. In the group that received an even code, paired samples were obtained at 6, 24, 72, and 96 hours.

Quantification of bupivacaine in the collected blood and milk samples was performed by liquid chromatography–tandem mass spectrometry, which was performed using a Quattro Ultima triple quadrupole mass spectrometer coupled with a Waters Acquity Ultra Performance Liquid Chromatography system. Limit of quantification was determined empirically by standard methods and found to be 0.7 ng/mL. Sample analysis was performed using MassLynx 4.1 software.

Our primary objectives were to evaluate bupivacaine concentrations in plasma and milk samples and to model bupivacaine transfer to breast milk and...
neonates by calculating milk/plasma area under the curve (AUC) ratios, neonatal dosage, and relative neonatal dosage using the below formulae. The safety analysis included adverse events in all neonates of participating mothers from the time of informed consent through the study safety follow-up period (up to day 14 postpartum). While in the hospital, adverse events were monitored through chart review; while at home, a follow-up phone call was conducted at day 14 postpartum. During the call, the neonates’ mothers were given the opportunity to report adverse events spontaneously, and a general prompt using open-ended questions was used. Neonatal adverse events of interest included central nervous system, gastrointestinal, respiratory, rash, seizures, and any reported hospital readmissions. No related maternal adverse events occurred with the administration. A total of 102 paired blood and milk samples were collected for the study. Reported adverse events (related or unrelated or both) were transient tachypnea of the newborn in two neonates (Table 1).

Bupivacaine was detected in all plasma and milk samples except for samples obtained before transversus abdominis plane block administration (Fig. 1). Concentrations in breast milk peaked at 6 hours (mean 58 ng/mL) followed by constant and steady decline to low almost undetectable levels at 96 hours (mean 5.2 ng/mL, Fig. 2). Maternal plasma concentrations had two peaks, first at 6 hours (mean 155.9 ng/mL) and then at 48 hours (mean 225.8 ng/mL) followed by steady decline (Fig. 2 and Table 2). Mean milk concentrations were measured at 44%, 36%, 28%, and 18% of mean plasma concentration at 2, 6, 12, and 24 hours, respectively, after liposomal bupivacaine infiltration (Table 2). Time intervals were 0-t (Table 3) and reflect bupivacaine exposure in plasma, breast milk, and milk/plasma ratios over that period of time, for example, milk/plasma AUC_{0-72} of 0.17 reflects the ratio over the period of 3 days. The estimated milk/plasma AUC ratios ranged between AUC_{0-2} of 0.45 (80% CI 0.38–0.52) and AUC_{0-96} of 0.15 (80% CI 0.14–0.17) (Table 3). The estimated neonatal dosage ranged between a mean of 355.9 at 0–2 hours and a mean of 15,155.4 ng/kg at 0–96 hours (Table 4). Relative neonatal dosage was less than 1% at all time intervals (Table 4).

**RESULTS**

Between March 2019 and October 2019, a total of 30 healthy participants were enrolled (Table 1). All intended paired samples were obtained as planned except for one mother in the odd code group owing to low milk supply and the neonate’s requiring milk supplementation. A total of 102 paired blood and milk samples were collected for the study. Reported adverse events (related or unrelated or both) were transient tachypnea of the newborn in two neonates (Table 1).

**DISCUSSION**

We evaluated breast milk transfer of bupivacaine after liposomal bupivacaine infiltration in transversus abdominis plane in patients undergoing cesarean birth. Bupivacaine was detected in breast milk shortly after infiltration and peaked at 6 hours, with a mean concentration of 58 ng/mL, which was 36% of mean plasma concentration at that time-point. Milk levels decreased slowly over the next 4 days to almost undetectable levels. Bupivacaine was transferred into...
mother’s milk such that an exclusively breastfeeding neonate would ingest less than 1% (relative neonatal dosage) of the maternal dose. None of the neonates of the enrolled mothers had clinically significant adverse events within the study follow up period, which was 14 days postpartum.

Prior reports have evaluated the transfer of the standard racemic bupivacaine into breast milk with reported milk/plasma AUC$_{0-12}$ of 0.34 with no reported calculated neonatal dosage or relative neonatal dosage.$^{29,35}$ However standard bupivacaine has a relatively short duration of action up to 8 hours if used for wound infiltration.$^{36}$ Liposomal bupivacaine plasma pharmacokinetics have been well established by prior studies.$^{15}$ In our study, plasma kinetics were consistent with those reports indicating a bimodal release profile with first peak within few hours and second between 12 and 36 hours of liposomal bupivacaine local infiltration. Although not systematically sought in our study, it is unknown whether systemic plasma

| Table 1. Patient Characteristics |
|---------------------------------|
| Mothers (n=30) Value            |
| Age (y)                         | 33 (21–40) |
| Parity                          |            |
| Nulliparous                     | 3 (10)     |
| Multiparous                     | 27 (90)    |
| Ethnicity                       |            |
| Caucasian                       | 16 (53)    |
| Black                           | 7 (23)     |
| Latina                          | 4 (13)     |
| Asian                           | 3 (10)     |
| Measurements at delivery        |            |
| Weight (kg)                     | 81.9 (60–132) |
| Height (cm)                     | 163 (152–167) |
| BMI category at delivery        |            |
| Underweight                     | 0 (0.0)    |
| Normal                          | 3 (10)     |
| Overweight                      | 14 (47)    |
| Obese                           | 13 (43)    |
| Gestational age at delivery (wk)| 39.2 (37.42) |
| Cesarean birth                  |            |
| Primary                         | 3 (10)     |
| Repeat                          | 27 (90)    |
| Neonates (n=30)                 |            |
| Sex                             |            |
| Male                            | 15 (50)    |
| Female                          | 15 (50)    |
| Birth weight (g)                | 3,480 (2,900–5,190) |
| Age of milk intake start (d)    | 1 (1–1)    |
| Required supplementing with      | 1 (3)      |
| formula or donor milk           |            |
| Length of hospital stay (d)     | 3 (3–4)    |
| Weight change at discharge (%)  | 6 (2–11)   |
| Neonates with related or unrelated AEs | 2 (7)* |
| Required hospital readmission within follow-up period | 0 (0.0) |

BMI, body mass index; AE, adverse event. Data are median (range) or n (%).

* Both admissions were for transient tachypnea of the newborn.
concentrations of bupivacaine correlate with local efficacy, despite evidence suggesting analgesia up to 72 hours after single dose local infiltration as compared with bupivacaine hydrochloride or placebo. By obtaining plasma samples, we were able to calculate milk/plasma AUC_0-t ratios, which ranged between 0.3 at day 1 and 0.15 at day 4 postinfiltration. These ratios indicate that very little plasma bupivacaine is transferred into breast milk and that bupivacaine does not accumulate in breast milk.

Passage of drugs into breast milk primarily occurs through passive diffusion in proportion to the drug’s concentration in maternal plasma, although this passage depends on different factors including lipophilicity, protein binding, molecular weight, and pKa. Our calculated milk/plasma AUC_0-t ratios correlate well with bupivacaine’s protein binding characteristics of 85–95%. Calculated neonatal dosage values ranged between a mean of 355.9 ng/kg at 0–2 hours and 15,155.4 ng/kg at 0–96 hours. As explained above, these time intervals reflect drug exposure in breast milk over that time period. Neonatal dosage was calculated based on the average daily milk intake of 150 mL/kg/d in an exclusively breastfed neonate. Milk intake varies with age of the neonates and among patients. Nevertheless, the value of 150 mL/kg/d is well established in the pharmacokinetic literature and provides a standard by which drugs can be compared with each other. Once neonatal dosage is calculated, it can be compared with the standard neonatal or infant dosage for the drug, if it is known. However, to circumvent the problem caused by a lack of known neonatal and infant dosages for many maternal drugs, the World Health Organization Working Group and others proposed calculation of relative neonatal dosage as we have done.

Relative neonatal dosage calculations have some pitfalls, which include the effect of variations in administered medications dosages, postnatal age, and milk volume. However, it is generally well accepted as a measure of safety of medication use during breastfeeding. Relative neonatal dosage is classified into acceptable if less than 10% of maternal dosage, caution if 10–25% of maternal dosage, and unacceptable if greater than 25% of maternal dosage. In our study, values were all less than 1% at all time intervals. Because bupivacaine is metabolized primarily in the liver, a neonate’s absorption will likely be even lower given the first-pass effect.

The use of liposomal bupivacaine in transversus abdominis plane block after cesarean birth provides a promising alternative in controlling pain and reducing opioid use, which will further reduce nausea, vomiting, delayed mobilization, and bowel

| Time Interval (h) | Milk AUC (ng-h/mL) | Plasma AUC (ng-h/mL) | Milk/Plasma Ratio |
|------------------|--------------------|----------------------|------------------|
| 0–2              | 56.9 (41.5–78.2)   | 126.9 (108.1–149.1) | 0.45 (0.38–0.52) |
| 0–6              | 286.8 (227.2–365.4)| 692.5 (581.1–825.6)| 0.41 (0.39–0.44)|
| 0–12             | 580.4 (477.3–711)  | 1,571.9 (1,339–1,848)| 0.37 (0.36–0.38)|
| 0–24             | 1,004.5 (819–1,237.4)| 3,396.4 (2,909–3,973)| 0.30 (0.28–0.31)|
| 0–48             | 1,643.1 (1,331.5–2,033.2)| 8,107.6 (6,945–9,478.2)| 0.20 (0.19–0.21)|
| 0–72             | 2,137.3 (1,685.4–2,732.5)| 12,777.9 (10,959.5–14,916.3)| 0.17 (0.15–0.18)|
| 0–96             | 2,424.9 (1,866.9–3,188.3)| 15,706.2 (13,176.7–18,865.9)| 0.15 (0.14–0.17)|

AUC, area under the curve.

Data are geometric mean (80% CI).
malfunction, all of which can improve enhanced recovery after surgery. However, studies evaluating the clinical benefit of liposomal bupivacaine incisional infiltration in patients undergoing cesarean birth had conflicting results. Although a retrospective case–control study of 80 patients showed significant reduction in postoperative opioid use, a prospective single-blind randomized controlled trial of 80 participants showed no significant differences in opioid use or pain scores in the first 48 hours postoperatively. More clinical data are needed on the benefit of its clinical use.

We acknowledge the limitations to our study, including that no mothers of preterm neonates were enrolled given that such analysis would have been outside the scope of this study. Drug effect on milk supply was not assessed in our study given the complexity of factors affecting breast milk supply including medical, obstetric, physiologic, and psychosocial. However, in our study only one mother was assessed for low milk supply for which the newborn received milk supplementation.

In conclusion, our study findings suggest that, after liposomal bupivacaine infiltration, the level of bupivacaine ingested by the sucking neonate is acceptable and compatible with breastfeeding.

REFERENCES

1. Sutton CD, Carvalho B. Optimal pain management after cesarean delivery. Anesthesiol Clin 2017;35:107–24.
2. Lavand’homme P. Postoperative cesarean pain: real but is it preventable? Curr Opin Anaesthesiol 2018;31:262–7.
3. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of postoperative pain: a clinical practice guideline from the American society of Anesthesiologists’ committee on regional anesthesia, executive committee, and administrative council. J Pain 2016;17:131–57.
4. Ituk U, Habib AS. Enhanced recovery after cesarean delivery. F1000Res 2018;7:F1000Res.
5. Gadsden J, Hart S, Santos AC. Post-cesarean delivery analgesia. Anesth Analg 2005;101:S62–9.
6. Garimella V, Cellini C. Postoperative pain control. Clin Colon Rectal Surg 2013;26:191–6.
7. Eisenach JC, Pan PH, Smiley R, Lavand’homme P, Landau R, Houle T. Severity of acute pain after childbirth, but not type of delivery, predicts persistent pain and postpartum depression. Pain 2008;140:87–94.
8. Postpartum pain management. ACOG Committee Opinion No. 742. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e35–43.
9. Jirasiritham S, Tantivitayatan K, Jirasiritham S. Perianal blockage with 0.5% bupivacaine for postoperative pain relief in hemorrhoidectomy. J Med Assoc Thai 2004;87:560–4.
10. Chester JF, Stanford BJ, Gazet JC. Analgesic benefit of locally injected bupivacaine after hemorrhoidectomy. Dis Colon Rectum 1990;33:487–9.
11. Moiniche S, Keleti H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology 2002;96:725–41.
12. Bramlett K, Onel E, Viscusi ER, Jones K. A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in hemmorhoidal surgery. Dis Colon Rectum 2011;54:1552–9.
13. Gorfine SR, Onel E, Patou G, Krivokapic ZV. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy in total knee arthroplasty. Knee 2012;19:530–6.
14. Smoot JD, Bergese SD, Onel E, Williams HT, Hedden W. The efficacy and safety of DepoFoam bupivacaine in patients undergoing bilateral, cosmetic, submuscular augmentation mammoplasty: a randomized, double-blind, active-control study. Aesthet Surg J 2012;32:69–76.
15. Hu D, Onel E, Singla N, Kramer WG, Hadzic A. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. Clin Drug Invest 2013;33:109–15.
16. Hutchins J, Argenta P, Berg A, Habeck J, Kaizer J, Geller MA. Ultrasound-guided subcostal transversus abdominis plane block with liposomal bupivacaine compared to bupivacaine infiltration for patients undergoing robotic-assisted and laparoscopic hysterectomy: a prospective randomized study. J Pain Res 2019;12:2087–94.
17. Hutchins J, Delaney D, Vogel RJ, Ghebrey RG, Downs LS, Carson L, et al. Ultrasound guided subcostal transversus abdominis plane (TAP) infiltration with liposomal bupivacaine

Table 4. Neonatal Daily Dose and Relative Neonatal Dose

| Time Interval (h) | Neonatal Dosage (ng/kg) (80% CI) | Relative Neonatal Dosage (%) (80% CI) |
|------------------|----------------------------------|--------------------------------------|
| 0–2             | 355.9 (259.1–488.9)              | 0.009 (0.006–0.013)                  |
| 0–6             | 1,792.4 (1,419.1–2,283.9)        | 0.047 (0.035–0.062)                  |
| 0–12            | 3,627.6 (2,983.2–4,443.7)        | 0.095 (0.074–0.121)                  |
| 0–24            | 6,278.1 (5,118.5–7,733.9)        | 0.164 (0.128–0.211)                  |
| 0–48            | 10,269.4 (8,321.9–12,707.6)      | 0.268 (0.208–0.347)                  |
| 0–72            | 13,357.9 (10,533.7–17,077.8)     | 0.349 (0.263–0.467)                  |
| 0–96            | 15,155.4 (11,667.9–19,926.8)     | 0.396 (0.291–0.545)                  |

Data are geometric mean (80% CI). Neonatal dosage (ng/kg) calculated using the formula: AUC0–t, milk (ng/h/mL)/t (h)×average milk volume ingested within t period (mL/kg). Average milk volume ingested in 24 hours: 150 mL/kg. Relative neonatal dose (%) was calculated using the formula: neonatal dosage (ng/kg)/maternal dosage (ng/kg)×100%.
for patients undergoing robotic assisted hysterectomy: a prospective randomized controlled study. Gynecol Oncol 2015; 138:609–13.
18. Baker BW, Villadiego LG, Lake YN, Amin Y, Timmins AE, Swain LS, et al. Transversus abdominis plane block with liposomal bupivacaine for pain control after cesarean delivery: a retrospective chart review. J Pain Res 2018;11:3109–16.
19. Brusko GD, Kolcun JPG, Heger JA, Levi AD, Manzano GR, Madhavan K, et al. Reductions in length of stay, narcotics use, and pain following implementation of an enhanced recovery after surgery program for 1- to 3-level lumbar fusion surgery. Neurosurg Focus 2019;46:E4.
20. Gasanova I, Alexander JC, Estrella K, Wells J, Sunna M, Minhajuddin A, et al. Ultrasound-guided suprainguinal fascia iliaca compartment block versus periauricular infiltration for pain management after total hip arthroplasty: a randomized controlled trial. Reg Anesth Pain Med 2019;44:206–11.
21. Hyland SJ, Deliberato DG, Fada RA, Romanelli MJ, Collins CL, Wasielewski RC. Liposomal bupivacaine versus standard periarticular injection in total knee arthroplasty with regional anesthesia: a prospective randomized controlled trial. J Arthroplasty 2019;34:488–94.
22. Iwanoff C, Salamon C. Liposomal bupivacaine versus bupivacaine hydrochloride with lidocaine during midurethral sling placement: a randomized controlled trial. J Minim Invasive Gynecol 2018;26:1133–8.
23. Burnett A, Faley B, Nyirienda T, Bamboat ZM. Liposomal bupivacaine reduces narcotic use and time to flatus in a retrospective cohort of patients who underwent laparotomy. Int J Surg 2018;59:55–60.
24. US Food and Drug Administration. Clinical lactation studies: considerations for study design guidance for industry. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-lactation-studies-considerations-study-design. Retrieved April 18, 2020.
25. Armbruster DA, Pry T. Limit of blank, limit of detection and limit of quantitation. Clin Biochem Rev 2008;29(suppl 1):S49–52.
26. Armbruster DA, Tillman MD, Hubbs LM. Limit of detection (LOD)/limit of quantitation (LOQ): comparison of the empirical and the statistical methods exemplified with GC-MS assays of abused drugs. Clin Chem 1994;40:1233–8.
27. Portillo J, Kumar N, Melibary S, Quevedo E, Bergese S. Safety of liposome extended-release bupivacaine for postoperative pain control. Front Pharmacol 2014;5:90.
28. Bolat E, Bestas A, Bayar MK, Ozcan S, Erhan OL, Ustundag B. Evaluation of levobupivacaine passage to breast milk following epidural anesthesia for cesarean delivery. Int J Obstet Anesth 2014;23:217–21.
29. Ortega1 D, Viviani X, Lorec AM, Gameire M, Martin C, Bruguerolle B. Excretion of lidocaine and bupivacaine in breast milk following epidural anesthesia for cesarean delivery. Acta Anaesthesiologica Scand 1999;43:394–7.
30. Anderson PO, Sauberan JB. Modeling drug passage into human milk. Clin Pharmacol Ther 2016;100;42–52.
31. Neville MC, Keller R, Seacat J, Lutes V, Neifert M, Casey C, et al. Studies in human lactation: milk volumes in lactating women during the onset of lactation and full lactation. Am J Clin Nutr 1988;48:1375–86.
32. Begg EJ, Duffull SB, Hackett LP, Ilett KF. Studying drugs in human milk: time to unify the approach. J Hum Lact 2002;18:323–32.
33. Atkinson HC, Begg EJ, Darlow BA. Drugs in human milk. Clinical pharmacokinetic considerations. Clin Pharmacokinet 1988;14:217–40.
34. Bennett PN, editor. Drugs and human lactation. 2nd ed. Amsterdam, The Netherlands: Elsevier; 1996.
35. Baker PA, Schroeder D. Interpleural bupivacaine for postoperative pain during lactation. Anesth Analg 1989;69:400–2.
36. Bethea JW Clinical anesthesia, 6th edition. Anesthes 2010;112:767–8.
37. Thomas J, Long G, Moore G, Morgan D. Plasma protein binding and placental transfer of bupivacaine. Clin Pharmacol Ther 1976;19:426–34.
38. Tsen LC, Tarshis J, Denson DD, Osaathanondh R, Datta S, Bader AM. Measurements of maternal protein binding of bupivacaine throughout pregnancy. Anesth Analg 1999;89:965–8.
39. Wulf H, Winckler K, Maier C, Heinzow B. Pharmacokinetics and protein binding of bupivacaine in postoperative epidural analgesia. Acta Anaesthesiol Scand 1988;32:530–4.
40. Anderson PO, Valdès V. Variation of milk intake over time: clinical and pharmacokinetic implications. Breastfeed Med 2015;10:142–4.
41. Committee on Gynecologic Practice. ACOG Committee Opinion No. 750. Perioperative Pathways: Enhanced Recovery After Surgery [published correction appears in Obstet Gynecol. 2019 Jun;133(6):1288] [published correction appears in Obstet Gynecol. 2019 Nov;134(5):1121]. Obstet Gynecol. 2018;132(3):e120–e130.
42. Parikh P, Sunesara I, Singh Multani S, Patterson B, Lutz E, Martin JN. Intra-incisional liposomal bupivacaine and its impact on postcesarean analgesia: a retrospective study. J Matern Fetal Neonatal Med 2019;32:966–70.
43. Prabhu M, Clapp MA, McQuaid-Hanson E, Ona S, O’Donnell T, James K, et al. Liposomal bupivacaine block at the time of cesarean delivery to decrease postoperative pain: a randomized controlled trial. Obstet Gynecol 2018;132:70–8.

Authors’ Data Sharing Statement
Will individual participant data be available (including data dictionaries)? No.
What data in particular will be shared? Not available.
What other documents will be available? Not available.
When will data be available (start and end dates)? Not applicable.
By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? Not applicable.

PEER REVIEW HISTORY
Received January 24, 2020. Received in revised form March 4, 2020. Accepted March 12, 2020. Peer reviews and author correspondence are available at http://links.lww.com/AOG/B878.