Chapter 5

# Pain Management for Pregnant Women in the Opioid Crisis Era

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Additional information is available at the end of the chapter

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**Abstract**

Acute and chronic pain management during pregnancy, after delivery and even during lactation are challenging even for experienced physicians. This chapter intends to cover pregnancy-induced physiological changes in relation to pain conditions. It also covers the most common pain disorders in pregnancy and provides a comprehensive summary of the pharmacological and non-pharmacological options for pain management in pregnancy. Additionally, pain management in context of opioid abuse will also be covered, as high prevalence of opioid prescription is linked to the very poor maternal and fetal outcomes. The possibility of maternal opioid abuse and fetal opioid withdrawal should be known to all physicians, given its rising trends. Multimodal protocols and opioid sparing strategies are highly essential for safe pain management during pregnancy and have been discussed. This chapter is intended to be a fast and detailed review for residents, pain fellows, and physicians who seek pain control in pregnant women.

**Keywords:** pain management during pregnancy, pregnancy related musculoskeletal pain, non-pharmacological pain management, opioid crisis, opioid use disorder, neonatal abstinence syndrome

## 1. Introduction

Pain during pregnancy is not necessarily limited to labor pain and includes musculoskeletal, urological, neuropathic, and psychosocial pain. This can pose a diagnostic and management challenges, especially in terms of medication selection. If left untreated, it can lead to anxiety,

depression, and even physical disability. Pain can persist postpartum with severe symptoms in 10% of patients and can sometimes last for more than 10 years after delivery [1]. There are multiple barriers to effective pain management in pregnancy. In addition to the complex and multifactorial nature of pain, there is a worldwide misconception that acute musculoskeletal pain during pregnancy is a normal physiological consequence that should be coped with. There is also fear of undesirable pharmacological effects of pain medicines on the fetus that prevent patients from pursuing treatment options.

Another challenge is the ongoing opioid crisis. Progressive increase in opioid prescription and lack of familiarity with non-pharmacological pain management or multimodal protocols have led to a sharp increase in opioid abuse, admission to rehabilitation facilities, and increased overall maternal and fetal morbidity and mortality [2].

## 2. Physiological changes in pregnancy affecting pain

Pain occurring in pregnancy could be a result of mechanical and/or biochemical changes arising from changing physiology. The average pregnant woman gains 10–18 kg of weight (an approximate of 20% increase from baseline), doubling the mechanical load on axial joints and ligaments [3, 4]. The core muscles responsible for core stabilization and balance are stressed as well. The gravid uterus stretches the abdominal muscles and pelvic floor muscles. There is an upward shift of the center of gravity leading to some compensatory hyperlordosis with stretching of lower back muscles, significant anterior pelvic tilt with rotation of the pelvis on the femur, and increased use of hip extensors and abductors. There is also more head flexion and drooping of the shoulders [5]. Enlarged breasts and malposition during breastfeeding could also lead to thoracic kyphosis.

Hormonally induced structural changes include increased ligament and joint laxity, decreased bone density and weaker collagen, all of which have been associated with back pain [6, 7]. The Relaxin hormone is secreted from the placental decidua and corpus luteum to increase the myometrium relaxation and cervical softening by altering the matrix metalloproteinase and glycosaminoglycan compositions [8]. While the correlation of Relaxin hormone level with pain has been inconsistent, it can contribute to joint and ligament laxity and symphysis pubis dilation [7]. There is fluid gain of 2–3 l, which are locally entrapped in legs and ankles which in addition to global water retention contributes to joint stress [9]. This further contributes to joint stress. Improper joint loading can persist in the postpartum period due to continued ligament laxity and core muscle weakness. The net effect is low back pain (LBP) and pelvic girdle pain (PGP).

## 3. Non-labor chronic pain

Acute and chronic pains are very common in pregnancy, with an incidence of at least 60% for LBP and 20% for PGP. Chronic non-labor pain is any subjective unpleasant sensory experience, both physically and emotionally, with actual tissue damage not relating to obstetric origin for more than 6 months. Some authors accept a 3-month timeframe if pure central neuromodulation has been documented [10]. Chronic pain has been associated with poor

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academic achievement, increased job loss, disability, anxiety, depression, sexual dysfunction and reduction in relationship satisfaction. These collectively contribute to a lower quality of life (QOL) [11]. Chronic pain guidelines classify chronic pain into pain with a specifically identifiable pathology (such as infection or malignancy) for which there is specific treatment or pain with non-specific pathology. Non-specific pain could be somatic, visceral, neuropathic, psychosocial, or combined. (**Table 1**) summarizes the type of chronic pain in pregnant women.

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| **Somatic** | **Musculoskeletal** | Pelvic floor dysfunction |
| | | Spondylosis |
| | | Myofascial syndrome—fibromyalgia |
| **Visceral** | **Gynecologic** | Endometriosis (most common) |
| | | Pelvic adhesive/congestion syndrome |
| | | **Infections**: |
| | | Tuberculous salpingitis—chronic PID |
| | | **Malignancy**: |
| | | Gynecologic malignancy |
| | | **Mechanical**: |
| | | Prolapse of pelvic contents |
| | | Adnexal cysts—cervical stenosis |
| | **Urological** | Congenital: Urethral diverticulum |
| | | **Malignancy**: Bladder neoplasm |
| | | **Infection**: |
| | | Nongynecologic—interstitial cystitis |
| | | Recurrent UTI—urethritis |
| | | **Stones**: (nephrolithiasis/urolithiasis) |
| | **Gastrointestinal** | **Inflammatory**: |
| | | Inflammatory bowel disease |
| | | Diverticulitis—colitis—celiac sprue |
| | | **Malignancy**: Colon neoplasm |
| | | **Functional**: Irritable bowel syndrome |
| | | Constipation |
| **Neuropathic** | • Herniated disk—cauda equina syndrome | |
| | • Neuralgia—nerve impingement | |
| **Psychosocial** | • Prior or current physical or sexual abuse | |
| | • Depression—somatization disorder | |
| | • Substance abuse | |

**Table 1.** Chronic pain conditions in pregnant women.

### 3.1. Musculoskeletal pain

Musculoskeletal pain is any pain that originates from muscles, tendons, or ligaments. Back pain and pelvic pain are among the most common types of chronic musculoskeletal pain in pregnancy [5]. Other less common types are cervical, thoracic, rib, abdominal wall, and chest wall pain. Acute musculoskeletal pain directly after labor could be due to sacral stress fracture, coccydynia (from coccygeal fracture, dislocation, or contusion), perineal tear after traumatic vaginal delivery, or symphysis pubis pain (from contusion or symphysis separation).

#### *3.1.1. Lower back pain*

**Lower back pain** (**LBP**) is any pain occurring between the 12th rib and the gluteal fold. **LBP** commonly occurs at lumbar spine level L4-5 and is believed to be a combination of mechanical strains, muscles weakness, joint laxity, and connective tissue edema without any identifiable etiology on imaging studies [12]. Less common causes are myofascial pain, lumbar disc herniations, and true sciatica. Magnetic resonance studies did not show any difference in the incidence of asymptomatic disc bulge or herniation in pregnant women compared with nonpregnant women [12].

#### *3.1.2. Pelvic girdle pain*

**Pelvic girdle pain** (**PGP**) is any pain occurring between the posterior iliac crest and gluteal fold down to the symphysis pubis. Also called lumbopelvic pain, it is the second most common pregnancy-related musculoskeletal complaint after LBP; however, it is even more disabling. **PGP** is classified into four categories: unilateral sacroiliac syndrome, bilateral sacroiliac syndrome, symphysiolysis (separation of the pubis), and pelvic girdle syndrome (pain in all three pelvic joint regions, namely the two sacroiliac joints and the pubis). The sacroiliac joint (**SIJ**) is the most common source of pelvic girdle pain in pregnancy [20], followed by pelvic floor muscle dysfunction, which is prevalent in 50% of pregnant women with pelvic pain. MRI studies have reported the pregnancy-induced SIJ changes to be SIJ-bone marrow edema (BME), joint fluid accumulation, capsulitis, enthesitis, and subchondral sclerosis [13].

#### *3.1.3. Risk for musculoskeletal pain*

While mechanical strain can occur routinely in pregnancy, musculoskeletal pain development is not universal. Risk factors include multiparity, preexisting joint disorders, obesity, and depression. LBP progressively increases with each trimester; however, it has a favorable postpartum course as the pain resolves at least in 80% of patients. Unfortunately, 20% of patients still report pain up to 3 years after delivery. The underlying etiology, severity of the symptoms and degree of anatomical changes (such as exaggerated symphysis widening and pelvic asymmetry) determine the intrapartum and postpartum prognosis. Bone marrow distension and joint capsular edema usually resolve after delivery, but autoimmune-related joint conditions such as multiple sclerosis and rheumatoid arthritis usually flare up in the postpartum period after the cessation of pregnancy-induced autoimmune modulation [14, 15].

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### 3.2. Management of musculoskeletal pain

#### *3.2.1. History and physical examination*

A comprehensive and structured history is the first step for pain management in any patient. This includes:

- Detailed nature of the pain (onset, course, duration, alleviating and aggravating factors, and radiation)
- Functional limitations, other persistent pain conditions
- History of other comorbidities (e.g., diabetes mellitus, autoimmune diseases)
- History of illicit drug abuse
- Social and family support, coping mechanisms
- Alarming neurological signs as urinary retention (with overflow incontinence), bladder or bowel incontinence, saddle anesthesia, loss of anal sphincter tone, major motor weakness in lower extremities, and fever
- Any suspicion of infection, fracture, or malignancy should be investigated, and tertiary neurosurgical referral is warranted urgently

The **general** examination starts with inspection of the skin, spine, and pelvic contour; palpation of surrounding muscles, SIJ, and facet joints for tenderness; and determination of gait pattern. In SIJ and facet joint arthropathy, there is localized tenderness over the affected joints with increased pain on axial rotation. Discogenic pain radiates to back of the thigh and worsens with the flexion of the spine.

**Special** physical tests for back pain are designed to provoke reproducible pain during the joint action with high specificity and sensitivity. Thus, they can be relied upon for preliminary diagnosis and follow up. These include active straight leg raise (ASLR) test for LBP and Patrick's Faber test for PGP, pubic symphysis palpation and modified Trendelenburg's test for symphysis pubis pain, posterior pelvic pain provocation (PPPP) test for posterior pelvic pain, and long dorsal sacroiliac ligament (LDL) palpation for SIJ pain. Physical examination can be helpful in identifying symptomatic herniated disc and its alarming signs. However, it is not very helpful to definitely locate the anatomic source of other non-discogenic pain even after imaging studies [16]. In general, a single physical test is less useful than combined tests for clinical decision, thus combined clusters of physical examinations are recommended for better test reliability [17].

#### *3.2.2. Laboratory investigations for musculoskeletal pain*

There are no recommendations for routine laboratory investigations for musculoskeletal pain unless there is suspicion of infection or malignancy. Consider CBC, ESR, and CRP in

suspected malignancy, or thyroid assay if hypothyroidism is suspected, and any blood investigations according to provisional diagnosis.

*3.2.3. Radiological investigations for musculoskeletal pain*

There are no recommendations for routine radiological scans in acute or chronic back pain without warning signs. The European guidelines for diagnosis and treatment of PGP recommends against routine imaging for musculoskeletal pain during pregnancy. No significant differences were found in short- or long-term pain outcomes or functional recovery outcomes between immediate imaging versus routine care in patients with LBP in the absence of warning signs [18]. Due to poor sensitivity in detecting the early degenerative stages of SIJ arthritis, computed tomography (CT) and conventional radiography are not recommended. MRI is more favorable as a diagnostic alternative as there is no exposure to radiation and it is more reliable in discriminating changes around joints and ligaments. MRI is recommended for LBP, PGP and SIJ pain only in case of traumatic injuries, tumor, ankylosing spondylitis, and alarming signs [19].

*3.2.4. Treatment of musculoskeletal pain*

Treatment of musculoskeletal pain should be in a structured, multimodal approach. This involves the combination of non-pharmacological and pharmacological options. Surgical intervention is only reserved for emergency situations (acute disc herniation and cauda equina syndrome).

Non-pharmacological modalities include physical exercise and other alternatives such as massage, acupuncture, relaxation techniques, and chiropractic care. Physical exercise helps strengthen muscles of the back, abdomen, and pelvic floor to maintain core stability and augment joint stabilization.

The first line pharmacological treatment for mild pain is a short course of analgesics such as acetaminophen. NSAIDs can be used for no more than 2 days at a time, and it is contraindicated in the third trimester and preferably to be avoided in first trimester. Opioids should also be avoided throughout the pregnancy. In chronic pain studies, prolonged opioid use did not show any benefit in functional outcome or reduction of pain intensity [20]. Moreover, it can increase pain sensitivity in the long run. Most medical societies agree about the judicious use of opioid in chronic pain, as summarized in **Table 2**.

### 3.3. Migraine

The incidence of new-onset migraine during pregnancy is around 2–3%. However, it is more common for pregnant women to have a prior history of migraine. Fortunately, severity and frequency of migraine symptoms reduce by 43–86%, mostly during the first trimester. Sumatriptan is considered safe and is recommended by the European Federation of Neurological Societies as abortive migraine therapy [21]. It is considered non-teratogenic and, despite the theoretical vasoconstrictor effect, no vascular malformations were reported. However, it has been associated with uterine atony and peripartum hemorrhage [22]. Ergot derivatives are contraindicated during pregnancy and lactation due to their high teratogenic

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| **Recommendation** 1: "**Strong Evidence**" | **Optimization** of non-opioid pharmacotherapy and non-pharmacological therapy **before** trial of opioids. |
| **Recommendation** 2: "Weak Evidence" | In persistent problematic pain despite optimized non-opioid therapy, **Opioid trial can be started** if,<br>1. Chronic non-cancer pain<br>2. No current/past substance use<br>3. No active psychiatric disorders |
| **Recommendation** 3: "**Strong Evidence**" | In Patients with current substance use disorder, **Opioid is strongly not recommended.** Substance use disorder as alcohol abuse and dependence, and narcotic abuse and dependence should be addressed by physician. |
| **Recommendation** 4: "Weak Evidence" | In Patients with current active psychiatric disorder, **Optimization of** psychiatric disorder **is strongly recommended before Opioid trial.** as long as<br>**1.** Optimal non-opioid, non-pharmacological therapy for chronic non-cancer pain has been achieved. |
| **Recommendation** 5: "**Strong Evidence**" | In **long term** opioid for non-cancer chronic pain patients should be **restricted to less 90 mg morphine equivalents** daily rather than no upper limit or a higher limit on dosing. |
| **Recommendation** 6: "Weak Evidence" | Starting **opioid** for non-cancer chronic pain patients should be **restricted to less 50 mg morphine equivalents** daily rather than no upper limit or a higher limit on dosing. |
| **Recommendation** 7: "Weak Evidence" | **Opioids rotation** and **tapering** for current opioid users in case of<br>**1.** Persistent non-cancer pain or 2. Adverse events<br>"*Rotation is parallel with the goal of dose reduction*" |
| **Recommendation** 8: "Weak Evidence" | **Tapering opioids** to the **lowest effective dose** with the aim to **discontinuation.** |
| **Recommendation** 9: "**Strong Evidence**" | **Multidisciplinary team** (MDT) program is highly recommended for patients using opioids and experiencing serious adverse events.<br>"*MDT is not limited to a primary care physician, a nurse, a pharmacist, a physical therapist, a chiropractor, a kinesiologist, an occupational therapist, an addiction specialist, a psychiatrist, and a psychologist*" |

**Table 2.** Summary of the 2017 Canadian Guidelines for Opioids for Chronic Non-Cancer Pain.

risk, uterine vasoconstriction, low birth weight, preterm contractions and miscarriage, and even convulsions in breastfed infant [23]. Beta-blockers are the first line prophylactic option during lactation and are considered safe during pregnancy. Angiotensin-converting enzyme inhibitors are contraindicated because of their nephrotoxicity and prematurity risk [22]. Non-pharmacological options include relaxation techniques, acupuncture, biofeedback, and behavioral cognitive therapy. Acetaminophen is ideal as first add-on medication. If acetaminophen fails, sumatriptan or NSAIDs could be added to the regimen based on clinical assessment and potential risk to the fetus.

### 3.4. Neuropathic pain

Causes of neuropathic pain in pregnancy include carpal tunnel syndrome, meralgia paresthetica, low intercostal nerve compression, and the pain of a previous cesarean section wound scar. Physiological water retention, obesity, and diabetes are contributory factors for neuropathic pain. Pregnancy-related carpal tunnel syndrome (PRCTS) is as prevalent as 43%, as confirmed by nerve conduction studies [24]. It manifests as pain and numbness in the distribution of the median nerve with progressive worsening at night. CTS usually subsides by conservative treatment and night splints. Physical therapy, infiltration of local anesthetic, and slow-release steroids could be added. Surgical decompression is rarely required and is reserved only for severe cases with motor neuropathy [25]. Differential diagnosis includes De-Quervain tendinopathy which presents with pain, swelling, and tenderness along the radial aspect of the wrist. Meralgia paresthetica is mononeuropathy of the lateral femoral cutaneous nerve (LFCN) which presents as tingling and numbness in the anterolateral aspect of the thigh.

## 4. Summary of non-labor pain management algorithm

A structured, multimodal approach is the essence of management of NLP. It is essential to set realistic goals based on functional status rather than chasing a pain score of zero. The impact of setting realistic goals of pain management has been shown to produce more patient satisfaction, better psychological well-being, higher quality of life and reduced anxiety [26, 27]. On the other hand, a patient feeling her pain is poorly controlled leads to more disability, increased pain intensity, anxiety, and depression [28, 29].

**Non-pharmacological** therapies are very valuable as they augment pain relief and minimize the utilization of drugs. These benefits are welcomed by pregnant women who often have concerns about medications and their side effects. Activity modifications, physical exercise, and a physiotherapy program have been shown to be effective in pain reduction in comparison with standard care. The additive benefit of combining different approaches such as adding acupuncture to stabilization exercises, has been proven in different studies. Pelvic belt bracing has been shown to improve SIJ stability by decreasing joint laxity and sagittal rotation by 19% [30].

## 5. Summary of pharmacological management

### 5.1. Teratogenicity and toxicity

Agents that are toxic and cause birth defects are known as teratogens [31]. During fetal development, teratogens impart their effect mostly during the time of organogenesis which begins in the third week of gestation. The severity of malformation depends on many factors, including type of teratogenic agent, dose and duration of exposure, time period of gestation, and

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| **Category A**: No fetal risk in human studies |
| **Category B**: No fetal risk in animal studies, but no human studies |
| **Category C**: Harmful fetal risk in animal studies, but no human studies |
| **Category D**: Harmful fetal risk in human studies, but use is acceptable in serious situation |
| **Category X**: Harmful fetal risk in both animal and human studies. |

**Table 3.** FDA classification for safety of medications in pregnancy.

maternal and fetal health prior to the exposure. Teratogenicity can be caused by fetal cell death leading to spontaneous abortion, impaired cellular functions, or placental toxicity [31].

The US Food and Drug Administration (FDA) classification for safety of medications in pregnancy is shown in "**Table 3**" [32].

### 5.2. Opioid medications

Codeine, hydrocodone, oxycodone, and propoxyphene are currently among the most commonly prescribed opioid agents in the United States [33]. Opioid medications should not be considered as a homogenous class of medications regarding its maternal and fetal effects, as some subclass are safer than the others. Evidence is still inconclusive regarding the relationship of opioid with poor fetal growth, preterm birth, and birth defects as most of the studies were biased with a lot of confounders. The general recommendation is that opioid usage should be avoided or minimized during pregnancy and should never be considered as a first line option. Usage during early pregnancy could be associated with neural tube defects and heart defects, and during late pregnancy, with neonatal abstinence syndrome (NAS) and neonatal respiratory distress syndrome. All opioid medications are classified as Class C (uncertain safety, no human studies; animal studies show an adverse effect).

Fentanyl patches seem to be safe, but there is still a risk of withdrawal. Methadone is associated with neonatal morbidity, such as preterm birth (<32 weeks of gestation), low birth weight, decreased head circumference, jaundice, thrombocytosis, arrhythmia, and admission to the neonatal intensive care unit [34, 35]. Codeine is classified as category C by the FDA [36]. It is neither teratogenic nor associated with congenital malformation. However, there have been reports of postpartum hemorrhage if it was taken near the end of pregnancy. Moreover, it could be rapidly metabolized into morphine, by CYP450 enzymes leading to a significant risk of fetal opioid toxicity during lactation [37]. Tramadol is classified as a category C medication. It has a risk of withdrawal with high maternal dosing [32]. It is not recommended to discontinue it during breastfeeding as only trace amounts cross into the breast milk.

The morphine equivalent daily dosage (MEDD) is a mean of calculating the daily cumulative intake of any opioid-related drugs. The aim is to reduce the risk of overdose, especially in chronic opioid use. Evidence has shown that there is no single dosage threshold below which overdose risk could be avoided, but opioid dosages of <50 MEDD/day (mg/day) would likely reduce the risk of fatal overdose.

### 5.3. Non-opioid analgesic medications

#### *5.3.1. Acetaminophen (paracetamol)*

Acetaminophen is widely used as an analgesic. In the USA, 65–70% of women used acetaminophen during pregnancy [38]. It has no known maternal adverse outcomes or fetal congenital defects as confirmed by analysis of registries [39]. Despite the reports about increased risk of attention deficit hyperactive disorder (ADHD) in children if used for over 6 weeks, the evidence was inconclusive according to the latest FDA warning [40].

#### *5.3.2. Non-steroidal anti-inflammatory agents*

Non-steroidal anti-inflammatory agents (NSAIDs) such as Ibuprofen, Naproxen, Diclofenac, and Celecoxib are very commonly prescribed for analgesia. It was reported that 18–25 and 4% of the USA pregnant women are exposed to over-the-counter (OTC) Ibuprofen, and Naproxen respectively [38]. In the third trimester, NSAIDs are linked with premature closure of the ductus arteriosus and development of pulmonary hypertension in a fetus. At high doses, NSAIDs decrease renal perfusion in fetus and lead to oligohydramnios. Despite NSAIDs being Category B drugs before the third trimester, it is generally recommended to be avoided as in the first trimester there is risk of miscarriage and in the third trimester there is a risk of oligohydramnios and ill effect on fetal circulation. Furthermore, NSAIDs are associated with a delay in onset of labor and increase in duration.

#### *5.3.3. Aspirin*

Aspirin is not commonly used to treat pain or fever in pregnancy. It is associated with neonatal hemorrhage, IUGR, gastroschisis and perinatal death. Similar to NSAIDs, they delay onset of labor and increase labor duration. An increased risk of bleeding during delivery has also been reported. Low-dose Aspirin (81 mg) is considered safe and is commonly given with heparin in conditions with recurrent miscarriage and in women with antiphospholipid syndrome [41].

### 5.4. Psychotropic medications

Psychotropic drugs are medications that affect mood, cognitive function or any other mental process [42]. These include antidepressants, benzodiazepines, antiepileptic agents and antipsychotics. Most of the safety profiles and recommendations for using these drugs are based on retrospective observational studies in pregnant patients with underlying psychiatric or mood disorders (such as bipolar or depression or anxiety) and are thus liable to bias and confounding. Some medications are well known to cause significant congenital malformations, such as Valproate, Carbamazepine, Lithium, and Lamotrigine. Therefore, they must be avoided in pregnancy. Most of other drugs are debated in their fetal outcome. In general, the risk-benefit ratio should be weighed, and the lowest dose should be applied.

### *5.4.1. Antidepressants*

Patients with chronic pain commonly experience depression. Selective serotonin receptor inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are widely used as antidepressants and also as adjuvant therapy for chronic pain. SSRIs have been the most commonly studied antidepressants in pregnancy and include Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, and Sertraline. There is little information about other SSRIs. Majority of studies report that SSRIs are not teratogenic; however, some consider them as low-risk teratogens as due to there has been associated increase, albeit minimal, in cardiac congenital anomalies in the form of small ventricular defects that spontaneously close in childhood [43, 44]. The use of SSRIs minimally increases the risk of antepartum and postpartum hemorrhage. There has been no increase in the risk of spontaneous abortions, perinatal deaths, or hypertensive disorders of pregnancy. Peripartum fetal exposure is not believed to be associated with postpartum withdrawal or toxicity symptoms in the neonate. Case reports that had reported an association were confounded by other psychotropic medications [45]. Among SSRIs, sertraline has the safest profile as its low levels in blood and breast milk [46].

TCAs are believed to be generally nonteratogenic except Clomipramine as reported by most studies. All drugs in this class could increase the risk of spontaneous abortion, hypertensive disorders of pregnancy, postpartum hemorrhage and transient fetal withdrawal symptoms [47]. There is still limited information and less usage of antidepressants drugs other than SSRIs, such as Selective Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and atypical antidepressants like Mirtazapine and Buspirone.

### *5.4.2. Benzodiazepines*

A majority of studies report benzodiazepines to be nonteratogenic. Even the few conflicting reports showed that the incidence of minor anomalies such as cleft palate is only minimally increased compared with the general population. Perinatal usage increases the risk of low birth weight, preterm labor and spontaneous abortion. Moreover, peripartum exposure is associated with withdrawal and toxicity symptoms [48].

### *5.4.3. Antiepileptic agents*

Antiepileptic drugs are now commonly used in pain management, particularly for the treatment of neuropathic pain such as, trigeminal neuralgia, diabetic neuropathy, post-herpetic neuralgia, post-stroke pain, phantom limb pain and pain after spinal cord injuries. Majority of studies have reported significant fetal morbidity due to in-utero exposure that including major anomalies like neural tube defects, congenital heart abnormalities, and urinary tract defects, skeletal abnormalities, cleft palate and impaired cognitive and motor development [49, 50]. Pregabalin, which is very commonly prescribed for chronic neuropathic pain, has a better safety profile than other antiepileptics. However, it is still associated with a higher risk for malformation than in the general population [51].

*5.4.4. Antipsychotic agents*

In recent times, Olanzapine, the atypical antipsychotic, has been gaining popularity in chronic pain management. A majority of studies report Olanzapine as nonteratogenic and not associated with spontaneous abortions or major congenital malformations. Nevertheless, it has been associated with an increase in birth weight [52].

## 6. Non-pharmacological management

### 6.1. Physical therapy

Physical therapy has been one of the cornerstones of chronic pain treatment, replacing the original approach of rest. Activities are aimed at restoring flexibility, strength, and endurance, as well as reducing the severity of chronic pain through modulation of the biochemical processes within the body [30, 53]. Numerous physical therapy programs exist (e.g., aerobic, yoga, tai chi, strength, pilates, flexibility, and range of motion), and each one differs in frequency, intensity, and design. Despite the high utilization of physical therapy and several studies that have demonstrated its benefits in chronic pain, the effectiveness of physical therapy is unclear and current high-quality evidence to support such claims are lacking [53–56]. Absolute contraindications are myocardial infarction, ongoing unstable angina, and severe aortic stenosis [56]. Adverse effects of physical therapy are rare with musculoskeletal injury being the most common. Other potential adverse events include pain exacerbations, soreness, rhabdomyolysis, dehydration, hypo- and hyperthermia, and cardiac and respiratory events [57]. Importantly, neither the AHA nor the systemic reviews site pregnancy as an absolute or relative contraindication to physical therapy. Currently, the consensus is that the potential benefits of physical activity in pain relief, and improved quality of life outweigh its risks. For maximum effectiveness and minimum adverse effects, the evidence suggests that supervised and structured program schedules are superior to self-supervised and varying program schedules [53]. Moreover, adding a specifically tailored training to a standard physical exercise has less disability and more functional recovery at 2 years postpartum in comparison with physical exercise alone [58].

### 6.2. Acupuncture

Acupuncture is a technique where needles or other modalities are used to stimulate predetermined locations throughout the body to promote the flow of 'Qi' and rebalance the body's energy. Although the practice originated in China thousands of years ago, the specific mechanism of action has yet to be uncovered. Current theories suggest that acupuncture boosts the body's intrinsic neuropeptide pathways, including endogenous opioids. However, these effects appear to be short term and do not explain the longer term benefits of acupuncture [59]. Due to the heterogeneity of acupuncture techniques, outcomes are hard to study and compare. A few studies have shown benefits, including several randomized controlled trials which demonstrated acupuncture to be an effective alternative to pharmacologic treatment [60]. However, these studies focused on labor-related pain and not chronic pain during

pregnancy. In addition, meta-analyses have suggested that any superiority of acupuncture over sham acupuncture is not clinically significant [61, 62]. The literature does not suggest any absolute contraindications to acupuncture, but relative contraindications are similar to other needling techniques used for the treatment of pain. The incidence of serious adverse risks is rare (estimated to be 0.05 per 10,000 treatments) and is generally associated with poorly trained or unlicensed acupuncturists. The two most common adverse risks reported in one study were needling pain (3.3%) and hematoma (3.2%). Other risks include bruising, syncope, exacerbation of symptoms, paresthesia, infection, retained needle, and damage to surrounding tissues [63]. Two studies have commented on the adverse effects of acupuncture during pregnancy, and both suggest that, provided the practitioner avoid locations associated with the cervix and uterus, acupuncture is safe for both the mother and the fetus [64]. Despite the lack of evidence for the efficacy of acupuncture, the overall consensus is that acupuncture's benefits outweigh its risks, and that a trial of acupuncture can be considered in interested patients when the availability of other safe treatment options is limited.

### 6.3. Botulinum toxin

Botulinum toxin has been reported safe during the first trimester of pregnancy [65]. Although research for the use of Botox as a treatment for several chronic pain syndromes (e.g., myofascial pain, neuropathic pain) is promising, the only FDA-approved indications of Botox (serological types A and B) related to the treatment of chronic pain conditions are spasticity and chronic migraine. Evidence suggests that Botox is effective in providing pain relief for several months as a result of its long half-life [66]. Animal studies have shown some fetal damage, but the risk is uncertain in humans due to lack of sufficient evidence. Botox is classified by the FDA as a pregnancy category C drug. The current recommendation by the FDA is that Botox should be "*administered during pregnancy only if the potential benefits justifies the potential risk to the fetus.*" In addition, other more conservative treatments should be exhausted first. If Botox is considered, the risk and benefits should be acknowledged by the patient prior to proceeding.

## 7. Interventions for pain management

### 7.1. Radiofrequency ablation

Radiofrequency ablation (RFA) is a process of nerve destruction via radiofrequency-generated heat by insertion of a catheter or electrode close to the target nerve under fluoroscopic guidance, confirming the correct location through sensory and motor testing, and applying a preset temperature for a fixed time period. This aims for neuromodulation of pain pathway by disruption of the transmission of nerve impulses from the pain generators to the central nervous system. The most common application of RFA is for the treatment of facet joint pain. Other applications include discogenic pain, radicular pain, and sacroiliac pain. Generally, a diagnostic and therapeutic block with local anesthetic with or without steroid is required to proceed with RFA. Current evidence suggests that RFA treatment has a modest, short-term benefit at best, with no long-term pain improvement, as supported by a recent meta-analysis

[67–69]. Contraindications to RFA are like those associated with other neuraxial procedures. Complications include increased pain, muscle spasms, numbness or paresthesias, infection, bleeding, superficial burns, damage to surrounding tissues, side effects of local anesthetics as well as fetal exposure to radiation. As a general rule, ultrasound and magnetic resonance imaging are the preferred imaging methods during pregnancy. Ionizing radiation (e.g., fluoroscopy) in large doses can have varying effects to the fetus via pregnancy loss, malformation, growth disturbances and mutagenic and carcinogenic effects depending on the stage of gestation. The most sensitive period of gestation to radiation occurs during organogenesis (weeks 2–8) [70]. The recommended maximum dose of radiation for the duration of pregnancy varies by source, but has been sighted as low as 500 mrem (or 0.5 Rads). For comparison, a pregnant interventional radiologist can expect an average dose of 30 mrem during a 40-week pregnancy if wearing double lead [71]. Radiation is not an absolute contraindication to RFA in the pregnant patient, and if clinically indicated RFA via fluoroscopy can be considered. Benefit–risk ratio of RFA is an important first step and if in doubt, a radiologist could be consulted. Since the average exposure of radiation during a fluoroscopic-guided RFA is not well defined in the literature, various methods should be employed to minimize the risk of exposure to the fetus. Some of these techniques include shielding the abdomen and pelvic region with lead, minimizing fluoroscopic exposure time, proper placement of the fluoroscope to maximize distance from the X-ray source, limit magnifications, narrowing of the fluoroscopic window (known as tight collimation) and proper gestational timing of the procedure [70]. Given the limited evidence of RFA, the lack of quality evidence of RFA during pregnancy, and the potential for radiation exposure to the fetus, RFAs should only be considered after failure of conservative treatments and an informed discussion with the patient.

### 7.2. Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) is a technique of delivering low level of constant electrical impulses of variable frequencies, intensities and pulse waveforms to the epidermal surface with aim of inhibition of spinal cord interneurons and descending pain pathways [62, 72]. The indications for TENs are various, and examples include lower back pain and myofascial pain. Onset of pain relief takes on average 20–30 min in 75% of patients and 1 h in 95% of patients. The duration of pain relief varies among patients and conditions, but appears to be short term, decreasing over past several months of use [73]. During labor, TENS has demonstrated a benefit in acute pain relief, decreased analgesic use, and patient satisfaction [61, 74]. In contrast, two systemic analyses and a Cochrane review have not shown a significant reduction in pain [62, 75]. Technical errors from electrodes placement and timing could lead to interference with fetal heart monitoring and possible premature labor. All can easily be corrected by proper timing, proper anatomical placement of the devices, and removing the TENs if necessary [61]. Overall, the benefit of TENS for the treatment of chronic pain during pregnancy is not well studied in the literature. The general consensus is that the device's benefits outweigh its risks. TENS is easy to use and accessible over the counter. It provides a cost-effective, noninvasive, and potential pharmacologic sparing effect in pregnant patients and may be considered as an adjuvant for the safe treatment of chronic pain during pregnancy.

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## 8. Special topics in pregnancy

### 8.1. Opioid use disorder in pregnancy

Opioid use during pregnancy has increased worldwide in recent years. In the United States, the prevalence of opioid abuse or dependence among pregnant women has increased from 1.7 per 1000 delivery admissions in 1998 to 3.9 per 1000 delivery admissions in 2011. The rate of unintended pregnancy has been reported as high as 86% in women with opioid use disorder, exposing the fetus right from conception [76]. Increase in opioid-related morbidity has been directly linked with the high prevalence of opioid prescription, which reaches 27–39% among pregnant women [77]. Opioid use disorder (OUD) is a pattern of opioid intake associated with significant clinical impairment and distress. OUD is diagnosed, as described in (**Table 4**) by the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5), by at least **two** criteria within a **12-month** period [78].

Treatment of pregnant women with OUD has been shown to improve maternal and fetal outcome by decreasing the risk of relapse, maternal withdrawal symptoms, drug-seeking behaviors, and repeated cycles of intoxications [79, 80]. It also enhances the adherence to prenatal care. Opioid dependence in pregnancy is directly linked to placental insufficiency, fetal growth restriction, fetal death, abortions, premature delivery, preeclampsia, abruptio placentae, premature rupture of membranes, and postpartum hemorrhage. However, clear causality could not be established in the studied populations because of confounders in from of polydrug abuse, opioid withdrawal symptoms or coexisting maternal conditions [81]. Medical, nutritional, financial, psychological and socio-economical rampant in this patient population and should be taken into consideration when formulating a treatment plan.

Opioid use disorder (**OUD**)—DSM-5 Diagnosis by at least **2** criteria over **12** months.

- **Opioids intake** in larger amounts or over a longer period than was intended
- **Craving**, "strong desire or urge" to use opioids
- A persistent **desire** or unsuccessful efforts to cut down or control opioid use
- A great deal of **time** is spent to obtain, use or recover from the opioid
- **Failure** to fulfill **major role** obligations at work, school, or home
- **Recurrent opioid use** in physically hazardous situations
- **Reduction in important** social, or recreational activities.
- **Continued opioid** use despite the opioid related physical or psychological problem **Continued opioid** use despite the opioid related social or interpersonal problems
- **Tolerance**
- **Withdrawal**

**Table 4.** DSM-5 diagnostic criteria for OUD.

Methadone is still the standard treatment for the opioid dependence in many institutions due to its proven safety profile and established efficacy. Recently, the American College of Obstetrics and Gynecology (ACOG) has recommended buprenorphine as the first line therapy in OUD [82]. The interest is growing for buprenorphine after retrospective reports for its benefit of lower rates, lesser severity of NAS, lower morphine doses used for NAS, and a shorter stay in NICU [83]. Buprenorphine has a ceiling effect with expected low risk for overdose compared with methadone. The efficacy of buprenorphine as a substitution therapy has been debated because it was found that the patients on buprenorphine have less compliance rate and more reversion to other opioid drug abuse; however, those reports were biased and have different patient characteristics [34]. Both buprenorphine and methadone are considered safe with no significant harm and have shown good outcomes in OUD treatment [35].

### 8.2. Neonatal abstinence syndrome

As a shadow of opioid crisis and high prevalence of maternal opioid exposure, the incidence of NAS has increased worldwide. In the USA, a 400% increase in the incidence of NAS were reported and 5.8 up to 30 per 1000 hospital births in 2012, compared with 1.2 in 2000 [84, 85]. In 2012, one NAS-affected infant was born every 25 min in the United States [85].

**Neonatal abstinence syndrome (NAS)** is a neonatal drug withdrawal syndrome that occurs after opioids exposure in utero. The opioid is the main culprit for the withdrawal; however, other substances have also been reported, including alcohol, benzodiazepines, nicotine, and psychiatric medications such as antidepressants or antipsychotics [86]. The source of the opioid could be from clinician-approved use of prescription opioids for pain relief, or abuse of prescription opioids or illicit use (e.g., heroin); or medication-assisted treatment (MAT) of opioid use disorder.

In utero, fetal exposure to opioids during pregnancy is associated with a 60–80% risk of NAS [87]. However, the onset and severity are multifactorial and variable. They depend on gestational age, birth weight, maternal opioid dosage, concomitant use of other psychoactive medications and pharmacogenomics. NAS usually manifests within 2–3 days after birth with clinical signs of withdrawal as summarized in **Table 5** [88].

Multiple brain volumetric studies have reported a small volume of cortex, deep midbrain, brainstem, and thin cerebellar cortex in infants with in utero polydrug exposure including opiates [86].

| | |
|---|---|
| **Autonomic nervous system activation** | **Central nervous system irritability** |
| Fever—sweating | High-pitched continuous crying |
| Temperature dysregulation | Irritability—decreased sleep |
| Increased respiratory rate | Tremors—muscle hypertonicity |
| Nasal stuffiness, sneezing | Seizures |
| **Gastrointestinal dysfunction** | **Cardiovascular dysfunction** |
| Feeding difficulties | Tachycardia—hypertension |
| Vomiting—loose diarrhea | Hypotension in case of collapse |

**Table 5.** Summary of neonatal abstinence syndrome (NAS).

Long-term neurodevelopmental sequelae such as attention deficit disorders (ADD) and disruptive behavior have been reported in NAS. Therefore, long-term psychiatric follow-up is warranted [89]. Inpatient monitoring for 4–7 days for neonates with known in utero exposure to opioids is recommended by the American Association of Pediatrics (AAP) [88].

Non-pharmacological management is the initial approach for NAS. It entails keeping the neonate in calm, soothing environment with minimal stimulation, repeated maternal contact, and frequent hypercaloric meals [90]. Pharmacologic treatment is usually needed. This constitutes oral morphine as the first line agent and either clonidine or phenobarbital as the second line agent [85]. Once withdrawal symptoms are stable for 48 h, pharmacological weaning can be started. Breastfeeding is recommended in general even for mothers on methadone or buprenorphine treatment, as long as no other contraindications are present (e.g., HIV, illicit drug use) [82].

## 9. Recommendations summary

Chronic pain management in pregnancy is challenging. A multidisciplinary team approach and multimodal pain protocols are highly recommended. Optimum management includes a detailed review of the patient's comorbidities and considerations for behavioral and other socioeconomic factors that could affect chronic pain conditions. The safest approach is by following a goal-directed strategy that minimizes or optimizes opioid usage. Opioid sparing strategies include early alternative pain therapies such as exercise, physical therapy, behavioral changes, and non-opioid analgesics. Lifestyle and behavioral changes start with open, effective, and compassionate communication with the patient. The initial and follow-up visits should include patient education on different pharmacological options and alternative non-pharmacological modalities. Patients should be encouraged to take an active role in their own treatment plan. Acetaminophen is usually the first line drug for mild to moderate pain in any stage of pregnancy. Although ibuprofen is the non-steroidal anti-inflammatory drug (NSAID) of choice, it is contraindicated after 28 weeks of gestation as it could cause premature closure of the ductus arteriosus and impair fetal kidney function. Only in severe acute musculoskeletal pain, opioids should be used. Caution should be taken as peripartum administration is associated with neonatal respiratory depression. Additionally, a long-term therapy, particularly in late pregnancy, is associated with adaptation disorders and neonatal withdrawal symptoms. Once the opioids are indicated in a reproductive age woman, the benefits and risks of opioid use should be discussed. However, concerns about NAS or opioid abuse should not be a barrier for optimal pain management in pregnancy as long as a cautious and balanced approach is followed. Opioid prescriptions should be initiated with a drug monitoring program that could help to identify opioid use disorder or drug misuse. Concurrent opioid and benzodiazepines use should be avoided whenever possible. Opioid overdose is associated with high maternal and fetal mortality and morbidity. In case of overdose, substance abuse disorder, or higher opioid dosages (≥50 MME/day), naloxone should be prescribed. To avoid relapse, which is associated with very high morbidity in pregnant women with opioid use disorder, an opioid agonist (buprenorphine or methadone) is the recommended first line therapy in combination with behavioral therapy. Antiepileptic drugs are contraindicated during pregnancy as they carry a teratogenic risk; however, well-studied antidepressants, such

as sertraline and amitriptyline can be used for chronic pain with the appropriate indications. Sumatriptan is safe to use in pregnant patients with migraine.

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## References

[1] Elden H, Gutke A, Kjellby-Wendt G, Fagevik-Olsen M, Ostgaard H-C. Predictors and consequences of long-term pregnancy-related pelvic girdle pain: A longitudinal follow-up study. BMC Musculoskeletal Disorders. 2016 Dec 12;**17**(1):276

[2] Martin CE, Longinaker N, Terplan M. Recent trends in treatment admissions for prescription opioid abuse during pregnancy. Journal of Substance Abuse Treatment. 2015 Jan;**48**(1):37-42

[3] Kristiansson P, Svardsudd K, von Schoultz B. Back pain during pregnancy: A prospective study. Spine (Phila Pa 1976). 1996 Mar;**21**(6):702-709

[4] Ritchie JR. Orthopedic considerations during pregnancy. Clinical Obstetrics and Gynecology. 2003 Jun;**46**(2):456-466

[5] Kovacs FM, Garcia E, Royuela A, Gonzalez L, Abraira V. Prevalence and factors associated with low back pain and pelvic girdle pain during pregnancy: A multicenter study conducted in the Spanish National Health Service. Spine (Phila Pa 1976). 2012 Aug;**37**(17):1516-1533

[6] To WW, Wong MW. Persistence of back pain symptoms after pregnancy and bone mineral density changes as measured by quantitative ultrasound—A two year longitudinal follow up study. BMC Musculoskeletal Disorders. 2011 Feb;**12**:55

[7] Marshall SA, Ng L, Unemori EN, Girling JE, Parry LJ. Relaxin deficiency results in increased expression of angiogenesis- and remodelling-related genes in the uterus of early pregnant mice but does not affect endometrial angiogenesis prior to implantation. Reproductive Biology and Endocrinology. 2016 Mar 22;**14**(1):11

[8] Soh YM, Tiwari A, Mahendroo M, Conrad KP, Parry LJ. Relaxin regulates hyaluronan synthesis and aquaporins in the cervix of late pregnant mice. Endocrinology. 2012 Dec;**153**(12):6054-6064

[9] Heenan AP, Wolfe LA, Davies GAL, McGrath MJ. Effects of human pregnancy on fluid regulation responses to short-term exercise. Journal of Applied Physiology. 2003 Dec;**95**(6):2321-2327

[10] McMahon SB, Dmitrieva N, Koltzenburg M. Visceral pain. British Journal of Anaesthesia. 1995 Aug;**75**(2):132-144

[11] Tripp DA, Nickel JC, Fitzgerald MP, Mayer R, Stechyson N, Hsieh A. Sexual functioning, catastrophizing, depression, and pain, as predictors of quality of life in women with interstitial cystitis/painful bladder syndrome. Urology. 2009 May;**73**(5):987-992

[12] Scriven MW, Jones DA, McKnight L. Current concepts review. Musculoskeletal considerations in pregnancy. The Journal of Bone and Joint Surgery. American Volume. 1995 Sep;**77**(9):1465

[13] Eshed I, Miloh-Raz H, Dulitzki M, Lidar Z, Aharoni D, Liberman B, et al. Peripartum changes of the sacroiliac joints on MRI: Increasing mechanical load correlating with signs of edema and inflammation kindling spondyloarthropathy in the genetically prone. Clinical Rheumatology. 2015 Aug 26;**34**(8):1419-1426

[14] Hughes SE, Spelman T, Gray OM, Boz C, Trojano M, Lugaresi A, et al. Predictors and dynamics of postpartum relapses in women with multiple sclerosis. Multiple Sclerosis. 2014 May 9;**20**(6):739-746

[15] Zrour SH, Boumiza R, Sakly N, Mannai R, Korbaa W, Younes M, et al. The impact of pregnancy on rheumatoid arthritis outcome: The role of maternofetal HLA class II disparity. Joint, Bone, Spine. 2010 Jan;**77**(1):36-40

[16] May S, Littlewood C, Bishop A. Reliability of procedures used in the physical examination of non-specific low back pain: A systematic review. The Australian Journal of Physiotherapy. 2006;**52**(2):91-102

[17] Petersen T, Laslett M, Juhl C. Clinical classification in low back pain: Best-evidence diagnostic rules based on systematic reviews. BMC Musculoskeletal Disorders. 2017 Dec 12;**18**(1):188

[18] Chou R, Fu R, Carrino JA, Deyo RA. Imaging strategies for low-back pain: Systematic review and meta-analysis. Lancet (London, England). 2009 Feb 7;**373**(9662):463-472

[19] Vleeming A, Albert HB, Ostgaard HC, Sturesson B, Stuge B. European guidelines for the diagnosis and treatment of pelvic girdle pain. European Spine Journal. 2008 Jun 8;**17**(6):794-819

[20] Adams SM, Blanco C, Chaudhry HJ, et al. First do no harm: Marshaling Clinician Leadership to Counter the Opioid Epidemic. Washington, DC: National Academy of Medicine; 2017

[21] Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine-revised report of an EFNS task force. European Journal of Neurology. 2009 Sep;**16**(9):968-981

[22] Amundsen S, Nordeng H, Nezvalová-Henriksen K, Stovner LJ, Spigset O. Pharmacological treatment of migraine during pregnancy and breastfeeding. Nature Reviews. Neurology. 2015;**11**(4):209-219

[23] Cassina M, Di Gianantonio E, Toldo I, Battistella PA, Clementi M. Migraine therapy during pregnancy and lactation. Expert Opinion on Drug Safety. 2010 Nov 27;**9**(6):937-948

[24] Padua L, Di PA, Pazzaglia C, Liotta GA, Librante A, Mondelli M. Systematic review of pregnancy-related carpal tunnel syndrome. Muscle & Nerve. 2010 Nov;**42**(5):697-702

[25] Turgut F, Cetinşahinahin M, Turgut M, Bölükbaşi O. The management of carpal tunnel syndrome in pregnancy. Journal of Clinical Neuroscience. 2001 Jul;**8**(4):332-334

[26] Roditi D, Robinson ME. The role of psychological interventions in the management of patients with chronic pain. Psychology Research and Behavior Management. 2011;**4**:41-49

[27] Hanna MN, González-Fernández M, Barrett AD, Williams KA, Pronovost P. Does patient perception of pain control affect patient satisfaction across surgical units in a tertiary teaching hospital? American Journal of Medical Quality. 2012 Sep 16;**27**(5):411-416

[28] Vallerand AH, Templin T, Hasenau SM, Riley-Doucet C. Factors that affect functional status in patients with cancer-related pain. Pain. 2007 Nov;**132**(1-2):82-90

[29] Arnstein P, Caudill M, Mandle CL, Norris A, Beasley R. Self efficacy as a mediator of the relationship between pain intensity, disability and depression in chronic pain patients. Pain. 1999 Apr;**80**(3):483-491

[30] Stuge B, Hilde G, Vøllestad N. Physical therapy for pregnancy-related low back and pelvic pain: A systematic review. Acta Obstetricia et Gynecologica Scandinavica. 2003 Nov;**82**(11):983-990

[31] Brent RL. Environmental causes of human congenital malformations: The pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. Pediatrics. 2004 Apr;**113**(4 Suppl):957-968

[32] U.S. Food and Drug Administration. Labeling – Pregnancy and Lactation Labeling (Drugs) Final Rule. 2014. Available from: https://www.fda.gov/Drugs/Development ApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm [Accessed: 2018-06-29]

[33] Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among medicaid-enrolled women. Obstetrics and Gynecology. 2014 May;**123**(5):997-1002

[34] Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Mattick RP, Editor. The Cochrane Database Systematic Reviews. 2008 Apr 16;**2**:CD002207

[35] Brogly SB, Saia KA, Walley AY, Du HM, Sebastiani P. Prenatal buprenorphine versus methadone exposure and neonatal outcomes: Systematic review and meta-analysis. American Journal of Epidemiology. 2014 Oct 1;**180**(7):673-686

[36] U.S. Food and Drug Administration. FDA has reviewed possible risks of pain medicine use during pregnancy. 2015. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm429117.htm [Accessed: 2018-06-29]

[37] Niesters M, Overdyk F, Smith T, Aarts L, Dahan A. Opioid-induced respiratory depression in paediatrics: A review of case reports. British Journal of Anaesthesia. 2013 Feb; **110**(2):175-182

[38] Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. American Journal of Obstetrics and Gynecology. 2005 Sep;**193**(3 Pt 1):771-777

[39] Rebordosa C, Kogevinas M, Horváth-Puhó E, Nørgård B, Morales M, Czeizel AE, et al. Acetaminophen use during pregnancy: Effects on risk for congenital abnormalities. American Journal of Obstetrics and Gynecology. 2008 Feb;**198**(2):178.e1-178.e7

[40] Cooper M, Langley K, Thapar A. Antenatal acetaminophen use and attention-deficit/hyperactivity disorder: An interesting observed association but too early to infer causality. JAMA Pediatrics. 2014 Apr 1;**168**(4):306-307

[41] Kaandorp SP, Goddijn M, van der Post JAM, Hutten BA, Verhoeve HR, Hamulyák K, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. The New England Journal of Medicine. 2010 Apr 29;**362**(17):1586-1596

[42] Schulz P, Steimer T. Psychotropic medication, psychiatric disorders, and higher brain functions. Dialogues in Clinical Neuroscience. 2000 Sep;**2**(3):177-182

[43] Antenatal and Postnatal Mental Health: Clinical Management and Service Guidance; Clinical Guideline; 2014. Available from: http://nice.org.uk/guidance/cg192

[44] Grigoriadis S, VonderPorten EH, Mamisashvili L, Roerecke M, Rehm J, Dennis C-L, et al. Antidepressant exposure during pregnancy and congenital malformations: Is there an association? A systematic review and meta-analysis of the best evidence. The Journal of Clinical Psychiatry. 2013 Apr 15;**74**(4):e293-e308

[45] Einarson A. Antidepressants and pregnancy: Complexities of producing evidence-based information. CMAJ. 2010 Jul 13;**182**(10):1017-1018

[46] Marcus SM, Heringhausen JE. Depression in childbearing women: When depression complicates pregnancy. Primary Care. 2009 Mar;**36**(1):151-165. ix

[47] Gentile S. Tricyclic antidepressants in pregnancy and puerperium. Expert Opinion on Drug Safety. 2014 Feb 3;**13**(2):207-225

[48] National Collaborating Centre for Mental Health (UK). Antenatal and Postnatal Mental Health: Clinical Management and Service Guidance: NICE Clinical Guidelines: Updated Edition. Leicester (UK): British Psychological Society; No. 192. 2014

[49] Meador KJ, Pennell PB, Harden CL, Gordon JC, Tomson T, Kaplan PW, et al. Pregnancy registries in epilepsy: A consensus statement on health outcomes. Neurology. 2008 Sep 30;**71**(14):1109-1117

[50] Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Dose-dependent risk of malformations with antiepileptic drugs: An analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurology. 2011 Jul;**10**(7):609-617

[51] Patorno E, Bateman BT, Huybrechts KF, MacDonald SC, Cohen JM, Desai RJ, et al. Pregabalin use early in pregnancy and the risk of major congenital malformations. Neurology. 2017 May 23;**88**(21):2020-2025

[52] Brunner E, Falk DM, Jones M, Dey DK, Shatapathy CC. Olanzapine in pregnancy and breastfeeding: A review of data from global safety surveillance. BMC Pharmacology and Toxicology. 2013 Aug 1;**14**(1):38

[53] Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: An overview of cochrane reviews. Cochrane Database of Systematic Reviews. 2017 Apr 24;**4**:CD011279

[54] Stagg NJ, Mata HP, Ibrahim MM, Henriksen EJ, Porreca F, Vanderah TW, et al. Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: Role of endogenous opioids. Anesthesiology. 2011 Apr;**114**(4):940-948

[55] Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, DeVita P, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: The IDEA randomized clinical trial. Journal of the American Medical Association. 2013 Sep 25;**310**(12):1263-1273

[56] Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: A scientific statement from the American Heart Association. Circulation. 2013 Aug 20;**128**(8):873-934

[57] Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, Estes NAM, et al. Exercise and acute cardiovascular events placing the risks into perspective: A scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. Circulation. 2007 May 1;**115**(17):2358-2368

[58] Stuge B, Laerum E, Kirkesola G, Vøllestad N. The efficacy of a treatment program focusing on specific stabilizing exercises for pelvic girdle pain after pregnancy: A randomized controlled trial. Spine (Phila Pa 1976). 2004 Feb 15;**29**(4):351-359

[59] Carlsson C. Acupuncture mechanisms for clinically relevant long-term effects–reconsideration and a hypothesis. Acupuncture in Medicine. 2002 Aug;**20**(2-3):82-99

[60] Nesheim B-I, Kinge R, Berg B, Alfredsson B, Allgot E, Hove G, et al. Acupuncture during labor can reduce the use of meperidine: A controlled clinical study. The Clinical Journal of Pain;**19**(3):187-191

[61] Simkin P, Bolding A. Update on nonpharmacologic approaches to relieve labor pain and prevent suffering. Journal of Midwifery & Women's Health;**49**(6):489-504

[62] Liddle SD, Pennick V. Interventions for preventing and treating low-back and pelvic pain during pregnancy. Cochrane Database of Systematic Reviews. 2015 Sep 30;**9**:CD001139

[63] Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. Acupuncture for tension-type headache. Linde K, Editor. Cochrane Database of Systematic Reviews. 2009 Jan 21;**1**:CD007587

[64] Melchart D, Weidenhammer W, Streng A, Reitmayr S, Hoppe A, Ernst E, et al. Prospective investigation of adverse effects of acupuncture in 97,733 patients. Archives of Internal Medicine. 2004 Jan 12;**164**(1):104-105

[65] Oh H-M, Chung ME. Botulinum toxin for neuropathic pain: A review of the literature. Toxins (Basel). 2015 Aug 14;**7**(8):3127-3154

[66] Patil S, Willett O, Thompkins T, Hermann R, Ramanathan S, Cornett EM, et al. Botulinum toxin: Pharmacology and therapeutic roles in pain states. Current Pain and Headache Reports. 2016 Mar 15;**20**(3):15

[67] van Wijk RMAW, Geurts JWM, Wynne HJ, Hammink E, Buskens E, Lousberg R, et al. Radiofrequency denervation of lumbar facet joints in the treatment of chronic low back pain: A randomized, double-blind, sham lesion-controlled trial. The Clinical Journal of Pain;**21**(4):335-344

[68] Cohen SP, Hurley RW, Buckenmaier CC, Kurihara C, Morlando B, Dragovich A. Randomized placebo-controlled study evaluating lateral branch radiofrequency denervation for sacroiliac joint pain. Anesthesiology. 2008 Aug;**109**(2):279-288

[69] Bogduk N. Lumbar radiofrequency neurotomy. The Clinical Journal of Pain. 2006 May;**22**(4):409

[70] Vu CT, Elder DH. Pregnancy and the working interventional radiologist. Seminars in Interventional Radiology. 2013 Dec 20;**30**(4):403-407

[71] Leggett LE, Soril LJJ, Lorenzetti DL, Noseworthy T, Steadman R, Tiwana S, et al. Radiofrequency ablation for chronic low back pain: A systematic review of randomized controlled trials. Pain Research & Management;**19**(5):e146-e153

[72] Sluka KA, Walsh D. Transcutaneous electrical nerve stimulation: Basic science mechanisms and clinical effectiveness. The Journal of Pain. 2003 Apr;**4**(3):109-121

[73] Johnson MI, Ashton CH, Thompson JW. An in-depth study of long-term users of transcutaneous electrical nerve stimulation (TENS). Implications for clinical use of TENS. Pain. 1991 Mar;**44**(3):221-229

[74] Chao A-S, Chao A, Wang T-H, Chang Y-C, Peng H-H, Chang S-D, et al. Pain relief by applying transcutaneous electrical nerve stimulation (TENS) on acupuncture points during the first stage of labor: A randomized double-blind placebo-controlled trial. Pain. 2007 Feb;**127**(3):214-220

[75] Carroll D, Tramèr M, McQuay H, Nye B, Moore A. Transcutaneous electrical nerve stimulation in labour pain: A systematic review. British Journal of Obstetrics and Gynaecology. 1997 Feb;**104**(2):169-175

[76] Heil SH, Jones HE, Arria A, Kaltenbach K, Coyle M, Fischer G, et al. Unintended pregnancy in opioid-abusing women. Journal of Substance Abuse Treatment. 2011 Mar;**40**(2):199-202

[77] Ailes EC, Dawson AL, Lind JN, Gilboa SM, Frey MT, Broussard CS, et al. Opioid prescription claims among women of reproductive age—United States, 2008-2012. MMWR. Morbidity and Mortality Weekly Report. 2015 Jan;**64**(2):37-41

[78] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth edition, American Psychiatric Association; 2013. DOI: 10.1176/appi.books.9780890425596

[79] WHO. Guidelines for Identification and Management of Substance Use and Substance Use Disorders in Pregnancy. Geneva, Switzerland: WHO Press, World Health Organization; 2014. ISBN: 9789241548731. Available from: http://apps.who.int/iris/bitstream/handle/10665/107130/9789241548731_eng.pdf;jsessionid=1778A5AE016CB48996021D538AF83F87?sequence=1

[80] Young JL, Martin PR. Treatment of opioid dependence in the setting of pregnancy. The Psychiatric Clinics of North America. 2012 Jun;**35**(2):441-460

[81] Maeda A, Bateman BT, Clancy CR, Creanga AA, Leffert LR. Opioid abuse and dependence during pregnancy: Temporal trends and obstetrical outcomes. Anesthesiology. 2014 Dec;**121**(6):1158-1165

[82] ACOG Committee on Health Care for Underserved Women, American Society of Addiction Medicine. ACOG Committee Opinion No. 524: Opioid abuse, dependence, and addiction in pregnancy. Obstetrics and Gynecology. 2012 May;**119**(5):1070-1076

[83] Zedler BK, Mann AL, Kim MM, Amick HR, Joyce AR, Murrelle EL, et al. Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child. Addiction. Dec 2016;**111**(12):2115-2128

[84] Patrick SW, Davis MM, Lehmann CU, Lehman CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009-2012. Journal of Perinatology. 2015 Aug 30;**35**(8):650-655

[85] Kocherlakota P. Neonatal abstinence syndrome. Pediatrics. 2014 Aug 1;**134**(2):e547-e561

[86] Walhovd KB, Moe V, Slinning K, Due-Tønnessen P, Bjørnerud A, Dale AM, et al. Volumetric cerebral characteristics of children exposed to opiates and other substances in utero. NeuroImage. 2007 Jul 15;**36**(4):1331-1344

[87] Doberczak TM, Kandall SR, Wilets I. Neonatal opiate abstinence syndrome in term and preterm infants. The Journal of Pediatrics. 1991 Jun;**118**(6):933-937

[88] Hudak ML, Tan RC, Committee on Drugs, Committee on Fetus and Newborn, American Academy of Pediatrics. Neonatal drug withdrawal. Pediatrics. 2012 Feb 1;**129**(2):e540-e560

[89] Ornoy A. The impact of intrauterine exposure versus postnatal environment in neurodevelopmental toxicity: Long-term neurobehavioral studies in children at risk for developmental disorders. Toxicology Letters. 2003 Apr 11;**140-141**:171-181

[90] Jansson LM, Velez M, Harrow C. The opioid-exposed newborn: Assessment and pharmacologic management. Journal of Opioid Management;**5**(1):47-55

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