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REVIEW ARTICLE

Persistent pain after cesarean delivery

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ABSTRACT

The incidence of persistent pain after cesarean deliveries (CD) varies but is much lower than after comparable surgeries. However, with over four million deliveries annually and a rising CD rate, even a low prevalence of persistent pain after CD impacts many otherwise healthy young women. Consideration of the pathophysiology of persistent pain after surgery and the risk factors predisposing women to persistent and chronic pain after CD provides insights into the prevention and treatment of persistent pain; and improves the quality of care and recovery after CD. The findings that the peripartum state and oxytocin confer protection against persistent pain may provide new and interesting perspectives for the prevention and treatment of chronic pain caused by trauma or surgery.

Predictive tools available to identify and target patients at high risk of acute and chronic pain have mostly weak to modest predictive correlations and many are either not clinically feasible or too time-consuming to apply. Persistent pain has been linked to the severity of acute postoperative pain and opioid exposure. Modified surgical techniques, neuraxial anesthesia and opioid-sparing analgesia may help limit the development of persistent and chronic pain. The goal of this narrative review is to examine the incidence of persistent pain after CD; review briefly the underlying pathophysiology of persistent pain and the transition from acute to chronic pain (with particular emphasis on the uniqueness after CD); and to review modifiable risk factors and prevention strategies that identify at-risk patients and allow tailored treatment.

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Introduction

Tissue trauma and nerve injury from surgery are common causes of debilitating chronic pain.¹ Persistent pain after surgery affects 10–50% of people after various common surgical procedures, such as groin hernia repair, breast and thoracic surgery, leg amputation, and coronary artery bypass surgery.¹ It was initially thought that persistent pain after cesarean delivery (CD) was an understudied and under-reported phenomenon, with one of the first prospective studies showing that the prevalence of persistent pain was similarly low for both CD and vaginal delivery (VD).^{2,3} However, the CD rate has increased by more than 10-fold over the last 70–80 years.^{4,5} Of the nearly four million births in the United States (U.S.) in 2016, 31.9% of deliveries were through CD, making it one of the most common surgeries performed.^{4,5} The increase in CD in recent years makes even a small prevalence of persistent pain after CD a significant burden, both financially and in

terms of quality of life, for a large number of otherwise healthy young women.^{5–8} Persistent pain after CD has been shown to be associated with postpartum depression, interferes with daily activities, and causes sleep disturbances, all of which negatively and directly impact the mother. As a result, the care of the baby by the mother is affected negatively.^{9–12}

To adequately control postoperative pain, healthcare providers use a one-size-fits-all multimodal analgesic approach and sensible opioid prescription with monitoring to prevent addiction.^{14,15} The challenge is in tailoring this approach to the outliers who may be opioid-tolerant or opioid-sensitive.¹⁶ However, the severity and duration of postoperative pain and its management may be predictive of developing persistent pain at two to 12 months or later.^{2,3,17,18} Several risk factors have been identified that predispose patients to the development of persistent pain after surgery. When compared to men, women are at higher risk of developing persistent pain after surgery that is of greater severity.^{19,20} In addition, a younger age increases the risk of persistent pain after surgery. This highlights the importance of studying and preventing persistent pain after CD in these otherwise mostly healthy young females.²¹

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The literature reports the incidence of persistent pain after CD as ranging from <1% to 23% at 12 months after surgery.^{3,6,11,22,23} Despite this wide range of values, the incidence of persistent pain after CD is reported to be less than that after similarly invasive surgeries, such as total abdominal hysterectomy or inguinal herniorrhaphy.^{3,24–26} The hormonal status of pregnancy and the peripartum period may convey some protection, likely mediated through oxytocin.^{27,28}

Many studies have been performed to assess for risk factors that can predispose young women to persistent pain after CD.^{1,6,7,11,24,29} An understanding of pathophysiology of persistent pain after surgery and the risk factors that can predispose women to it can provide insight into prevention and treatment of persistent pain and improve the quality of care and recovery after CD. The goal of this narrative review is to examine the incidence of persistent pain after CD, review briefly the underlying pathophysiology and the transition from acute to chronic pain, and identify modifiable risk factors and prevention strategies.

Incidence and characteristics of persistent pain after cesarean delivery

The International Association for the Study of Pain (IASP) defined persistent pain as clinical discomfort lasting more than two months post surgery, after exclusion of other causes such as postoperative chronic infection or pre-existing chronic pain conditions.³⁰ The International Classification of Diseases defined the associated duration to be more than three months after surgery, with pain intensity greater than, or characteristics different from, pre-operative pain, in order to incorporate varying recovery durations from a wide range of surgeries.³¹ For the purpose of this review, the definition of persistent pain used by the IASP is applied unless otherwise qualified with the specific time period. Persistent pain lasting more than three months would generally be considered as chronic pain.

The reported incidence of persistent pain after surgery varies widely among different surgical types and even within the same type of surgery. The inclusion criteria for persistent pain reported by various authors has often differed by the definition of pain onset, duration, intensity and location.^{3,23,29,32} Furthermore, many reports evaluating persistent pain after delivery have focused on the incidence of pain, without determining or clarifying if pain predated delivery or even pregnancy.^{7,10,29,33,34} These differences in definition and inclusion criteria most likely contribute to the wide variability in the reported incidence of persistent pain after surgery. In addition, other factors that are still poorly understood, such as genetic or population characteristics, may also contribute to the difference in the reported incidence across studies.³⁵ Although race has not been

studied as a risk factor for persistent pain after surgery, there is a disparity in CD rates among different races.³⁶ Studies have also shown that minorities are at higher risk for inadequate acute pain control.^{37–39}

Many studies have been conducted regarding the incidence of persistent pain after CD, but results, like those of many other surgeries, have shown a wide range in values from <1% to 23% up to 12 months after CD.^{2,3,6,7,8,12,22,23,32,40,41} Table 1 summarizes some of the clinical data on persistent pain at two to 12 months after CD. Niklasson et al. conducted a prospective study of 260 healthy women who underwent elective CD in Sweden.⁶ They reported the incidence of women suffering from persistent pain in one or more locations to be 40%, 27% and 22% at three, six and 12 months after CD, respectively. Fifty-six percent reported pain around the surgical site at three months, while 32% and 25% reported pain at more than one location at three and six months, respectively. The abdomen was the most commonly reported location at three and six months, shifting to the back or low back at 12 months postpartum. Overall, more than one-fifth of patients with moderate to very severe pain described the pain as impacting their enjoyment of life.⁶ In one of the initial studies on chronic pain after CD, Nikolajsen et al. used a mail questionnaire to inquire about chronic pain after CD in 244 consecutive patients, reporting an 18.6% incidence of persistent pain three months after CD and 12.3% at the mean observation time of 10.1 months, with 5.9% reporting daily, or almost daily, pain.¹¹

In a prospective study of 527 Chinese women, Jin et al. examined the presence of pain by interviewing the patients in person pre-operatively and 24 h postoperatively, followed by phone interviews at three, six and 12 months after surgery.⁷ They reported the incidence of pain to be 18.3%, 11.3%, and 6.8% at three, six and 12 months, respectively. Most women in the study reported mild pain at rest and only 3% of those reporting pain had moderate to severe pain at 12 months.⁷ Declercq et al. used the data from Listening to Mothers II in a 2006 national survey of English-speaking U.S. mothers to conduct a retrospective study on mothers' reports of postpartum pain. They found that 79% of mothers reported experiencing pain at the incision site in the first two months and 18% had persistent pain at least six months after birth.⁴²

Some of the studies published on the topic of persistent pain after CD do not specifically evaluate pain at three, six and 12-month intervals or pain that started with delivery. A meta-analysis conducted by Weibel et al. on 38 articles reported an overall 15.4% of women experiencing wound pain at the scar or abdominal area between three and six months after CD. The overall incidence fell to 11.5% at six months and further to 11.2% at least 12 months after CD.²⁹

Table 1 Summary of the incidence of persistent pain at 3, 6 and 12 months after cesarean delivery, as presented in the literature

Study	3 months n/N (%)	6 months n/N (%)	12 months n/N (%)	Study design
Niklasson et al. ⁶ (2015)	93/231 (40.3)	63/228 (27.6)	46/215 (21.4)	Prospective
Daly et al. ³² (2017)	35/98 (36) at 4 months			Prospective
Jin et al. ⁷ (2016)	92/502 (18.3)	55/487 (11.3)	32/472 (6.7)	Prospective
Eisenach et al. ³ (2013)	95/972 (9.8) at 2 months	17/942 (1.8)	3/937 (0.3)	Prospective
Liu et al. ¹² (2013)	62/426 (14.6) at 2 months		18/426 (4.2)	Prospective
Richez et al. ³⁴ (2015)	75/268 (28.0)	45/239 (18.8)		Prospective
Kainu et al. ²² (2016)			85/379 (22.4)	Prospective
Kainu et al. ⁴⁷ (2010)			42/229 (18.3)	Prospective
Moriyama et al. ⁷⁶ (2016)	69/225 (30.7)			Prospective
Eisenach et al. ² (2008)	26/283 (9.2) at 8 wks			Prospective
Ortner et al. ²³ (2014)	37/335 (11.0) at 8 wks	11/335 (3.3)	2/335 (0.6)	Prospective

n is number of patients with persistent pain, N is the number of patients assessed (denominator) and (%) is the percentage of those evaluated having persistent pain at the corresponding assessment time.

In contrast, Eisenach et al., using a definition of persistent pain as new onset pain from delivery, undertook a prospective study of 1228 women to assess for pain immediately after delivery (vaginal and cesarean) and then two, six and 12 months later. They interviewed patients within 36 h of delivery and again by telephone at two months. Those patients who still had pain at two months were followed using a phone interview at six months, and those who still reported pain were followed to 12 months.^{2,3} The incidence of pain was reported to be 9.8 and 1.8% at two and six months after vaginal and CD, respectively.³ The pain reported at six months was from a median of two locations per patient. The abdominal surgical site and the pelvis were the most common locations of pain after cesarean and vaginal delivery, respectively. At 12 months postpartum, the incidence was 0.3%, representing three of the patients studied, all of whom had a vaginal delivery.³ Eisenach et al. concluded that persistent pain after CD was not a major health problem but that it does affect individual people who experience pain after delivery. The three women who had pain at 12 months postpartum reported a high burden of pain from activities of daily living, and all of them met the threshold for depression on the Edinburgh postpartum depression index.³ The much lower incidence of persistent pain after CD reported in this study may be due to a combination of a more precise definition for persistent pain and missing some patients who might have developed persistent pain after the two- or six-month interviews and therefore, did not receive follow-up. Similarly, a prospective study involving 786 Chinese women showed 12.2%, 3.8% and 0.8% incidence of persistent pain at three, six and 12 months postpartum respectively. At three months, over 40% of those with persistent pain experienced pain daily and the pain interfered with one or more daily activities, mood, sleep or child care. However, by 12 months the impact and frequency of pain was significantly less.⁴³ Ortner et al. also reported a low incidence of chronic

pain after CD of 0.6% at 12 months. They followed 335 women who had planned CD in a prospective longitudinal cohort study using the Short-Form McGill Pain Questionnaire-Revised. Similar to the findings of Wang et al. and Eisenach et al., Ortner et al. reported the incidence of new onset pain as 11% and 3% at two and six months after surgery, respectively.^{2,3,23,43}

Many studies have also looked at the incidence of chronic pain after CD compared with vaginal birth, with conflicting results.^{8,22,29,44-47} Some report that chronic pain after CD is less than that after vaginal birth,^{8,29} whereas others state that pain after CD is greater than from vaginal birth.^{22,44-47} Eisenach et al. reported that it is the severity of pain after childbirth, not the mode of delivery, that predicts persistent pain and depression eight weeks after delivery.² The data on how mode of delivery affects the incidence of chronic pain deserve further investigation with a larger cohort.

Many of the studies published rely on questionnaires by mail or telephone to qualify and quantify patients' pain.^{8,11,23,33,42,48} Retrospective studies depend on recall of the pain at the time of delivery, which sometimes occurred many months to years prior to the study survey.^{8,11,42,45} Most previous studies measured the dichotomous outcome of presence of persistent pain at one or more fixed time points after surgery, but limited information is known about the daily recovery trajectory and the transition from acute to persistent pain. Booth et al. studied the daily pain characteristics of 530 post elective CD patients for two months using daily text messaging questionnaires to the patients.⁴⁹ Using cluster analysis, they found that the initial trajectory of pain recovery was similar in all subjects, but divergence of pain recovery trajectory occurred at two to four weeks post CD, resulting in six unique clusters of recovery speed and patterns. In their cluster analysis and modelling, 9% of the women were predicted to have persistent pain lasting more than two months after CD, similar to previous observations.^{2,3} Future studies

should further characterize the day-to-day dynamic trajectory of normal surgical pain recovery over time and the various deviant trajectories, and identify predictors for those with slow recovery or persistent pain.⁴⁹

Pathophysiology of persistent pain after surgery

The cascade of neurochemical changes initiated by a surgical incision that lead to peripheral and central sensitization and a hyperalgesic state are probably an evolutionary protective mechanism, temporarily shielding injured tissue from further use or damage until healing is complete. The development of persistent pain after surgery can be viewed as a disequilibrium from the body's normally allostatic state of low-level balance between pro- and antinociceptive systems. With surgery, sustained activation of the pronociceptive system leads to hyperalgesia and allodynia, which resolves during normal healing and recovery aided by subsequent activation of the antinociceptive system. This establishes a new allostatic state with a balance of similarly elevated levels of pro- and antinociceptive systems.⁵⁰ Pre-existing pain or severe acute pain can potentially increase vulnerability to persistent pain sensitization in some patients due to an insufficient compensatory antinociceptive response during recovery or exhaustion of compensatory response by high levels of presurgical antinociceptive activation. Thus, insufficiency or absence of tonic nociceptive inhibition leads to sustained hyperalgesia and allodynia, and consequently persistent pain after surgery.⁵⁰⁻⁵²

Persistent pain represents a failure of the hyperalgesic state to return to the pre-injury or presurgical state, despite completion of tissue healing.^{1,21,50} Pain after surgery results from a combination of the inflammatory response and nerve injury – even if direct nerve injury is not involved. The intensity of pain is related to the magnitude of nociceptive inputs and the peripheral and central sensitization that amplify pain sensation for a given nociceptive input. There are three commonly discussed factors associated with acute and persistent pain after surgery; these include nociceptive, inflammatory and neuropathic pain.¹ Nociceptive pain is due to stimulation of nociceptors from actual or threatened nerve damage to non-neural tissue during the CD.⁴⁸ Nociceptors relay sensory information such as the presence, location, intensity and duration of noxious stimuli from the periphery to the central nervous system.^{11,46} The decreased threshold and greater responsiveness of these nociceptors is thought to be partly responsible for the development of hypersensitivity at the location of injury.²⁴ Inflammatory pain comes from the release of inflammatory mediators at the site of direct tissue trauma. These mediators cause an increase in local sensitization to pain by decreasing the firing threshold of the nociceptors, a phenomenon called primary hyperalgesia. Xing et al. studied the inflammatory cytokine IL-6

and anti-inflammatory cytokine IL-10 as mediators of postoperative pain after CD. They used IL-6 levels as a measure of surgical wound severity and these rose postoperatively by four hours, peaking at 12 and 24 h before declining. The anti-inflammatory cytokine IL-10 may balance the effects of IL-6 and was found to have a similar increase in serum level postoperatively at four hours, with peak levels at 12 and 24 h.⁵³

Surgical procedures can also damage nerves in the body, leading to neuropathic pain. Peripheral nerve damage leads to sensory loss at the site of injury and a paradoxical hypersensitivity. Nerve damage and/or primary hyperalgesia from sustained activation of primary afferent neurons can lead to neuroplastic changes that increase neuronal sensitivity of the central nervous system. This results in central sensitization which can present as clinical findings of hyperalgesia and allodynia,^{1,24,46} and secondary hyperalgesia (defined as hyperalgesia outside of the injury/surgical site).

Although neuropathic pain is present in many patients who have chronic pain after CD, nerve injury alone does not explain its incidence. Other factors must play a role in the development of chronic pain as not all patients with nerve damage develop neuropathic pain.^{1,24} In particular, the Pfannenstiel incision is frequently used for CD due to its lower risk of subsequent incisional hernia and its aesthetic benefits.^{24,54} The persistent pain present after CD has been characterized as neuropathic and could be the result of nerve entrapment at the incision site.^{44,54} With the Pfannenstiel incision, there is a risk of ilio-inguinal and iliohypogastric nerve entrapment leading to pain at the scar.^{44,55} Loos et al. indicated there could be some utility to diagnostic and therapeutic nerve blocks for these patients.⁵⁴ Eisenach et al. found pain was reported at a median of two locations per patient, with the most common location being at the abdominal CD scar.³ Chin et al. studied postpartum pain descriptors to help qualify neuropathic and nociceptive pain in patients between 24 and 48 h of CD and six weeks after. They identified 28 words used to describe neuropathic pain, for example aching, itchy or shooting; and 26 words to describe nociceptive pain, for example cramping, tender and sharp. Twenty-nine of the 30 participants chose an average of 3.5 neuropathic words to describe their pain at 24–48 h after CD, while all 30 participants chose an average of 5.8 nociceptive words. Six weeks after surgery this number decreased to 26 women choosing an average of 2.5 neuropathic words to describe their pain and all 30 participants choosing an average of 4.6 nociceptive words.⁴⁸

Pathophysiology unique to persistent pain after cesarean delivery

The incidence of persistent pain after CD is, remarkably, almost 10-times lower than persistent pain after

similarly invasive surgical procedures such as total abdominal hysterectomy or inguinal herniorrhaphy.^{3,24–26} Many mechanisms have been proposed to explain this discrepancy, such as a shorter operation duration for CD and less peripheral nerve injury, or a positive psychological factor in expecting or caring for a newborn.^{3,27,34} It is possible that the pregnant state or the high prevalence of spinal anesthesia use for CD is somewhat protective against the development of chronic pain. Oxytocin, an endogenous nonapeptide hormone released in large amounts at the time of parturition and during lactation, has been proposed as a possible explanation for this lower incidence of chronic pain.^{24,27,28,56}

Gutierrez et al. examined the development of hypersensitivity in the rat model.²⁷ Spinal nerve ligation at mid-pregnancy produced similar hypersensitivity to hind-paw mechanical stimuli it did as in non-pregnant rats. Partial resolution of hypersensitivity began with delivery but removal of the pups prevented this resolution, suggesting the postpartum state, and not the pregnant state, as protective against hypersensitivity.^{27,28,56} Spinal nerve ligation performed on another group of rats within 24 h of delivery resulted in hypersensitivity that resolved over two to three weeks. However, weaning the pups led to temporary return of hypersensitivity that was reversible with intrathecal oxytocin. Postpartum resolution of hypersensitivity was also inhibited by an intrathecal injection of atosiban (an oxytocin receptor antagonist) but not naloxone (an opioid receptor antagonist), suggesting oxytocin works by a different mechanism than opioids in reversing hypersensitivity during the postpartum period. At the same time, lumbar punctures performed on a different group of animals showed elevated spinal oxytocin levels in postpartum rats compared to non-pregnant controls.²⁷ Severino et al. reported that intrathecal injection of oxytocin and vasopressin receptor antagonists similarly reduced the withdrawal threshold in both male and female rats with L5 spinal nerve ligation, but not in those without ligation. Furthermore, spinal nerve ligation produced a significant increase in oxytocin fiber immunoreactivity in lumbar spinal cord regions, and oxytocin and vasopressin 1A-receptor messenger ribonucleic acid (RNA) expression in ipsilateral dorsal root ganglion. Collectively, this suggests that oxytocin signaling increases in the spinal cord after surgery and contributes to recovery from mechanical hypersensitivity in both genders. The role of oxytocin as an analgesic agent and its mechanism in the prevention of, or recovery from, development of hypersensitivity and chronic pain, especially in the postpartum period, is an area needing further research.^{27,28,57–59}

Risk factors

Identification of risk factors for the development of persistent pain after CD may help prevent or better predict

the condition. These risk factors can be broken down into three main categories of pre-operative, intra-operative and postoperative factors. Table 2 summarizes proposed risk factors that have been identified from clinical or experimental data. Table 3 lists some of the clinical findings reported specifically about risks associated with persistent pain after CD. As the level of evidence increases, future studies should utilize the proposed risk factors for building models to study persistent pain after CD.

Pre-operative risk factors

Pre-operative risk factors are important to recognize in patients who may be predisposed to developing persistent pain after CD. However, a comprehensive risk stratification or modelling tool with high sensitivity and specificity, that reliably identifies patients at risk for developing persistent pain after CD in the clinical context, has not been developed. Daly et al. examined the deprivation status of patients as determined by the Scottish Index of Multiple Deprivation ranking-year 2012. They reported that greater deprivation level predicted the incidence of pain at four months after elective CD.³² Non-private insurance status was also determined to be a risk factor for the development of chronic pain in a cohort of women who delivered at a Singapore hospital.³³

Niklasson et al. studied a cohort of 260 Swedish women undergoing elective surgery and found that first-time CD was a risk factor, with odds ratios (OR, 95% confidence intervals (CI)) of 1.96 (1.11 to 3.44; $P=0.02$) and 2.31 (1.23 to 4.44; $P=0.01$) for pain at three and six months, respectively.⁶ Furthermore, Niklasson et al. determined that if the reason for CD was psychological (defined as CD at maternal request), there was a significantly higher risk for chronic pain at three months, while emergency CD was also associated with an increased OR (1.56, 1.01 to 2.40; $P=0.02$) for developing chronic pain.⁶ In a prospective cohort study of 527 Chinese women, Jin et al. used the Edinburgh Postnatal Depression Scale (EPDS) to assess depressive symptoms in pregnant women prior to CD. They found that pre-operative depression, defined as an EPDS score ≥ 12 , had a statistically significant association with chronic pain at three and six months postoperatively, with OR 4.64 (2.08 to 10.36; $P<0.001$) and 5.53 (2.19 to 13.93; $P<0.001$), respectively.⁷ It has also been shown experimentally that pre- or postsurgical stress prolongs the duration of incision-induced hyperalgesia. This prolongation can be abolished by removal of the adrenal gland or by blocking spinal glucocorticoid receptors.⁶⁰ Various psychosocial factors may play an important role and require further investigation, even though findings from previous studies are not always consistent or conclusive.

Pain that exists prior to pregnancy or during pregnancy may be a risk factor for development of chronic

Table 2 Factors associated with an increased risk of persistent pain after surgery, based on experimental and/or clinical studies

	Factors	Clinical examples	References
Pre-operative	Psychological and social factors	Anxiety, depression, stress, lower socioeconomic or deprivation status, elective request or emergency cesarean delivery	1,6,7,25,32,33,34
	Opioid-induced hyperalgesia	Pre-operative opioid use, previous opioid exposure or repeated exposure	66–71
	Pre-existing pain and pain elsewhere	Pre-operative pain severity, previous surgery/injury	11,26,33,46,47,61,63–65
Intra-operative	Surgical technique*	Pfannenstiël incision (number and length), surgical duration, nerve injury/entrapment	7,25,54,55,93,107
	Anesthetic technique*	General vs neuraxial/regional anesthesia, spinal morphine, dose of spinal medication, high/repeat opioid dose use	6,11,46,54,62,75,76,107
Postoperative	Acute postoperative pain	Severity of acute postoperative pain	2,3,11,22,32,33,46,47,65,77,78
	Depression	Postpartum depression	2,32

*These intraoperative factors are also associated with increased severity of acute postoperative pain, which can in turn, in part or indirectly be associated with the risk of persistent pain after cesarean delivery.

pain;⁶¹ however, many studies of persistent pain specifically list pre-existing pain as an exclusion criterion.^{6,12,23,62} Reports of pain elsewhere in the body were also a risk factor, with back pain and migraines being the most common locations.³³ A history of CD was found in a significantly higher percentage of patients with chronic pelvic pain as compared to the control group without CD. Furthermore, previous CD is an established risk factor for persistent pain after hysterectomy.^{26,63} The propensity for persistent pain with pre-existing pain or previous injury or surgery fits the disequilibrium concept, with the loss of balance from the allostatic state due to exhaustion of compensatory antinociceptive systems from pre-existing pain or injury, as described in the pathophysiology section earlier.

The increasing prevalence of patients having multiple CDs may put this patient population at higher risk for persistent pain after surgery and these women should be more aggressively targeted for prevention of persistent pain.^{11,33,47,64,65} Along with pre-existing pain, both clinical and experimental data support opioid-induced hyperalgesia, which associates pre-operative and peri-operative opioid exposure with an increase in persistent pain after surgery.^{66–71} It was shown in a rat model that a single opioid dose could lead to exaggerated hyperalgesia, while repeated opioid doses resulted in persistent central sensitization that was preventable with N-methyl-D-aspartate (NMDA) receptor antagonists, such as ketamine.⁶⁶ Thus, multimodal opioid-sparing analgesic and anesthetic regimens in the peri-operative period should be implemented to avoid or minimize repeated opioid exposures, especially in patients with multiple CDs.

Intra-operative risk factors

The identification of intra-operative risk factors may help in understanding which components of the surgery

itself can be targeted to decrease the incidence of subsequent persistent pain. In a study of 866 Dutch women, having more than two Pfannenstiël incisions and emergency CD were significant risk factors for developing chronic pain with OR of 2.92 (1.44 to 5.93; $P=0.003$) and 1.56 (1.01 to 2.40; $P=0.02$), respectively.⁵⁴ It was proposed that an increase in length and/or number of Pfannenstiël incisions may result in damage or trapping of the nerves innervating the suprapubic and lower abdominal areas and formation of neuromas, which contribute to the development of neuropathic pain.^{54,72–74}

The type of anesthesia used for CD has been studied as a potential means of preventing chronic pain. Regional and neuraxial anesthesia have been shown to be superior to general anesthesia in reducing persistent pain after CD.^{11,75,76} The nerve blocks may work by inhibiting the transmission of inflammatory and nociceptive pain from the periphery to the central nervous system, thereby inhibiting the mechanism by which central sensitization occurs. This reduces the opioid requirement intra-operatively and may decrease opioid-induced hyperalgesia.^{50,75} Nikolajsen et al. performed a retrospective questionnaire study of 220 women with a mean follow-up time of 10.2 months and determined that more than twice the number of patients who reported chronic pain at the time of the survey had received general rather than spinal, anesthesia.¹¹ In a Cochrane review, Weinstein et al. established that pooled data from four randomized controlled trials totaling 551 patients favored regional/neuraxial anesthesia (OR 0.46 (0.28 to 0.78; $P=0.004$)) over general anesthesia for a lower risk of persistent pain three to eight months after CD.⁷⁵

Intra-operative anesthetic management can have effects extending to postoperative pain control, in which

Table 3 Risk factors evaluated and associated odds ratio (OR) (when applicable or available) for persistent pain after cesarean delivery, based on clinical studies

Risk factors	References	OR (95% CI) <i>P</i> -value
Pre-operative factors		
Psychosocial	Daly et al. ³² (2017) Richez et al. ³⁴ (2015)	1.00 (1.00 to 1.00) <i>P</i> =0.27
Non-private insurance status	Sng et al. ³³ (2009)	1.68 (1.03 to 2.73) <i>P</i> =0.036
Pre-operative depression	Jin et al. ⁷ (2016)	3 months: 4.64 (2.08 to 10.36) <i>P</i> <0.001 6 months: 5.53 (2.19 to 13.93) <i>P</i> <0.001
Maternal request for caesarean delivery	Niklasson et al. ⁶ (2015)	3 months: 1.96 (1.11 to 3.44) <i>P</i> =0.02 6 months: 2.31 (1.23 to 4.44) <i>P</i> =0.01
Low maternal weight	Moriyama et al. ⁷⁶ (2016)	0.96 (0.92 to 0.99) <i>P</i> =0.011
Pre-existing pain ^a	Nikolajsen ¹¹ (2004), Vermelis ⁴⁶ (2010), Kainu ⁴⁷ (2010)	
Pain present elsewhere	Nikolajsen et al. ¹¹ (2004) Sng et al. ³³ (2009)	2.47 (1.49 to 4.11) <i>P</i> =0.001
Intra-operative factors		
Emergency vs. elective cesarean delivery	Loos et al. ⁵⁵ (2008) Niklasson et al. ⁶ (2015)	1.56 (1.01 to 2.40) <i>P</i> =0.02 2.04 (1.15 to 3.70) <i>P</i> =0.02
Type of anesthesia (GA vs. NA/RA)	Weinstein et al. ⁷⁵ (2018) Nikolajsen et al. ¹¹ (2004)	0.46 (0.28 to 0.78) <i>P</i> =0.004
Intrathecal morphine	Moriyama et al. ⁷⁶ (2016)	0.42 (0.20 to 0.89) <i>P</i> =0.023
Lower dose of spinal local anesthetic	Cancado et al. ⁶² (2012)	8.26 (1.17 to 39.90) <i>P</i> =0.009
No use of nonsteroidal anti-inflammatory drugs	Cancado et al. ⁶² (2012)	8.86 (1.87 to 42.00) <i>P</i> =0.006
Pfannenstiel incision more than twice	Loos et al. ⁵⁴ (2008)	2.92 (1.44 to 5.93) <i>P</i> =0.003
Longer duration of surgery	Jin et al. ⁷ (2016)	1.07 (1.02 to 1.11) <i>P</i> =0.001
Postoperative factors		
Pooled complications ^b	Kainu et al. ⁴⁷ (2010)	
Postpartum depression ^c	Daly et al. ³² (2017), Eisenach et al. ² (2008), Eisenach et al. ³ (2013)	
Severe acute pain ^d	Sng et al. ³³ (2009) Jin et al. ⁷ (2016)	1.35 (1.22 to 1.49) <i>P</i> =0.0001 3 months: 2.40 (1.62 to 3.54) <i>P</i> <0.001 6 months: 2.51 (1.56 to 4.04) <i>P</i> <0.001 12 months: 2.74 (1.45 to 5.18) <i>P</i> =0.002
Presence of numbness	Eisenach et al. ² (2008) Nikolajsen et al. ¹¹ (2004) Kainu et al. ²² (2016) Kainu et al. ⁴⁷ (2010) Loos et al. ⁵⁴ (2008)	3.01 (2.05 to 4.40) <i>P</i> =0.000

GA: general anesthesia. NA/RA: neuraxial anesthesia (spinal or epidural anesthesia) with or without regional local anesthetic block or infiltration. ^aStudies^{11,46,47} reported an increase in frequency of persistent pain after cesarean delivery in correlation with pre-existing pain or with pain present elsewhere.

^bPooled complications (mainly wound infection, endometritis and excessive bleeding) were associated with a higher frequency of persistent pain after cesarean delivery (*P*=0.004)⁴⁷

^cEisenach et al.^{2,3} after controlling for propensity scores developed from a non-parsimonious logistic model with all 16 designated predictors entered simultaneously, showed a significant bidirectional correlation between persistent pain at two months after delivery and postpartum depressive symptoms (*P*=0.001). Daly et al.³² reported a significant correlation (*P*<0.001) between postnatal depression (Edinburgh postnatal depression scores) and persistent pain (pain inventory severity scores) assessed at four months after cesarean delivery.

^dEisenach et al.² after controlling for propensity scores developed from a non-parsimonious logistic model with all 16 designated predictors entered simultaneously, showed a one-point increase in acute pain score after delivery was associated with a 12.7% increase in the odds of persistent pain at two months after delivery (*P*=0.018). Nikolajsen et al.¹¹ and Kainu et al.^{22,47} reported separately that the presence of persistent pain after cesarean delivery was significantly (*P*<0.04, *P*=0.023 and *P*=0.004, respectively) associated with severe postoperative pain scores (*P*<0.04).

severe acute postoperative pain may in turn increase the risk of persistent pain after surgery. Cancado et al. performed a prospective randomized study of 443 women, dividing the patients into five groups receiving different doses from 8 to 15 mg of 0.5% hyperbaric bupivacaine and opioids in the spinal anesthesia for CD, and with

or without intra-operative systemic nonsteroidal anti-inflammatory drugs (NSAIDs). The authors determined that the group with the lower dose (8 mg vs 15 mg) of spinal bupivacaine and the group without the use of intraoperative NSAIDs had higher acute postoperative mean pain scores at rest and with movement, and also

had a higher incidence of persistent pain three months after surgery.⁶²

Postoperative factors

A preponderance of evidence supports high severity of acute postoperative pain as a risk factor associated with transition of acute pain to chronic pain.^{2,7,11,22,32,33,47,66,77,78} Early studies showed patients who reported persistent pain after CD were more likely (66% vs 44%) to have recall of severe acute postoperative pain compared to those without persistent pain.^{11,65} Jin et al. measured average pain score at rest and on movement within 24 h of CD. They determined that higher average pain scores on movement within 24 h of surgery were a significant predictor of chronic pain at three, six and 12 months (OR at 12 months of 2.7 (1.5 to 5.2; $P=0.002$)).⁷ Sng et al. conducted a prospective study of 857 patients who underwent an elective CD with spinal anesthesia and intravenous morphine patient-controlled analgesia for the first 24 h postoperatively. They found that a higher pain score in the immediate 24-h postoperative period was a risk factor for the development of chronic pain at a mean follow-up time of 14.5 months.

Similarly, Eisenach et al. found that severity of acute pain, but not mode of delivery, predicts persistent pain and postpartum depression eight weeks after delivery. Every one point (on a 0–10 scale) increase in acute pain was independently associated with a 12.7% increase in the odds of experiencing pain at eight weeks and a 8.3% increase in the risk of depressive symptoms at that time. The latter were also independently associated with an increase in persistent pain.² Likewise, Hannah et al. found no difference between mode of delivery (planned CD or vaginal birth for a term singleton breech fetus) with respect to persistent pain and other maternal outcomes by two years postpartum.⁷² Whether mode of delivery affects persistent pain after delivery needs to be validated with larger cohorts, as others have also reported a higher incidence of persistent pain after CD than vaginal delivery.²²

In summary, many risk factors for the development of persistent pain after CD have been identified. The evidence collectively points towards optimal control of intra-operative and postoperative pain, using multimodal opioid-sparing regimens for analgesia, as yielding a lower risk of developing persistent pain and other complications. More information is needed to determine which risk factors have the greatest impact and, therefore, are the best targets to try and reduce the incidence of chronic pain.

Prediction of acute and persistent pain

With increasing understanding of the pathophysiology and potential risk factors for development of persistent

pain, it is important to discuss the prevention strategies that have been studied to combat this growing problem. Ideally, identifying pre-operatively those patients at high risk of developing persistent pain would allow them to be targeted more aggressively with tailored prevention.^{61,79,80} Despite recognizing various risk factors, the sensitivity and specificity of being able to identify individual patients at risk is still low. Quantitative sensory testing, such as using heat pain threshold, and extensive psychosocial questionnaires such as the Spielberger State-Trait Anxiety Inventory, may provide some predictive information about the risk of acute severe postoperative pain.^{32,34,80,81–83} This approach is not only too time-consuming beyond the usual short pre-anesthetic visit, but it has also not been proven to reliably predict persistent pain after surgery with high specificity. A three-item pre-operative screening questionnaire has been studied as an alternative to the more time consuming and costly quantitative sensory testing to predict postoperative pain. The questionnaire, which assessed maternal anxiety, anticipated post-caesarean pain and anticipated analgesic need and was found to correlate moderately with evoked pain intensity 24 h after CD.⁸⁴ Interestingly, Booth et al, who reported six unique clusters for speed and trajectories of pain recovery after CD, found that perceived stress score, acute pain intensity after CD, number of previous CDs and smoking status were predictors for the unique cluster membership in their multinomial logistic regression model.⁴⁹ The authors suggested that unique cluster membership of pain recovery trajectories in the initial two months after CD could be strong predictors of pain lasting for years, as has been observed in studies on non-obstetric surgeries (OR 18.4).^{85–87}

The role of genetic factors should be studied, as only a percentage of patients who have the same surgery, tissue injury or nerve damage will progress to persistent pain.^{1,35,88,89} For example, the melanocortin-1 receptor gene, that associates with fair skin and red hair, mediates greater female-specific kappa opioid analgesia.⁸⁸ The CYP2D6 phenotype has been recognized in individuals who have increased metabolism of codeine to morphine, which may have implications for opioid dosing.³⁵ Similarly, CYP2D6 and CYP3A4 gene variations have been linked with altered oxycodone metabolism. The A118G polymorphism of the μ -opioid receptor has been associated with variability in morphine consumption in post-CD patients.⁸⁹ Other genes, such as the catechol-O-methyltransferase and μ -opioid receptor genes, have been studied for their effects on variability of morphine response and consumption, partly through varied modulation of the neurotransmission of dopamine and norepinephrine.^{35,90} On the other hand, the effects of UGT2B7 variants on hepatic glucuronidation activity related to morphine metabolism (converting morphine to morphine-3-glucuronide and morphine-6-

glucuronide) have been studied but results are inconsistent, in part due to different methodologies used in the studies.^{35,90} In the future, genetic studies to correlate a single nucleotide polymorphism in multiple genes with development of persistent pain may help identifying those at risk for persistent pain more reliably.

Tissue and nerve injury are the main initiating causes of persistent pain. Thus, potential modification of surgical technique to reduce tissue injury, inflammation or adhesion response, and to reduce or avoid nerve injury or entrapment, may help alleviate the risk of persistent pain.^{55,91} Coutinho et al. found that uterine exteriorization resulted in a higher frequency of moderate or severe pain six hours after surgery when compared with in situ uterine repair.⁹² Careful and gentle dissection, muscle sparing techniques, peritoneal non-closure, avoidance of uterine exteriorization, smaller incisions and surgery of shorter duration should be considered to combat persistent pain after CD. These modifications have not been proven to reduce persistent pain but do reduce acute postoperative pain.

Optimizing acute pain management to prevent persistent pain

Multimodal analgesic regimens use a combination of medications with different mechanisms of action to optimize analgesia as a result of additive or synergistic drug interactions, while minimizing the associated side effects. They typically include a combination of neuraxial and systemic opioids and NSAIDs with acetaminophen.⁹³ There has been a trend towards using enhanced recovery after surgery (ERAS) programs, including the use of multimodal analgesia, to control postoperative pain and improve recovery.^{9,94} A preponderance of evidence suggests that severe acute postoperative pain or opioid (single, repeated or high-dose) exposure can increase the risk of persistent pain. Thus, multimodal opioid-sparing regimens might play a significant role in the strategy to minimize persistent pain after CD.¹⁴ It should be noted that reducing the amount of opioids patients take while in the hospital and after going home plays a role in persistent pain and also in combating the “opioid epidemic”. Even though Bateman et al. has shown that only 1 in 300 opioid-naïve patients becomes a persistent opioid user a year after CD, the absolute number is likely to be significant given the high prevalence of CD.¹⁶ They also reported that clinicians in the U.S. routinely prescribed opioids significantly exceeding patients’ needs after CD in a multicenter study of 720 women.⁴⁰ Patients consumed more opioid when more was prescribed, independent of patient characteristics and without better pain scores or patient satisfaction than those prescribed lower amounts of opioid. It is concerning that 95.3% of the left-over opioid was not disposed of by the patients,

and had the potential to be introduced into the community.

Nonsteroidal anti-inflammatory drugs and acetaminophen inhibit cyclooxygenase and can be used as part of multimodal postoperative analgesia regimens to target acute pain and reduce opioid consumption by 30–50%. Continuous infiltration of local anesthetics and NSAIDs at the wound site using an indwelling catheter, especially when neuraxial analgesia is not possible, has been shown to decrease pain scores and opioid consumption for the first 24 h after CD, but has not been proven to be of benefit in decreasing chronic pain.^{14,24,50,95,96} Transverse abdominis plane block has been shown to improve postoperative acute pain scores and reduce opioid consumption in patients undergoing CD who did not receive intrathecal morphine but an impact on chronic pain is unproven.^{97,98}

Gholipour Baradari et al., in a randomized double-blind placebo-controlled study, found that a small bolus of 1.5 mg/kg of intravenous lidocaine during induction of general anesthesia for elective CD decreased postoperative morphine consumption over the first 24 h after surgery.⁷⁶ Ketamine blocks NMDA receptors and inhibits central sensitization following peripheral injury.^{24,50} Bauchat et al. studied the effects 10 mg intravenous ketamine in the peri-operative period in a randomized double-blind placebo-controlled study.⁹⁹ Although there was no difference in the incidence of breakthrough pain in the first 24 h, the study suggested there may have been benefit in reducing pain two weeks after CD. The psychomimetic effects of ketamine were recorded using a validated questionnaire: 35% of patients reporting dizziness, lightheadedness or blurred vision during the infusion but no lasting effects postoperatively.⁹⁹ Suppa et al. conducted a double-blind randomized study that administered S-ketamine, an enantiomer of ketamine, peri-operatively and found that it may have anti-hyperalgesic effects that lead to reduced morphine consumption in the first 24 h after surgery.¹⁰⁰ S-ketamine has an analgesic potency twice that of racemic ketamine, although no studies have been done to compare the two drugs for CD analgesia.¹⁰¹ More studies are needed to study the effects of ketamine and other NMDA receptor blockers, such as dextromethorphan and nitrous oxide, on the development of chronic pain after surgery.

Gabapentin and pregabalin are involved in decreasing glutamate transmission and blocking sodium and calcium channels, the latter being upregulated in the process of central sensitization.^{24,50} Studies have shown that these medications decrease opioid use and pain in the immediate postoperative period at the expense of severe maternal sedation.^{14,102} A study of gabapentin in lactating mothers showed low plasma concentrations of gabapentin in suckling infants and did not observe adverse effects in the newborn but more data are

needed.¹⁰³ In a randomized double-blind placebo-controlled study by Monks et al. a peri-operative course of gabapentin had a statistically significant but clinically unimportant effect in reducing pain in the first 24 h after CD.¹⁰⁴ The efficacy of gabapentin in preventing postsurgical pain is weak and the side effects likely outweigh the benefits. Additional investigation is necessary to determine the optimal dosing and potential effects on the risk of persistent postsurgical pain.¹⁰⁵

Clonidine and dexmedetomidine, both α_2 -adrenoreceptor agonists, have antinociceptive properties within the descending pathways of the dorsal horn of the spinal cord and may have a role in targeting one of the mechanisms of chronic pain development after surgery, though limited data are available.²⁴ Neostigmine, a cholinesterase inhibitor, produces analgesia by increasing spinal endogenous acetylcholine, reducing opioid requirement and pain scores.⁴¹ Neuraxial administration of clonidine or neostigmine has been studied and deserves further, larger investigation for both acute postoperative analgesia and reducing persistent pain after surgery.^{24,41} In a randomized double-blind placebo-controlled trial Bollag et al. found that the addition of clonidine to a transversus abdominis plane (TAP) block with bupivacaine did not affect short- or long-term pain scores.¹⁰⁶

In summary, many pharmacologic mechanisms for the prevention of progression of acute postoperative pain to chronic pain have been studied. Further studies are needed on this topic to specifically determine appropriate medications, dosages and duration of administration for post CD patients; and the effect of drug transfer, if any, to the neonate. Information gained on mechanisms of peripheral and central sensitization offers opportunities for novel targeted pharmacological interventions. In particular, the protective effects of oxytocin against hypersensitivity should be further investigated and validated. Investigation into glial cell line-derived neurotrophic factor may offer a novel target for preventing injury-induced transcriptional changes in sensory neurons.

Summary and future directions

Due to a high prevalence of CD, even a low incidence of persistent pain affects a large number of young women. Several different testing modalities may be used to help predict severe acute pain and/or persistent and chronic pain. However, these modalities, while associated with statistically significant results in the research setting, remain clinically impractical or unfeasible at present because of their time-consuming nature and weak or moderate sensitivity and specificity. As these tests are refined and improved, so as to be time efficient and highly sensitive and specific, they may be applied to tailor treatment for patients at risk of developing severe

acute pain and/or chronic pain. The current predominance of evidence suggests an association between acute pain severity after surgery and the development of persistent and chronic pain. Thus, current approaches to chronic pain prevention aim to optimize multimodal analgesia and reducing nociception and acute pain, by modifying the surgical technique, choosing neuraxial anesthesia/analgesia, supplementing with regional anesthesia and local anesthetic when a neuraxial technique is not possible, and implementing a multimodal opioid-sparing analgesic regimen. With the increasing understanding of the pathophysiology and risk factors, it is essential to continue the quest to identify novel target sites that will help to prevent and treat persistent pain after CD.

Disclosure of interests

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