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Enhanced Recovery for Cesarean Deliveries in the United States: Perspectives From the Front Lines – Part 1

Approximately 1.2 million women undergo cesarean delivery in the United States each year, accounting for 32% of all births.¹ Cesarean delivery can be associated with moderate to severe postsurgical pain, which is caused by a complex combination of nerve ending trauma and inflammation.^{2,3} This pain may contribute to suboptimal bonding between mother and infant, a delay in recovery, ongoing pain, and challenges with breastfeeding.² Therefore, for this patient population, it is critical to effectively manage pain and improve postoperative recovery, which has the potential to improve mother-infant bonding, breastfeeding, and even postpartum depression.⁴ To address this need, Enhanced Recovery after Surgery (ERAS) protocols are being developed and implemented in the postsurgical environment.⁵ Although cesarean delivery is one of the most prevalent abdominal surgeries globally, no randomized trials on ERAS for cesarean birth have been completed and published in the United States,⁴ and ERAS society guidelines on cesarean delivery were not released until 2018. These guidelines have supported standardized care processes and have increased access to data that demonstrate the value of advancing ERAS. Because obstetrics is one of the most recent disciplines to adopt ERAS protocols, obstetricians, gynecologists, and obstetric anesthesiologists are encouraged to explore and implement these protocols now to support improved results for their patients.⁴

The protocols for post-cesarean delivery pain management involve multimodal analgesia to reduce patient exposure to opioids.⁵ Opioid minimization is of great importance. Opioid use after childbirth may be linked to a hindered ability of the mother to safely increase mobility (thereby potentially increasing her risk for thromboembolism) and to attend to the daily activities of infant care. In addition, infants of mothers who receive opioid-based pain medication and who breastfeed may experience drowsiness or potential toxicity.³ Opioid use is also associated with a higher risk of serious opioid-related events, according to a 2020 retrospective study that reviewed 209,215 births to opioid-naïve women (N = 161,318) enrolled in Tennessee Medicaid between January 1, 2007, and August 20, 2014. Of the 64,438 cesarean delivery births included in the study, 91% of the women who underwent such deliveries filled at least 1 opioid prescription. Serious opioid-related events were identified in 4582 women; 69.1% of these events were associated with persistent use, which was defined as receiving a supply of opioids for more than 90 days within 180 days following surgery, with no more than 30-day breaks in supply (postpartum exposure prescriptions were not included).⁶ Persistent use has also been noted as a concern by the American College of Obstetricians and Gynecologists (ACOG), which estimates that 1 of every

300 patients who receives opioids following cesarean delivery becomes an ongoing user.⁷

Women undergoing surgery often have concerns about opioids. Results from a recent survey of 500 women aged 30 to 50 years who received orthopedic, soft tissue, or obstetrics and gynecology-related surgery demonstrated that 84% of women were concerned about being prescribed or taking opioids, with the highest concerns related to the physical effects and potential dependence or addiction. Despite this concern, 67% of the women consumed an opioid after their surgery.⁸ Regarding women's concerns about opioids, it may be beneficial to implement enhanced recovery protocols for cesarean delivery that involve either reduced or no opioid use and discuss nonopioid options available to women having surgery.

Enhanced Recovery after Surgery and Multimodal Pain Management: A Call to Action

The recently published ERAS society guidelines for cesarean delivery have increased access to data on improving and standardizing perioperative care for this patient population.⁴ ERAS involves patient-centered, evidence-based, multidisciplinary care to help reduce the stress response following surgery and to optimize recovery.⁵ The multimodal analgesia approach followed in ERAS can include either systemic opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), or acetaminophen; a local anesthetic; epidural or intrathecal opioids; and transversus abdominis plane (TAP) block or local wound infiltration.² Combining medications and analgesia techniques may result in greater pain relief following cesarean delivery than that of opioids alone, diminished opioid use, and the potential for reduced overall episode-of-care costs.^{2,5}

It may be beneficial to implement enhanced recovery protocols for cesarean delivery that involve either reduced or no opioid use and discuss nonopioid options available to women having surgery.

The multimodal analgesia approach is supported by guideline recommendations for postpartum pain management. ACOG states that although neuraxial opioids can provide substantial anesthesia following cesarean delivery, their effects wane over time, which warrants implementation of additional pain management therapies.⁷ In addition to recommending standard oral and parenteral analgesic therapies such as acetaminophen and NSAIDs, ACOG guidelines state that pain may also be effectively

managed with local anesthetics administered via wound infiltration or TAP block following cesarean delivery. Although limitations can be experienced with many of these local anesthetics because of a short duration of action, some options (such as bupivacaine liposome injectable suspension [EXPAREL]) exhibit long-lasting pain management effects for the first few days following surgery.⁹ If opioids are prescribed, ACOG recommends limiting their use to the briefest duration possible and counseling for women at risk of central nervous system depression for both the woman and her infant, if breastfed.⁷

The Society for Obstetric Anesthesia and Perinatology also recommends multimodal analgesia following delivery to help reduce in-hospital and postdischarge opioid use, potentially diminishing opioid-related adverse effects (AEs; eg, nausea, vomiting, sedation, constipation, misuse) by 30% to 50%. Their recommendations include mention of regional block or peripheral nerve block and continuous wound infiltration.¹⁰ An example of how these recommended local/regional analgesia techniques can be effective is with long-lasting nonopioid EXPAREL, or liposomal bupivacaine.¹¹

ERAS protocols can be applied easily to all cesarean births, including unplanned or emergency deliveries, regardless of whether cesarean birth is the chosen approach to delivery. Therefore, ERAS protocols are appropriate for all patients undergoing cesarean delivery. With demonstrated success in other surgical specialties, ERAS should be widely implemented for postpartum care.⁴

EXPAREL® (bupivacaine liposome injectable suspension)

EXPAREL is a suspension composed of multivesicular liposomes carrying bupivacaine that offers a long-lasting, nonopioid option for local and regional postsurgical pain control.^{2,11} EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks. It can be administered by anesthesiologists as a regional field or interfascial plane block, such as a TAP block, or by surgeons as a direct infiltration in the surgical area.¹¹

EXPAREL has been shown to be safe and efficacious in multimodal approaches for pain management following cesarean delivery. In addition, EXPAREL has decreased opioid use in the in-hospital, outpatient, and after-discharge settings across a variety of women's health procedures. These outcomes were demonstrated in the results of a single-center, retrospective study of patients who underwent a cesarean delivery between 2012 and 2015 (N = 201); 111 of these patients had previously delivered by cesarean birth. All patients received a multimodal pain management protocol, which included intrathecal morphine and supplemental analgesics, and 101 of these patients also received EXPAREL via a TAP block as part of the protocol. Efficacy end points included opioid consumption overall and following surgery; the number of patients who consumed no opioids; area under the curve (AUC) of numeric rating scale pain intensity scores during the 3 days

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following surgery; the times to discharge readiness from the postanesthesia care unit; time to ambulation, to intake of solid food, and to bowel movement; discharge readiness and location; and hospital length of stay.²

Study results indicated that patients who received EXPAREL experienced significantly reduced mean times to ambulation (39%, $P < .001$) and solid foods (31%, $P = .008$), and a 26% mean time reduction to first bowel movement ($P = .05$). In addition, they had significantly shorter mean times for duration of hospital stay (2.9 vs 3.9 days; $P < .001$), discharge readiness (2.9 vs 3.6 days; $P = .006$), and postanesthesia care unit readiness (138 vs 163 minutes; $P = .028$). EXPAREL use resulted in a 46% improvement in AUC pain scores overall and a 44% improvement in AUC of numeric rating scale pain scores on day 3 following cesarean delivery ($P < .001$). EXPAREL use was also associated with a significantly reduced consumption of opioids following cesarean delivery (47% reduction for all patients, 54% for first cesarean delivery, 42% for repeat cesarean delivery; $P < .001$ for each group).^{*} A significantly higher number of patients who received EXPAREL consumed no opioids post cesarean delivery compared with those who did not (12% vs 3%; $P = .017$).²

AEs occurred less frequently in the group who received EXPAREL than in the multimodal-alone group (33.7% vs 49.5%; $P = .026$). Opioid-related AEs, including nausea, pruritus, vomiting, and abdominal pain, were experienced by 43 patients in the EXPAREL group and 76 in the multimodal-alone group.²

Similar results regarding opioid reduction with EXPAREL were achieved in a randomized, controlled, double-blind, prospective study on EXPAREL vs bupivacaine hydrochloride (HCl) in patients at least 18 years of age undergoing elective cesarean deliveries (N = 186). Patients were randomized to receive either EXPAREL or bupivacaine HCl, administered following cesarean delivery through a bilateral, 2-point classic TAP block. All patients received

spinal anesthesia with morphine and bupivacaine. The multimodal postsurgery treatment approach also included acetaminophen and ibuprofen administered up to 72 hours post surgery or until discharge. The primary end point was total opioid use following cesarean delivery through 72 hours. Secondary end points included opioid use following cesarean delivery through 24 hours, 48 hours, 1 week, and 2 weeks, AUC of visual analog scale pain intensity scores through 72 hours, and the percentage of patients following cesarean delivery who were "opioid spared." This was the percentage of patients who took less than or equal to 10 mg of oxycodone (15-mg morphine equivalent dose) and graded their bother or stress from the following opioid-related AEs as "not at all": vomiting, itching, sweating, freezing, and dizziness.¹

Through 72 hours, patients in the EXPAREL group experienced a 52% reduction in total postsurgical opioid consumption vs bupivacaine HCl (least squares mean [LSM] morphine equivalent dosing [MED], 15.5 mg vs 32.0 mg).^{*} This group also experienced a statistically significant reduction at 48 hours (LSM MED, 9.1 mg vs 20.5 mg; $P = .010$) and 7 days (LSM MED, 23.3 mg vs 45.8 mg; $P = .018$). At 2 weeks, opioid reduction trended toward statistical significance, with a 41% reduction in opioid use (LSM, 28.2 vs 47.8 mg, respectively; $P = .054$). Fifty-four percent of women in the EXPAREL group were spared opioid use through 72 hours versus 25% in the bupivacaine arm (53.5% vs 24.7%; $P = .001$).¹

Conclusions

Guideline recommendations for a multimodal pain management approach after cesarean delivery can be implemented with ERAS protocols that include long-lasting, nonopioid therapies such as EXPAREL. Evidence indicates that ERAS protocols that include EXPAREL may help effectively manage post-cesarean delivery pain vs ERAS protocols alone, which in turn may help improve postpartum outcomes, including recovery from surgery.² EXPAREL can also help address concerns about opioid use, given the opioid reduction and opioid-sparing results of recent studies in cesarean delivery.^{3,6} In addition, given concerns around breastfeeding after surgery, results from a recently published study demonstrated that bupivacaine excreted in breast milk following use of liposomal bupivacaine and bupivacaine hydrochloride admixture after cesarean delivery resulted in a relative neonatal dose that was excreted at less than 1%, which is considered minimal risk for breastfeeding healthy full-term neonates.¹² ERAS protocols for cesarean delivery that include EXPAREL may help minimize opioid consumption and improve recovery after delivery vs a multimodal protocol alone, for the immediate postsurgical period and into the early postpartum period, affecting women's overall recovery and return to normal activities of daily living.¹ ■

^{*}The clinical benefit of the decrease in opioid consumption was not demonstrated in the pivotal trials.

Editors from *Contemporary OB/GYN*[®] spoke with Elizabeth Cherot, MD, MBA, FACOG, obstetrician-gynecologist and chief medical officer at Axia Women's Health in Voorhees Township, New Jersey, and Cynthia English, DO, FACOG, an obstetrician-gynecologist practicing at Fort Worth Obstetrics & Gynecology in Fort Worth, Texas, to learn about their experiences with enhanced recovery protocols for cesarean deliveries in the United States, including multimodal pain management and the use of EXPAREL[®] (bupivacaine liposome injectable suspension).

Disclosure: Both Dr Cherot and Dr English have a consulting relationship with Pacira Pharmaceuticals, Inc., the manufacturer of EXPAREL.

Contemporary OB/GYN[®]: Can you explain why pain management is important for procedures such as cesarean delivery?



Cherot: [Pain management] comes to mind for every obstetrician and gynecologist because pain can have lasting effects on patients both mentally and physically as they recover. Patients should be comfortable enough

to be able to move and take care of themselves, but without experiencing a lot of adverse effects (AEs).

Cesarean delivery presents an ideal situation for enhanced recovery after surgery (ERAS) programs because the focus is on getting patients home sooner and having them recover better. In 2016, we started a pilot program of ERAS at our institution and now it is standard in my particular hospital as well as at a few other hospitals in our area. I have not written a prescription for an opioid in a long time because of the ERAS pathways at our institution. It has been eye-opening to see that with these protocols, we can make some real differences in people's lives.



English: As obstetricians, we are always thinking about how to get patients back to normal functioning and lessen the physical and mental stress of cesarean delivery. Multimodal pain management is a key component.

ERAS protocols allow patients to potentially avoid many of the AEs of opioids, while supporting them in their recovery. In my experience, when patients are able to resume their normal activity without fear or worry of severe pain or AEs of medications, they recover faster, bond well with their infant, and are more satisfied with their experience.

Contemporary OB/GYN[®]: Can you describe your ERAS program and the pain management options that are available through a multimodal approach?

Cherot: Enhanced recovery is, at a fundamental level, a standardized pathway, which emphasizes outcomes with improved patient engagement, information, and some autonomy. It improves patient outcomes and increases patient satisfaction. Multimodal pain management is a [major] component of ERAS and

involves addressing pain from different levels. It is multidisciplinary.⁵ Partnering with anesthesia is important. Anesthesiologists and obstetricians must work together to ensure patients have a better recovery experience. Selecting an obstetrician champion and an anesthesia champion for multimodal pain management at your institution will help the program to be effective. Nursing also needs to be your partner because they are going to be the face of the program.

We have patients drink a carbohydrate load the night before surgery and allow them to consume clear liquids up to 2 hours prior to surgery. When they come into the hospital, they will have also taken some preoperative medications that can help with food digestion. We also give them warm fluid and they are placed on a warmer in the operating room. This is to ensure that the pH of their stomach [will not] drop.

Anesthesiologists place [the epidural], which blocks the nerves from the middle of the abdomen, down, and then the obstetrician can perform either a local infiltration into the incision, as one would for numbing medication in a dental procedure. For example, a regional analgesic approach, such as local infiltration with liposomal bupivacaine (EXPAREL)¹¹ is used to provide long-lasting nonopioid pain control. Nerve pathways are blocked distally rather than centrally and then a nonsteroidal or a narcotic could be administered intravenously. Multiple pathways are used to get to the pain. As a result, less systemic narcotic or opioids are used. With an epidural, [physicians] can add a small amount of opioid, such as a morphine injection, which is not systemically absorbed. As a result, we have seen a reduction in the first 48 hours of narcotic use. The opioid reduction alone was reason enough for us to continue to use the long-acting liposomal bupivacaine.

[After surgery] we allow patients to eat sooner [than before] and we remove the catheter sooner. [Normally, we] would leave a catheter in for 24 hours after surgery; however, at our hospital we have not done that [practice] since 2016. In addition, we encourage patients to get up and move not long after surgery. Mobilization is important to avoid blood clots and [muscle] atrophy. We discuss mobilization with patients via a digital app that is used by Axia Women's Health prior to surgery as well, explaining to them that although they may feel uncomfortable, moving is part of the recovery process.

Through a process of shared decision-making, we explain the protocol to our patients and discuss options

for pain management. One of the most important elements of ERAS that we found was engaging with patients about the program starting at 36 weeks. We take them through a process, [using] an app to deliver the information. The app delivers timely information to patients to educate them, not only [about] where to park at the hospital, but also what they need to do to prep for surgery and what information they need to know. They can educate themselves by reading information about the process and provide them with the milestones that we are hoping they are going to be able to hit, and when.

Many patients know what opioids are, but they may not know that they can cause drowsiness, constipation, itching, nausea, and vomiting. With ERAS protocols, nonopioid medications, such as acetaminophen and ibuprofen, are the go-to medications immediately post OP [operative], which was a big change for a lot of physicians. The first medication given to the patient normally lasts for 6 hours and then next medication is given 3 hours before it runs out. I call this a shingle effect of overlapping these medications, so most patients do not require extra pain relief in that first 24-hour period. This is something that is very novel in the past few years.

English: Similar to Dr Cherot, I agree that ERAS is a fundamental pathway that emphasizes outcomes with improved patient engagement. Two years ago, my partners and I piloted an ERAS and multimodal pain management for cesarean delivery program in conjunction with the anesthesia department and the nursing leadership and staff. [We found that] education is key to a successful program. Patients are engaged in the early stages of their pregnancy to identify pain control concerns, past experiences with surgery, and any barriers they may have encountered. We work on [mitigating] modifiable risks that may impact their pregnancy and recovery. Most patients research pain control options that are available during labor, but they have minimal insight into post-OP pain medications [that are available] aside from opioids.

Addressing the concerns of patients who have had prior cesarean deliveries and had poor experiences with pain control is a first step for alleviating anxiety. We focus on how we are going to do things differently [for this delivery] and how we are going to assist them to have an improved recovery.

Patients are informed that there are different types of pain [after surgery] and are shown how these types of pain will be addressed. Some additional options that are provided include heat packs, ice packs, and abdominal binders. Knowing that there are many alternatives [for pain management] helps patients so that they do not feel that they are going to be at the mercy of the pain.

Our approach has been that pre-OP, the night before surgery, patients take oral acetaminophen, and this is repeated 1 hour before surgery. During surgery, our institution uses neuraxial anesthesia without long-acting opioids. Long-acting, nonopioid EXPAREL® (bupivacaine liposome injectable suspension) is used for local infiltration.¹¹ Because we do not utilize intrathecal morphine nor have the

ability to perform transversus abdominis plane (TAP) blocks, to provide additional postsurgical pain control beyond the spinal anesthesia, long-acting liposomal bupivacaine has substantially changed our practice and helped to provide pain control postoperatively.

Oral acetaminophen is then alternated with intravenous or oral nonsteroidal anti-inflammatory drugs, with 1 medication being administered every 3 hours so patients always have a baseline level of pain [management]. We then build on this foundation. We use oral opioids on an as-needed basis for breakthrough pain and advise patients that we are trying to minimize their use to maximize [the patient's] function and have the best post-OP experience.

Contemporary OB/GYN®: Anecdotally, what impact has a multimodal pain management and enhanced recovery program had on women and their recovery?

Cherot: The biggest outcome we saw at our hospital was that not only have we had a reduction in our opioid use [but] the majority of our patients go home with no narcotic at all. If I do have to write a prescription [for an opioid], it is for a small amount (eg, 5 tablets).

Patients have been engaged in the process, actively participating, and in my experience, after surgery they are ambulating and are ready to go home. To my knowledge, hospital stays also were reduced and the cost savings on that was meaningful.

In doing this, it has had a major impact in all our practices across Axia [Women's Health]. Patients come tell us great things about their recovery. Their anecdotal stories comparing their first cesarean delivery [without multimodal] to their second relay that their recovery was substantially different, for the better.

English: When we considered multimodal pain management [as part of ERAS], we had concerns about decreasing opioid exposure while still optimizing pain control. ERAS, multimodal pain management, and incorporating EXPAREL intraoperatively have made this possible. We have been amazed at the results. Our patients are ambulatory, without a [Foley] catheter, and tolerating a regular diet, 6 to 8 hours after surgery. To my knowledge, this has decreased our length of stay, reduced our opioid use [both in and out of the hospital], and improved the experience of our patients. Patients are happy to share their [birth] experience and many leave [the hospital] using minimal to no opioids after surgery.

Contemporary OB/GYN®: What is the next evolution of enhanced recovery? What should providers expect?

English: I want to see more widespread implementation and standardization across specialties. I would encourage my colleagues to research multimodal pain management and ERAS and find their physician and nursing champions in this endeavor. I think they would be amazed at the results they could get for their patients and the enhancement in pain control. ■

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Indication

EXPAREL® (bupivacaine liposome injectable suspension) is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks.

The infiltration indication includes regional field or interfascial plane blocks such as, but not limited to Transversus Abdominis Plane (TAP) block, Pectoralis (PEC) and Serratus plane blocks, Erector Spinae Plane (ESP) block, Thoraco-Lumbar Interscalene Plane (TLIP) block, interspace between the Popliteal Artery and Capsule of the Posterior Knee (iPACK), and Quadratus Lumborum (QL) block.

Important Safety Information

- EXPAREL is contraindicated in obstetrical paracervical block anesthesia
- Adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via infiltration were nausea, constipation, and vomiting; adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via interscalene brachial plexus nerve block were nausea, pyrexia, and constipation
- If EXPAREL and other non-bupivacaine local anesthetics, including lidocaine, are administered at the same site, there may be an immediate release of bupivacaine from EXPAREL. Therefore, EXPAREL may be administered to the same site 20 minutes after injecting lidocaine
- EXPAREL is not recommended to be used in the following patient population: patients <18 years old and/or pregnant patients
- Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease

Warnings and Precautions Specific to EXPAREL

- Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL
- EXPAREL is not recommended for the following types or routes of administration: epidural, intrathecal, regional nerve blocks **other than interscalene brachial plexus nerve block**, or intravascular or intra-articular use
- The potential sensory and/or motor loss with EXPAREL is temporary and varies in degree and duration depending on the site of injection and dosage administered and may last for up to 5 days, as seen in clinical trials

Warnings and Precautions for Bupivacaine-Containing Products

- **Central Nervous System (CNS) Reactions:** There have been reports of adverse neurologic reactions with the use of local anesthetics. These include persistent anesthesia and paresthesia. CNS reactions are characterized by excitation and/or depression
- **Cardiovascular System Reactions:** Toxic blood concentrations depress cardiac conductivity and excitability which may lead to dysrhythmias, sometimes leading to death
- **Allergic Reactions:** Allergic-type reactions (eg, anaphylaxis and angioedema) are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients
- **Chondrolysis:** There have been reports of chondrolysis (mostly in the shoulder joint) following intra-articular infusion of local anesthetics, which is an unapproved use
- **Methemoglobinemia:** Cases of methemoglobinemia have been reported with local anesthetic use

Please refer to full **Prescribing Information**, which is available at www.EXPAREL.com.