Perioperative pain management strategies among women having reproductive surgeries

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This review presents opioid-sparing strategies for perioperative pain management among women undergoing reproductive surgeries and procedures. Recommendations are provided regarding the use of nonsteroidal anti-inflammatory drugs, acetaminophen, other adjunctive medications, and regional anesthetic blocks. Additional considerations for chronic opioid users or patients using opioid replacement or antagonist therapy are discussed. (Fertil Steril® 2017;108:200–6. ©2017 by American Society for Reproductive Medicine.)

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Women undergoing procedures or surgeries related to infertility experience pain, which is often treated with opioid medication. This creates some important clinical considerations. For patients who are opioid naive, exposure to these addictive medications may be a trigger for persistent use. Data from reproductive procedures are limited, but recent data suggest that opioid exposure after other surgeries confers an increased risk for chronic opioid use (1, 2). For women who are taking chronic opioids or opioid replacement therapy, tolerance to opioids has the potential to make pain management more difficult. Likewise, women who have a history of an opioid use disorder may wish to avoid opioid medications, given concerns about the potential relapse. For these reasons it is important for all patients, but particularly those with a history of opioid use disorder or dependence, to optimize the treatment of pain in the perioperative period with non-opioid analgesics. In this review we present evidence-based strategies for non-opioid perioperative pain management demonstrated to improve postoperative pain scores and/or decrease consumption of opioids, and provide recommendations for implementation following common reproductive surgeries and procedures.

NON-OPIOID ANALGESICS

A variety of non-opioid analgesics are available, which can be used as part of a multimodal analgesic regimen to reduce the need for opioid analgesics. The two most commonly used classes of non-opioid analgesics are nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Gabapentinoids are also becoming an increasingly popular component of multimodal analgesia and are now included in many enhanced recovery after surgery protocols (3–5).

Nonsteroidal anti-inflammatory drugs inhibit cyclooxygenase (COX) enzymes to prevent the metabolism of arachidonic acid released from damaged tissue to prostaglandins, which in turn lowers the pain threshold in peripheral nociceptors (6). These medications can be administered preoperatively, intraoperatively, or postoperatively. Preoperative administration of NSAIDs may be beneficial as a preemptive analgesic. They have been demonstrated to improve pain control for many surgical procedures. Though there is a theoretical concern owing to their effect on platelet function, evidence suggests that the use of NSAIDs generally does not increase the risk for periprocedural bleeding (7, 8).

Evidence regarding preoperative NSAIDs use in reproductive surgeries or infertility-related procedures is limited. Among women having combined

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outpatient hysteroscopy–laparoscopy for infertility under general anesthesia, preoperative naproxen administration resulted in lower postoperative pain scores, shorter time to discharge, and less need for postoperative pain medications (9). In contrast, administration of preoperative diclofenac for outpatient hysteroscopy alone did not demonstrate improved pain scores during or after the procedure (10, 11). Although more work needs to be done to determine the exact role of preoperative NSAID administration in reproductive surgeries, it is reasonable to administer NSAIDs either preoperatively or intraoperatively for most patients given the favorable safety profile.

For postoperative patients, data suggest NSAIDs result in a 20%–40% reduction in opioid consumption over the first 24 hours after a variety of major and minor surgical procedures (12). There is no proven benefit of IV over oral NSAIDs, and no comparative efficacy data exist to drive selection of specific NSAIDs (13, 14). There are also currently no high-quality data specifically demonstrating the impact of postoperative NSAIDs on opioid consumption after reproductive surgeries. However, it is likely that the findings showing benefit in other surgical populations are relevant to these procedures.

Perioperative/periprocedural NSAIDs have traditionally been avoided during fertility treatment, given concerns about COX inhibition on pregnancy implantation (15, 16), but the importance of this has recently been questioned. In a retrospective cohort study of women undergoing oocyte retrieval for a planned fresh transfer cycle, a third of whom received postprocedure IV ketorolac, there were no differences in pregnancy rates or live birth rates, and postoperative pain scores were significantly lower among women who received ketorolac (17). No prospective or randomized, controlled trial data are available. Until better evidence accumulates it may be prudent to avoid NSAIDs in association with oocyte retrieval with a planned fresh transfer cycle.

Acetaminophen, or paracetamol, likely functions via central COX enzyme inhibition and central serotonergic activation, although the mechanism of analgesia is incompletely understood (18, 19). The addition of acetaminophen to opioid-based postoperative pain management results in a reduction in opioid consumption of 20%–40% over the first 24 hours after various major and minor surgical procedures (12, 20–23). Whether efficacy of acetaminophen differs by route of administration is controversial: although some studies suggest benefit to IV acetaminophen (24), the majority of studies have not shown any significant benefit to the administration of IV over oral acetaminophen in decreasing opioid use (25–27). There are also currently no high-quality data specifically demonstrating the impact of postoperative acetaminophen on opioid consumption after reproductive/gynecologic surgery, but it is likely that the benefits observed for other surgeries will translate.

The mechanism of action of gabapentinoids is complex and occurs along several pathways. The suspected pathway for pain modulation is via calcium channel–dependent inhibition of synaptic neurotransmitter release, which results in peripheral blocking of pain due to tissue injury (28, 29). A meta-analysis among women undergoing total abdominal hysterectomy has demonstrated decreased opioid consumption and decreased pain scores for the first 24 hours after surgery with preoperative gabapentin (30). Preoperative gabapentin or pregabalin has also been shown to significantly decrease postlaparoscopy shoulder pain in women undergoing laparoscopic gynecologic surgery (31, 32). The use of gabapentinoids should be considered in patients undergoing major reproductive/gynecologic surgeries, particularly patients at high risk for difficult-to-control postoperative pain.

No randomized trial directly compares the relative opioid-sparing effects of acetaminophen, NSAIDs, and gabapentinoids. A network meta-analysis comparing non-opioid analgesics after major surgery has demonstrated decreased opioid consumption over the first 24 hours after surgery with both acetaminophen and NSAIDs, with a mean reduction in IV morphine equivalents of 6 mg for acetaminophen and 10 mg for NSAIDs, with no statistically significant difference between these drugs (33). The combination of analgesics with different mechanisms of action results in even greater pain relief. Acetaminophen and ibuprofen co-administration yield a number needed to treat of 1.5–1.6 to effect 50% pain relief (23, 34). Taken together, the data suggest that women should be routinely treated with acetaminophen and NSAIDs, and potentially with the addition of a gabapentinoid provided no contraindication exists.

Misoprostol, used to facilitate cervical dilation, has been suggested as another adjunctive analgesic option for patients undergoing intrauterine procedures, particularly in the outpatient setting. However, a recent systematic review and meta-analysis investigating the impact of preoperative misoprostol on intraoperative pain during outpatient hysteroscopy demonstrated no clinically meaningful improvement in pain over placebo (35). Other trials comparing preoperative misoprostol with lidocaine cervical spray or NSAIDs also showed no superior benefit for pain management (11, 36, 37). A single trial that examined the preoperative administration of misoprostol well before (8–12 hours) outpatient hysteroscopy did show benefit in reducing intraoperative pain, perhaps suggesting the importance of timing of administration (38). However, given the side effect profile of a single dose of misoprostol (nausea, vomiting, diarrhea, abdominal cramping, fever (39, 40)) and the limited data suggesting benefit, this medication should probably not be used routinely for patients undergoing these procedures in the outpatient setting.

REGIONAL ANESTHETIC BLOCKS

Regional blocks with local anesthetics can serve the role of the primary intraoperative anesthetic, with or without sedation, or of adjunctive postoperative pain control. Depending on the approach (vaginal, laparoscopic, or abdominal), procedure under consideration (oocyte retrieval, hysteroscopy, dilation and curettage, hysterectomy), and patient characteristics (pain history or risks of conscious sedation or general anesthesia), regional blocks may be considered. The neuraxial approach with epidural anesthesia can be used for postoperative pain control for major open surgeries. A full review of the use of neuraxial anesthesia is out of the scope of this review, and we focus on other regional anesthetic blocks that may be useful in reproductive surgeries.

Incisional Blocks

Incisional blocks constitute single-dose or continuous infiltration of local anesthetic at the surgical incision site. The choice of local anesthetic, and whether epinephrine is added to prolong the duration of anesthesia, is provider dependent. Incisional blocks with longer-acting anesthetics such as bupivacaine or ropivacaine have been demonstrated to result in improvement in postoperative pain in most, but not all, trials and meta-analyses of various surgical procedures, and no high-quality data exist specifically for gynecologic procedures (41–43). A new liposomal formulation of bupivacaine has been created with the goal of providing long-acting local pain control. In a study of women undergoing abdominal hysterectomy randomized to transversus abdominis plane blocks with short-acting bupivacaine vs. surgical site infiltration with liposomal bupivacaine, surgical site infiltration resulted in lower pain scores and decreased oral opioid use postoperatively (44). However, in one trial among women undergoing laparoscopic hysterectomy, incisional infiltration of liposomal bupivacaine did not significantly improve patients' postoperative pain or opioid use compared with short-acting bupivacaine. A Cochrane review has concluded that although liposomal bupivacaine seems to decrease postoperative pain, its efficacy for all surgeries is difficult to quantify owing to the limited number of high-quality studies (45, 46).

Continuous wound infiltration of local anesthetic, whereby a multi-holed catheter is placed in the preperitoneal or subcutaneous space and attached to a pump that delivers the local anesthetic, may also provide improvements in postoperative pain control and decreased opioid use, with no increased risk of wound complications (3, 47). A meta-analysis across major surgeries has demonstrated no significant differences in postoperative pain control between epidural analgesia and continuous wound infiltration, also suggesting significant benefit of continuous wound infiltration (48). However, consistently favorable results among women undergoing laparotomy for gynecologic indications have not been demonstrated (49, 50). It is likely that incisional blocks are beneficial among women undergoing reproductive surgeries; however, there are insufficient data to inform whether single-injection or continuous infiltration is more effective at relieving pain. Consideration of the surgical approach and provider preference/experience should inform block selection until better data are available.

Transversus Abdominis Plane Block

Transversus abdominis plane (TAP) blocks are a technique in which local anesthetic is infiltrated under ultrasound guidance in the plane between the internal oblique and transversus abdominis muscles to anesthetize the nerves of the abdominal wall. Transversus abdominis plane blocks require anesthesiologists trained in the procedure, and may require additional intraoperative or postanesthesia care unit time for placement. Meta-analyses evaluating the efficacy of TAP blocks on postoperative pain for open and laparoscopic procedures have demonstrated significant reduction in early postoperative pain, as well as decreased opioid consumption in the first 24 hours after surgery (51, 52). Results in gynecologic procedures are mixed. In three studies randomizing women undergoing total laparoscopic hysterectomy (TLH) to TAP blocks vs. sham or no sham blocks, there were no significant differences in postoperative recovery or opioid use in the first 24 hours after surgery (53–55). However, in a different trial randomizing women undergoing TLH to preoperative TAP blocks with two different concentrations of ropivacaine or sham saline blocks, TAP blocks with the higher ropivacaine concentration resulted in overall improved postoperative recovery, decreased opioid consumption in the first 24 hours postoperatively, and faster time to discharge from the postanesthesia care unit (56). Moreover, a randomized trial of TAP blocks with liposomal bupivacaine vs. short-acting bupivacaine for TLH demonstrated an approximate 50% decreased opioid use in the first 72 hours postoperatively with liposomal bupivacaine (57). Preoperative TAP blocks among women undergoing total abdominal hysterectomy (unknown surgical incision) and receiving other preoperative analgesics have also resulted in decreased opioid consumption for the first 48 hours postoperatively (58, 59). Nevertheless, as above, surgical site infiltration with liposomal bupivacaine provided better pain control than TAP blocks with short-acting bupivacaine, and in a comparison of unilateral surgical site infiltration vs. a contralateral TAP block for gynecologic laparoscopy, no significant differences between either approach existed (44, 60). More evidence is needed, but the available data suggest this block may be useful in improving pain control in patients undergoing some reproductive/gynecologic surgeries.

Paracervical Block

In a paracervical block, local anesthetic is infiltrated into the lateral cervicovaginal junctions at 3 o'clock and 9 o'clock or 4 o'clock and 8 o'clock. The choice of local anesthetic is provider-dependent. However, paracervical blocks for uterine procedures have been extensively studied, and meta-analyses suggest they result in little improvement in intraoperative pain control (61, 62). Moreover, parcervical blocks do not provide significant improvement in intraoperative pain control over conscious sedation for oocyte retrieval (63). On the basis of these data, routine use of paracervical blocks for outpatient intrauterine procedures or oocyte retrieval is likely to be of little clinical benefit.

Intrauterine Block

Instillation of local anesthetic into the uterine cavity results in an intrauterine block. A 2012 systematic review of trials for intrauterine anesthesia for a variety of outpatient gynecologic procedures suggests favorable results for endometrial biopsy or uterine curettage, mixed results for hysteroscopy, no benefit for hysterosalpingogram, and insufficient evidence for dilation and curettage and saline-infusion sonogram (64). Subsequently, one additional trial has demonstrated lower postoperative pain scores and analgesic use with intrauterine instillation of local anesthetic after hysteroscopy (65). However, the design of this trial is of limited quality. Until higher-quality data are available, intrauterine block with local anesthesia is not recommended for routine use in reproductive procedures, with the possible exception of endometrial biopsy and uterine curettage.

SPECIAL CONSIDERATIONS IN PATIENTS WITH CHRONIC OPIOID USE OR OPIOID USE DISORDERS

Patients with current or prior opioid use or use disorder can pose a number of specific perioperative challenges. Patients with chronic opioid use undergoing major abdominal surgery incur $2,341 in excess hospital costs, have longer hospital stays, and experience higher rates of complications and readmissions (66). Among benign gynecologic patients, preoperative opioid use is associated with twice the risk of chronic postsurgical pain compared with non-opioid users (67).

A thorough preoperative evaluation is essential to identifying patients with chronic opioid use or opioid use disorders, to make appropriate plans for intraoperative anesthesia, postoperative analgesia, and postoperative recovery counseling, if appropriate (68). To elicit this history, patients should be questioned about use of alcohol, tobacco products, opioids, and illicit drugs (69). If a patient with chronic opioid use or opioid use disorder is identified, complete cessation of opioids is often not feasible preoperatively, and in most cases, not recommended (69); however, establishing a commitment to decrease preoperative use may provide the framework for successful pain management postoperatively, and opioid independence thereafter. An opioid contract, a formal and detailed written agreement that describes key aspects of opioid therapy, may be used to establish boundaries and expectations (70). A structured pain management plan should also be created preoperatively to maximize multimodal non-opioid therapy and potentially take advantage of regional anesthesia techniques described above (71). Although maximizing non-opioid approaches to analgesia is a rational approach, there is a paucity of high-quality evidence regarding optimal perioperative pain management of chronic opioid users.

One adjunctive medication that may have particular utility in opioid tolerant patients is ketamine. Ketamine modulates glutamatergic *N*-methyl-D-aspartate pain receptors, and its minimally sedating properties have made it a new option for the management of patients with chronic pain. In a trial of opioid-dependent chronic back pain patients undergoing major lumbar spine surgery randomized to IV ketamine upon induction of anesthesia or saline, 24-hour and 48-hour total morphine consumption and postoperative pain scores were significantly reduced in the ketamine group (72). An exploratory analysis of this cohort revealed that ketamine may be most efficacious in patients who consume at least 40 mg of daily oral morphine (72). However, the addition of postoperative low-dose ketamine infusions in subanesthetic doses to parenteral hydromorphone has not been demonstrated to decrease postoperative opioid use (73–75). Other opioid-sparing intraoperative and postoperative strategies, such as lidocaine and dexmedetomidine infusions, are also potential options but have not been rigorously studied in trials focusing on chronic opioid users (76–78). A discussion with the anesthesiologist may allow for optimal selection of adjunctive intraoperative agents, to improve postoperative pain control.

Postoperatively, patients chronically using opioids (or on opioid replacement therapy) must continue their total daily opioid dose to control ongoing chronic pain and/or avoid withdrawal. Additional analgesia is generally necessary to manage acute postoperative pain, and tolerant patients will often require higher doses of opioids to achieve satisfactory analgesia. However, these higher doses may also lead to more frequent unwanted opioid side effects, including sedation, respiratory depression, ileus, and paradoxical worsening of pain secondary to opioid-induced hyperalgesia (79). It is thus imperative to optimize the use of multimodal non-opioid analgesia in these patients, as described above.

Patients Using Methadone, Buprenorphine, or Naltrexone

Buprenorphine is a unique opioid with activity in multiple receptors, including μ (partial agonist), κ (antagonist), and δ (antagonist). Patients taking buprenorphine–naloxone formulations can be expected to have higher than average analgesic requirements owing to the competitive binding of buprenorphine for the μ-opioid receptor and its slow dissociation times (80). Several approaches regarding management of patients taking buprenorphine have been recommended, with limited clinical data (69). Commonly used approaches include [1] continuing buprenorphine at the preprocedural dose throughout the perioperative period, [2] discontinuing buprenorphine at the time of admission for scheduled procedure and substituting with either short- or long-acting opioids, or [3] administering buprenorphine in fractionated doses during the postoperative period, to maximize its analgesic effect.

Methadone, a μ-receptor agonist with *N*-methyl-D-aspartate antagonist properties, is recommended to be continued perioperatively to avoid fluctuations in drug levels and potential withdrawal (69, 81–83). Patients who have not taken their regular methadone dose may be given an equivalent loading dose preoperatively with any number of biosimilar agents (69, 84).

Naltrexone is often used in the treatment of alcohol and opioid dependence as a once-daily agent or depot injection and is a competitive μ-receptor antagonist. Patients receiving oral opioid antagonist therapy with naltrexone should generally discontinue the medication 3 days before surgery (85). The depot form should be discontinued at least 30 days before scheduled procedures (82).

Patients receiving opiate replacement therapy often require higher than expected opioid doses to achieve analgesia, resulting in increased risk for respiratory depression and warranting careful postoperative monitoring (73). It is also important to avoid treating opioid-dependent patients with mixed antagonists/agonists, such as nalbuphine or butorphanol, often used for treatment of opiate-induced pruritus, because these can precipitate withdrawal. A multidisciplinary approach to postoperative pain control with co-management by a pain specialist is often helpful for these complex patients.

OUTPATIENT POSTOPERATIVE PAIN MANAGEMENT

Although many strategies presented above will result in decreased in-hospital opioid consumption, it is important to

maintain opioid-minimizing approaches to prescribing practices upon discharge. Leftover opioids from unused prescriptions are an important source of opioid misuse, and long-term opioid use is linked to high-intensity opioid prescribing in the acute setting (2, 86–88). With increasing interest in understand opioid use patterns, survey studies have documented a high proportion of unused opioids remaining in the home after common surgeries, without proper disposal (89–91). One institution's approach to decreasing the amount of opioids prescribed after common surgeries was to emphasize the value of non-opioid analgesics and discharge patients with the number of opioids that satisfied 80% of their postoperative pain needs, on the basis of prior work (90). This change in practice was implemented via provider education (90, 92). Another institution's approach was to engage patients in the decision for opioid prescribing after cesarean delivery, using the model of shared decision making. In this approach, providers present the risks and benefits of opioids, NSAIDs, and acetaminophen, normative opioid consumption, and education on routes of disposal of unused opioids. Patients then self-selected the number of tablets they wanted to be prescribed up to the usual quantity dispensed for that procedure (91). This approach led to a 50% decrease in the number of opioids prescribed after cesarean delivery (93). Although additional work is necessary to understand analgesic consumption necessary to provide adequate postoperative pain relief after reproductive surgeries, the above approaches represent promising strategies to decrease outpatient opioid prescribing.

Outpatient postoperative pain management is particularly complex in chronic opioid users or patients receiving opioid replacement or antagonist therapy. Much of the management is driven by expert opinion and prior experience caring for these patients. Close follow-up should occur in a pain management clinic if pain is difficult to control or if downtitration to the baseline opioid dose does not occur quickly. We also recommend close follow-up with the primary surgeon, to ensure postoperative recovery is appropriate despite significant analgesic need.

In conclusion, perioperative care of the opioid-naïve patient and chronic opioid user requires thoughtful consideration of preoperative, intraoperative, and postoperative strategies to minimize opioid use. Considerable data exist to recommend preoperative administration of NSAIDs, consideration of regional anesthesia and surgical blocks, and postoperative multimodal analgesia. Additional strategies are often necessary for patients using opioid replacement therapy or chronic opioid users, but the above principles of preoperative analgesic administration, intraoperative opioid minimization strategies, and multimodal postoperative analgesia still apply.

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