Holistic Pain Management in Pregnancy

What RNs, APRNs, Midwives and Mental Health Professionals Need to Know

Theresa Mallick-Searle
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Preface

In conducting my research for this book, along with my personal experiences as a registered nurse for over 25 years and a nurse practitioner in pain management for over 20, caring for patients with chronic and acute pain during pregnancy, I discovered a real need in the community to provide a practical education guide for the advanced practice registered nurse, bedside and clinic nurse, and Midwife. My objective is to provide the reader with the most up-to-date clinical information available on assessment and management of pain during pregnancy, applying a nurturing and holistic approach to the patient. An overview to the scope of the need, including a discussion on the use of opioids and the incidence of opioid use disorder will be covered. Things that you can do to help your patient in preparation for a healthy pregnancy will be reviewed, including optimization of diet, nutrition, fitness, mental health, and stabilization of chronic pain conditions. A few of the most common pain conditions that can present or worsen with pregnancy will be evaluated, including low back pain, pelvic girdle pain, migraine, and fibromyalgia.

Redwood City, CA, USA — Theresa Mallick-Searle

Contents

Introduction to Pain in Pregnancy

1

Theresa Mallick-Searle

Pain is as common to being human as breathing. Pain is a physiologic response to the exposure of noxious stimuli that is built into our DNA [1]. Pain is protective; the "pain response" is what helps us escape or remove ourselves from potential further harm or even death. Our current understanding as to the pathophysiology of pain is broken down into four distinct phases: transduction, transmission, perception, and modulation (Fig. 1.1). It is through these phases that pain is experienced [2]. Transduction occurs at the point of tissue insult, where primary afferent neurons are activated by a noxious stimulus, such as a burn. Transmission occurs when the nerve impulses are transmitted from the periphery (site of injury) to the dorsal horn of the spinal cord. Perception occurs as part of the ascending pain pathway, when the nerve impulse ascends to the regions of the brain responsible for pain perception (somatosensory cortex, insular cortex, prefrontal cortex, anterior cingulate cortex, thalamus, amygdala, nucleus accumbens). Finally, modulation occurs in parallel to the activation of the ascending and descending pathways. Where within the periphery, the spinal cord, and in the brain, chemical changes are occurring in the nervous system to bring about homeostasis and reduce the noxious impact of the pain response [2].

To best set the stage for a robust discussion about pain in pregnancy, we will spend some time here defining some basic concepts in pain. Pain is generally defined as being acute or chronic. Acute pain is pain that is anticipated, generally has a known cause, and is short-lived. Chronic pain is maintained pain that general outlasts its protective benefit, often has multiple causes, is associated with much emotional suffering and disability, is ongoing or recurrent, and continues beyond the anticipated time of tissue healing (3–6 months) [3]. A newer term that has been

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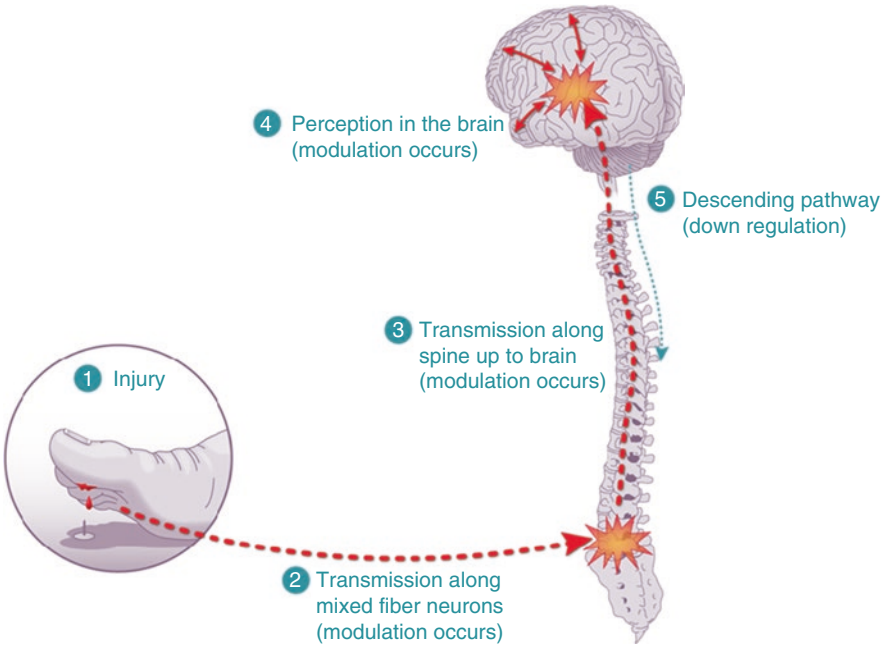

Fig. 1.1 Neuromechanisms of pain. (Adapted from CORE-REMS: Pain Management and Opioids: Balancing Risks and Benefits. WWW.CORE-REMS.ORG)

Table 1.1 Types of pain [5, 6]

Nociceptive/inflammatory	Nociplastic	Neuropathic
• Pain in response to injury or stimuli; typically acute	• Pain arising from altered nociceptive function; typically chronic	• Pain that develops when the nervous system is damaged; typically chronic
• Examples: postoperative pain, sports injuries, arthritis, sickle cell disease, mechanical low back pain	• Examples: fibromyalgia, irritable bowel syndrome, nonspecific low back pain	• Examples: postherpetic neuralgia, trigeminal neuralgia, distal polyneuropathy, neuropathic low back pain

coined, to define pain presentation is "high-impact chronic pain." This term is used to define chronic pain that is experienced with such regularity that it interferes in patients' lives (work, social, self-care activities) on most days or every day during the last 6 months [4]. There are three types of pain characteristics which are descriptive and to some degree may identify sources of ongoing stimulus: neuropathic, nociceptive, and nociplastic (Table 1.1). Nociceptive pain is defined as pain that is related to insult of somatic or visceral tissues due to trauma or inflammation. Examples of nociceptive pain would be childbirth or chronic axial low back pain. Neuropathic pain is defined as pain related to insult of peripheral and/or central

nerves. Examples of neuropathic pain would be diabetic peripheral neuropathy or lumbar radiculopathy. Nociplastic pain, a new term introduced by the International Association for the Study of Pain (IASP) in 2017, defined as pain without identifiable nerve or tissue insult, thought to result from persistent neuronal dysregulation. An example of nociplastic pain is fibromyalgia [5].

After 40 years, the IASP introduced a revised definition of pain, in the hopes that it would lead to improved assessment and management of those with pain. The new definition is: "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [7]. This revised definition was put forth to try and encapsulate the subjective and objective nature of pain. A reflection that:

- Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
- Through their life experiences, individuals learn the concept of pain.
- A person's report of an experience as pain should be respected.
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain [7].

Pregnancy and childbirth are essential to the existence of any species. In humans, ethnicity and cultural influences play a powerful role in the experience. Although we will not spend a lot of time in the discussion of cultural influences on the pain experience, I think that it is important to examine some common cultural influences on pain management. Having a better understanding of the role that ethnicity and culture play in pain, pregnancy, and childbirth will provide the healthcare provider with greater insights to the best, acceptable treatment approaches compatible with the patient's beliefs and needs. There has been much written about the influence that culture and ethnicity have on the pain experience [8–12]. Additionally, there have been writings published on the influence of culture and ethnicity on pregnancy and childbirth [13–16]. What is lacking in the literature is a combined examination of the role that cultural influences directly have on the pain experience in pregnancy. We can surmise that when the cultural beliefs and practices of the individual are supported and respected by the healthcare community, then there is much more harmony during the pregnancy. However, when the mainstay of the healthcare community conflicts with the values and culture of the individual, this can lead to not only a negative experience for the pregnant female, but also possibly worsen the pain experience.

The experience of a healthy pregnancy, safe childbirth, and successful bonding during the perinatal period is what we all strive for in the care of our patients. With many other critical aspects of care to be knowledgeable about and competent to

provide, often the importance of making pain management a priority gets overlooked. Pain during pregnancy is common, and its management is complex. Poorly managed pain can result in adverse maternal outcomes such as depression, sleep deprivation, hypertension, as well as poor fetal outcomes [17–19]. Advanced practice registered nurses (APRNs), nurses, and midwifes need to have a basic understanding of patient assessment and the basics of a pain history. If there is a history of chronic pain and substance use, the assessment needs to be expanded to include a standard pain history and assessment.

Aspects of a complete pain history include the follow:

- Pain assessment (Fig. 1.2): descriptors (location, intensity, severity, quality, duration, variations), treatments trialed, effects of pain on physical, emotional, psychosocial function, and examination (focus of general observation, musculoskeletal, neurological, cutaneous) [20].
- Inclusion of past medical and treatment history (Fig. 1.3): nonpharmacologic strategies trialed and effectiveness, pharmacologic strategies trialed and effectiveness, relevant illness, and past and current opioid use [21].
- Complete social and psychological history (Fig. 1.4).

The use of validated pain assessment tools (Fig. 1.5) can help structure the evaluation and expedite the process. Commonly use assessment tools in pain management include the brief pain inventory (BPI), 5-As, chronic pain grade questionnaire (CPG), PEG three-item scale [22].

We will cover the risk assessment that should be covered in patients with an opiate use disorder, substance abuse disorder, or you considering for chronic opioid use, in Chap. 3.

Fig. 1.2 Pain assessment

Nonpharmacologic Strategies and Effectiveness

Pharmacologic Strategies and Effectiveness

Relevant Illnesses

Past and Current Opioid Use

- Query your state's PDMP to confirm patient report
- Contact previous healthcare professionals and obtain prior medical records
- For opioids currently prescribed, note the opioid, dose, regimen, and duration
- Determine whether the patient is opioid tolerant

General Effectiveness of Current Prescriptions

Fig. 1.3 Past medical and treatment history

Social History

Employment, cultural background, social network, relationship history, legal history, and other behavioral patterns

Psychological History

Screen for:

- Mental health diagnoses, depression, anxiety, PTSD, current treatments
- Alcohol, tobacco, and recreational drug use
- History of adverse childhood experiences
- Family history of substance use disorder and psychiatric disorders
- Depression and anxiety can be predictors of chronic pain

Fig. 1.4 Obtaining a social and psychological history

In addition to mastering the ability to do a good pain assessment, it is also important to know when to refer to a specialist (pain management, interventionalist, high-risk OB, addictionologist), as well as what are your legal responsibilities, which is important particularly given the nature of caring for the pregnant female, fetus, and the family during the fragile and emotional time.

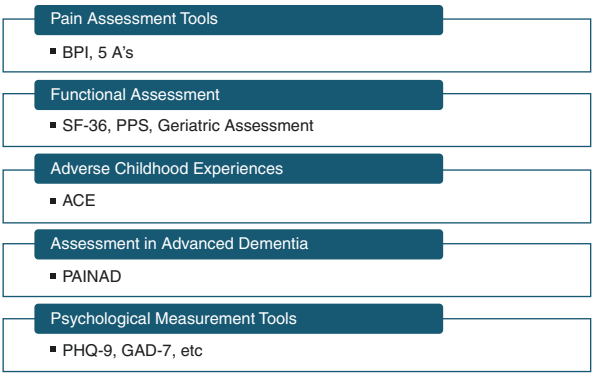

Fig. 1.5 Pain assessment tools. (Adapted from CORE-REMS: Pain Management and Opioids: Balancing Risks and Benefits. http://core-rems.org/opioid-education/tools/)

1.1 Summary

In summary, many clinicians find themselves apprehensive about managing all aspects of pain in pregnancy. This can be for a multitude of reasons including time commitment, knowledge, and fear. An understanding of basic pain mechanisms and assessment, as well, and where and when to refer will go a long way to easy the anxiety and care hesitation in this patient population. An integrated care approach of multimodal and multidisciplinary care should be applied for best outcomes.

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Background and Medication Overview

2

Theresa Mallick-Searle

In 2011, the Institute of Medicine (IOM) released a report on pain, estimating that 100 million adults in the United States live with chronic pain conditions, and it is the most common cause of long-term disability [1]. The Global Burden of Disease Study 2016 reaffirmed that the high prominence of pain and pain-related diseases as the leading cause of disability and disease burden worldwide [2]. Studies have shown that women compared with men experience a greater burden of disease and functional disability when it comes to chronic pain [3, 4]. In the United States, the latest figures report upward of six million pregnancies for 2010, reflecting that pregnant women represented approximately 5% of the total US population [5]. Sedgh and colleagues reported the global pregnancy rate in 2012 to be upward of 213 million pregnancies [6]. There is no doubt that both pain and pregnancy are prevalent in our society. Although the precise/exact incidence/prevalence of chronic pain in pregnant women is unknown [7], it is estimated to be significant. One study of 156 pregnant women who presented to the Women's Mental Health Program at the University of Arkansas for Medical Sciences for an initial evaluation from July 2013 to June 2016 showed chronic pain conditions were reported by 44 (28.2%). The most common chronic pain complaints included neck and/or back pain (34.1%) and headaches (31.8%) [8]. Bateman and colleagues, in their article published in 2014, looking at patterns of opioid utilization in pregnancy in the United States, found that in a cohort of over 500,000 pregnant women, 14% filled a prescription for an opioid at least once during their pregnancy, and 6% received opioids throughout all trimesters [9]. A study published in the Journal of Obstetrics and Gynecology reported an opioid prescribing rate of 20% in over a million pregnant women surveyed [10]. Approximately one out of every five

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women was prescribed opioids during pregnancy. The statistics above, along with many other smaller studies that have been done over the past decade, lead us to believe that the prevalence of both acute and chronic pain during pregnancy is greater than anticipated and has personal, economic, societal, and medical consequences.

The epidemiology of chronic pain is similar in pregnancy compared to that of the general population of nonpregnant women. Studies have shown that the development of chronic pain is determinant on many factors, including sociodemographic, clinical, psychological, and biological [11]. Pain researchers continue to examine the likelihood of developing chronic pain, as a direct result of poorly managed acute pain [12–14]; however, many experts in the field of pain research believe that evidence does support that poorly managed pain is an established risk factor for the development of chronic pain states. Poorly managed pain may also lead to maternal stress, depression, sleep deprivation, and hypertension, thereby potentially affecting the developing fetus and adversely affecting pregnancy outcomes [15].

Health-related behaviors and their outcomes are the most important modifiable risk factors in the genesis, duration, and impact of chronic pain [16].

Numerous articles have been written examining specific chronic pain disorders during pregnancy [7]. By far, the most common chronic pain conditions that women struggle with/suffer from during pregnancy headaches/migraine, musculoskeletal pain (pelvic pain, low back pain), and generalized body pain (fibromyalgia, rheumatological conditions). We will cover these specific pain disorders in more detail in separate chapters.

It has been well researched and subsequently recommended that the optimal approach to chronic pain management is a multidisciplinary approach focusing on biopsychosocial treatment [16–18]. An epidemiologically informed multidisciplinary and patient-centered approach is key to the successful management of chronic pain [19]. This also applies to the management of chronic pain in pregnancy, using a multimodal focus with and understanding of the risks to both the pregnant female and the developing fetus. The use of opioids for chronic pain in the prepregnancy period and subsequently during the antepartum, intrapartum, and postpartum period has been a matter of discussion among all healthcare providers who care for these women and their newborns. The introduction of the 2016 Centers for Disease Control (CDC) guidelines for safe opioid prescribing [20] has put a special focus not only on the safety of opioid use during pregnancy but also started another discuss about the risk and management of opioid use disorder (OUD) during pregnancy. The topic of opioid use disorder (OUD) in pregnancy will be more broadly covered in Chap. 3, so we will not spend too much time in discussion here. Suffice it to say, statistics have shown us that the percentage of opioid-related deaths in the United States continues to rise [21]. The risks of mortality and morbidity related to opioid use during pregnancy is the same if not worse (related to physiological changes during pregnancy and risks to the fetus) [22–24] and must be considered in the development of a treatment plan for the management of acute and chronic pain during pregnancy.

2.1 Use of Opioids in Pregnancy

Overall, when it comes to general considerations with opioid prescribing in pregnancy, outside of an identified opioid use disorder (OUD), the following apply:

- Continue to practice routine "risk evaluation and mitigation" strategies (REMS), including goal setting, compliance monitoring, and risk assessment [20, 24].
- Avoid synthetic opioids during the first trimester [25].
- If prepregnancy use of chronic opioids and decision is to wean opioids, it should be weaned before conception (if able) or during the second trimester: increase in incidence of miscarriage in the first trimester; increase in preterm birth if withdrawal in the third trimester [26–28].
- Avoid codeine during lactation: codeine is a prodrug metabolized to morphine, the amount and rate of metabolism is highly variable from none to producing very high peak levels, and neonatal deaths have been attributed to mismatch between ultrarapid metabolizing woman and slow in infants with immature morphine metabolism [29, 30].

The use of opioids during pregnancy, outside of OUD, has demonstrated to be beneficial in the right patient population, situation, and with appropriate monitoring. Short courses of opioids (preferably at lower doses) are generally safe in pregnancy, although neonatal abstinence syndrome must be monitored following third trimester exposure [31, 32]. Bateman and colleagues evaluated a nationwide sample of publicly and commercially insured pregnant women, to evaluate the association of first trimester prescription opioid use with congenital malformations in the offspring. Looking at a sample size of 1,602,580 publicly insured and 1,177,676 commercially insured pregnant women, they concluded that "prescription opioids used in early pregnancy are not associated with a substantial increase in risk for most of the malformation types considered, although a small increase in the risk of oral clefts associated with their use is possible" [32].

One last comment on the use of opioids during pregnancy related to stigmatization. There may be circumstances where the use of intermittent or daily opioids is necessary and the benefits outweigh the risks. I would like to share a commentary written by Meryl Kornfield for the Washington Post—online on June 24, 2021 (assessable at https://www.washingtonpost.com/nation/2021/06/24/pregnant-woman-charged-prescription/). In brief, a *36-year-old, who says she has chronic back pain, battled excruciating aches during her most recent pregnancy and was prescribed opioids by her doctor. Her baby tested positive for the opioid, which precipitated an investigation that led an Alabama prosecutor to charge the new mother with prescription fraud in a case her attorneys say is an unprecedented violation of a pregnant woman's privacy and freedoms*. Without going in to all the details of this case, it demonstrates the scrutiny that patients and healthcare providers are put under, to the extent of criminal prosecution for the use of opioids in a safe, controlled, and monitored medical setting.

2.2 Non-opioid Pharmacotherapy

Prescription and over-the-counter medication use during pregnancy and lactation is fairly common. An estimated 94% of women use at least one medication while pregnant or lactating, with nearly 70% taking a medication in the first trimester of pregnancy [33]. As the use of pharmacotherapy is common and part of a multimodal approach in pain management, it will be discussed broadly in this chapter. All medication use during pregnancy should include shared decision-making on the part of the pregnant female and her care providers. The patient's providers have the responsibility to make recommendations about medications that are appropriate to treat the condition (acute/chronic/episodic/neuropathic/nociceptive/nociplastic pain) and provide the patient with education about risks and benefits to help the patient make an informed decision. In the late 1970's, the US Food and Drug Administration (FDA) had provided regulation for drug labeling for pregnancy and lactation. This was the introduction in 1979 of a categorical system to guide healthcare providers regarding the risks and benefits of medications. The system consists of five lettered categories (A, B, C, D, X), which designate drugs as ranging from no evidence of risk, as demonstrated by adequate and well-controlled studies (A), to animal and human studies showing clear evidence of fetal risk, with the risk of drug use outweighing any possible benefit (X). In 2015, the FDA implemented the Pregnancy Lactation Labeling Rule (PLLR), which amends the previously issued Physician Labeling Rule. The PLLR provides a set framework for drug manufacturers to provide information about the risks and benefits of using prescription drugs and biologic products during pregnancy and lactation. The PLLR replaces the pregnancy letter categories (A, B, C, D, and X) previously printed on drug labels and allows for providers and patients to have a more thoughtful discussion about medication use, risks, benefits, and evidence [34].

The fundamental considerations when choosing to use a particular medication include what is known about the medications use in pregnancy (some medications have a longer history of use during pregnancy), duration of time the medication will be recommended, proposed "safety" at which stages of pregnancy [35]. The most critical period for minimizing drug exposure is during early development, the first trimester. Clinicians' need to keep in mind that physiological changes associated with pregnancy may affect the pharmacokinetics and pharmacodynamics of medication. An increase in maternal plasma volume, body fat, and drug distribution volume and changes in renal and hepatic functionality, gastrointestinal motility, and passage of drug through the placenta all need to be considered [35–37].

There are numerous resources available to assist clinicians in data collection regarding potential medication safety in pregnancy and lactation, and several of those will be listed for you below. It is not the aim of this text to provide and exhaustive list of all medications and substances possibly to be used for pain during pregnancy, but we will present considerations for commonly used medications and

provide resources. Another additional valuable resource is access to "pregnancy registries." A pregnancy exposure registry is a study that collects health information from women who take prescription medicines or vaccines when they are pregnant. Information is also collected on the newborn baby. This information is compared with women who have not taken medicine during pregnancy. Pregnancy registries are generally sponsored by interested organizations (pharmaceutical companies, academic institutions, government sponsored), ongoing for a finite period, and often listed on the US FDA website: https://www.fda.gov/science-research/womens-health-research/pregnancy-registries. Below is a selection of currently ongoing pregnancy registries for some common medications used for pain management (not an all-inclusive list) (Table 2.1).

There are certain medications/substances that are known to have teratogenic effects on the fetus and should be avoided as the risks outweigh the benefits of use. An easy way to remember these is with the mnemonic "TERATOWA" [38].

Thalidomide
Epileptic medications (Valproic acid, Phenytoin)
Retinoid (Vitamin A)
ACE inhibitors, **A**RBs
Third element (Lithium)
Oral contraceptives, Hormones
Warfarin
Alcohol

2.3 Acetaminophen/Paracetamol

Acetaminophen/paracetamol is one of most used analgesic and antipyretic drugs around the world, available without a prescription, and often self-dosed. Findings from two US studies indicate that 65–70% of pregnant US women reported using acetaminophen anytime during pregnancy [39]. It is thought to be the safest analgesic medicine for pregnant women. Although generally considered safe, there are recent studies that have raised some additional considerations: acetaminophen use in pregnancy can cause child attention-deficit disorder (ADHD), premature closing of the ductus arteriosus, and asthma [40–43].

Acetaminophen is generally considered to be a weak inhibitor of the synthesis of prostaglandins (PGs). There is considerable evidence that the analgesic effect of acetaminophen is central and is due to activation of descending serotonergic pathways, but its primary site of action may still be inhibition of PG synthesis [44]. Recommendations are to take the least dosing for the shortest during; however, dosing of 2000–4000 mg daily in divided dosing, in conditions of normal liver function, is considered safe. Clinicians need to be mindful to the toxic effects of acetaminophen on the liver in setting of hepatitis, concomitant use of other medications that have effects on the liver, and alcohol use.

Table 2.1 List of pregnancy registries

Medication	FDA indication	Pain type	Contact/more info.
Erenumab (Aimovig)	Migraine	Neuropathic/ nociplastic	Phone: 1-833-244-4083 www.genesispregnancyregistry.com
Fremanezumab (Ajovy)	Migraine	Neuropathic/ nociplastic	Phone: 833-927-2605 www.TevaMigrainePregnancyRegistry.com
Zolpidem (Ambien)	Insomnia	Insomnia	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Trazodone (Desyrel)	Depression	Insomnia	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Venlafaxine (Effexor)	Depression	Neuropathic/ nociplastic	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Amitriptyline (Elavil)	Depression	Neuropathic/ nociplastic	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Galcanezumab (Emgality)	Migraine	Neuropathic/ nociplastic	Phone: 1-833-464-4724 http://www.migrainepregnancyregistry.com
Cannabidiol (Epidiolex)	Seizure	Neuropathic/ nociplastic	Phone: 1-888-233-2334 http://www.aedpregnancyregistry.org
Triazolam (Halcion)	Insomnia	Insomnia	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Eszopiclone (Lunesta)	Insomnia	Insomnia	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Pregabalin (Lyrica)	Seizure	Neuropathic/ nociplastic	Phone: 1-888-233-2334 http://www.aedpregnancyregistry.org
Desipramine (Norpramin)	Depression	Neuropathic/ nociplastic	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Rimegepant (Nurtec ODT)	Migraine	Neuropathic/ nociplastic	Phone: 1-877-366-0324 http://nurtecpregnancyregistry.com
Armodafinil (Nuvigil)	Narcolepsy	Sedation	Phone: 1-866-404-4106 http://www.nuvigilpregnancyregistry.com
Nortriptyline (Pamelor)	Depression	Neuropathic/ nociplastic	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Desvenlafaxine (Pristiq)	Depression	Neuropathic/ nociplastic	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Modafinil (Provigil)	Narcolepsy	Sedation	Phone: 1-866-404-4106 http://provigilpregnancyregistry.com

Medication	FDA indication	Pain type	Contact/more info.
Mirtazapine (Remeron)	Depression	Sleep	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Temazepam (Restoril)	Insomnia	Sleep	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Milnacipran (Savella)	Fibromyalgia	Neuropathic/ nociplastic	Phone: 877-643-3010 www.savellapregnancyregistry.com
Quetiapine (Seroquel)	Depression	Sleep	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Doxepin (Sinequan)	Depression	Sleep	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Imipramine (Tofranil)	Depression	Sleep	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry
Bupropion (Wellbutrin)	Depression	Mood	Phone: 1-866-961-2388 https://womensmentalhealth.org/research/pregnancyregistry

2.4 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

It is estimated that the use of NSAIDs in pregnancy varies from between 2% and 15% [45, 46]. Use of NSAIDs tends to decrease over the course of pregnancy, consistent with its known teratogenic effects in the third trimester [47]. All NSAIDs cross the placenta, and their safety profile in pregnancy depends on the timing, dose, and duration of exposure. Use of NSAIDs after 30 weeks' gestation is contraindicated due to the association between third trimester maternal NSAID use and premature closure of the ductus arteriosus as well as fetal oligohydramnios and the same hemostatic abnormalities seen with third trimester aspirin use [48, 49]. A safety warning issued by the US Food and Drug Administration (FDA) in 2020 recommends that pregnant women avoid NSAIDs at 20 weeks or later because they can result in low amniotic fluid and may cause rare kidney problems in unborn babies [50].

Ibuprofen (similar to most NSAIDs) has multiple actions on different inflammatory pathways and cellular systems involved in acute and chronic inflammation. The principle pharmacodynamic (PD) actions of ibuprofen, like that of other NSAIDs, that are involved in control of acute pain, fever, and acute inflammatory reactions are the inhibition of COX-1- and COX-2-derived pro-inflammatory prostanoids (mainly PGE2) [48]. Recommendation, like any over-the-counter analgesics, is to take the least dosing for the shortest duration; however, dosing of 1200 mg daily in divided dosing is considered sage in adults. Clinicians need to be mindful to the toxic effects of NSAIDS on renal, gastrointestinal, and cardiovascular systems.

2.5 Gabapentin

Gabapentin is a gamma-aminobutyric acid (GABA) analog with GABA agonist activity. Its action is in modulation of excitatory neurotransmitter release, in part by blocking voltage-dependent calcium channels [51]. In addition to being currently US Food and Drug Administration (FDA)-approved for the treatment of partial seizures and postherpetic neuralgia, gabapentin is extensively used off-label for many pain conditions, including diabetic neuropathy and other neuropathic pain, fibromyalgia, postoperative pain, anxiety disorders, hot flushes, alcohol withdrawal, and tremor [52]. Gabapentin doses vary greatly, especially when being used for an off-label indication. Main side effects in adults include sedation, confusion, and edema. As gabapentin is renally excreted unchanged in the urine, dosing adjustments need to be considered in renal disease.

Gabapentin use during pregnancy has been studied and, based on the limited human studies evaluated, is not considered a risk for teratogenicity; however, caution with use is advised. A large population-based cohort study in Denmark found no association between first trimester exposure to gabapentin and risk for congenital malformations, although the number of exposed cases was small [53]. A more recent cohort study looking at the US Medicaid Analytic eXtract (MAX) dataset; a population-based study of 1,753,865 Medicaid-eligible pregnancies between

January 2000 and December 2013, examining the risk of major congenital malformations and cardiac defects associated with gabapentin exposure during the first trimester (T1); and the risk of preeclampsia (PE), preterm birth (PTB), small for gestational age (SGA), and neonatal intensive care unit admission (NICUa) associated with gabapentin exposure early, late, or both early and late in pregnancy. The authors found no evidence for an association between gabapentin exposure during early pregnancy and major malformations overall, although there was some evidence of a higher risk of cardiac malformations. Maternal use of gabapentin, particularly late in pregnancy, was associated with a higher risk of PTB, SGA, and NICUa [54].

2.6 Pregabalin

Pregabalin binds to the alpha2-delta subunit of calcium channels reducing neurotransmitter release and has many of the same attributes regarding mechanism of action, indication and side effects associated with gabapentin [55]. The main difference between gabapentin and pregabalin with regard to pharmacodynamics is in its physiological bioavailability, dosing, and FDA indications. Standard dosing for neuropathic pain related to diabetes is 50–100 mg oral three times daily, for postherpetic neuralgia 150–300 mg twice to three times daily, and for pain associated with fibromyalgia 150–225 mg twice daily.

Studies on the safety of pregabalin in pregnancy are lacking. One small (164 exposed pregnancies) multisite, prospective cohort study using data from Teratology Information Services in seven European countries found that pregabalin use during the first trimester of pregnancy was associated with significantly higher rates of major congenital malformations when compared with unexposed pregnancies [56]. Another larger cohort study evaluating the data base of 1,323,432 pregnancies resulting in a live-born infant between 2000 and 2010 and data from US Medicaid Analytic eXtract (MAX), looking at the use of pregabalin in early pregnancy and risks of major congenital malformations, found that of the 477 infants exposed to pregabalin during the first trimester, there was no suggested teratogenic effects of pregabalin, although they could not rule out the possibility of a small effect [57].

2.7 Selective Serotonin Reuptake Inhibitors (SNRI) and Tricyclic Antidepressants (TCAs)

Antidepressants are often used for the management of a diverse range of chronic pain syndromes as well as depression [58]. Research on the use of SNRIs and TCAs for neuropathic/nociplastic pain is robust and considered first-line treatment in many chronic pain conditions [59–63]. Evaluating safety of using antidepressants in pregnancy is difficult as most studies have been done looking at small sample sizes and associated with confounding illnesses, behaviors, and other risk factors connected with psychiatric disorders. Studies that have looked at venlafaxine and

duloxetine, two commonly used SNRIs in pain management, have shown inconclusive findings because of the reasons mentioned above. A small number of studies have evaluated outcomes following SNRI (venlafaxine or duloxetine) use in pregnancy and have found no major teratogenic effects [25]. A recent systematic review found no association between first trimester exposure to venlafaxine and an increased risk for major congenital malformations [64]. Conversely, studies have found a possible association with an increased risk for some perinatal complications, including a withdrawal syndrome with venlafaxine use in the third trimester [65]. The amount of data for duloxetine is much smaller but does not suggest a clinically important increased risk for teratogenic effects during pregnancy. A recent study published in 2020, looking at a cohort study nested in the Medicaid Analytic eXtract for 2004–2013, of women who had been exposed to duloxetine during the etiologically relevant time window, compared with no exposure to duloxetine, exposure to selective serotonin reuptake inhibitors, and exposure to duloxetine, is unlikely to be a major teratogen but may be associated with an increased risk of postpartum hemorrhage and a small increased risk of cardiac malformations [66]. Most studies evaluating the risks of exposure to TCAs in pregnancy have found no increased risk for malformations. However, one retrospective cohort study found an increased risk for spina bifida in infants exposed to TCAs, but not for other types of congenital malformations [67].

2.8 Low-Dose Naltrexone (1–5 mg/Daily) [68]

Naltrexone and naloxone are well-known opioid antagonists used in chronic or acute states of abuse or accidental overdose. Naltrexone is prescribed in daily doses of at least 50 mg to be taken orally for medication-assisted treatment of alcoholism or opioid use disorders. Naloxone is classically used as an opioid antagonist for reversal of opioid-induced respiratory depression (can be delivered SC/IM/IV/IN). Low-dose naltrexone (LDN) has been introduced into clinical practice following Dr. Bihari's initial off-label usage of naltrexone in doses ranging from 1.5 to 3 mg as an adjuvant therapy for acquired immune deficiency syndrome (AIDS) in the 1980s [69]. Low-dose naltrexone (LDN), considered in a daily dose of 1–5 mg, has been shown to reduce glial inflammatory response by modulating Toll-like receptor 4 signaling in addition to systemically upregulating endogenous opioid signaling by transient opioid-receptor blockade [68, 69]. Since the 1980s there have been many publications reporting the safety and efficacy of LDN for many disorders, including pain [70–74].

There is very limited human data on the use of LDN during pregnancy. Animal studies of perinatal exposure to naltrexone (1–50 mg/kg/day) suggest altered aspects of adult offspring behavior pertaining to emotionality, exploratory drive, and analgesic response to morphine [74, 75]. Although the data in humans is lacking, there is a potential to its utility for pain and symptom management in pregnancy. A review of the literature shows an increasing interest in the use of LDN in infertility medicine, possibly to correct "clinical endorphin deficiency" [76–80]. DR. Phil Boyle,

MICGP, MRCGP, CFCMC (https://neofertility.ie/about/), founder and director of NeoFertility, presented data in New Orleans, USA, August 2013, reported several case reports of naltrexone use, low dose for infertility management (https://byits-fruit.org/research/low-dose-naltrexone-novel-uses-for-a-licensed-medication).

Dr. Boyle reports "50% of our patients take Low Dose Naltrexone (3–4.5 mg nightly) often throughout pregnancy" and has also presented findings of the use of LDN in his practice.

2.8.1 Low Dose Naltrexone in Pregnancy: Comparison of Outcomes Between Users and Nonusers During Pregnancy

- 120 used LDN in pregnancy (50.6%).
- 30 did not take LDN during pregnancy.
- 30 LDN only until 25 weeks.
- 47 LDN beyond 26 weeks.
- 13 unconfirmed duration LDN use (https://ldnresearchtrust.org/sites/default/files/inline-files/Dr-Phil-Boyle.pdf)

There have been several studies published looking at the use of naltrexone in the treatment of OUD during pregnancy [81–83]. In these three studies evaluating the use of naltrexone in OUD during pregnancy, naltrexone appeared well-tolerated by both mother and fetus, and newborn infants did not experience symptoms of neonatal abstinence syndrome. The authors in all three studies agreed that more research is needed to determine naltrexone safety and benefits in pregnant women.

2.9 OnabotulinumtoxinA (Botox)

OnabotulinumtoxinA via intramuscular injection is used routinely for multiple painful conditions (muscle spasticity, migraine, dystonia) [84]. OnabotulinumtoxinA injected via a studied paradigm is FDA-approved standard dose, fixed injection sequence treatment for chronic migraine prevention [84, 85]. Given the tremendous benefit that patients receive with this treatment, and as many of the patients studied were women of childbearing age, the question was raised about the safety and efficacy of continuing treatment during pregnancy. Many studies, including reporting from the Allergan pregnancy registry [86], have shown no evidence of teratogenic effects on the fetus. Botulinum toxin is a large molecule and, when injected intramuscularly in recommended doses, is not expected to enter systemic circulation [87]. Therefore, onabotulinumtoxinA is unlikely to cross the placenta. A question posed to Motherisk Team at the Hospital for Sick Children in Toronto and Ontario about Botox in pregnancy prompted a review of the existing literature. Tan and colleagues concluded that of the 38 pregnancies reported in the literature, including

women who had botulism poisoning during pregnancy, exposure to onabotulinumtoxinA does not appear to increase the risk of adverse outcome in the fetus [88].

Wong and colleagues reported their experience of 45 patients exposed to onabotulinumtoxinA during pregnancy. Although the numbers are small, they found no impact of the toxin found on the pregnancy outcomes [89]. A 24-year retrospective review of the Allergan safety database shows that the prevalence of fetal defects in onabotulinumtoxinA-exposed mothers before/during pregnancy (2.7%) is comparable with background rates in the general population. Pregnancy outcome monitoring in onabotulinumtoxinA-exposed women continues [86].

2.10 Topicals (Aspirin, Menthol, Lidocaine, NSAIDS)

Over-the-counter and prescription topical analgesics are popular and often considered safer compared with the side effects of oral equivalent medications [90–92]. Generally, the same considerations should be advised as with oral acetaminophen and NSAIDs as mentioned earlier; however, with an appreciation for the studies that have shown decreased systemic circulation, clinicians can be comforted that the side effects reported with oral dosing should be considered less with standard dosing of topical equivalent analgesics.

The use of topical lidocaine during pregnancy remains questionable. No studies in human pregnancy have been published. However, the use of limited amounts of lidocaine as single injections has been studied (see Chap. 9). Animal reproductive studies of topical lidocaine have failed to demonstrate a risk to the fetus. As lidocaine as a molecule is seen to cross the placenta and the lack of human studies, it has conditioned US clinicians to proceed with caution when using topical lidocaine in pregnancy. In Australia, topical lidocaine is categorized as pregnancy category A: drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed [93].

2.11 Melatonin

There is no clear evidence of harmful adverse events when using melatonin during pregnancy. However, it is suggested that administration of exogenous melatonin during pregnancy can interfere with the development of the postnatal circadian rhythm [94]. Melatonin is a natural substance of breast milk and is excreted in a circadian cycle. Hypothetically the use of exogenous melatonin can be thought to have a negative influence on postnatal sleep patterns and other hormonal cycles. There is no relevant data available to support this hypothesis [94]. Melatonin in low doses seems compatible with breastfeeding. Poor sleep is often a comorbid presentation in patients with chronic pain; equally sleep disturbances are seen in pregnancy.

Table 2.2 Common medications used for pain: safety in lactation

Medications that are considered safe with breastfeeding	Acetaminophen, ibuprofen, caffeine, gabapentin, topical analgesics, duloxetine, amitriptyline, desipramine, opioids, propranolol, valproate, lidocaine, melatonin
The pharmacological effects in human infants is unknown; caution is advised	Pregabalin, milnacipran, synthetic opioids, LDN, onabotulinumtoxinA
Should be avoided during breastfeeding	Codeine, ergotamine

Use of medications in breastfeeding is dependent on a number of factors, lipid solubility, molecular weight, minimal protein binding, half-life of the medication, and timing of administration [95–99] (Table 2.2).

Resources

- Hale's Medications and Mothers Milk 2021: https://www.halesmeds.com
  Updated regularly, available as an online subscription and Published: Springer Publishing Company.
- Pregnancy and birth cohort resources in Europe: a large opportunity for etiological child health research: http://www.birthcohorts.net
- American Academy of Pediatrics Committee on Drugs (COD) https://publications.aap.org/pediatrics/article/132/3/e796/31630/The-Transfer-of-Drugs-and-Therapeutics-Into-Human
- Drugs and Lactation Database (LactMed)—https://www.ncbi.nlm.nih.gov/books/NBK501922/
  Smartphone APP available for free
- REPROTOX www.reprotox.org
  World Health Organization—https://www.who.int/health-topics/breastfeeding#tab=tab_1
- American College of Obstetricians and Gynecologists—Resource Center: https://www.acog.org/clinical-information/resource-center
- LifeCycle Project & EU Child Cohort Network:
  - LifeCyce Project https://lifecycle-project.eu
  - Birthcohorts.net www.birthcohorts.net

2.12 Summary

Research is showing that more pregnant women than previously thought are reporting struggling with chronic pain. This biopsychosocial model of care benefits this patient population, as women in pregnancy struggle with not only the physical effects of pain but also anxiety, stress, poor sleep, and other medical comorbidities associated with the physiological changes in pregnancy. The importance of appropriate/adequate pain management during pregnancy has been urged by American College of Obstetricians and Gynecologists, Department of Health and Human

Services, American Academy of Pediatrics, and World Health Organization, among many others. Pharmacotherapy is one of the tools in multimodal management of pain. Many medications are safe and appropriate to use in pregnancy and lactation; however, clinicians must be educated and knowledgeable of certain considerations in this patient population.

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Opioids and Opioid Use Disorder (OUD) in Pregnancy

3

Theresa Mallick-Searle

Research has shown that women have more acute and chronic pain than men [1, 2]. "Women compared with men, experience a greater burden of disease and functional disability when it comes to chronic pain as well as lower therapeutic effects with use of long-term opioid use," according to a study published by Darnall and colleagues [3]. According to a 2020 report from the National Center of Health and Statistics, 5.7% of US adults used one or more prescription opioids in the 30 days prior to sampling between 2015 and 2018. This prescription opioid use was significantly higher among women than men (women, 6.4%, vs. men, 4.9%), and overall use increased with age (20–39 years, 2.8%; 40–59 years, 6.6%; 60+ years, 8.2%) [4]. These differences in opioid prescribing to women is not isolated to the US population [5], and biological along with sociological factors have been partially identified to explain gender differences in pain, opioid use, and addiction [6]. Another surprising statistic, reported that opioid prescription doses were often higher in women during pregnancy who were also co-prescribed anxiolytics [7].

With an estimated four million term pregnancies each year in the United States, incidence of opioid prescriptions to pregnant women has seen a steady increase. In a recent national survey, 6.6% of respondents reported prescription opioid use during pregnancy [8]. Looking at insurance claims data, Carter and colleagues, reported an opioid use increase from 1 to 6/1000 births from 2000 to 2006 [9]. Additionally, they reported out that during this same 6 years, 39% of Medicaid recipients (women of childbearing age) filled an opioid prescription, and 28% of women covered by private insurance [9]. The use of prescription opioids during pregnancy is associated with a low absolute risk of neonatal abstinence syndrome (NAS) in the absence of

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additional risk factors. Long-term use compared with short-term use and late use compared with early use of prescription opioids are associated with increased NAS risk independent of additional risk factors [10]. Weighing the risks and benefits of continuing or initiating opioid therapy during pregnancy, outside of an identified opioid use disorder (OUD) should be done in the setting of informed consent and joint decision-making between the patient and her provider. We have discussed this in more detail in Chap. 2.

Given the inherent risk of poorly managed pain in the setting of OUD during pregnancy (previously identified or not), it is imperative that the patient be screened and monitored as with any patient on opioid therapy for pain management. Management of OUD in pregnancy often requires a team effort among mental health providers, pain management, maternal health provider, and the patient. All providers involved in the patients care need to be mindful, compassionate, and well educated to care for this high-risk population. Maternal and newborn providers and staff face an increasing number of opportunities to care for women and newborns affected by OUD, as well as substance abuse disorder (SUD).

Goals of care should include:

- Every pregnant woman should be screened for substance abuse. Routine screening should rely on validated screening tools (see Table 3.1).
- Every pregnant woman with OUD should be on medication-assisted treatment (MAT).
- An increasing evidence base supports the use of non-pharmacologic treatment for newborns with neonatal abstinence syndrome (NAS).

Table 3.1 Screening tools for prenatal substance use/abuse. These tools have been well studied and demonstrated high sensitivity [11]

Screening tool	Questions
SURP-P (Substance Use Risk Profile-Pregnancy) [12][a]	1. Have you ever used marijuana?
	2. How many alcoholic drinks have you consumed in the month before knowing you were pregnant?
	3. Do you feel the need to cut down on your alcohol or drug use?
4-Ps Plus [13][b]	1. Parents: Did any of your parents have a problem with alcohol, or other drug use?
	2. Partner: Does your partner have a problem with alcohol or drug use?
	3. Past: In the past, have you had difficulties in your life because of alcohol or other drugs, including prescription medications?
	4. Present: In the past month have you drunk any alcohol or used other drugs?

[a] Scoring involves classifying the number of alcoholic drinks consumed in the month before pregnancy as none versus any and then counting the number of affirmative items. Negative response for all items = low-risk; one affirmative response = moderate-risk; two to three affirmative responses = high-risk

[b] Any "yes" response should trigger further questions

- Mothers and babies should receive support to keep them together.
- Support needs to continue into the postnatal period.
- Excellent communication and collaboration among all providers.

Several studies now report that opioid overdose deaths decline during pregnancy but peak in the year following pregnancy and are now one of the leading causes of mortality among women during that period [6, 14]. A recent national US data tracking the percent of pregnant women hospitalized specifically for treatment of prescription opioid abuse showed a dramatic increase from 2% to 28% between 1992 and 2012 [15]. Significant morbidity and costs may be associated with infants exposed to opioids, particularly when pregnant mothers have not been in treatment prior to delivery. Wachman and colleagues reported that the incidence of newborns with NAS increased fivefold from 2000 to 2012, from 1.2 to 6 per 1000 live births, and continues to increase, with recent data citing as many as 20 cases per 1000 live births [16]. The importance of early identification and treatment of patients with SUD/OUD has been sited in many studies. One study in particular looked at a cohort of women, addicted to heroin, during pregnancy, not offered MAT. These pregnancies showed an association with lack of prenatal care, increased risk of fetal growth restriction, abruptio placentae, fetal death, and preterm labor [17]. Untreated addiction (regardless of pregnancy status) has also been shown to be associated with an increased engagement of high-risk activities. Two evidence-based medications that are used for MAT in patients with OUD are methadone and buprenorphine. Both have been researched in women during pregnancy, and reports suggest that each can be prescribed without apparent significant adverse outcomes for patients or neonates [18].

The use of methadone for MAT in patients with OUD has been the "gold standard" since 1974. It generally is regimented by daily dosing co-treating with psychological support. In a recent study, it was reported that 86% of women required an increase in dosing during pregnancy and many did better with split dosing. Doses were reduced roughly after 6 weeks, and no increase in NAS was appreciated [9].

The introduction of buprenorphine for MAT during pregnancy has shown to result in fewer preterm births and lower risk of NAS. Studies have shown that pregnant patients with OUD who received buprenorphine compared to those receiving methadone used significantly less morphine at delivery and had shorter hospital stays [19, 20]. The American College of Obstetricians and Gynecologists (ACOG) supports the use of methadone or buprenorphine as a potential first-line medication for pregnant women with OUD [21, 22].

The full discussion of assessment and treatment of addiction goes beyond the scope of this chapter; however, the following resources are being provided for further follow-up reading and information that should help guide the clinician in the ongoing management of this special patient population.

Resources

- Mother & Baby Substance Exposure Toolkit—A part of the California Medication Assisted Treatment Expansion Project. https://nastoolkit.org/

- American College of Obstetricians and Gynecologists—Opioid Use and Opioid Use Disorder in Pregnancy https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/08/opioid-use-and-opioid-use-disorder-in-pregnancy
- Centers for Disease Control and Prevention (CDC)—Resources on Opioid Use During Pregnancy https://www.cdc.gov/pregnancy/opioids/resources.html
- National Center on Substance Abuse and Child Welfare—Treatment of Opioid Use Disorders in Pregnancy https://ncsacw.samhsa.gov/resources/opioid-use-disorders-and-medication-assisted-treatment/treatment-of-opioid-use-disorders-in-pregnancy.aspx
- European Monitoring Center for Drugs and Drug Addiction—Pregnancy and opioid use: Strategies for treatment https://www.emcdda.europa.eu/system/files/publications/807/TDAU14006ENN_483434.pdf
- https://www.drugsandalcohol.ie/23001/

3.1 Summary

An appreciation for the higher incidence and disability associated with acute and chronic pain in women is important knowledge to have. The use of opioids, either acutely, episodically, or chronically (outside of a diagnosis of OUD), is a shared decision that should be made after full disclosure of the risks, between a patient and her clinician. As with pain management in general, especially in the setting of opioid use, a multidisciplinary team should be sought to care for these high-risk patients. The team at minimum should include mental health, pain management, and maternal health providers. When the care of a patient with known, suspected, or newly identified SUD is undertaken, a multidisciplinary team is priority. The mother should also be included in the shared decision-making and supported well after her delivery. Use of non-opioid analgesics should be prioritized when able. Interventional, body, and behavioral therapies must be part of the ongoing care, and patients must be given access to MAT for best outcomes.

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Nutrition and Microbiome: In Preparation for Pregnancy

4

Cynthia Belew

4.1 Underlying Etiologies of Chronic Pain

Many studies have identified the intersection of mitochondrial dysfunction, oxidative stress, and inflammation as key factors in the etiology of fibromyalgia syndrome and chronic pain [1, 2]. In addition, an altered gut microbiota and intestinal permeability are etiologies of chronic pain. Impaired mitochondrial function and disruptions in the microbiome are known to negatively impact pregnancy outcomes as well. Many promising nutritional interventions for chronic pain act through the pathways of repairing mitochondrial function, modulating the immune system, enhancing the intestinal microbiome, and repairing intestinal barrier integrity (Fig. 4.1). A foundational understanding of these systems and their interactions with chronic pain enables the healthcare provider to understand the rationale for selecting dietary interventions and nutritional supplements in managing chronic pain. To that end, this review provides a brief description of the physiology of these systems (mitochondrial, immune, microbiome) in relation to chronic pain. It focuses on dietary and supplemental interventions that have significant evidence to support their benefit for the management of chronic pain and are considered safe for use during pregnancy, emphasizing those that also address underlying conditions of mitochondrial function, inflammation, intestinal dysbiosis, and impaired intestinal barrier function.

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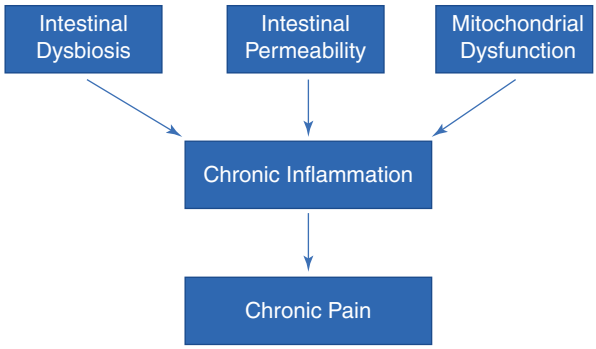

Fig. 4.1 Etiologies of chronic pain [3–12]

4.2 Inflammation and Oxidative Stress Underlie Chronic Pain

The central role of oxidative stress and inflammation in the development and maintenance of fibromyalgia and other chronic pain disorders has been well described [3, 4]. Oxidative stress and chronic inflammation are closely related processes, and these two interdependent processes coexist in many chronic diseases. Oxidative stress can induce inflammation, and inflammatory processes can induce oxidative stress. Symptom severity in chronic pain conditions is directly correlated with high levels of inflammatory molecules and low levels of antioxidants. A decrease in biomarkers for oxidative stress and inflammation has a direct association with decreased pain perception [13]. Therefore, strategies for modulating oxidative stress and inflammation are of particular interest in managing chronic pain disorders.

4.3 Mitochondrial Function

Recent advances in our understanding of the pathophysiology of chronic disease have led to an even deeper understanding of the etiology of chronic inflammation: the role of mitochondrial function [5]. Mitochondria, known as the "powerhouse of the cell," are organelles with their own genome and essential players in the control of normal physiology. Mitochondrial dysfunction is the primary etiology in a wide range of inflammation-driven chronic diseases [5]. Strategies using dietary interventions and nutritional supplements to support normal mitochondrial function are valuable for managing chronic inflammation-based disorders [5].

An essential function of the mitochondrion is to convert oxygen and glucose from food into adenosine triphosphate (ATP). ATP is produced through the citric acid cycle, or Krebs cycle, which provides more than 90% of the energy needed for cellular function [14]. Pro-inflammatory molecules called reactive oxygen species (ROS) are produced as a by-product of ATP production and include both free radicals and strong oxidizing agents [14]. At low levels, ROS serve as essential signaling molecules that enable the cell to respond to changing environmental conditions [14].

In a healthy physiologic state, equilibrium occurs when the mitochondrial scavenging systems neutralize ROS with antioxidants. If this equilibrium is disrupted and there are more ROS than can be managed by the body's antioxidant defense system, their accumulation leads to oxidative stress and damage to the mitochondria, lipids, proteins, and cellular DNA, impairing energy production and activating chronic inflammation [14].

In addition, when mitochondria are stressed, the lipid bilayer of the mitochondrial membrane becomes unstable, and mitochondrial DNA is released from the cell, triggering production of inflammatory molecules [5]. Researchers have described the role of these inflammatory cytokines in the development of fibromyalgia syndrome and inflammatory pain [4].

4.4 Mitochondrial Function: Role in Chronic Pain

Muscle and nerve cells require significant amounts of ATP to function normally and are especially sensitive to mitochondrial defects [15]. Dysfunctional mitochondria contribute to chronic pain by causing cellular ATP deficiency, as they are unable to produce the same amount as healthy organelles: this leads to excessive ROS and impaired calcium buffering thus affecting membrane excitotoxicity and synaptic plasticity [2]. Reduced ATP in muscle and neural cells contributes to muscle pain and central sensitization seen in patients with FMS [2] and neuropathic pain. Additionally, excessive ROS generated by mitochondrial dysfunction induces altered nociception through peripheral and central nervous system sensitization and increase cytokine production, which is involved in inflammatory pain, chronic pain, and fibromyalgia [6, 15]. Pro-inflammatory cytokines are positively correlated with excessive mitochondrial ROS as well as increased pain scale scores [15]. In muscle cells, mitochondrial dysfunction causes cellular injury, leading to widespread muscular pain, decreased neuronal synaptic function, and contributes to central sensitization [2]. Considering the large body of evidence linking mitochondrial dysfunction with various chronic pain and inflammatory conditions, the protection of mitochondrial function is considered a key therapeutic strategy in their management.

4.5 Mitochondrial Function and Pregnancy

Interventions to improve mitochondrial function are likely to enhance optimal pregnancy outcomes as well as support the management of chronic pain. Researchers have described a critical role of mitochondrial function in fertility, including oocyte quality, fertilization, implantation, epigenetic programming, and early embryo development [7]. Failure of mitochondrial-mediated communication can adversely impact the growing embryo [7]. A growing number of researchers describe the impact of impaired mitochondrial production of ATP in the placenta, which may be linked to placental insufficiency and preeclampsia [16].

Associations between diet during pregnancy and oxidative stress markers and mitochondrial damage indicate that lifelong mitochondrial dysfunction in the offspring may result from an altered nutritional environment during intrauterine life. These factors impact fetal programming and the lifelong health of the offspring [17].

4.6 Mitochondrial Function and Nutrition

It is well established that a range of micronutrients are required for optimal mitochondrial function [7, 18]. Micronutrient deficiencies are highly prevalent among persons of childbearing age in the United States, with substantial percentages having intake below the estimated average requirement for calcium; magnesium; vitamins A, B12, C, D, and E; as well as folate, iron, zinc, copper, choline, potassium, dietary fiber, and DHA [19]. In Wesselink's review of the literature, the role of the food-derived supplements in mitochondrial dysfunction are described: these include B vitamins, vitamins C and E, selenium, zinc, CoQ10, melatonin, carnitine, taurine, lipoic acids, and resveratrol [18]. In addition, Bordoni describes the role of green tea catechins, curcumin, pomegranate-derived polyphenols, quercetin, vitamin K1, *N*-acetylcysteine, and sulforaphane in mitochondrial function [20]. Since many nutrients work synergistically in metabolic pathways, it is unlikely that supplementation with a single nutrient will improve mitochondrial function if another is deficient, which underlines the importance of a diverse and nutrient-dense diet.

In addition to micronutrient deficiencies, excessive or inadequate macronutrient intake (fat, carbohydrates, protein) contribute to mitochondrial dysfunction and oxidative stress [7]. Although the antioxidant system is designed to protect against mitochondrial damage, specific amino acids are needed for the optimal functioning of these systems, and their deficiency may directly impact pregnancy [17].

In summary, the mitochondrion is an essential organelle that either aids in optimal cellular functioning or may contribute to multiple inflammatory states and chronic pain conditions. When the mitochondrion's ROS scavenging system is unable to mitigate the damage of ROS, oxidative stress occurs, promoting inflammation and contributing to chronic pain disorders. Mitochondrial dysfunction has widespread implications in various pathologic states and may negatively impact pregnancy outcomes and the long-term health of the offspring. Dietary supplements to support mitochondrial function are discussed in the supplements section of this chapter.

4.7 Microbiome and Intestinal Barrier Function

Human health is dependent on the intersecting factors of a diverse microbiome and an intact intestinal mucosal barrier. Impairment of these factors underlies a wide array of chronic inflammatory diseases. The gut barrier, consisting of the intestinal

epithelium and a protective mucus layer, is required to maintain its digestive and absorptive functions while maintaining its barrier function to separate the contents of the gut lumen (the external environment) from internal tissues and organs, preventing the passage of harmful substances into circulation [21]. It acts as a selective filter, allowing absorption of nutrients while keeping pathogens and toxins out. A disrupted intestinal barrier function (aka intestinal permeability) is linked with many chronic diseases. Another key factor for health is the intestinal microbiota, which consists of more than a trillion bacteria in a symbiotic relationship with the host. A balanced microbiota is essential for adequate intestinal barrier function and applies broadly to reducing inflammation, supporting healthy immune response; improving vitamin and lipid metabolism, intestinal homeostasis, and maintenance of the intestinal barrier function; and improving liver and kidney function–all priorities both for pain management and for a healthy pregnancy.

As understanding of the widespread impacts of a balanced microbiome continues to develop, there is evidence connecting the microbiota with many types of chronic pain, including visceral, inflammatory, and neuropathic expressions. Targeting gut microbiota through dietary intervention and targeted supplementation represents a fruitful strategy for managing chronic pain [22]. Alterations in the gut microbiota are observed in chronic pain conditions [8]. Intestinal dysbiosis induces central sensitization through well-described pathways, regulating the neuroinflammation that accompanies chronic pain disorders [22, 50]. Several reviews examine the evidence showing the physiologic and neurochemical mechanisms through which the intestinal microbiota modulate chronic, inflammatory, visceral, and neuropathic pain, fibromyalgia, and headache [22, 50]. Some have suggested that the association between specific changes in the microbiome and fibromyalgia is so strong that microbiome analysis could be used as a diagnostic tool for fibromyalgia [8].

In addition, the gut microbiota mediates neuroinflammation and produces psychoactive metabolites, including serotonin, dopamine, and noradrenaline, with implications for the modulation of mood [10]. Disturbances in the microbiome are linked with depression, anxiety, and poor stress resilience. Mood can be improved by dietary interventions designed to support a healthy microbiome and the use of prebiotic or probiotic supplements.

The gut microbiota also plays a critical role in health during pregnancy. Intestinal dysbiosis is strongly linked with pregnancy complications, including gestational diabetes, fetal growth restriction, infections during pregnancy, and preeclampsia [23]. In addition, the status of the maternal microbiota during pregnancy impacts the metabolic, immune, and neurologic health of the offspring throughout their lifespan [24].

Understanding the fundamental physiology of the gut microbiome equips the healthcare provider with specific rationales for the use of selected dietary and nutritional interventions in the management of chronic pain (Table 4.1). The microbiome has taken multiple hits from the modern lifestyle that drive down its diversity, including a low-fiber diet, antibiotic use, Cesarean birth, a lack of human milk feeding [44], and glyphosate-sprayed foods [45].

Table 4.1 Strategies to improve the microbiome

Remove substances that harm the microbiota and the intestinal barrier	Refined sugars refined carbohydrates [25, 27], gluten [28–30], processed foods, food additives [31]		
Rebalance the microbiome by selecting nourishing beneficial microbes	Dietary soluble fiber in abundance and variety [32–34]		
	Polyphenol-rich foods [35, 36]		
	Prebiotic supplements such as inulin		
Replace beneficial bacteria	Fermented foods [37, 38]		
	Probiotic supplements		
Repair the intestinal barrier	Postbiotic supplements (butyrate) [39–41]		
	Fermented foods		
	Dietary fiber and prebiotics		
	Definition	**Examples**	**Notes**
Prebiotics	A nondigestible substrate that is selectively utilized by host microorganisms conferring a health benefit [42]	Fructans (FOS, inulin) polyphenols, galactans (GOS)	Obtained in dietary fiber or supplements
Probiotics	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [42]	Bifidobacteria, *lactobacillus*	Obtained in supplements or in probiotic-like bacteria in fermented foods
Postbiotics	Inactivated microbial cells and/or their metabolites that confer a health benefit on the host [43]	Butyrate (butyric acid), inactivated probiotic bacteria	Obtained by consumption of dietary fiber, fermented foods, or in supplements

4.8 Short-Chain Fatty Acid Essential Modulators of Inflammation and Neurology

Microbial-accessible carbohydrates (MACs) are fibers ingested from dietary sources or in the form of prebiotic supplements. MACs are fermented by intestinal bacteria to short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate. SCFAs, also known as postbiotics, are potent modulators of human health. SCFAs modulate pain sensitization [22, 46]. They provide an energy source for colonic cells and maintain the stability of the intestinal barrier [32]. They enter the circulation and regulate immune, metabolic, and neural pathways, providing beneficial anti-inflammatory, metabolic, neuroprotective, and stress- and mood-modulating effects [47].

Dietary fibers including psyllium, inulin, and pectins from fruits and vegetables increase butyrate production, and butter has a butyrate content of 2.7% [47]. Prebiotic supplements can increase butyrate production.

Butyrate (butyric acid), a postbiotic available as a supplement, modulates systemic immune, nervous system, and metabolic function [43]. It has a critical role in enhancing intestinal barrier function by promoting assembly of tight junctions and stimulating intestinal mucus production and well as providing the primary fuel source for colonocytes [39]. It has such potent beneficial effects that its use has been proposed as a treatment for mental health and neurodegenerative disorders [40]. Several trials have reported its effectiveness in improving symptoms in patients with irritable bowel syndrome [41]. It also has an important role in the prevention of obesity and obesity-related diseases [48].

4.9 Intestinal Barrier Function

Intestinal permeability (also known as leaky gut) is a crucial driver of localized and systemic inflammation and is believed to play a pathogenic role in many chronic diseases [46]. An understanding of the intestinal barrier function is beneficial for understanding the rationales for recommended dietary and supplemental interventions.

Altered intestinal permeability has been reported in chronic pain conditions, including fibromyalgia, complex regional pain syndrome, and irritable bowel syndrome. The degree of intestinal permeability is associated with the severity of pain [50]. Beneficial microbes produce short-chain fatty acids and other signaling molecules, which provide an energy source for colonocytes and promote the integrity of the gut barrier [32].

The integrity of the gut barrier depends on the relationship between the gut microbiota and the intestinal epithelium. In the setting of inadequate dietary fiber, the microbiota is deprived of a food source and begins to digest the protective layer of mucus and eventually the intestinal epithelial cells, which leads to intestinal inflammation [51].

The intestine is an interface between what is inside the human body and the outside. The intestinal epithelium allows absorption of nutrients but prevents bacteria and harmful bacterial metabolites from the lumen of the gut from entering into circulation [51]. Intercellular tight junctions (TJs) have immense complexity and tightly control the trafficking of antigens across the intestinal barrier and into the system, dictating the balance between immune tolerance and immune response. Breakdown of the intestinal barrier results in translocation of antigens and harmful bacterial endotoxins across the intestinal wall, triggering inflammatory responses. Proinflammatory molecules can then cross the blood-brain barrier and trigger systemic inflammation [51]. One of the antigens, lipopolysaccharide (LPS), is a highly inflammatory bacterial endotoxin. When LPS gets into the system (known as metabolic endotoxemia), it initiates chronic inflammation, activates the HPA axis, and reorganizes the sensitivity of the pain system [52]. It is proposed that LPS endotoxins are a causative factor in obesity and diabetes [46]. Researchers state that intestinal permeability is a precursor to autoimmune and other diseases [51].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common cause of gastric mucosa injury. Proton-pump inhibitors (PPIs) are often given with NSAIDs to protect the upper gastrointestinal tract from NSAID-induced gastropathy; however, PPIs disrupt the intestinal microbiome and contribute to the development of intestinal permeability. In one RCT, the use of PPIs with NSAIDs increased the incidence of NSAID-induced small intestinal mucosal injury from 16% to 44% compared to the use of an NSAID with a PPI [12].

4.10 The Role of Gluten in Intestinal Permeability and Chronic Pain

The opening and closing of the tight junctions between intestinal epithelial cells must be tightly regulated. Zonulin, currently the only known mediator of the permeability of tight junctions, is used as a marker for intestinal permeability. If not closely regulated, zonulin opens the gate and allows inappropriate and uncontrolled antigen trafficking, leading to the production of proinflammatory cytokines and the breakdown of immune tolerance. Elevated zonulin is implicated in the pathogenesis of many chronic inflammatory diseases, including autoimmune, metabolic, intestinal, and neuroinflammatory disorders [46].

Two of the most potent factors that trigger zonulin release and the accompanying intestinal permeability are intestinal dysbiosis and gliadin, a molecule found in gluten. In some individuals, the zonulin pathway "misinterprets" gluten as a potentially harmful component of a microorganism [51, 53].

An increase in intestinal permeability is seen in all who consume gluten, including those with celiac disease, non-celiac patients with gluten sensitivity, and non-celiac controls, with the greatest permeability seen in those with non-celiac gluten sensitivity and those with celiac disease [53]. Gluten is clearly implicated in the damaged barrier seen in those with celiac disease, but evidence also supports the benefits of a gluten-free diet in those with IBS or non-celiac gluten sensitivity [28]. Several studies have shown that treatment with a gluten-free diet in non-celiac disease subjects with IBS improves IBS symptoms and reduces intestinal permeability [29].

Non-celiac gluten sensitivity (NCGS) is a clinical diagnosis describing individuals who develop intestinal and extraintestinal symptoms when consuming gluten-containing foods and have a resolution of symptoms on a gluten-free diet but do not have celiac disease or wheat allergy [28]. Impaired intestinal barrier function is seen in these patients. The prevalence may be as high as 6%. It is prevalent in patients with functional GI disorders such as IBS and dyspepsia. Chronic muscle/joint pain, fatigue, headache, and difficulty concentrating are common symptoms in persons with NCGS [54]. NCGS is associated with chronic severe low back pain, and a gluten-free diet improves symptoms in those patients [55]. A gluten-free diet (GFD) also improves musculoskeletal pain, fatigue, weakness, and GI symptoms in patients with refractory functional dyspepsia; symptoms recur when gluten is reintroduced [56].

Consumption of soluble fiber is the only dietary intervention currently known to fortify the intestinal barrier function in humans [49]. In addition to gluten, dietary sugar, fructose, emulsifiers, and alcohol increase gut permeability and reduce mucus thickness, allowing for enhanced translocation of LPS leading to increased inflammation [46, 49].

4.11 Dysbiosis

Many studies have shown that intestinal dysbiosis reduces the production and function of immune cells and increases inflammation, and restoration of the microbiome reverses these effects. Dysbiosis increases intestinal permeability and inflammation and disrupts the function of the gut-brain axis that may play a role in the pathogenesis of depression and chronic fatigue syndrome [57].

4.12 Microbiome and Pregnancy

During pregnancy, the maternal gut microbiome shapes the maternal vaginal microbiome and, in turn, the microbiome of the newborn infant, with lifelong implications for health. The primary source of the vaginal microbiota is the translocation of both beneficial and pathogenic species from the gut to the vagina. A complex cross talk of bacteria across the gut and vagina modulates both local and systemic immune responses with an effect on overall health [58]. A disrupted vaginal microbiome is associated with increased risks of preterm birth, gestational diabetes, and preeclampsia [59]. Infant exposure to the vaginal maternal microbiome during birth determines the initial colonization of the newborn gut, which is largely sterile prior to birth. The initial colonization takes place in successive waves over the first year of life [59]. Infant exposure to the vaginal and fecal microbiome at birth is a critical "priming" event that impacts the brain health and immune and metabolic functions in the offspring for the rest of their life [59]. *Bifidobacterium* species, the most abundant bacteria in the GI tract of healthy newborns and considered a "keystone" species, has broad benefits for health, including decreased development of common allergic disorders such as eczema and asthma [60]. Prenatal diet, prenatal antibiotic use, Cesarean birth, and formula feeding are shown to decrease the levels of *Bifidobacterium* species in the newborn gut.

The maternal diet during pregnancy shapes the composition of the infant microbiome up to at least 1 year of life, independent of the mode of delivery [59]. An altered gut microbiota at birth associated with prenatal diet may have adverse health consequences related to immune, neurologic, and metabolic health throughout life [59]. A low-glycemic diet rich in multiple vitamins and minerals is associated with a healthier vaginal microbiome [61].

4.13 Diet and the Microbiome

A broad range of vitamins, minerals, and trace elements is required for the optimal function of the human microbiota. Additional dietary components contributing to microbiota health include fiber, phytochemicals, and fermented foods. In a recent large-scale study, researchers showed that the quality of foods included in a diet impacts the composition and function of the microbiota and human health. A diet rich in fresh, unprocessed, nutrient-dense plant and animal foods supports the presence of gut microorganisms lined to good health. In contrast, high intake of sugar or processed foods (sweetened beverages, refined grains and processed meats) is related to gut dysbiosis and poor health [25].

Overweight pregnant women with higher intakes of omega-3 fatty acids, fiber, and a range of 12 vitamins and minerals had greater gut microbiota diversity with fewer pro-inflammatory species and reduced serum zonulin concentrations, indicating protective effects for the intestinal barrier [62]. These findings strengthen similar findings by other researchers in pregnant and nonpregnant female populations and again highlight the importance of a nutrient-dense diet for human health.

4.14 Remove Sugar, Gluten, Food Additives, and Pesticides

As discussed previously, gluten is a potent driver of intestinal permeability. In addition, a number of food additives, such as monosodium glutamate and artificial sweeteners promote dysbiosis and intestinal permeability and are associated with symptoms in patients with fibromyalgia and IBS, underscoring the importance of avoiding processed foods [31].

The intake of refined sugars also promotes inflammation, dysbiosis, and intestinal permeability, which in turn influences neurotransmitter metabolism and brain function [26]. Several authors have reviewed a growing body of preclinical and clinical evidence that supports a link between high levels of refined sugars and dysbiosis and a loss of intestinal barrier function. Sugar intake also increases the cortisol response to stress [27].

While refined sugars undermine health, fruit contains fiber and polyphenols that are beneficial to health. Several studies have connected the intake of fruit juice with adverse health outcomes, but the consumption of whole fruit with an improved diversity and composition of the gut microbiota reduced risk of type 2 diabetes and cardiovascular disease and enhanced psychological well-being [63, 64]. Research consistently shows that fruit consumption has an anti-obesity effect [65]. Similarly, honey, rich in prebiotic and highly bioavailable polyphenol compounds, has paradoxical hypoglycemic effect and may even provide benefits in the management of diabetes mellitus [66].

Pesticides and herbicides used in conventional food production methods disrupt the gut microbiota, leading to intestinal inflammation and permeability. These disruptions in the microbiome may account for the fact that the incidence of obesity is closely related to the level of pesticides in the body [67]. The herbicide glyphosate

inhibits the growth of beneficial bacterial and increases the growth of pathogenic microbes. The consumption of organic food may benefit the gut microbiota, not only because of the absence of microbiota-disrupting pesticides but because organic foods have a higher polyphenol and carotenoid content than conventionally farmed foods [68]. The Shopper's Guide to Pesticides in Produce from the Environmental Working Group provides an annually updated "Dirty Dozen and Clean Fifteen" list with guidance regarding which conventionally grown fruits and vegetables contain the most and least harmful pesticides.

4.15 Replenish: Fiber, Prebiotics, and Polyphenols

Dietary fiber is a potent force for preventing and alleviating chronic inflammatory diseases through its role in shaping the microbiome and fortifying intestinal barrier function. Vegetables, fruits, and legumes are the primary dietary sources of fiber, and numerous studies have shown that these foods favorably alter the gut microbiota. Lesser amounts of fiber are found in cereal grains and tubers [69]. Fibers are classified as prebiotics if bacteria metabolize them in the large intestine [69]. Fermentation of prebiotic fibers by a diverse microbiota produces signaling molecules including SCFAs, critical molecules for maintenance of the intestinal barrier, immune modulation, and support of healthy metabolic function [32].

A low-fiber diet starves the intestinal microbiota. It rapidly causes changes in the microbiome composition, driving down diversity and decreasing beneficial bacteria [32]. The fiber intake of hunter-gatherer peoples average 150 g per day. The current recommended daily allowance (RDA) for women aged 19–50 is 25–28 g (USDA), and only 5% of Americans meet recommendations. A growing body of research suggests that daily fiber intake of at least 50 g provides the most optimal health benefits [32].

Sonnenburg and colleagues have shown in animal studies that a low-fiber diet over several generations results in progressive loss of diversity and that key bacterial species could not be restored when fiber intake was resumed [44]. They propose that the solution to the epidemic of chronic disease stemming from an impaired microbiome is to commit to a dietary fiber intake that "borders on the comical" [70]. A variety of dietary fibers is as important as abundance, as different types of fibers support different microbial species. A diet with 30 or more different types of fruits and vegetables each week is correlated with a much higher diversity in gut microbiota than a diet with 10 for fewer plant types [33].

Prebiotics increase the production of beneficial SCFAs such as butyrate, maintain intestinal barrier function, improve the composition of the microbiota, improve mineral absorption, and modulate immunity and metabolism, satiety, neurotransmitters, and stress hormones [42]. Extensive research exists on the benefit of various prebiotic supplements including improved metabolic function and reduced obesity. Normalized cortisol patterns, anxiolytic effects, and reduction in IBS symptoms are all reported, all would be beneficial in individuals who are living with chronic pain [42].

Inulin is a prebiotic found in artichoke, asparagus, leeks, onions, garlic, Jerusalem artichoke, burdock, chicory, and dandelion root and is also available as an inexpensive supplement. Inulin stimulates the growth of beneficial bacteria, reduces zonulin, and improves intestinal permeability [71]. It modulates inflammation, regulates blood sugar, and enhances the absorption of minerals [71]. Consuming a diet high in inulin-containing vegetables for 2 weeks leads to beneficial modifications of the microbiome as well as greater satiety and a reduced desire to eat sweet, salty, and fatty foods [34]. Inulin supplementation is beneficial for the treatment of constipation and irritable bowel syndrome, for improvement of parameters of glycemic control, and for inflammation in overweight and obese adults [72]. Inulin supplements are available in powders, capsules, and gummies. The addition of any new dietary or supplemental fiber or prebiotic can cause uncomfortable intestinal symptoms at first until the microbiome adjusts. Initial dosing of any prebiotic should be low. Inulin dosing should start at not more than 1–3 g a day for the first 1–2 weeks, gradually increasing the dose as tolerated up to 10–20 g/day [73] (Table 4.3). Some people may be unable to adjust to inulin intake, especially those who are intolerant to FODMAPs.

Phytochemicals are a broad group of plant metabolites other than vitamins and minerals, encompassing polyphenols, carotenoids, lignans, and sulfur-containing compounds They are widely present in vegetables, fruits, grains, nuts, seeds, and flowers. Their dietary intake is associated with a lowered risk of chronic inflammatory diseases [74]. They have direct influence on health through modulation of the microbiome, protection of the gut barrier function, antioxidant, and immunomodulating effects [75].

Polyphenols have powerful anti-inflammatory and antioxidant effects and are utilized by intestinal microbiota to synthesize health-producing metabolites. They are found in fruits, vegetables, green tea, coffee, and wine and include the flavonoids quercetin and resveratrol. They have antinociceptive and anti-inflammatory effects. Substantial preclinical evidence describes how polyphenols can attenuate nociceptive, neuropathic, and inflammatory pain [76]. Polyphenols can attenuate or reverse the inflammation seen in conditions like obesity and dysbiosis [75]. A meta-analysis has shown that supplementation of polyphenol-rich foods results in increased abundance of beneficial intestinal microbes with a decrease in pathogenic species. Apples, berries, green tea, red wine, and other fruits and vegetables were used in the studies [77].

Polyphenols are particularly rich in green tea, olive oil, berries, cherries, mushrooms, and culinary herbs and spices, including garlic, turmeric, black pepper, cinnamon, ginger, and rosemary [78]. Strawberries, blueberries, cherries, and pomegranate are among the polyphenol-rich foods that have evidence supporting their pain-relieving properties in humans.

Pomegranate fruit (*Punia granatum*) has been used in traditional medicine for relief of various types of pain. A large body of preclinical evidence and some clinical evidence supports its pain-relieving effects on nociceptive, inflammatory, neuropathic, acute, and chronic pain [35]. Pomegranate juice is shown to decrease the glycemic response to foods with a high glycemic index, reduce systematic inflammation, and reduce blood pressure [35].

Anthocyanins are polyphenols responsible for the red, orange, purple, and blue hues found in plant foods. They have potent anti-inflammatory and immunomodulatory effects and play an important role in prevention of chronic inflammatory diseases [79]. Their health-promoting effects are in part attributed to the impact on the intestinal microbiota, where they both inhibit the growth of pathogenic bacteria and increase beneficial bacteria that produce anti-inflammatory SCFAs [74]. A dietary intervention conducted on 60 patients at a tertiary pain clinic that included polyphenol-rich foods along with counseling on diet quality and nutrient density resulted in significant improvement in pain and quality of life. In that intervention, cherry juice, rich in anthocyanins, was provided as a dietary supplement [36].

Another flavonoid, apigenin, has prebiotic effects in the human gut and is also a potent antioxidant and anti-inflammatory with neuroprotective effects [80]. It protects against the inflammation caused when the harmful bacterial metabolite LPS translocated from the gut into the systemic circulation [80]. Dietary intake of apigenin is associated with better-quality sleep. Apigenin is found in parsley, celery, onions, artichokes, oranges, chamomile, calendula, basil, thyme, and oregano. The apigenin content in chamomile and dried parsley far exceeds that of other foods. Chamomile (*Matricaria chamomilla*) has the added benefit of antinociceptive and anxiolytic effects. Several trials have reported its benefits for improved sleep quality and the treatment of generalized anxiety disorder [81].

Ginger (*Zingiber officinale*) also contains potent polyphenols and has potent anti-inflammatory compounds. It is under investigation for use in neurodegenerative, autoimmune, and other chronic inflammatory diseases. Ginger intake enhances diversity and increases the presence of anti-inflammatory microbes in the human gut [82]. Ginger has such potent gut-protective effects that it can restore intestinal barrier function and alleviate antibiotic-associated diarrhea [82]. It is also effective for a variety of types of pain. Randomized controlled trials have shown its effectiveness in dysmenorrhea, osteoarthritis, and migraine [83]. It improves fasting blood sugar and serum insulin in [83]. Doses of 500–1500 mg/day are as effective as the antiemetics pyridoxine and metoclopramide and more effective than placebo [83]. Two cohort studies have reported that ginger did not affect the risk of teratogenicity or abnormalities in birth [83]. Ginger is also shown to enhance human milk production after vaginal births. Ginger can be used fresh or dried as a culinary spice and in teas. In supplement form, it can cause heartburn in some people at doses of 500–2000 mg per day [83] (Table 4.3).

Cruciferous vegetables, which include broccoli, cauliflower, cabbage, Brussels sprouts, and kale, are especially potent benefits for health. They contain sulforaphane, a compound with demonstrated capacity to prevent inflammation, oxidative stress, and fatigue. Sulforaphane also protects the healthy function of human mitochondria [84] and microbiota as well as having neuroprotective, cardioprotective, and anticancer effects. In preclinical research sulforaphane shows promise for reducing various types of pain [85].

Nuts and seeds contain anti-inflammatory polyphenolic and prebiotic compounds that protect intestinal barrier function, enhance butyrate synthesis, and

improve anti-inflammatory status [86]. They have a broad range of health benefits including glucose modulation and improved maintenance of healthy weight. It may be best to avoid peanuts, which often are contaminated with aflatoxin, a mold with hepatotoxic and carcinogenic effects.

Flaxseed contains lignans and polyphenols with anti-inflammatory and antioxidant effects. It is also a rich source of alpha-linolenic acid, a precursor molecule to DHA and EPA. In humans, flaxseed has displayed powerful cardioprotective, antihyperglycemic, anticancer, and neuroprotective effects [87]. In addition, the fibers in flax have a prebiotic effect in the human gut, increasing the abundance of microbes that produce beneficial SCFAs. Several trials have found it to be effective for constipation, but it also has anti-diarrheal effects [88]. A review of 45 RCTs concluded that flaxseed is beneficial for weight reduction in overweight and obese adults [89].

The oils in flaxseed are highly susceptible and become rancid through oxidation, unfavorably altering taste and health benefits [87]. Flaxseed is commonly used in baked goods, and baking does not alter the composition of the ALA. Milling, crushing, or grinding the seed decreases stability. However, these processes are required to make the components of flaxseed bioavailable. Rather than buying flaxseed preground, it is best to purchase whole seeds and grind small amounts at home, refrigerating it after grinding. Ground flax can be mixed with water, hot cereal, yogurt, smoothies, or applesauce for consumption. Doses used in studies range between 15 and 40 g/day, with doses of at least 30 g being the most effective for weight management [89]. Thirty grams is equivalent to approximately three tablespoons of whole flaxseed. As with any substance with prebiotic effects, the user should start with small amounts (½–1 tsp) and gradually increase the dose up to 2–3 tablespoons daily (Table 4.3).

4.16 Replace Fermented Foods, Fresh Produce, and Probiotics

Fermented foods have anti-inflammatory and immunomodulating properties. Fermented foods are not classified as probiotics because they do not always contain specific strains of bacteria in specific quantities; however, they contain live bacteria with health-promoting properties. The consumption of safe microorganisms every day in food is such an important part of preventing or ameliorating disease a group of scientists have recommended that fermented foods be included in national dietary recommendations [90].

Metabolites with antioxidant, gut-protective, and immunomodulatory functions are synthesized during fermentation. Much research describes the anti-inflammatory effects of fermented foods, including kefir, kimchi, and fermented soy [37].

Several clinical trials have shown improvements in blood pressure, waist-hip ratio, fasting glucose, and percent body fat with dietary intake of kimchi [38]. There is evidence that fermented vegetable consumption can alter mood and brain activity, decreasing stress hormones and social anxiety in young adults [91].

Fermented foods include beverages (kvass, kombucha, dairy products (yogurt, kefir), fermented dairy alternatives (coconut, soy, almond, cashew yogurts), soy products (miso, tempeh), and fermented vegetables (sauerkraut and kimchi, pickled beets, cucumbers, ginger). Shelf-stable fermented foods such as beer, coffee, chocolate, soy sauce, and wine have been processed after fermentation and do not contain live bacteria. Pasteurization kills the live organisms in fermented foods, and labeling foods as containing "live and active cultures" is used to confirm the health benefits of fermented products [90]. Fermented foods contain histamine, so caution is advised for those with histamine intolerance.

4.17 Fresh Produce

Emerging research reveals a wide variety of beneficial bacteria are found both on the surface and in the flesh of fresh fruits and vegetables. Each type of produce has substantially different bacterial communities. A whole apple, including the core and seeds, contains a 100 million bacteria, far more than is found in many probiotic supplements [92]. Most of the bacteria are inside the apple, not on the skin.

4.18 Probiotics

Probiotic supplements may be the most expensive and least reliable of strategies for supporting healthy intestinal function. While more than 2000 randomized controlled clinical trials exist on probiotic supplementation for various disorders, evidence of benefit is inconsistent. Thousands of strains of probiotic bacteria exist, and the effects on health are highly strain specific. While overall probiotics are shown to downregulate inflammation and improve intestinal barrier function and increase SCFAs, each strain has unique effects. It is difficult to accumulate a consistent body of knowledge because varying strains, doses, routes, and treatment durations are used in research. Often the strain with demonstrated efficacy in a clinical trial is not available commercially. In addition, adequate numbers of bacteria must be used to see benefits. Furthermore, inter-individual variability in the composition of the individual's microbiome with variation in the diet leads to differences in individual response to probiotic supplements. Dietary and prebiotic strategies may be less complex and easier to implement.

Robust evidence does exist for specific probiotic strains for specific conditions. Expert consensus recommendations on the use of probiotics are available from the International Scientific Association for Probiotics and Prebiotics (ISAPP). The ISAPP website contains a wealth of quality resources for both clinicians and consumers, including patient education infographics and videos. The Alliance for Education on Probiotics contains a clinical guide to probiotic products, which is also available as an app. This resource provides evidence-based and referenced recommendations regarding the indications for specific probiotic strains, along with ratings of the quality of evidence, dosing information, and brand names. Evidence

supports the use of specific probiotic strains to prevent and treat many gastrointestinal conditions, including IBS, constipation, antibiotic-associated diarrhea, *Clostridium difficile*-associated diarrhea, traveler's diarrhea, inflammatory bowel disease, and *Helicobacter pylori* infection. Other conditions with AEP recommendations include anxiety, weight management, mastitis, bacterial vaginosis, and vulvovaginal candidiasis. Another source of evidence-based guidelines is from the American Gastroenterological Association (AGA). The AGA recommends that healthcare providers consider recommending appropriate strains of probiotics when prescribing antibiotics [93].

4.19 Probiotics and Fibromyalgia

The most robust evidence for probiotic benefits is for various disruptions in intestinal function, such as IBS and IBD. These effects could be beneficial for patients with fibromyalgia (FM), considering that it is reported that more than 80% of patients with fibromyalgia had disrupted bowel patterns. While several small trials have reported that probiotics have benefits on the symptoms of chronic fatigue syndrome, limited research exists on probiotics in the treatment of fibromyalgia.

4.20 Probiotics and Pregnancy

Some individual trials regarding the benefits of probiotic supplementation during pregnancy have been promising. For example, supplementation with *Lactobacillus reuteri RC-14* and *Lactobacillus rhamnosus GR-1* is shown to reduce Group B *Streptococcus* colonization rates [94]. The overall evidence from clinical trials regarding the benefits of probiotic supplementation during pregnancy is decidedly mixed. There is inconclusive evidence of transfer from mother to infant of bacteria from ingested supplements. Recent meta-analyses have reported no beneficial impact of probiotics on preterm birth or gestational diabetes [95], with inconclusive evidence for an impact on hypertensive disorders of pregnancy. A review of 21 RCTs reported evidence that prenatal probiotic supplementation may reduce the risk of eczema, but not asthma in the offspring [96]. The optimal strain, dose, and timing have not been identified.

4.21 Dietary and Supplemental Interventions for the Management of Chronic Pain

The use of dietary and supplemental nutrients with antioxidant or anti-inflammatory properties and supporting healthy mitochondrial and gastrointestinal function form a crucial part of the therapeutic strategy for managing chronic pain (Table 4.2). Forty-one percent of women age 19–50 and 47% of pregnant or breastfeeding women in the United States are deficient in one or multiple

Table 4.2 Dietary strategies for the management of chronic pain

Consume an abundance and variety of high-fiber foods [63]
Vegetables, fruits, beans, whole grains, nuts, and seeds [64, 86]
Aim for a minimum of 30–50 g of fiber per day [32, 69]
Eat inulin-rich foods: onions, leeks, garlic, artichoke, asparagus, dandelion, and burdock roots [34, 71–73]
Eat a wide variety of vegetables and fruits
Aim for 30 different plant foods per week [33]
Consume polyphenol and carotenoid-rich foods
Daily intake of green, red, orange, purple, and blue plant foods [76, 77]
Regular use of culinary herbs such as ginger, garlic, parsley, basil, thyme, oregano [78]
Regular consumption of olive oil, berries, cherries, and pomegranate [35, 79]
Eat cruciferous vegetables daily
Cabbage, cauliflower, broccoli, Brussels sprouts, kale, turnip, bok choy [84]
Consume fermented foods daily [37, 91]
Fermented vegetables, beverages, dairy or dairy alternatives labeled "contains live and active cultures"
Consume foods high in magnesium [97–99]
Darky leafy greens, nuts and seeds especially pumpkin seeds, and fatty fish (tuna, halibut, salmon), avocado, prunes, figs
Eat 8–12 ounces of fatty seafood per week [100, 101]
Wild salmon, sardines, herring, trout, mackerel, oysters, anchovies
Use cooking methods other than frying
Reduce intake of omega-6 fats [102, 103]
Soy, corn, sunflower, safflower, canola, sesame, and peanut oils
Minimize intake of refined sugars, gluten, artificial sweeteners, food additives, and processed foods [25–27]
Whole fruit and honey are beneficial to health [63, 66]
Avoid foods with glutamate and aspartate [31]
MSG, soy and fish sauce, aged cheeses, cured meats, hydrolyzed vegetable protein, plant protein extracts, yeast extract, food additives (sodium or calcium caseinate, modified food starch, smoke flavoring, artificial flavoring)
Eat organic food as much as possible [68]
Use the Shopper's guide to pesticides in produce from the environmental working group

micronutrients [104]. An expert panel of pain researchers has recommended that all patients with chronic pain should have nutritional counseling at the onset of treatment [105]. *Diet therapy* is a prescribed diet modification that manipulates the whole diet to increase and decrease the intake of specific nutrients. This section provides an overview of the impact of nutrition on chronic pain, focusing on evidence-based diet therapy to improve pain and comorbidities of chronic pain (depression, anxiety, IBS) and optimize health during pregnancy. It also reviews selected dietary supplements that are safe for use during pregnancy and evidence-based for treating chronic pain and mitigating the underlying etiologies of inflammation, mitochondrial dysfunction, intestinal permeability, and microbiome disruption.

4.22 Diet and Pain

A large and rapidly growing body of research describes the diet as an essential modulator of chronic inflammation and that diet has a noticeable impact on pain . Studies that examine the impact of diet on chronic pain especially highlight the role of dietary intake on oxidative stress and inflammation. Specifically, a diet with refined carbohydrates, processed sugar, and saturated and trans fats promotes inflammation. Both chronic inflammation and oxidative stress are biological precursors to chronic pain.

A systematic review and meta-analysis of 43 studies examined the impact of dietary interventions on managing a variety of disorders involving chronic pain. An overall positive effect of whole-food diets was seen, with no single diet standing out in effectiveness [106]. The common features of the effective dietary approaches are diet quality, whole foods, and nutrient density, which are all involved in modulating the physiology of pain. In addition, weight loss often occurs when nutrient-dense whole-food diets are implemented.

Brain and colleagues reported that personalized telehealth dietary consultations in adults with chronic pain led to improvements in perceived pain, quality of life, and quality of dietary intake [36]. The intervention included counseling about nutrient density and diet quality and the inclusion of polyphenol-rich foods, which are discussed in the section on the microbiome.

Rondanelli reviewed 172 studies and recommended a low-glycemic diet with a minimum of 5 portions of fruits and vegetables daily to reduce proinflammatory states associated with chronic pain [107].

Holton reviewed evidence showing that fibromyalgia is associated with a low dietary intake of micronutrients and high dietary intake of free glutamate and aspartate [108]. Glutamate, an excitatory neurotransmitter, mediates pain transmission and plays a key role in central sensitization. Clinical trials restricting the intake of foods and additives containing free glutamate and aspartate resulted in symptom improvement in people with FM and IBS, and reintroduction of these foods resulted in a return of symptoms [108].

4.23 The Dietary Inflammatory Index (DII)

The Dietary Inflammatory Index (DII) is a tool for estimating the inflammatory nature of a person's diet based on the overall dietary composition. It is a validated tool for predicting levels of six of the most studied inflammatory biomarkers, with higher DII scores associated with biomarkers of inflammation. It is an approach that considers the diet as a whole rather than individual nutrients, which allows the capture of nutrient interactions within the diet. The DII is based on a broader range of human populations worldwide, study designs, and nutritional assessment methods than other diet indices and includes evidence from cell culture and animal experiments [109]. Six thousand five hundred articles on the effect of dietary parameters on six inflammatory markers and food consumption data sets from around the world were used to develop the DII [109].

Correa-Rodriguez and colleagues reported that pain hypersensitivity in women with fibromyalgia syndrome was positively correlated with high scores on the Dietary Inflammatory Index. The researchers concluded that strategies to promote an anti-inflammatory diet should be considered to improve pain in women with FM [110]. Similarly, a survey showed that those with a pro-inflammatory diet on the DII scale were 42% more likely to have low back pain [111].

The DII utilizes a food frequency questionnaire and evaluates 45 food parameters in creating the score, including macronutrients and micronutrients and commonly consumed foods, herbs, and spices that contain 16 flavonoids linked with anti-inflammatory effects. Food categories counted as pro-inflammatory include added sugar, refined grains, red meat, and saturated fat. Anti-inflammatory foods include fruit, non-starchy vegetables, fish/seafood, and whole grains. It is a tool for research, and the researchers have launched a company (https://imaginehealthy.org/) where the individual can obtain their DII score for a fee.

An anti-inflammatory diet supports healthy pregnancy outcomes as well as supporting the management of chronic pain. Prior to pregnancy, a pro-inflammatory diet as measured by the DII score is associated with worse outcomes of in vitro fertilization, early pregnancy loss, and increased risk of preterm birth [112]. The DII score has been used during pregnancy in numerous studies that demonstrate an association between high DII scores and increased risk of preterm birth and low birth weight [112]. The effects on the offspring when a pro-inflammatory diet is consumed during pregnancy include increased neonatal and childhood adiposity, increased risk of attention deficit hyperactivity disorder symptoms at preschool age, emotional and behavioral problems, and asthma [113]. A pro-inflammatory diet as measured by the DII is linked with an increase of intrapartum fetal asphyxia, as measured by umbilical cord gases at birth [114]. The authors hypothesize that maternal systemic inflammation caused by a high DII diet can cause intrauterine inflammation and impaired fetal oxygenation.

The components that make up an anti-inflammatory diet overlap with those of a diet for support of a healthy gut—a diverse and balanced microbiota and intact intestinal barrier function. Essential foods for gut function are discussed in the section of this chapter covering the microbiome.

4.24 Supplements

This section reviews selected supplements that are safe and beneficial during pregnancy and treat chronic pain and inflammation while also improving mitochondrial function and supporting a healthy microbiome and intact intestinal barrier.

4.25 Magnesium

More than half of the population has a dietary magnesium intake below the estimated average requirement [97]. Magnesium is the fourth most common mineral in the body and is a cofactor in more than 300 enzymes systems needed for a variety of essential functions. Low dietary intake leads to chronic inflammatory states and is associated

with numerous chronic diseases [98]. Symptoms of mg deficiency include fatigue, irritability, anxiety, and headache [98] . A bidirectional link between magnesium and stress is proposed, with stress causing magnesium loss, which leads to a deficiency. In turn, magnesium deficiency increases the body's susceptibility to stress disorders [98].

Magnesium has an antinociceptive effect and inhibits central sensitization [99]. Patients with fibromyalgia have low magnesium status, and magnesium deficiency is related to the pain intensity of fibromyalgia and migraine [99]. Tartelon and Littenberg found that for every additional milligram of dietary magnesium consumed per kilogram of body weight, the odds of experiencing chronic pain decreased by 7% [97]. The use of magnesium to treat chronic pain has been studied in patients with chronic low back pain, fibromyalgia, and neuropathic pain [115]. The Canadian Headache Society and the American Academy of Neurology have recommended that magnesium be offered for migraine prophylaxis, with a recommended dose of 600 mg of elemental magnesium daily as magnesium citrate [116].

An association of low magnesium intake with depression is well documented [97]. In a meta-analysis of 11 studies, the authors found significant effects of dietary magnesium intake in relation to decreased risk of depression. The largest risk reduction was seen with 320 mg/day of magnesium intake. Several trials have demonstrated the efficacy of supplementation for a reduction in depression and anxiety stress scores, decreased cortisol, and improved heart rate variability (a measure of stress) [98]. In Europe, authorized health claims about magnesium include statements that magnesium contributes to a reduction of tiredness and fatigue, normal muscle function, normal psychological function, and normal functioning of the nervous system [117].

Soil magnesium levels vary widely across the United States, and geographic variations in magnesium intake exist [118]. Public water systems typically remove magnesium before distribution. Many other factors, including obesity, oxidative stress, high calcium intake, deficiency in other nutrients, low intake of dietary protein and fiber, caffeine intake, and the use of medications such as diuretics, proton-pump inhibitors, and antibiotics, increase the risk of magnesium deficiency. The current DRI of 350 mg for women (IOM) is considered inadequate [119].

In pregnancy, in a recent meta-analysis of 6 RCTs, the preterm birth rate was decreased by more than 40% in the magnesium supplementation groups compared with control groups [118].

Counseling on foods containing magnesium is appropriate for patients with chronic pain. Nuts, seeds, and some beans are good sources of magnesium, with pumpkin seeds, sesame seeds, brazil nuts, almonds, black beans, and kidney beans being the highest (USDA). Dark leafy greens (spinach, chard, broccoli), fatty fish (tuna, salmon, halibut) figs, avocado, and dried plums are other good sources of magnesium.

Magnesium supplements come in multiple forms with different benefits specific to different physical functions. Absorption and bowel tolerance are key issues to consider along with physiological need as a basis for recommendations. Magnesium has a laxative effect and patients with compromised digestion need extra support and careful dosing.

Magnesium citrate is one of the most bioavailable forms of magnesium and magnesium oxide is poorly absorbed. Magnesium bisglycinate is highly bioavailable and is the least likely to cause diarrhea [120] (Table 4.3).

Table 4.3 Functional foods and supplements for the management of chronic pain in pregnancy

Functional foods				
Name	Actions/indications	Dosages	Cautions	Considerations
Chamomile [81]	Anti-inflammatory, gut-protective and neuroprotective	Strong tea 2–3×/day, liquid extract (3–6 mL/day)	Rare allergic reactions, more likely in those with allergy to ragweed [121]	
	Useful for anxiety, insomnia, migraine, GI discomfort, premenstrual syndrome			
Flaxseed [87–89]	Anti-inflammatory, neuroprotective, gut-protective, prebiotic	15–40 g/day (one TB = 9 g)	May case GI discomfort in some until microbiota adapt	Start with ½-1 tsp/day and gradually increase dose to gut tolerance
	Helps with achieving healthy weight		Oils susceptible to rancidity	Buy whole seed and grind at home, refrigerate after grinding
	Useful for either diarrhea or constipation			
Ginger [82, 83]	Pain-relieving, anti-inflammatory, antispasmodic, digestive aid, gut-protective, balances microbiota	Use fresh or dried, in tea or cooking	May cause heartburn in some people at high doses. Caution if you have peptic ulcers	
	Effective for management of pain, migraine, GI discomfort, and nausea, including nausea of pregnancy	Supplement: 250–500 mg BID-TID		
Pomegranate and cherry [35, 36]	Pain-relieving, gut-protective	4–12 oz/day of juice		May be used in juice or powder form. Juice reduces glycemic response to foods

(continued)

Table 4.3 (continued)

Functional foods				
Name	Actions/indications	Dosages	Cautions	Considerations
Supplements				
Coenzyme Q10 [122–129]	Anti-inflammatory	100–200 mg/day	Inadequate information for use in those with kidney or liver disease or during chemotherapy	Use ubiquinol form
	Supports mitochondrial function		May lower blood glucose, caution in people with diabetes	
	Reduce pain, anxiety and depression.		May increase metabolism of warfarin	
	Improve fertility and pregnancy outcomes			
Curcumin [130–138]	Potent anti-inflammatory actions	500 mg BID-TID	May be best avoided when trying to conceive and in the first weeks of pregnancy [136]	Meriva and BCM-95 are well-researched formulations [136]
	Pain: as effective as ibuprofen in some studies		Curcumin does not interfere with the action of common antiplatelet medications or alter the INR values in stable patients on warfarin [138]	Doses of 1.5 g are well tolerated. Dose for chronic pain 1.0–1.2 g/day, doses of >2 g/day of Meriva used for acute pain may cause gastric upset some users [136]
	Mood: as effective as antidepressants in some studies			
	May be beneficial for improving IBD			

Fish oil [100–103, 139–149]	Dietary intake of fish: Anti-inflammatory, mood-enhancing, pain-relieving effects	Adequate intake for adult women 1.1 g/day; 1.4 g/day during pregnancy	But from manufacturers who are GEOD members to ensure supplements without rancidity or contaminants, do not exceed 2 g/day of combined EPA and DHA supplements [121]	Fish consumption is the best option. The benefits of supplementation are unclear
	Beneficial for headache, depression, reduced risk of preterm birth, and improved visual, verbal, and motor development skills in the offspring		https://www.goedomega3.com/	If supplements are used, take with a high-fat meal. If used for depression, take a product with at least 60% EPA
Inulin [34, 71, 72]	A prebiotic, improves microbiota and intestinal barrier function. Beneficial for constipation, IBS, glycemic control, mood, cognition	Start with low dose of not more than 1–3 g/day, gradually increasing as tolerated to 10 g/day	May cause GI discomfort at first if started with too high dose	
Magnesium [97–99, 115–120]	Decreases inflammation. Deficiency increases susceptibility to stress, and symptoms include fatigue, anxiety, headache	RDA for adult women is 310 mg of elemental magnesium, but some experts recommend more, and 600 mg/day is recommended for migraine prevention	High doses may cause diarrhea. May interact with antibiotics, diuretics, proton-pump inhibitors [121]	Magnesium citrate and magnesium glycinate (bisglycinate) are best absorbed, glycinate least likely to cause diarrhea
	Indications: pain, migraine, anxiety, migraine			
	May decrease risk of preterm birth			

(continued)

Table 4.3 (continued)

Functional foods				
Name	Actions/indications	Dosages	Cautions	Considerations
Probiotics [42, 43]	Research supports use for a variety of gastrointestinal conditions and for vaginitis	–	Any side effects are minor and consist of GI symptoms like gas. Caution in those with severe illness or immunocompromised	Must use specific strains for specific conditions
	Specific strains may decrease group B streptococcus colonization during pregnancy (*lactobacillus reuteri RC-14 and lactobacillus rhamnosus GR-1*) [94]			Use evidence-based guidelines: the ISAPP website, the Alliance for education on probiotics clinical guide (app), American Gastroenterological Association guidelines
Vitamin D [150–164]	Treatment of deficiency improves chronic pain and supports a healthy microbiota	Sun exposure 10 am–2 pm is the best source. Supplement: vitamin D3, 1200–4000 IU/day treatment of deficiency: 50,000 IU/weekly × 12 weeks	Upper safe intake: 4000 IU/day (IOM) 10,000 IU/day (Endocrine Society). May interact with statins, thiazide diuretics [114]	Deficiency is common
				Risk factors for deficiency include the presence of chronic pain, obesity, having dark skin, and limited sun exposure
				Take with vitamin K2, 70 μg

4.26 Coenzyme Q10

Coenzyme Q10 (CoQ10) is a fat-soluble vitamin-like molecule found in nearly every cell in the body. It is a normal part of the diet and also is endogenously synthesized. (It is one of the most widely researched and utilized antioxidant supplements in treating and preventing a broad range of chronic diseases) [122]. In recent years its essential role in mitochondrial function has been highlighted. It is indispensable for mitochondrial and cellular function, and inadequate levels have severe consequences for health.

CoQ10 plays a crucial role in mitochondrial ATP production and cellular metabolism [123]. It also increases the production of critical antioxidants and reduces pro-oxidative compounds, protecting against oxidative damage [15].

A meta-analysis of nine RCTs reported that supplemental CoQ10 significantly reduced inflammatory markers in patients with chronic disease [123]. Patients with fibromyalgia (FM) have lower CoQ10 levels than healthy subjects, and lower levels of CoQ10 are positively correlated with proinflammatory cytokines and pain scores [6]. In two small RCTs, supplementation with CoQ10 in patients with FM resulted in improved markers of mitochondrial function, reduced oxidative stress and inflammation, and improved pain scores [15, 124]. In other studies, CoQ10 supplementation improved anxiety and depression and the pain of FM [124]. In patients with migraines, a 2019 meta-analysis showed that CoQ10 was more effective than placebo at reducing the duration and number of migraine days per month [125].

CoQ10 supplementation has potential benefits for human reproduction and perinatal disease prevention. In a meta-analysis of 5 RCTs with 449 infertile women, supplementation with CoQ10 improved clinical pregnancy rates compared with placebo [126]. In women with intrahepatic cholestasis of pregnancy (ICP) CoQ10 levels in maternal and umbilical cord blood are lower than in normal pregnancy [127]. CoQ10 significantly improved cholestasis in animal models by attenuating liver oxidative stress and in humans is more effective than the standard treatment of ursodeoxycholic acid [127]. The authors suggest that given its excellent safety record, it can be considered as a treatment for ICP.

In data from clinical studies, CoQ10 has been highly safe and well tolerated. Adverse effects are mild and rare [128]. Inadequate information exists on the use of this supplement in patients with kidney or liver disease or using chemotherapeutic agents, so it should be avoided in those patients. It may lower fasting glucose, so caution may be required in patients with diabetes. It may increase the metabolism of warfarin. Toxicity is unlikely even in doses up to 1200 mg/day [126]. Typical doses are 100–200 mg/day. No mutagenicity and no adverse effects on the pregnancy or offspring were noted in reproductive toxicity studies on pregnant rats and mice [129] (Table 4.3).

4.27 Curcumin

Turmeric (*Curcuma longa* L.) has been used for centuries as a culinary herb and for medicinal benefits. Curcumin is a primary component of turmeric. Curcumin is one of the most extensively studied plant compounds, with nearly 300 randomized controlled trials, many showing benefit in an extensive range of chronic inflammatory diseases. It has anti-inflammatory, immunomodulating, antioxidant, neuroprotective, and antidiabetic properties [130].

The analgesic effects of curcumin are described as equivalent to ibuprofen, without the adverse effects [130]. When added to conventional therapy, curcumin improves clinical parameters in subjects with inflammatory bowel disease [130]. Multiple randomized clinical trials have demonstrated its benefits in reducing cortisol and improving depression and anxiety, mood states that often coexist with chronic pain, as well as improving insulin sensitivity and reversing metabolic abnormalities [131, 132].

A large body of preclinical and animal research supports the strong potential for curcumin's benefit in people with migraines, and small clinical trials show a reduced severity and duration of headache [133].

Curcumin is beneficial for supporting healthy mitochondrial function. It also is shown to have potent effects in maintaining intestinal barrier function and improving symptoms in patients with inflammatory bowel disease [130].

4.28 Curcumin During Pregnancy

The European Food Safety Authority reports that there are no concerns about genotoxicity [134]. Several authors have reviewed a large body of preclinical evidence supporting the use of curcumin for the prevention and management of pregnancy complications such as gestational diabetes, preeclampsia, depression, fetal growth restriction, and preterm birth [135]. Curcumin has the potential to counteract the effects of cytotoxic and teratogenic agents, such as lead, alcohol, polychlorinated biphenyls (PCBs), arsenic, and mercury [135]. Some reviewers summarize in vivo and animal studies showing no significant teratogenic or adverse effects associated with curcumin consumption on pregnancy outcomes [135], while others report that some animal studies show detrimental effects on oocyte maturation and blastocyst implantation and development [136]. Until there is more data, curcumin is best avoided in early pregnancy and during attempts to conceive a pregnancy [136].

See Table 4.4 for information about the use of curcumin supplements.

Curcumin has low bioavailability and needs to be processed in a way that enhances absorption. Formulations for increased bioavailability include binding to phospholipids or lecithins or mixing with adjuncts such as piperine found in black pepper. Meriva and BCM-95 are two of the most-researched formulations of curcumin. Meriva in doses of 1.5 g/day is well tolerated, whereas doses of 2 g/day, used for acute or severe pain, causes gastric upset in approximately some subjects [137]. Recommended dosing for chronic pain is 1–1.2 g/day [137]. Curcumin does not

Table 4.4 Recommended daily allowances

	Endocrine Society [156]	Institute of Medicine [114]
RDA adults	1500–2000 IU/day	600 IU/day
RDA obese adults	3000–6000 IU/day	No recommendation
Safe upper limit	4000 IU/day	10,000 IU/day
Pregnancy RDA	1500–2000 IU/day	600 IU/day
Pregnancy safe upper limit	10,000 IU	4000 IU/day

interfere with the action of common antiplatelet medications or alter the INR values in stable patients on warfarin (Table 4.3) [138].

4.29 Vitamin D

Adequate vitamin D levels are crucial for many aspects of a healthy pregnancy and have particular relevance to pain management. Sixty-seven percent of the adult population in the United States has insufficient vitamin D levels. The prevalence of vitamin D deficiency is higher in African American and Hispanic adults and in people with BMIs in the overweight or obese category [166].

4.30 Vitamin D and Pain

A review of 81 studies reported a significantly lower serum vitamin D level (25(OH) D concentration) in patients with widespread chronic pain and muscle pain [166]. Vitamin D levels are lower in those with low back pain than in healthy controls [151]. In patients with FM, the severity of anxiety and depression is worse in the setting of vitamin D deficiency [151]. Several studies have found vitamin D supplementation to improve pain in patients with nonspecific musculoskeletal pain [152]. The results of a qualitative meta-analysis concluded that eight studies support the benefits of vitamin D supplementation for chronic pain. Dosing of at least 1000 IU/day was required to see an effect [154]. Another meta-analysis explicitly focused on widespread chronic pain and fibromyalgia concluded that vitamin D supplementation decreases pain scores in patients with those conditions. They recommend screening and treating for vitamin D deficiency in those with FM [154].

4.31 Sources of Vitamin D

The primary source of vitamin D is skin exposure to sunlight in the spring, summer, and fall seasons. When skin exposure to the sun occurs between 10:00 AM and 3:00 PM, ultraviolet B rays stimulate the synthesis of cholecalciferol in the skin. An adult in a bathing suit exposed to enough sun to cause slight skin pinkness 24 h after exposure produces vitamin D equivalent to ingesting between 10,000 and 25,000 IU of vitamin D [156]. The amount of sun exposure required to synthesize adequate

vitamin D varies by season, time of day, latitude, cloud cover, skin pigmentation, sunscreen use, body weight, and age [156].

Few foods naturally contain vitamin D. The best sources are wild-caught fatty fish, such as trout, salmon, tuna, and mackerel. Smaller amounts are present in beef liver, egg yolks, and cultured cheeses (such as ricotta, cheddar, fontina, muenster, Monterey, bleu, brie, gouda) [154]. Most of the milk supply in the United States is fortified with vitamin D3 at low levels of about 120 IU per cup. Vitamin D2 is found in mushrooms [154]. Many of the vitamin D-rich foods are not typically consumed on a regular basis.

4.32 Vitamin D Serum Status and Recommendations for Testing

A serum concentration of 25(OH)D is used to indicate vitamin D status. It reflects vitamin D obtained through endogenous production, food, and supplements. (Office of Dietary Supplements ODS). Serum concentrations are reported either in nanomoles per liter (nmol/L) or nanograms per milliliter (ng/mL). One nanogram per milliliter is equal to 2.5 nmol/L.

In 2010 the Institute of Medicine defined vitamin D deficiency as serum 25(OH)D of less than 12 ng/mL and vitamin D insufficiency as less than 20 ng/mL (IOM). The Endocrine Society defines *deficiency* as below 20 ng/mL and *insufficiency* as 21–29 ng/mL, while stating that 40–60 ng/mL is the preferred range for health [156]. The Institute of Medicine (IOM) recommendation is based exclusively on bone health, while the Endocrine Society based their recommendations on information about the impact of vitamin D on immune function, cancer risk, and pregnancy complications. Many vitamin D experts support 40 ng/mL as the optimal level for health in nonpregnant [158] and pregnant individuals [159].

The Endocrine Society recommends screening those at risk of vitamin D deficiency. Groups at risk of vitamin D deficiency include but are not limited to people with limited sun exposure, people with dark skin, and people who are obese [156]. The Endocrine Society Recommendations states that "at risk" should be defined based on the most current literature. Since fibromyalgia and other chronic pain disorders are associated with vitamin D deficiency and supplementation improves symptoms, testing serum vitamin D levels would be indicated in these populations.

4.33 Recommended Intake

The recommended daily intake varies by organization and BMI (Table 4.4). There is an extensive debate about the relative value of the IOM versus the Endocrine Society Guidelines. Researchers have noted inaccuracies in the IOM analyses of evidence that led to underestimating both the serum 25(OH)D threshold and the required daily intake [160].

Supplementation of 1000 IU daily for 2 months was insufficient to raise blood level to at least 30 ng/mL in those with mild insufficiency [161]. In an analysis of

108 studies, Veugelers and colleagues reported that a daily intake of 2909 IU is needed to achieve 25(OH)D concentrations of 20 ng/mL in 97.5% of healthy adults [162]. In addition, they reported extensive variation among doses needed for normal weight, overweight, and obese individuals and recommend that recommendations be specific for body weight. No toxicity has been seen in adults taking between 10,000 and 20,000 IUs daily for more than a year [163].

To treat vitamin D deficiency, the Endocrine Society recommends 50,000 IU weekly for 8 weeks, followed by 50,000 IU every 2 weeks to maintain vitamin D sufficiency [157].

4.34 Sun Exposure

Sunlight has health benefits that are independent of vitamin D. Although vitamin D deficiency is associated with an elevated risk of chronic pain, cancer, diabetes, cardiovascular disease, depression, and autoimmune conditions, clinical trials on vitamin D supplementation have been mixed and have not consistently decreased the risk of these diseases (Alfredsson) [164]. The benefit of vitamin D synthesized in the skin may be greater than that vitamin D obtained through supplements, since vitamin D produced in the skin may last in the circulation at least twice as long compared with ingested vitamin D. In addition, sun exposure stimulates the syntheses of serotonin, nitric oxide, and endorphins, key molecules for health [164]. Improved health outcomes are seen related to sun exposure independent of vitamin D, and improved health outcomes are seen related to serum 25(OH)D levels but not vitamin D supplementation [167]. These observations have led to hypotheses that vitamin D serum status is a proxy for rather than a mediator of beneficial effects of sun exposure and that vitamin D supplements are not an adequate substitute for sun exposure [164, 167]. Sun exposure is associated with a reduced incidence of blood clots, breast, prostate, and colorectal cancer, pancreatic cancers, and all-cause mortality [164, 169] and is estimated to be responsible for 340,000 deaths per year in the United States [164].

Public health authorities in the United States recommend minimizing sun exposure to decrease the risk of skin cancer. An expanding understanding of the role of sun exposure in health has led researchers to express concern that these recommendations have contributed to an epidemic of vitamin D deficiency and associated disease and need to be revised to emphasize the benefits of adequate sun exposure while warning against exposure that produces sunburn [164, 167]. Several reviewers have noted that melanoma is rare. The risk factor for melanoma appears to be intermittent intense sun exposure leading to sunburn rather than chronic sun exposure [164]. Most studies have found that chronic lifetime sun exposure is associated with a protective effect on the development of malignant melanoma [168]. Outdoor workers have half the melanoma rate of indoor workers, and tanned people have lower rates in general [164, 167]. In a study of nearly 30,000 Swedish women, those with more sun exposure had half the all-cause mortality rate as those who habitually avoided sun exposure [169]. Lindqvist found that people who spend more time in the sun have lower blood clots and diabetes rates and half the overall mortality of those who avoid sun exposure [169].

Light-skinned people living at 40° latitude can produce adequate vitamin D by spending 15 min in the sun with face, arms, and legs exposed 2–3 times a week between 11 AM and 3 PM during May through October [164]. However, multiple factors influence the amount of sun exposure required for adequate vitamin D production. Those with darker skin require more sun exposure to produce vitamin D. The dminder app, by ontometrics, developed by researcher Michael Holick, is a tool that uses age, weight, skin type, amount of exposed skin, latitude, season, time of day, and cloud cover to track the amount of sunlight needed for vitamin D production. The app can notify the user of the optimal duration of sun exposure to maximize vitamin D production and avoid sunburn. Grassroots Health, an organization with an international panel of vitamin D researchers, contains a wealth of resources for moving research about vitamin D into clinical practice [170, 171].

4.35 Pregnancy

Vitamin D deficiency and insufficiency are common during pregnancy, with some authors reporting that 97% of African Americans, 81% of Hispanics, and 67% of white people were deficient or insufficient [158]. Observational studies have consistently found an association of vitamin D deficiency during pregnancy with an increased risk of pregnancy complications, including gestational diabetes, preeclampsia, preterm birth, and low birth weight [170]. Vitamin D mediates placental function and optimal neurodevelopment and lung maturation in the fetus [170]. Adequate vitamin D levels during pregnancy are associated with improved mood and sleep quality. For the offspring, insufficient vitamin D status during gestation is associated with increased incidences of allergies, asthma, autism spectrum disorder, and multiple sclerosis [170].

While the results of studies reviewing the impact of vitamin D supplementation on health outcomes outside of pregnancy have been mixed, systematic reviews have shown that vitamin D supplementation during pregnancy safely elevated circulating 25(OH) D levels and is associated with improved insulin sensitivity and reduced risk of low birth weight [165]. Wagner and colleagues reported that supplementation of 4000 IU/day during pregnancy reduced the incidence of preterm birth by more than half and may reduce preeclampsia and gestational diabetes. Their findings resulted in a program to supplement all pregnant women with 5000 IU/day of vitamin D at five hospitals in the medical university system in South Carolina [172]. Vitamin D supplementation during pregnancy results in decreased risk of asthma in the offspring [170].

4.36 Vitamin D Dosing During Pregnancy

Supplementation with 2000 IU/daily compared with 1000 IU is more effective at promoting adequate vitamin D status and ameliorating pro-inflammatory markers in the mother and cord blood and leading to higher birth weight and head

circumference [173]. In a randomized controlled clinical trial with 500 pregnant women comparing doses of 4000 IU/day with 2000 or 400 IU/day, only the 4000 IU dose effectively achieved sufficient 25(OH)D serum levels [172].

4.37 Considerations for Vitamin D Supplementation

Vitamin D3 is preferred over vitamin D2 for supplementation. Vitamin D and vitamin K2 work synergistically to regulate calcium homeostasis. While vitamin D3 improves calcium absorption, vitamin K2 ensures that calcium is deposited into bone rather than into soft tissues, thus enhancing vascular elasticity. Vitamin D supplementation in the setting of vitamin K deficiency might induce soft tissue calcification, negatively impacting cardiovascular and joint health [174]. Supplement manufacturers offer products pairing K2 with D3. Dark leafy green vegetables, especially kale, chard, parsley, broccoli, and spinach, liver, and fermented foods such as cheese and natto are sources of vitamin K. Menaquinone-7 is the best absorbed of the various forms of vitamin K and shows benefit in clinical trials.

In summary, sun exposure is a safe way to maintain optimal vitamin D status and has health benefits beyond those of vitamin D synthesis. The dminder app can be used to guide sun exposure on an individualized basis. Some experts in vitamin D research recommend that preconception and pregnancy levels of 25(OH)D be maintained at a minimum concentration of 40 ng/L, which would require 4000 IU/day of vitamin D intake [165]. Others recommend attaining a minimum concentration of 20 ng/mL [158], which would require an intake of 1200 IU/day. An intake of 4000 IU/day of vitamin is within the safe upper limit recommended by the IOM and the Endocrine Society [159]. Given the many factors that impact the vitamin D status of individuals, including skin pigmentation, body weight, and sun exposure, along with the critical importance of vitamin D for health, the Endocrine Society guidelines recommend measuring serum 25(OH)D concentrations in individuals at risk for vitamin D deficiency. Indications for testing include pregnancy, obesity, and dark skin pigmentation [156].

4.38 Polyunsaturated Fatty Acids: Omega-3 and Omega-6

Polyunsaturated fatty acids (PUFAs) are essential components of the human diet. They are divided into two categories: omega-3 ($n-3$) and omega-6 ($n-6$). Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are the two primary omega-3 fatty acids and have powerful pain-relieving properties and benefits for maternal health and fetal and infant development.

Omega-3 fatty acids are transformed into antinociceptive and anti-inflammatory molecules, whereas omega-6 fatty acids are transformed into compounds with pronociceptive and proinflammatory properties [102]. A higher omega-6 to omega-3 ratio contributes to chronic inflammatory states, and the excessive intake of omega-6 fats in the modern diet is a driver for signaling pathways involved in persistent pain [106].

EPA and DHA are most abundant in cold-water fish and found in grass-fed ruminant animals' fat [175]. Plant foods such as nuts and seeds contain alpha-lipoic acid, a precursor to DHA and EPA. When fish consume algae or ruminant animals eat grass, they convert ALA to DHA and EPA and concentrate the $n-3$ PUFAs in their fat. The human liver is inefficient in converting ALA to DHA and EPA Studies show that ALA sources, like flax oil, have a very minimal effect in raising DHA levels in humans [139]. DHA but not EPA supplements can be produced from microalgae in a laboratory, and those supplements effectively increase DHA serum levels in humans [140].

The optimal intake of $n-3$ PUFAs depends on the intake of omega-6 fatty acids. Omega-6 PUFAs, including linoleic and arachidonic acid, are found in vegetable oils (safflower, sunflower, corn, sesame, peanut, soy, and canola oils) and foods derived from livestock and poultry raised on grain rather than on green pasture. The same set of enzymes competitively metabolizes omega-6 and omega-3 PUFAs. The lipid mediators produced from their metabolism produce antagonistic functions in the human body [102]. Omega-6 PUFAs enhance inflammation, platelet aggregation, and vasoconstriction, while omega-3 PUFAs have the opposite effects. The higher the intake of $n-6$, the more $n-3$ is needed to neutralize the detrimental effects of $n-6$ [102]. Humans evolved with a ratio of omega-6 and omega-3 fats of roughly 1:1. With the advent of the modern vegetable oil industry, this ratio has shifted to approximately 20–50:1. The recommended ratio of $n-6$:$n-3$ is 4–5:1 [102].

Because of the value of sufficient omega-3 intake for optimal health combined with the inefficient conversion of ALA to EPA and DHA and the overwhelming amount of omega-6 fats in the modern diet, the intake of omega-3 fats is of considerable importance.

4.39 PUFAs and Pain

Dietary intake of adequate $n-3$ leads to decreased inflammatory markers and improved symptoms in chronic inflammatory disorders [102]. The mechanisms of action include, among others, a shift from pro-inflammatory to anti-inflammatory prostaglandin production and an impact on plasma membranes' fluidity and physical properties, leading to improved cellular and mitochondrial function [102]. In addition, $n-3$ intake leads to increased production of a family of compounds known as "specialized pro-resolving mediators" (SPMs). SPMs promote the resolution of inflammation after an injury or trauma and support tissue healing, preventing acute inflammation from becoming chronic inflammation.

Overconsumption of $n-6$ PUFAs with low intake of $n-3$ PUFAs is highly associated with the pathogenesis of many inflammatory diseases, and reducing $n-6$ intake is as important as increasing $n-3$ intake. A high intake of $n-6$ fatty acids creates a biochemical susceptibility to develop chronic pain, whereas high serum levels of $n-3$ fatty acids are associated with antinociception and lower inflammatory mediators [102]. In subjects with chronic daily headache, an

intervention that increased dietary $n-3$ PUFA intake while reducing $n-6$ PUFA intake led to a significant reduction in headache frequency and intensity pain and use of acute pain medication [103]. In addition, dietary supplementation of $n-3$ has been shown to reduce joint pain, neuropathic pain, and discogenic neck and low back pain [103, 141].

4.40 Fish Intake Versus *n* − 3 Supplements

A food-based rather than supplement-based approach may be optimal in promoting the health benefits of adequate $n-3$ PUFA status (Table 4.5). Fish as a food contains many compounds that modulate immune and neurologic function and decrease inflammation, including melatonin, selenium, vitamin D, tryptophan, and taurine [100]. In addition, regular fish consumption enhances microbiota diversity and increases bacteria that produce beneficial short-chain fatty acids, leading to decreased gut inflammation and preservation of intestinal barrier function [100].

EPA and DHA in fish are better absorbed than those in fish oil supplements, leading to plasma levels of $n-3$ PUFAs as much as nine times higher [142]. Fish consumption is associated with a lower risk of depression and somatic complaints, especially in women [143].

While fish consumption consistently correlates with a reduction in chronic inflammatory diseases [145], the results of systematic reviews and meta-analyses of fish oil supplementation have been inconsistent or negative for many conditions [146].

Table 4.5 Omega-3 content of fish and seafood (per 3 ounce cooked portion) [149, 176]

>1000 mg	500–1000 mg	250–500 mg	<250 mg
Anchovies	Barramundi	Alaska Pollock	Catfish
Herring	Mussels	Crab	Clams
Mackerel	Salmon (chum, coho, pink, and sockeye)	Flounder/sole	Cod
Oysters (Pacific)	Sea bass[a]	Mackerel (king)[b]	Crayfish
Sablefish (black cod)[a]	Swordfish[b]	Rockfish[a]	Grouper
Salmon (Atlantic and Chinook)	Tilefish[b]	Snapper[a]	Haddock
Sardines	Trout	Tuna (skipjack, canned)	Halibut[a]
Tuna (bluefin)	Tuna (albacore)[a]	Walleye	Lobster
Whitefish			Mahi-mahi[a]
			Scallops
			Shrimp
			Tilapia
			Tuna (yellowfin)[a]

[a] Limit to one serving a week if pregnant or preparing for pregnancy
[b] Avoid if pregnant or preparing for pregnancy

Mood disorders are common in people living with chronic pain. The American Psychiatric Association (APA) and the International Society for Nutritional Psychiatry Research recommend the consumption of fish as part of treating depressive disorders [147]. Meta-analyses show that dietary intake of fish is very strongly correlated with a lower risk of mood disorders [144]. A review by a subcommittee of the International Society for Nutritional Psychiatry Research concluded that supplements with dosages of 1–2 g daily of EPA from either pure EPA or EPA/DHA formulas is effective for the treatment of depression [148].

4.41 Pregnancy

Over 95% of pregnant women in the United States do not meet the recommended daily intake of 250 mg of EPA and DHA. Data has shown that more than 20% of pregnant people report eating no fish in the previous month, and for those who did eat fish, half ate less than 2 oz per week [149]. The FDA emphasizes the health benefits of fish intake and recommends that pregnant people consume at least 8 oz and up to 12 oz of lower-mercury fish per week [149] (Fig. 4.2).

During pregnancy, meta-analyses have shown that adequate $n-3$ fatty acid consumption from fish is correlated with lower risks of depression [177] and anxiety and improved neurocognitive outcomes for the offspring [178]. Preterm birth and low birth weight are lowest with a dietary $n-3$ intake of 8–12 oz/week [179]. A review of 44 publications highlights the substantial benefits of fish consumption for brain development. Consistent evidence of moderate quality indicates that seafood consumption during pregnancy is associated with improved visual, verbal, and

Fig. 4.2 Advice about eating fish for women who are or might become pregnant [149]

motor development skills in the offspring compared with eating no seafood [180]. Compared with no seafood consumption, when 2–4 servings/week of fish were consumed during pregnancy, children reach developmental milestones more quickly and gain an average of 7.7 IQ points [181]. Others have reported that mothers who consume fish experience less psychological distress during pregnancy and postpartum depression [182].

However, in contrast with strong evidence consistently showing the benefit of dietary $n-3$ intake during pregnancy, supplementation trials have had inconsistent and often negative results. While some reviewers have found moderate-quality evidence for the effectiveness of $n-3$ supplementation in reducing the risk of preterm birth and low birth weight [183], another review of 143 studies concluded that $n-3$ supplementation did not have any consistent effects on maternal or infant health outcomes [184].

Despite concerns about the potentially detrimental effects of mercury exposure in dietary seafood consumed during pregnancy, no study has found any adverse effects from maternal consumption of more than 12 oz/week [178]. Most seafood contains selenium, which binds with mercury, protecting against its harmful effects. Higher mercury levels are unexpectedly correlated with higher seafood intake and associated with cognitive benefits, likely reflecting the nutritional effects of seafood. Higher seafood consumption through 30 oz/week was associated with more favorable language and communication scores and higher IQ scores [178]. Oken reported that even with an intake of greater than 100 oz/week, no adverse effects were found for neurocognition [184]. The authors concluded that there is no evidence to support an upper limit of 12 oz/week of seafood intake during pregnancy and state that pregnant people can be confident that seafood consumption will have cognitive benefits for their offspring [178, 184].

4.42 Considerations Regarding Fish Oil Supplements

Several quality issues have been reported with fish oil supplements, including the presence of oxidized lipids and contaminants such as polychlorinated biphenyls, both of which have adverse health effects [146]. Fish oil supplements should undergo molecular distillation to remove toxins, be free of oxidation as indicated by the "peroxide value," and be bioavailable, criteria which can be verified by examining the Certificate of Analysis from the manufacturer. The Global Organization for EPA and DHA Omega-3s (GOED) is an industry group that sets strict quality criteria for fish oil supplements, including oxidative quality and environmental contaminants [185]. Supplement manufacturers who are members are required to meet those standards and their products are subject to randomized testing. A list of GOED members is available on the GEOD website at https://www.goedomega3.com/.

Fish oil supplements should be consumed with a high-fat meal. Taking supplements with a meal containing 44 g of fat compared with a meal with 8 g of fat led to a threefold increase in absorption of DHA and EPA [186] (Table 4.3).

4.43 Summary

The characteristics of a diet for the management of chronic pain overlap with those needed for optimal health during pregnancy. An abundance of evidence supports a therapeutic diet of a whole-food diet with abundant intake of a wide variety of plant foods, emphasizing those high in fiber, polyphenols, magnesium, and omega-3 fats while including fermented foods and minimizing exposure to omega-6 fats, pesticides, and food additives. This diet plan can be expected to reduce pain; improve quality of life; improve associated disorders such as depression, anxiety, and IBS; and optimize health during pregnancy. By addressing the underlying etiologies of inflammation, intestinal dysbiosis and permeability, and mitochondrial dysfunction, this approach also promotes long-term health for individuals living with chronic pain and their offspring. In addition, supplementing the diet with functional foods such as chamomile, culinary herbs, flaxseed, ginger, green tea, pomegranate, and cherries provides pain-relieving, anti-inflammatory, gut-protective, and mood-modulating effects. Supplements that are safe during pregnancy and useful for reducing pain, anxiety, and depression include CoQ10, curcumin, and magnesium. Vitamin D supplementation is beneficial in those with vitamin D deficiency, and fish oil supplements may be helpful for those who lack dietary intake of fish.

4.44 Resources

FDA Handout "Advice About Eating Fish for Women (stet) Who Are or Might Become Pregnant" at https://www.fda.gov/media/102331/download
Seafood Nutrition Partnership: well-organized and high quality toolkit for providers and patient education handouts at https://www.seafoodnutrition.org/resources/health-professionals/
Global Organization for DHA and EPA (GOED): resources for providers and list of fish oil manufacturers that meet quality standards at https://goedomega3.com/
Gut Microbiota for Health: website by the European Society of Neurogastroenterology and Motility. Infographics for patient education, news regarding the microbiota. At https://www.gutmicrobiotaforhealth.com/
International Scientific Association for Probiotics and Prebiotics (ISAPP). Guidelines for evidence-based use of prebiotics and probiotics, resources for providers and for patient education Downloadable app Clinical Guide for Probiotic Products (USA version) provides level of evidence and dosing for probiotic products by indication
Vitamin D Society: provider resources, news
dminder app for individualized tracking of vitamin D status and recommended sun exposure at https://dminder.ontometrics.com/
Imagine Healthy, website for the Dietary Inflammatory Index, food frequency questionnaire that generates a DII score and diet recommendations for a fee. At https://imaginehealthy.org/
Institute for Functional Medicine explanation of the functional medicine approach to disease: https://www.ifm.org/functional-medicine/what-is-functional-medicine/

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Behavioral Management for Pain in Pregnancy

5

Valerie W. Jackson, Iulia Gambro Irina Ivan, and Karen Choe

5.1 Making the Case for Psychological Interventions

Pregnancy is a period characterized by numerous changes in the body. Physical and hormonal changes can lead to new complaints of pain or exacerbation of a chronic pain condition, leave women vulnerable to mood and sleep disturbances, as well as potentially affect their work and social roles. Your patient may have concerns around pharmacological treatments for pain and thus embrace a more holistic and natural approach to pain management. These factors and the interplay between them bring to light the importance of treatment emphasizing the mind-body connection, with physical and psychological health being inextricable.

5.2 The Gate Control Theory

One theoretical model that accounts for both body and mind in the perception of pain is the gate control theory [1]. The gate control theory suggests that when injured, the peripheral nervous system transmits pain signals up the spinal cord and to the brain. When the pain message travels toward the brain, nerve gates can be "open or closed." In addition to other sensory factors (e.g., touching, rubbing),

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cognitive and emotional factors can modulate how the pain signal is processed. Factors that "open the gate," therefore increasing pain, include depression, anxiety, stress, negative cognitions, focus on pain, and lack of activity. Factors that "close the gate," therefore decreasing pain, include medications, relaxation training, positive emotions, optimism, distraction, and exercise.

5.3 The Biopsychosocial Model

The experience of chronic pain is more than a sensory experience. Pain can be understood as the multidimensional interaction of biological, psychological, and social factors (Fig. 5.1).

Psychological factors such as depression, anxiety, sleep, and social factors such as support, culture, and socioeconomic status play an important role in patients' reactions to pain. These responses can be helpful or harmful as they can ameliorate, maintain, or perpetuate pain. For example, patients may respond to pain by avoiding movement due to fear of worsening pain or causing injury. This may lead to deconditioning, negative emotions and cognitions, and further avoidance or withdrawal from valued and meaningful activities. This may strain relationships, decrease quality of life, and place patients at increased risk of depression, anxiety, and insomnia, all of which may also exacerbate pain. Cultural factors may also impact whether

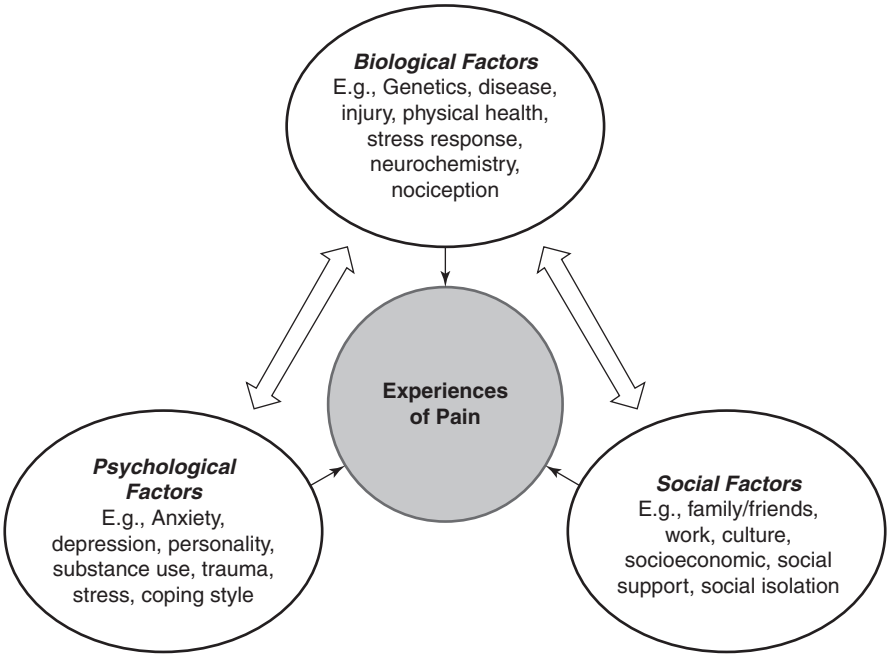

Fig. 5.1 The biopsychosocial model of pain

patients ask for support, "push through the pain," or experience stigma associated with certain treatments. Assessing and understanding the relationship between biological, psychological, and social factors for each individual is crucial to successfully manage chronic pain.

Within the framework of the biopsychosocial model, there are important pain-specific psychological factors that can impact pain outcomes. Specifically, these include pain catastrophizing, pain anxiety, and coping style.

Pain Catastrophizing. Pain catastrophizing is defined as exaggerated negative beliefs and emotions in response to actual or anticipated pain. The tendency to magnify the threat of pain, feel helpless, and ruminate about the pain is common in pain catastrophizing. It is associated with a reduction in quality of life, increase in anxiety, depression, opioid use, suicidal ideation, pain disability, and severity [2–4]. High levels of pain catastrophizing can undermine behavioral and medical interventions and is further associated with poor outcomes to treatment [2]. For this reason, patients benefit from screening for pain catastrophizing even in medical settings. For example, in acute pain settings, pain catastrophizing is a useful construct as it is a risk factor for the progression from acute to chronic pain [4].

In pregnancy, women with higher pain catastrophizing are more likely to have pain postpartum and restricted physical activity than women with lower pain catastrophizing [5]. Among women with lumbopelvic pain, 10% endorsed catastrophizing during all three trimesters of pregnancy, while for 32% of women, the levels of catastrophizing varied over time [5]. Given that pain catastrophizing may not be stable across time, assessment of this throughout pregnancy may be valuable. The Pain Catastrophizing Scale (PCS) is a 13-question self-report scale in which higher scores indicate higher levels of pain catastrophizing [6, 7]. Cognitive behavioral therapy can reduce the impact of counterproductive pain-associated cognitions and is the most common approach used to treat pain catastrophizing.

Pain Anxiety. Research around the fear avoidance model of chronic pain demonstrates a significant relationship between fear, avoidance of pain, and increased disability from chronic pain. Fear avoidance (also known as kinesiophobia) is a component of pain anxiety in which individuals avoid activities that can increase pain. While fear avoidance can be defensive or protective across many situations (e.g., avoiding touching a hot stove), it can negatively affect daily functioning, particularly in cases where there is no significant threat to injury (e.g., walking increases back pain, so patient chooses to avoid walking as much as possible). In fact, fear avoidance can lead to loss of function and secondary pain effects such as work disability and low mood. Patients may wait for the pain to get better before engaging in daily activities. They may avoid activities such as seeing friends or family for fear of experiencing increased pain. Activity avoidance due to fear can lead to deconditioning, worsening of the pain condition, and reduced quality of life. Helping patients recognize this pattern and learn new ways to cope with pain can be a difficult but meaningful shift in outlook for patients that allow for increased quality of life.

In pregnancy, there are a limited number of studies looking at pain anxiety and the relationship to pain outcomes. Catastrophic and anxious thoughts have been associated with magnifications of pain, including acute and persistent perineal pain [4]. The Pain Anxiety Symptoms Scale (PASS) is a common scale measuring fear and anxiety responses specific to pain, available in validated 40- and 20-item versions [8].

Coping Style. Pain coping, which could be active or passive, is defined as an intentional effort to manage or relieve pain. Active pain coping skills include PT, stretching, breathing exercises, pacing activities, and engagement in valued activities, with the patient taking an active role in managing the pain. Passive pain coping skills include taking medications, surgical procedures, and resting. Passive coping can increase pain catastrophizing and lead to further physical deconditioning. Alternatively, individuals with active coping skills feel higher self-efficacy to manage pain and continue regular activities.

Among pregnant women with lumbopelvic pain in Taiwan, pain interfered most with sleep, walking ability, enjoyment of life, work, general activity, and mood. Pain interference was associated with a number of coping strategies (i.e., asking for assistance, resting, guarding, coping self-statement, relaxation, seeking social support), but pain intensity was associated only with resting and asking for assistance. The most commonly used coping strategies were resting, task persistence, and guarding [9]. Researchers examined the association between fear avoidance beliefs and pelvic girdle pain in a study among pregnant women in Pakistan. Not only were fear avoidance beliefs significantly anticipated during pregnancy, but increased levels of fear avoidance beliefs were also associated with increased levels of pain [10]. Encouraging active versus passive pain coping can improve mood, anxiety, and overall functioning for pregnant women experiencing pain.

5.4 Depression and Anxiety in Pregnancy

In terms of mental health, depression and anxiety are the most prevalent disorders during pregnancy [11, 12]. A systematic review identified risk factors for prenatal depression and anxiety, which included lack of social support/partner, history of abuse or domestic violence, personal history of mental illness, unplanned/unwanted pregnancy, adverse events in life, low education level, low income, low self-esteem and self-efficacy, childhood abuse, and history of or current smoking [13]. Ethnicity, age, parity, unemployment, and family history of mental illness were identified as risk factors, but results were inconsistent across studies [13].

The variability in prevalence rates noted below is attributed to differences in methods of measurement (i.e., EPDS, PHQ-8, SCID, clinical interview), sampling methods, gestational age, and overestimation due to the potential overlap between pregnancy physiological changes (e.g., energy level/fatigue, appetite, sleep) and mood. Although some point to the potential for overestimation, other factors like stigma may impact response rates during a period that is associated with happiness making the case of underestimation.

5.4.1 Depression

Data using DSM-5 criteria for major depressive disorder suggests that rates have increased over the last 15 years, with prevalence rates of 10.4% for 12-month and 20.6% for lifetime [14], an increase from previous rates of 6.6% and 16.2%, respectively [15]. Consistent with previous research, women are at higher risk for major depressive disorder than men [14–16]. The 12-month prevalence rate among women was 13.4%, almost double that of men [14], and the same was true for lifetime prevalence (26.1% versus 14.7%). In addition to this gender difference, the age of onset for major depression is in the middle 20s [17] and for mood disorders overall 31 years [18], increasing the risk of developing depression during pregnancy.

Depression is well-documented as the most prevalent mental health disorder during pregnancy [19]. In the United States, prevalence rates of depression during pregnancy range from 4% to 25% [20]. This may range by socioeconomic status, with low-income populations reporting prevalence rates from 25 to 50% compared to middle-class populations reporting 9–28% [20]. Among depressive disorders during pregnancy, prevalence rates range between 3.1 and 6.1% for major depression and 16.6% for minor (subthreshold) depression [21, 22]. History of depression and prenatal depression is found to be the strongest predictors of postpartum depression [22, 23].

5.4.2 Anxiety

Anxiety is a common mental health disorder, with estimates suggesting as many as 33.7% of adults suffer from an anxiety disorder at some point in their lives [24]. A 2016 systematic review found that women are almost twice as likely and at higher risk to have anxiety disorders than men [25]. In pregnancy, rates vary considerably, with rates as low as 5.1% [26] to as high as 37.5% [27]. Overall, pregnant women are at an even higher risk of elevated anxiety and OCD prevalence than the general population [25]. A 2019 review found that 20.7% of pregnant women have at least one anxiety disorder, and 5% meet the criteria for at least two anxiety disorders [28].

5.5 Overview of Mental Health Treatment in Pain Management

Although pain has an adaptive function, when persistent, it has adverse effects on mood, relationships, and overall quality of life. Mental health disorders like depression, anxiety, post-traumatic stress disorder, and substance use are therefore significantly correlated with pain. Studies demonstrate higher odds of having these comorbidities in individuals with chronic pain [29]. While causal factors have not yet been identified, studies have found a bidirectional relationship between mental distress and pain [30]. Patients with chronic pain are at higher risk of developing mental health disorders, while individuals with pre-existing anxiety and/or

depression are at higher risk of developing chronic pain [31, 32]. Moreover, symptoms associated with pain overlap with various mental health conditions. For example, social isolation is associated with depression and pain—when patients with comorbid physical and mental health challenges experience social isolation, their symptoms are magnified [33]. In contrast to patients without mental health diagnoses, patients with both pain and mental health diagnoses have greater disability, lower quality of life, and greater pain-related anxiety and suffering [32]. Thus, screening for need for psychological services can reduce pain-related disability. Simple, free tools to evaluate depression (Edinburgh Postnatal Depression Scale; EPDS, appropriate for pregnancy) [34] and anxiety (generalized anxiety disorder-7; GAD-7) can be self-administered by patients and easily interpreted by clinicians.

5.6 Evidence-Based Treatments

Extensive research indicates that psychological interventions can improve pain, reduce pain-related disability, help patients achieve functional goals, improve mood, and improve subjective quality of life [35, 36]. CBT for pain is the current gold standard for pain psychology interventions, although evidence also suggests that structured mindfulness approaches like mindfulness-based stress reduction (MBSR) similarly improve pain-related outcomes compared to treatment as usual [37].

Psychological and non-pharmacological interventions (e.g., TENS, PT, massage) for chronic pain in pregnancy have been studied much less, with efficacy being unclear [38]. Despite this fact, psychological interventions (i.e., cognitive behavioral therapy, mindfulness-based stress reduction, acceptance, and commitment therapy) have been found to be safe, reduce distress, and improve mood and sleep in pregnant women [39–42].

In this section, we will introduce the interventions cognitive behavioral therapy (CBT), acceptance and commitment therapy (ACT), biofeedback, relaxation training, hypnosis, and mindfulness approaches. See Table 5.1 for a summary of biobehavioral interventions.

5.6.1 Cognitive Behavioral Therapy (CBT)

Cognitive behavioral therapy utilizes the theoretical framework that our thoughts (cognitions), behaviors (action or inaction), and feelings (both emotional and physical) are interrelated. Numerous studies back CBT as an evidence-based practice for pain management and anxiety and depression.

Throughout treatment, clinicians can help individuals formulate goals in either group or individual settings and support them to achieve their goals. Patients learn strategies to identify, challenge, and modify their unhelpful thoughts and behaviors, thus improving functioning. Specific maladaptive beliefs such as pain catastrophizing and pain anxiety may be challenged. Active coping strategies can replace

Table 5.1 Pain psychology modalities, research support, and access

Therapeutic modality	Research support	Access
Cognitive behavioral therapy (CBT) Utilizes the biopsychosocial approach to pain targeting behavioral and cognitive responses to pain, including cognitive restructuring, behavioral activation, pacing, and psychoeducation about pain and healthy behaviors	Moderate [43, 44]	Licensed clinician, self-guided books, apps can introduce concepts
Acceptance and commitment therapy (ACT) Encourages an acceptance-based approach to pain, accompanied by personal awareness and engagement in meaningful activities	Low to moderate [44, 45][a,b]	Licensed clinician, self-guided books
Mindfulness-based stress reduction (MBSR) Utilizes a nonjudgmental approach to pain through daily mindfulness practice (e.g., meditation, body scanning, yoga) intended to increase awareness of the body and breath	Moderate [37, 43, 46][c]	8-week group workshop (free online or available in hospital/clinic settings for a fee)
Relaxation Teaches patients to control their autonomous nervous system through breath and meditation exercises (e.g., progressive muscle relaxation, biofeedback, hypnosis) to produce a sense of calmness and reduce adverse reactions to pain	Low to moderate [47]	Widely accessible
Biofeedback (BFB) Provides immediate feedback via device to show body's response to relaxation exercises or cognitive restructuring	Moderate for migraine; low-moderate for other pain conditions [48, 49][d]	Often limited to specialized clinics and headache centers
Hypnosis Uses verbal and nonverbal suggestions to influence perceptions, mood, and behavior to promote relaxation and dissociate or change perceptions away from pain	Low [47, 50][a]	Clinician, can be self-trained

[a] There is limited data overall for this modality
[b] Few studies indicate large benefits in ACT for reducing disability and pain, high support for pain interference, and low support for pain intensity
[c] Excludes migraines
[d] Meta analysis for migraines only

unhelpful behaviors such as passive coping. Additional pain-specific behaviors target sleep, activity pacing, exercise, and healthy lifestyle such as limiting caffeine and tobacco. CBT often includes relaxation training as a part of the behavioral change, for instance, diaphragmatic breathing. Overall goals of pain CBT involve improving quality of life, reducing psychological distress, improving coping skills, and improving function. See Tables 5.2 and 5.3 for additional resources to recommend to patients seeking CBT, such as the app *Cureable* or website www.tamethebest.org for books and virtual classes on pain. Referral to a mental health provider for further evaluation or discussion may also be appropriate.

Table 5.2 Mobile apps for mood, relaxation, and pain management

Smart phone applications for mood, relaxation, and pain management	Modalities	Cost
What's up?—a mental health app includes diary, habit tracker, catastrophe scale, grounding game, breathing techniques	CBT and ACT for mood	Free
MoodKit	includes 200+ mood improvement activities, mood charts, customizable journal templates, thought checker	CBT for mood	Low cost
CBT Thought Diary—mood tracker and CBT journal	includes mood log, gratitude practice, journaling	CBT, ACT, DBT for mood	Free
Breathe2Relax	A personalized stress management tool that provides detailed information on the effects of stress on the body and diaphragmatic breathing	Stress management	Free
Headspace	Teaches you the basics of meditation and mindfulness in 10 min a day	Meditation and mindfulness	Free and paid options
Module on pregnancy: https://www.headspace.com/articles/mindful-pregnancy-1			
Cureable	Helpful in understanding the mind-body connection and pain coping skills. There are many free and interesting podcasts on pain research and treatments	Persistent pain symptom self-management	Free and paid options
Insight Timer	An extensive library of guided meditations for sleep, anxiety, and stress with effective search and filter functionality that allows the user to find specific content	Meditation	Free
MyLife Meditation: Mindfulness (Stop, Breathe & Think)	Meditation guide to relaxation and calming sleep	Meditation	Free

Note: These are applications available on mobile or tablet devices current as of the publishing of this text (2022). Pricing and availability may vary based on your location and are subject to change

Table 5.3 Websites for mood, relaxation, and pain management

Websites
Online Mindfulness-Based Stress Reduction | Complete self-paced MBSR free online course https://palousemindfulness.com
American Chronic Pain Association | Peer support and education https://www.theacpa.org
Retrain Pain | Pain education, science-based approach with lessons available in many languages https://www.retrainpain.org
Tame the Beast | Focus on psychoeducation and activity avoidance with online treatment options https://www.tamethebeast.org
painACTION | Resource written by health educators, pain experts, and people with pain to help people improve their pain self-management https://www.painaction.com
Meditation scripts for pregnancy https://womensmeditationnetwork.com/pregnancy-meditation https://www.innerhealthstudio.com/relaxation-during-pregnancy.html http://www.cheyenneregional.org/wp-content/uploads/2012/11/RelaxationScripts.pdf
Relaxation scripts (audio files, general and focus on migraine) https://dawnbuse.com/relaxation/

5.6.2 Acceptance and Commitment Therapy (ACT)

Acceptance and commitment therapy (ACT) is an empirically supported intervention, transdiagnostic in nature and gaining popularity for pain management in recent years. The broad target of ACT is "psychological flexibility," which is defined as one's ability to engage in chosen valued activities despite unpleasant sensations, feelings, and thoughts that may arise [51]. The central focus of ACT is to help patients realize that the experienced negative thoughts, emotions, and physical sensations are part of the human experience, and they are not themselves the problem. The problem exists when the efforts to avoid these unpleasant internal experiences prevent the patient from valued living. In ACT, this agenda to "get rid of" is not workable and leads to a number of negative consequences, including increased distress, dysfunction, and disability.

To increase psychological flexibility, six core skills are addressed in treatment. These include values, present moment, acceptance, defusion, committed action, and self as context (Table 5.4).

These six skills are used fluidly in treatment and practiced through experiential exercises and metaphors.

5.6.3 Mindfulness-Based Stress Reduction (MBSR)

Mindfulness interventions have increasing research to show efficacy in pain management and an existing base of evidence for mood. Mindfulness is an awareness of mind and body and can be taught through movement, meditation, and guided

Table 5.4

Six core skills in ACT	
Values	This process is focused on addressing lost direction and helping patients identify values and goals related to interpersonal relationships, work, spirituality, hobbies, family, and health
Present moment	This skill teaches remaining in the present moment, aware of thoughts, physical sensations, emotions, with nonjudgment, whether distressing or pleasant. In addition, it increases awareness of the mind's tendency to be in the past or future
Acceptance	This process encourages willingness to be with unpleasant thoughts, feelings, and physical sensations in service of valued living versus striving not to have these, avoid them. This skill is the antidote to avoidance, identifying "control of internal experiences as the problem"
Defusion	This skill teaches patients to take perspective on thinking and feeling, gaining insight that these thoughts, emotions, and physical sensations do not have to lead to avoidance behavior
Committed Action	This process encourages taking behavioral steps, "committing to" doing things in line with chosen values
Self as context	This skill encourages being a witness to thoughts, feelings, and unpleasant sensations and seeing oneself as an "experiencer" of these versus "being" the thoughts, feelings, and sensations

Table 5.5 Books for pain and stress management

Pain and stress management books	Modality
Managing Pain Before it Manages You	Margaret A. Caudill	CBT
Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness	Jon Kabat-Zinn	MBSR
The Pain Survival Guide: How to Reclaim Your Life	Dennis C. Turk	CBT
The Opioid-Free Pain Relief Kit: 10 Simple Steps to Ease Your Pain	Beth Darnall	CBT
Living Beyond Your Pain: Using Acceptance and Commitment Therapy to Ease Chronic Pain	Joanne Dahl	ACT
Living A Healthy Life with Chronic Pain	Sandra M. Lefort	CBT

practice. In particular, mindfulness-based stress reduction (MBSR), an 8-week program, has significant research to demonstrate reduction in depression, anxiety, and pain symptoms in patients with chronic pain, ranging from back pain to fibromyalgia [37]. Importantly, this approach can be effective and useful for various populations, including those looking for wellness and stress management strategies. Thus, this recommendation is appropriate for most patients, ranging from those diagnosed with mental health disorders to those disinterested in potentially stigmatizing treatments provided in a mental health clinic. Mindfulness-based approaches can also be particularly useful in patients who are either resistant or do not have access to mental health treatment or are looking for self-management strategies. There are numerous mindfulness tools available in the form of mobile applications, online guided meditations, and a variety of classes and books depending on patients' access and interest level, some of which are provided below in Tables 5.2, 5.3, and 5.5. MBSR has the added benefit of being a structured course that can be completed in person or online. Some patients may be more likely to adhere to treatment with the accountability of a course, while a free, evidence-based course with flexibility in scheduling may be more appropriate for others.

5.6.4 Relaxation Training

Formal relaxation training teaches individuals to gain control of their autonomic nervous system, using breath and meditation practices. Diaphragmatic breathing is a simple-to-use tool that patients may learn and use anywhere to decrease sympathetic nervous system activity, thus producing a sense of calm and reducing negative reactions to pain. Other relaxation training can occur through courses, guided meditations, exercises such as progressive muscle relaxation, and hypnosis. Relaxation training can include biofeedback, which has moderate evidence to demonstrate efficacy in pain management, most significantly for migraines [48, 49].

5.6.5 Biofeedback

Biofeedback is an evidence-based behavioral treatment in which patients understand and control their physiological responses (e.g., heart rate, breath, sweat, brainwaves, muscle tension, and peripheral temperature) via immediate feedback of their physiological processes from a device or computer screen [48]. This method involves skills that can be developed in relaxation training while providing greater concrete insight into the relationship between mind and body. Patients are provided visual evidence of how they can control their bodily reactions (e.g., heart rate, muscle tension) by merely slowing their breath, completing exercises such as progressive muscle relaxation, or thinking of something calming, making this both a transformative and accessible form of intervention for those with chronic pain.

Biofeedback is sometimes used in conjunction with CBT to demonstrate the mind-body connection. For instance, a patient describes a stressful experience and observes their physiological stress response increase on a computer screen and then discusses alternative perspectives on the problem. The patient then watches decreases in their "fight or flight" response such as decreased heart rate and muscle tension. Biofeedback practitioners can be found through www.bcia.org.

5.6.6 Hypnosis

Hypnosis has been used as a treatment for various medical conditions with some evidence of its benefits with chronic pain. Hypnosis is defined as "a state of consciousness involving focused attention and a reduced peripheral awareness characterized by an enhanced capacity for response to suggestion" [52]. There are only two steps to this treatment, the induction phase and suggestion phase. The induction phase is simply bringing ones full attention on a single object or experience (breath, being in a safe place), while the suggestion phase is designed to focus on changing the patient's subjective experience, emotions, thoughts, and behaviors [52]. Hypnosis research suggests that when applied to chronic pain, the suggestion phase focuses on a number of pain-related concepts like changing cognitions related to pain, decreasing awareness of pain, increasing activity, improving sleep, or any number of outcomes important to the patient treated [53].

Aside from the psychological interventions mentioned, successful pain management includes integration with multidisciplinary approaches. Combining medical interventions with other modalities such as physical therapy, mindfulness courses, or cognitive-behavioral therapy can optimize treatment. In particular, integrating psychological and physical therapy treatments can improve physical reconditioning, safe movement, fear avoidance, and goal setting. Overall, emphasizing the role

of self-management of pain can empower patients to continue meaningful activities despite pain.

5.7 Techniques That Nurses Can Use with Patients

There are a number of techniques that can be pulled from psychological interventions and used independently. Below we will focus on psychoeducation, mindfulness practices, activity pacing, and diaphragmatic breathing.

5.7.1 Psychoeducation

Psychoeducation or providing brief pain science education can help patients be more open to nontraditional approaches to pain management (e.g., meditation). Clinicians may teach patients how pain is not always an accurate assessment of a physiological problem. One useful example is phantom limb pain, which can be a clear way to demonstrate that pain does not always signify tissue damage: those who experience phantom limb pain continue to experience pain in limbs despite amputation. Clinicians can thus use the concept of phantom pain as a selling point for mind-body practices to reduce pain. This example is tangible for many patients and a non-stigmatizing approach to discuss the role of perception beyond nociception as contributing to the experience of pain. Further education about the gate control theory may also be appropriate here to highlight the broad psychosocial factors that can affect the pain experience.

5.7.2 Mindfulness Practices

A simple grounding exercise is presented below (Table 5.6) that can be completed together with patients and taught as a skill to take home. Further mindfulness practices such as guided imagery for patients are presented in Tables 5.2 and 5.3.

5.7.3 Activity Pacing

This strategy may help pregnant women break the chronic pain cycle, where "pushing through" or overdoing may be followed by "crashing" or resting. The broad goal is to help the patient identify valued activities, slowly increasing the activity level over time, and balancing rest and activity. Below (Table 5.7) are directions for activity pacing that could be shared with the patient adapted from the book *Living a Healthy Life with Chronic Pain* [54].

Table 5.6 Relaxation training: grounding exercise

5–4–3–2–1 grounding exercise
When you notice yourself feeling overwhelmed or distracted, this mindfulness exercise can help reconnect you with the present moment by tapping into your parasympathetic "rest" part of our nervous system. This short exercise is about paying close attention to each of your five senses at a time to bring yourself to the *here and now*. The goal is to be present and experience your surroundings without necessarily defining them. To ground yourself, focus on the following (you can say them out loud or silently in your head):
1. Take a few deep breaths and settle into your body. First, notice **five things you can see** in the room (e.g., the color and texture of your walls, the table, the curtains).
2. Second, notice **four things you can feel** (e.g., texture of your clothing, the soft surface of the couch you're sitting on, holding and letting an ice cube melt in your hands). You can try to identify how different parts of your body are feeling as well—is your jaw clenched? Are your feet planted on the floor?
3. Third, notice **three things you can hear** (e.g., birds chirping, cars driving, clock ticking, your own breath, a relaxing tune). Try to tune into calm-inducing sounds.
4. Fourth, notice **two things you can smell** (e.g., essential oils, light a scented candle, food cooking in the kitchen, fresh flowers).
5. Finally, notice **one thing you can taste** (e.g., piece of dark chocolate, sip of a soothing drink, mint/gum).
As you complete this exercise, remember to pay attention to inhales and exhales as you're simultaneously focusing on your senses.

Table 5.7

Activity pacing
1. **Take an activity inventory**. Note what activities (including rest breaks) you do and how it impacts your pain depending on duration of the activity.
2. **Make a plan**. Write down an activity schedule that includes rest breaks. For example, take 5 min of rest for every 30 min of activity that increases pain.
3. **Focus on duration of activity, not pain**. You can work to prevent pain flares by setting time limits to your activities.
4. **Build in breaks**. Avoid pushing through activities that flare pain and stick to your schedule.
Tips to stay on track
• **Set a timer** to remind you when to take a break.
• **Break up large tasks** into smaller chunks.
• **Prioritize** your to-do list.
• **Be mindful of overscheduling**. Set realistic goals.
• **Practice self-compassion**. Remember that pregnancy can be a challenging time with many transitions, and practice compassion if you do not accomplish all that you set out to today.

5.8 Diaphragmatic Breathing

Stress can contribute to a cycle of increased pain and disability. Identifying life stressors, personal reactions to stress, and physiological response to stressors can all

Table 5.8 Relaxation training: diaphragmatic breathing exercise

Diaphragmatic breathing
1. Sit or lie down in a comfortable position on a flat surface. Sit up straight and pull your shoulders back to relax them.
2. Place one hand on your chest and one hand on your stomach.
3. Breathe in through your nose and hold for a few seconds. As you breathe in, your chest expands, and your diaphragm contracts downward. Feel your hands rise as your belly rises.
4. Purse your lips, press gently on your stomach and slowly exhale through your mouth. As you breathe out, your chest contracts, and your diaphragm relaxes upward.
5. Repeat steps as necessary for best results for 5–10 min.

help patients better manage pain and make the connection between the variables that amplify pain experience. Diaphragmatic breathing (Table 5.8) is a short exercise that can be practiced for any duration of time in any place and serve to reduce muscle tension and stress in the body. It can be practiced together briefly with patients, and many apps (Table 5.2) provide easily accessible guidance for patients.

5.9 Resources

Additional resources are presented here, which are current as of 2022. In the spirit of encouraging self-management of pain, these may be shared with patients interested in pursuing pain psychology concepts outside of the clinical encounter. Mobile apps are listed in Table 5.2, websites in Table 5.3, and books in Table 5.5 [54–59].

5.10 Conclusion

In sum, pain is a mind-body experience and can be treated as such. Patients undergoing antenatal care often have an interest in non-pharmacological and noninvasive interventions. In the case of pain management, behavioral interventions can be particularly effective. Thus, we recommend (1) evaluating pain through the lens of a biopsychosocial model, (2) educating patients on the mind-body relationship, (3) encouraging self-management techniques, (4) practicing brief tools and strategies as appropriate during clinical encounters, (5) providing resources, and (6) considering referral to a mental health provider for additional treatment if necessary.

5.11 Case Study

Case study
A 28-year-old female with anxiety, migraine, 28 weeks pregnant with her first child presents to her PCP regarding increase in migraine and new onset of pelvic girdle pain. She discusses with her provider that she has stopped receiving Botox for migraine due to pregnancy and is also no longer using abortives such as Imitrex. She has been coping with pelvic pain and migraine by lying down, rest, and avoiding movement which worsens her pain. What can her provider recommend?

Case study
Evaluating the patient's pain experience through the lens of the **biopsychosocial model** can be a helpful first step. Identifying the biological (e.g., migraine, pelvic girdle pain), psychological (e.g., anxiety, passive coping tools, fear of movement), and social factors (e.g., potential social isolation) can create an opportunity to discuss a number of non-pharmacological interventions for pain. The provider can highlight that despite the patient not being able to use Botox and abortives which address the biological component of the pain experience, there are a number of effective strategies to managing pain that focus on the psychological and social factors of the patient's pain experience. The use of these strategies is associated with improved pain, quality of life, and functioning. Below are a number of recommendations that may be beneficial for this provider to consider in visits with the patient:
– Educating the patient on the **mind-body relationship** and introducing **relaxation training**.
– Engaging the patient in a 2-min **diaphragmatic breathing** (see Table 5.8) exercise in the visit.
– Helping the patient recognize the **pattern of activity avoidance** and worsening pain, deconditioning, and reduced quality of life.
– Educating the patient on **activity pacing** (see Table 5.7).
– Encouraging use of **self-management tools**.
– **Providing resources** for pain and mood management (see Tables 5.2, 5.3, and 5.5).
– Recommending **biofeedback**.
– Considering a **referral to a mental health provider** for cognitive behavioral therapy if appropriate (listening for language indicating high pain catastrophizing, worsening anxiety symptoms, and decreased function can be an indicator that additional treatment is necessary).

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Musculoskeletal Pain during Pregnancy

6

Laurel Short and Shannon DeSalvo

6.1 Occurrence/Incidence

Pregnancy is often described as a journey, and it is well-understood that even prior to obvious physical changes, there are physiologic shifts that impact the musculoskeletal system. Hormonal shifts lead to joint laxity and mobility that starts within the first trimester [1], and increased weight accompanied by the growing uterus yields changes to the center of gravity [2]. This adjustment results in compensatory stress to the lumbar spine, pelvis, and lower extremities [1–3] (Fig. 6.1). Therefore, it is not surprising that low back pain (LBP) is the most common orthopedic issue reported in pregnancy [4, 5]. Approximately half of musculoskeletal problems during pregnancy are related to lumbar or pelvic pain [6], with an estimated 50–75% of pregnant women experiencing pain in these areas [7]. Lumbar and pelvic pain can be severe, significantly impacting activity tolerance, sleep, mood, and overall quality of life. Additional consequences can include impaired sexual activity, increased risk of thromboembolism related to immobility, and missed work that can disrupt plans for maternity leave [3, 8].

Hormonal and weight changes are also associated with fluid retention, which increases risk of compression to soft tissue and nerves [3]. Elevated levels of relaxin, progesterone, and estrogen cause increased joint laxity, which is recognized as one of the causes of lumbar and pelvic pain during pregnancy [2]. Mid-back pain can also occur in relation to changes in breast size and ribcage alignment. Risk factors associated with lumbar and pelvic girdle pain in pregnancy include previous pregnancy, prepregnancy lumbar pain, depression or anxiety, prepregnancy lack of

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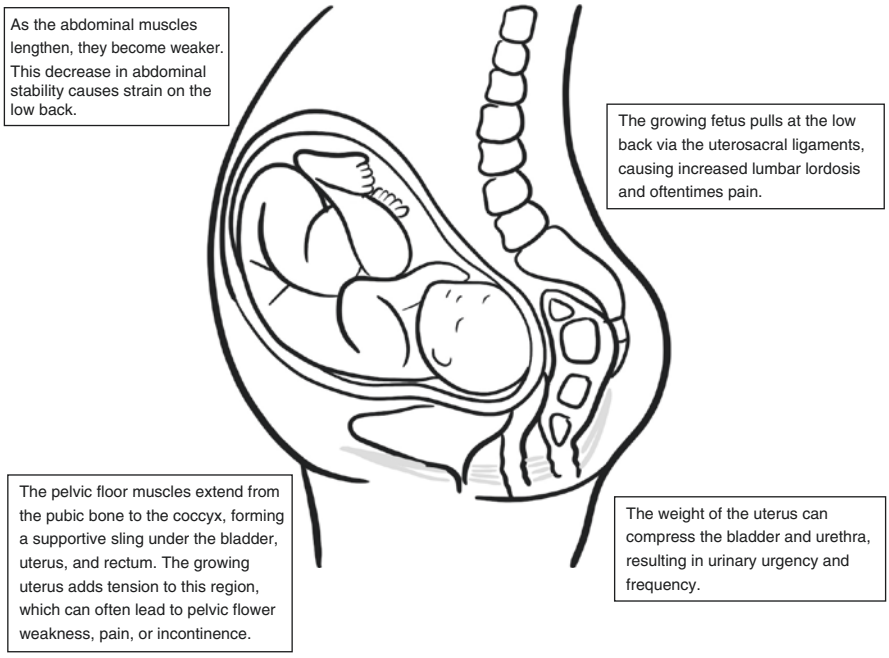

Fig. 6.1 Postural compensations associated with pregnancy. © Kim Bogart. Illustration commissioned for the book *Holistic Pain Management in Pregnancy*. Ed. Theresa Mallick-Searle, Springer Nature 2022

exercise, history of pelvic trauma, advanced maternal age, obesity, and history of joint hypermobility [2, 3].

In addition to exercise reducing the risk of back pain, the American College of Obstetrics and Gynecologists (ACOG) recommends at least 150 min of moderate-intensity aerobic activity per week for general health during pregnancy [9]. Lumbar or pelvic pain may limit exercise tolerance, which in turn increases risk of deconditioning, constipation, and other issues associated with decreased physical activity. Women who experience lumbopelvic pain may also have concern of exercise aggravating the problem, leading to a negative cycle of pain and inactivity.

Wrist and hip pain are also frequently encountered during pregnancy. Common diagnoses during pregnancy include carpal tunnel syndrome, trochanteric bursitis, and meralgia paresthetica. The most common mononeuropathy in pregnancy is median nerve entrapment, causing carpal tunnel syndrome. This is the second most prevalent orthopedic problem in pregnant women [1]. During pregnancy, at least one out of five women report symptoms of CTS [10]. A recent study showed a 34% prevalence of self-reported pregnancy-associated CTS and correlation with higher fluid retention [11], where a prior systemic review showed prevalence of up to 62% [12]. Meralgia paresthetica is a mononeuropathy of the lateral femoral cutaneous nerve, with an incidence rate in the general population of 0.43 per 10,000 person years [13]. Pregnancy is one of the predisposing factors for meralgia paresthetica.

All these conditions can impact a woman's daily function, sleep, and mood. Women who have musculoskeletal pain during pregnancy may even avoid future

pregnancy due to fear of recurrent issues [1]. As a patient may assume musculoskeletal discomfort is part of the pregnancy journey, it is important to assess for orthopedic symptoms as part of prenatal care.

6.2 Diagnoses (Table 6.1)

6.2.1 Low Back and Pelvic Pain

The presenting chief complaint in pregnancy is often low back pain; however, pelvic girdle pain (PGP) is a specific classification of back pain during pregnancy caused by a reduction in pelvic stability. The reduction in force closure within the pelvic girdle leads to a 32–68% increase in pelvic joint motion, which places increased demand on the pelvic musculature to accept and transfer the load between the trunk and lower extremities [14]. Pregnant women with PGP have decreased strength and endurance of their trunk musculature as compared with pain-free pregnant women. Research with this population [14] supports a positive relationship between strengthening of deep core musculature (transverse abdominus, pelvic floor, and multifidus) with improved stiffness of the sacroiliac joints and thus improved pelvic stability.

A detailed history combined with physical exam techniques can assist with differentiating between lumbar and pelvic girdle pain [3]. Low back pain is defined as pain or discomfort below the costal margin (12th rib) and gluteal fold, whereas pelvic girdle pain is "between the posterior iliac crest and gluteal fold, particularly in the vicinity of the sacroiliac joints" [3, 8, 15]. The term lumbopelvic pain encompasses pain in the low back and/or pelvic girdle regions (symphysis pubic, sacroiliac joint, and gluteal region) [7, 16].

6.2.2 Lumbopelvic Pain Features

The diagnosis of lumbar versus pelvic girdle pain is based on provocative orthopedic tests and symptom characteristics. In general, pelvic girdle pain tends to be located between the posterior iliac crest and gluteal fold. This can be unilateral or bilateral near the sacroiliac joint(s), and pain can also occur on the anterior aspect

Table 6.1 Differential diagnoses of lumbar and pelvic pain in pregnancy

Common conditions	Uncommon conditions
Sciatica [3]	Femoral vein thrombosis [2]
Sacroiliac joint dysfunction [2, 30]	Preterm labor [2, 3, 30]
Pelvic floor dysfunction [2, 30]	Placental abruption [2, 3]
Urinary tract infection [3]	Lumbar radiculopathy/cauda equina syndrome [2, 3, 30]
Coccydynia [30]	Spondylolisthesis [2, 3]
Pubic symphysis dysfunction [2, 3, 30]	Lumbar spine degenerative disc disease [30]
Round ligament pain [3]	Stress fracture [2]
Visceral pathology (gastrointestinal, urologic) [2, 3, 30]	Vulvar varicosity [30]
Meralgia paresthetica [27]	Osteonecrosis of the hip (AVN) [1]
Trochanteric bursitis [23]	Rupture of symphysis pubis [3]
Myofascial pain [2, 3, 30]	

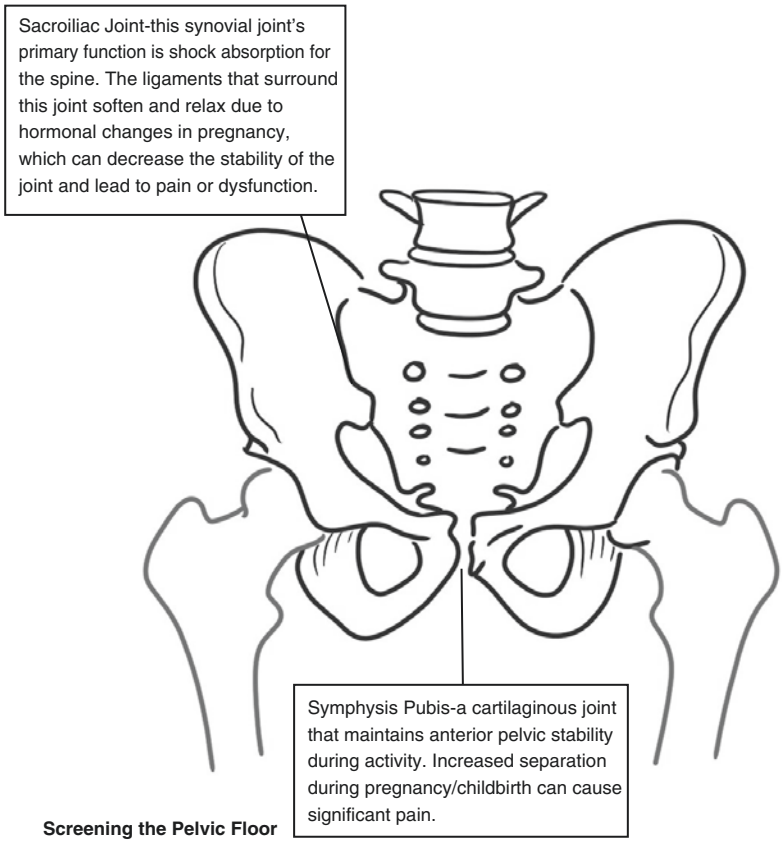

Fig. 6.2 Sacroiliac joint and symphysis pubis. © Kim Bogart. Illustration commissioned for the book *Holistic Pain Management in Pregnancy*. Ed. Theresa Mallick-Searle, Springer Nature 2022

of the pelvis in the region of the pubic symphysis (Fig. 6.2). Common characteristics include intermittent pain aggravated by longer periods of time in a position or activity such as standing, walking, or sitting [2, 5].

Frequently pain of the lumbopelvic region is multifactorial, and pubic pain often occurs in conjunction with lumbar and sacroiliac pain. There are common presenting features that can assist in differentiating the source of pain:

- Sacroiliac Joint(s) – Pain is at the posterior pelvis, often worse with longer periods of standing and walking. Single leg stance and stair climbing will often provoke the pain. SIJ pain may be unilateral or bilateral and is quite common in pregnancy.
- Pubic Pain – Pain may refer distally to the anteromedial aspect of the thigh, and patients often report discomfort with single leg activities such as walking and stair climbing. Sharp pain may be reported in the joint or as a rubbing sensation when they take a step. This often leads to a "waddle" type of gait.
- Round Ligament Pain – More common in the first trimester and second trimesters, round ligament pain can also occur unilaterally or bilaterally. Pain is felt at

the lower quadrant(s) of the abdomen, into the groin and even the vagina where the ligaments insert into the labia bilaterally.
- Low Back Pain – More common in the second and third trimesters, related to weight gain, change in center of gravity, and weakness of core musculature. Low back pain is often provoked with longer periods of standing, lifting, and bending/twisting motions.

Research supports that the instability of the pelvic girdle is the primary reason for pelvic joint pain in pregnancy [17]. As previously discussed, this instability is caused by the increase in reproductive hormones that results in laxity of connective tissues.

6.2.3 Screening the Pelvic Floor

When addressing musculoskeletal pain in the pregnant patient, it is important not to neglect the pelvic floor. During pregnancy, a pelvic exam is performed in the first trimester to obtain a PAP smear. After this, another pelvic exam is often not performed until the last few weeks of pregnancy when cervical dilation is assessed. If the patient is seeing a certified nurse midwife, often internal assessment of the cervix is not assessed to allow for a less invasive experience. However, when an internal exam is not performed, issues such as pelvic floor muscle tension or weakness, vulvar dermatoses or varicosities, and skeletal asymmetries may be unrecognized. In many European countries, it is standard practice to refer pregnant and postpartum patients to a pelvic floor physical therapist (PFPT) for a thorough pelvic floor evaluation, to determine if treatment would be beneficial [18].

The area of PFPT, though still unknown to many, was founded by the late Elizabeth Noble in the 1970s. She was a physiotherapist (PT) from Australia, who established the Academy of Pelvic Health within the American Physical Therapy Association APTA) in 1977. This area of healthcare has evolved immensely since the 1970s, and currently there are thousands of PFPTs in the United States. To specialize in this area, the therapist completes specific continuing education in pelvic health rehabilitation following graduation from a doctoral program in PT. There are also several residency programs offered in the United States for continuing education. The therapist then has the option to complete the CAPP certification (Certificate of Pelvic Physical therapy) through the American Physical Therapy Association's Academy of Pelvic Health or the PRPC (Pelvic Rehabilitation Practitioner Certification) through the Herman and Wallace Pelvic Rehabilitation Institute. Beyond these certifications, therapists can also sit for the WCS (Women's Health Clinical Specialist) board examination, which further validates the high level of training that goes into this area of physical therapy. Physical therapists with these certifications can be found at www.aptapelvichealth.org or www.hermanwallace.com. It is important to ensure the therapist is certified in pelvic floor therapy when referring a patient for evaluation. Common conditions they specialize in treating include pre-/postnatal musculoskeletal pain, urinary or fecal incontinence, pelvic organ prolapse, bowel dysfunction, diastasis recti, core stabilization, and preparation for labor and delivery [19–22].

Screening questions to determine if a referral to a pelvic physical therapist is warranted:

1. Do you have pain with intercourse, pelvic exams, or use of tampons?
2. Do you have urinary or fecal leakage (incontinence) or difficulty holding back gas?
3. Do you have urinary frequency or feel the need to strain when voiding?
4. Do you have constipation or frequently strain to have a bowel movement?
5. Do you have pain with sitting or pain in the tailbone/buttocks region?
6. Do you have pubic symphysis pain or any pain within the pelvic girdle?
7. Do you have concerns about your vulvar tissue such as itching, burning, swelling, or difficulty wearing tight clothing that may rub this area?
8. Do you ever have a "falling out feeling" or extreme pressure within the vagina?

A "yes" to any of these questions warrants a pelvic muscle exam and then a referral to a pelvic floor physical therapist.

What Does a Typical Pelvic Floor Physical Therapy Evaluation Look like? All PFPTs are trained in orthopedics prior to specializing in the pelvic floor. Therefore, they conduct a thorough orthopedic evaluation in addition to the pelvic floor examination. If a patient has never had a pelvic exam due to age or pain, this part of the evaluation will be deferred until appropriate. During the orthopedic portion of the exam, the PT will evaluate posture, strength, range of motion (ROM), joint mobility, and reflexes. An additional component of the exam includes muscle tissue integrity of the spine, trunk, and extremities. If the patient consents to a pelvic floor exam, the patient is then prepared for this. PFPTs are trained in making the exam comfortable for the patient, as well as knowing when it is not appropriate to complete (e.g., due to fear or past trauma).

A typical PFPT consultation is 1 hour in duration. This allows for a gentle, thorough approach to this intimate examination. During the pelvic floor exam, the PFPT evaluates skin, screening for vulvar dermatoses, signs of hormonal imbalance, or irritation. After reflexes are assessed, an internal exam is performed. By performing a digital vaginal exam, the PFPT can evaluate the integrity and strenght of the pelvic floor muscles, while also palpating for scar tissue or adhesions. Determining how well the patient can relax her pelvic floor muscles is key information for labor and delivery preparation. In addition, the PFPT assesses abdominal strength, diastasis recti, and general breathing patterns. The exam is comprehensive and reveals important information about the patient's pelvic health as it relates to labor and delivery [20–22].

6.2.4 Lumbar Radiculopathy

Lumbar radiculopathy is not a common cause of back pain in pregnancy, though it is important to be aware of symptoms and clinical features. Radiculopathy caused by disc herniation has a low incidence of 1 of 10,000 pregnancies, with less that 2%

of lumbar disc herniations causing cauda equina syndrome [3]. The pain associated with a herniated disc is often acute in onset, starting in the low back or gluteal area followed by radiating pain and paresthesias in the lower extremity. The pain may be aggravated by walking, sitting, or standing, and lying on the side in a lumbar flexion position can provide relief [23]. Straight leg maneuver, strength, reflex, and sensory testing are important in assessing for radiculopathy. Saddle anesthesia, incontinence, and progressive weakness in one or both legs are worrisome signs of cauda equina syndrome and considered an emergency. MRI diagnostic testing is recommended if neurologic deficits are present, as this can confirm a diagnosis and is not contraindicated imaging in pregnancy [3].

6.2.5 Trochanteric Bursitis

Trochanteric bursitis is a cause of lateral hip pain and can present in pregnancy secondary to altered gait, change in body habitus, and muscle imbalance. It is caused by inflammation of the greater trochanteric bursa and can occur in conjunction with lumbar, hip joint, or pelvic pain [23]. Trochanteric bursitis presents with pain and tenderness over the greater trochanter and can radiate distally to the lateral thigh. Patients often report difficulty side-lying due to increased pain and may feel better after walking a short distance.

6.2.6 Physical Exam Techniques

Whether the presenting chief complaint is low back pain, pelvic pain, or hip pain, a thorough physical exam of the lumbar spine and hip areas is required for honing the diagnosis. It is not uncommon for more than one pain area to occur simultaneously. Observation is performed to assess for skin changes, muscle spasm, and obvious swelling. General strength and reflex testing are recommended to assess for any areas of weakness, symmetry, and abnormal reflex findings. It is important to screen for hip strength, as often gluteal weakness (especially the gluteus medius) results in poor biomechanics and hip pain. The most effective position to assess gluteus medius strength is with the patient side lying. The examiner has the patient actively abduct the hip (with toes pointed up to isolate gluteus medius) and then assesses for ability to resist pushing into adduction.

Active and passive range of motion of the unaffected and affected side allows for comparison in joint flexibility and assessment of any movement that elicits pain. Palpation of the spine, SI joints, gluteal, and lateral hip can determine focal tender areas that may indicate joint inflammation or muscular pain. Sensory testing is useful to rule out radiculopathy and to assess for changes in a specific nerve distribution (e.g., lumbar radiculopathy or meralgia paresthetica). Gait can easily be observed as the patient enters the exam room or as part of the back and hip exam.

Following these exam techniques, special testing is used to identify specific diagnoses. The straight leg raise (SLR) maneuver is used to assess for lumbar radiculopathy. Depending on the gestation of the woman, care should be made not to remain in a supine position for an extended period due to risk of hypotension [3].

Raising the head of the bed to a 45-degree angle is recommended. A seated slump test can also be conducted in place of a supine SLR to prevent the risk of supine hypotensive syndrome [24]. In this test the patient is seated with full flexion of her entire spine and then asked to extend the knee and dorsiflex the foot. With overpressure provided by the examiner to maintain the spinal and ankle position, the patient is then asked to extend her cervical spine to assess if symptoms change with the release of dural pressure. This type of sensitizing maneuver detects neural tissue sensitivity or nerve root impingement [14].

There are also special orthopedic tests for the sacroiliac joint. Rather than one specific test to assess for SIJ dysfunction, several provocation tests are used in combination to thoroughly evaluate the area. The most common provocation tests are the SIJ compression/distraction, thigh thrust, FABER, and Gaenslen's (Photos 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 6.10 and 6.11). As these tests are taught in the supine position, it is important to raise the head of the bed 45 degrees or roll the patient a quarter turn to one side to prevent supine hypotensive syndrome. The Gillet test is also a good option, as it is in a standing position. The website https://si-bone.com/providers/resources/diagnostic/provocative-tests is an excellent resource with visual demonstrations for each provocative test.

Photo 6.1 Physical therapy alignment assessment (Permissions granted by Amanda Fisher, Emily Steinwart, Shannon DeSalvo, and Laurel Short)

Photo 6.2 Abdominal support binder (Permissions granted by Amanda Fisher, Emily Steinwart, Shannon DeSalvo, and Laurel Short)

Photo 6.3 Sacroiliac belt (Permissions granted by Amanda Fisher, Emily Steinwart, Shannon DeSalvo, and Laurel Short)

Photo 6.4 Pregnancy exercise class (Permissions granted by Amanda Fisher, Emily Steinwart, Shannon DeSalvo, and Laurel Short)

Photos 6.5 and 6.6 Pregnancy yoga class (Permissions granted by Amanda Fisher, Emily Steinwart, Shannon DeSalvo, and Laurel Short)

Photo 6.7 Physical exam, straight leg raise test (Permissions granted by Amanda Fisher, Emily Steinwart, Shannon DeSalvo, and Laurel Short)

Photo 6.8 Physical exam, FABER test (Permissions granted by Amanda Fisher, Emily Steinwart, Shannon DeSalvo, and Laurel Short)

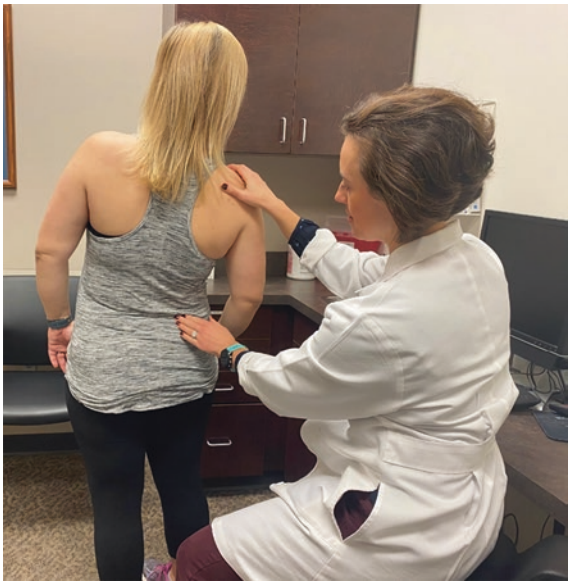

Photo 6.9 Physical exam, standing sacroiliac joint palpation and range of motion (Permissions granted by Amanda Fisher, Emily Steinwart, Shannon DeSalvo, and Laurel Short)

Photo 6.10 Physical exam, palpation of sacroiliac joint and trochanteric bursa (Permissions granted by Amanda Fisher, Emily Steinwart, Shannon DeSalvo, and Laurel Short)

Photo 6.11 Physical exam, Gaenslen's test (Permissions granted by Amanda Fisher, Emily Steinwart, Shannon DeSalvo, and Laurel Short)

6.2.6.1 Red Flags and Supine Hypotensive Syndrome

Considerations for musculoskeletal exam in pregnancy include assessing for red flag signs and supine hypotension syndrome. Red flag symptoms should be assessed to rule out a secondary cause of pain. Pelvic pain varies in severity and can be related to joint laxity or separation (diastasis) of the pubic symphysis. More serious and rare diagnoses include pubic symphysis separation, rupture of the pubic symphysis, and avascular necrosis (AVN) of the hip [1]. Pain of the symphysis pubis and altered gait or inability to walk are signs consistent with possible pubic symphysis diastasis [3]. Avascular necrosis occurs secondary to loss of blood supply to the femoral head and is uncommon in pregnancy, though there have been case reports in pregnancy and the postpartum period [25]. This diagnosis should be considered if there is significant pain with hip range of motion, radiating pain to the thigh from the groin, and poor walking tolerance. Prompt referral to an orthopedic specialist should be made for further evaluation if AVN is suspected or there are concerning findings on physical exam.

It is important to note that many of the lumbar spine and hip exam techniques are performed in a supine position. The examiner should take care to avoid extended periods of time in this position due to supine hypotensive syndrome. This is defined as a decrease in systolic blood pressure of at least 15–30 mmHg, due to compression of the vena cava and aorta from the gravid uterus [26]. Supine hypotensive syndrome is usually not a concern until at least 20 week of gestation, when the uterus is of a more substantial size. This compromise in venous return results in decreased cardiac output, which can affect the blood supply to the placenta. Symptoms usually occur within 3–10 min of lying down and include dizziness, weakness, pallor, nausea, diaphoresis, or tachycardia. To prevent these symptoms, after 20 weeks of gestation, women should lie on their left side, place a wedge or pillow under their right hip to, or recline back at a 45-degree angle in a recumbent position for an exam, procedure, or exercise. If an exercise can be performed in an alternate position (e.g., on hands and knees vs supine), this is recommended to avoid the risk of hypotensive syndrome.

6.2.7 Neuropathies

As previously noted, nerve compression can occur in pregnancy related to hormone fluctuation, weight change, and fluid retention. Common associated conditions include gestational diabetes and elevated blood pressure [27]. Peripheral neuropathies are common in pregnancy and can cause considerable discomfort [27, 28]. Carpal tunnel syndrome (CTS) and meralgia paresthetica are prevalent in this population. In general, CTS is the most common peripheral entrapment neuropathy and is more common in women compared to men.

CTS is caused by compression of the median nerve at the wrist, as the median nerve traverses along the flexor tendons to the hand [29]. Presenting symptoms include pain, paresthesias, and numbness of the thumb, first two full digits, and half of the third digit. There may be associated pain of the wrist and hand, as well as grip weakness. All symptoms tend to be more pronounced at night, with a description of waking with the hand(s) feeling "asleep" and potential relief by shaking the upper limb. Activities that often elicit CTS symptoms include driving, holding an object such as a book or phone, and/or when washing or brushing hair [30]. CTS in pregnancy can be unilateral or bilateral, with prevalence increasing in the third trimester [27]. Additional risk factors for CTS should be assessed for, including diabetes, hypothyroidism, rheumatoid arthritis, and repetitive movement tasks of the upper extremity [28].

Diagnosis of CTS is based on specific physical exam techniques that are easily performed in the clinic setting. Similar to the back and hip exam, a general upper limb physical exam is recommended. The Tinel and Phalen signs are both provocative tests that assess the median nerve at the carpal tunnel [31]. The Tinel sign is performed by gentle percussion over the median nerve area, with positive finding of tingling into the hand. The Phalen test is performed by having the patient bring the dorsum of the hands together with the wrists in a flexed position for 1 min to determine if symptoms are reproduced [27]. Pin prick sensation testing should also be completed to assess for decreased or altered sensation in the distribution of the median nerve (Fig. 6.3).

Meralgia paresthetica is a mononeuropathy of the lateral femoral cutaneous nerve (LFCN) (Fig. 6.4), a sensory nerve with distribution to the anterolateral region of the thigh. Though less frequent compared to CTS, it is related to stretching or compression of the LFCN under the inguinal ligament as the abdomen expands [27].

Meralgia paresthetica can be experienced as burning pain and paresthesias or numbness and altered sensation of the anterolateral thigh [28]. The symptoms are most often unilateral but can occur bilaterally [13]. Often symptoms are worse with standing and alleviated with sitting or lying down. The affected area is usually quite specific, and sensory testing is helpful to confirm the affected area. Pelvic compression testing and passive hip extension, which stretches the nerve, can also provoke the symptoms [13]. Comprehensive hip and low back exam techniques are recommended to rule out other potential etiology. As the LFCN is strictly a sensory nerve, weakness and change in reflexes are not associated with meralgia paresthetica [13].

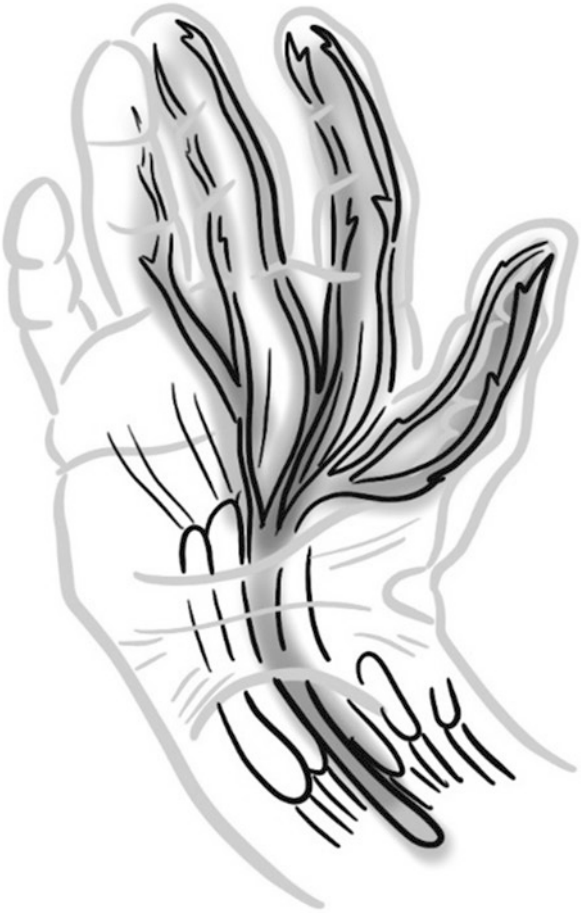

Fig. 6.3 Median nerve sensory distribution. © Kim Bogart. Illustration commissioned for the book *Holistic Pain Management in Pregnancy*. Ed. Theresa Mallick-Searle, Springer Nature 2022

6.2.8 Diagnostic Testing

Imaging is not routinely needed to initiate treatment for musculoskeletal issues in pregnancy. ACOG recommends MRI only in cases where the test is needed to answer a clinical question/determine treatment plan. MRI and ultrasound are not associated with risk to women who are pregnant [1]. MRI is indicated if lumbar disc herniation, cauda equina syndrome, or AVN is suspected.

Nerve conduction and electromyography (EMG/NCS) studies can be used to confirm the diagnosis of a peripheral nerve entrapment and to determine severity. As both CTS and meralgia paresthetica are anticipated to resolve in the postpartum phase, it is reasonable to monitor symptoms prior to completion of diagnostic testing. If there is concern for radiculopathy or weakness is present, EMG/NCS is safe to perform in pregnancy and effective to confirm the etiology. A board-certified electromyogram physician can be identified at aanem.org.

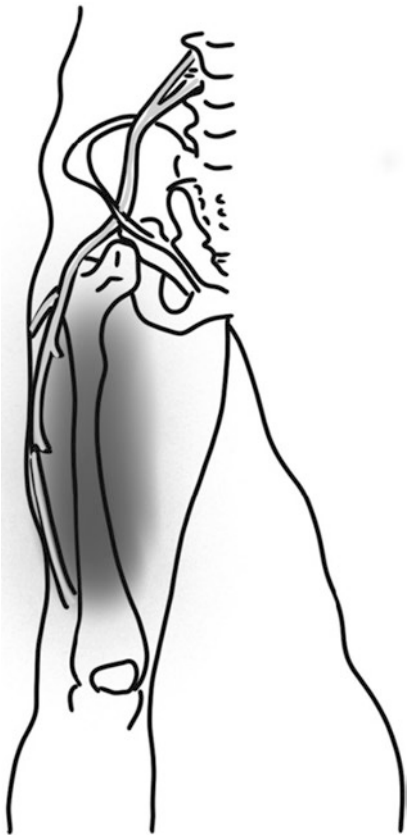

Fig. 6.4 Lateral femoral cutaneous nerve (LFCN) sensory distribution. © Kim Bogart. Illustration commissioned for the book *Holistic Pain Management in Pregnancy*. Ed. Theresa Mallick-Searle, Springer Nature 2022

6.3 Treatments

Given the significant disability associated with musculoskeletal pain in pregnancy, a multimodal treatment approach is recommended for optimal outcomes. In the absence of red flag or worrisome neurologic signs, conservative treatment options should be outlined with the patient to facilitate shared decision-making.

6.3.1 Pharmaceutical

Pregnant women may have concerns about taking medication for pain, and when considering options the provider should assess how the pain is impacting daily function, mood, and quality of life. This facilitates educated decision-making about medication use in pregnancy. Medication recommendations in pregnancy are currently guided by the pregnancy and lactation labeling rule (PLLR) [32]. This approach instructs prescribers to utilize labeling data to make informed guidance for pregnant women. The updated labeling requirement from the FDA replaced the

pregnancy letter categories with the intent of providing clearer communication [32]. As this text is not meant to provide specific medical advice, any medication use in pregnancy should be discussed with the woman's healthcare provider prior to use.

Acetaminophen is the most frequently used analgesic in pregnancy. It is a non-salicylate medication with demonstrated efficacy and relative safety in all trimesters of pregnancy [33] due to no known teratogenic properties. Though there have been more recent trials indicating a possible link between acetaminophen and behavioral disorders such as ADHD and autism [34], these have been shown to be weak associations with limitations in data [35].

Nonsteroidal anti-inflammatory drugs (NSAIDs) function by peripheral inhibition of cyclooxygenase and associated inhibition of prostaglandin synthetase [33]. NSAIDs have been shown to cause premature closure of the ductus arteriosus in late pregnancy; therefore this category is not recommended in the third trimester. NSAIDs are recommended only for short-term use in the first and second trimesters [2]. In October of 2020, the FDA published an updated recommendation that warns against use of NSAIDs at 20 weeks of gestation or later due to the risk of causing low levels of amniotic fluid [36]. This is a result of renal development in the unborn baby, as after about 20 weeks of gestation a majority of amniotic fluid is produced by the baby's kidneys [36]. Many over-the-counter medications include NSAIDs alone or combined with other medication(s); therefore it is imperative to review this recommendation with pregnant women.

Muscle relaxants have been used in pregnancy but have inconsistent recommendations. The skeletal muscle relaxant cyclobenzaprine has similar precautions as NSAIDs in the third trimester, also associated with premature ductal closure [35, 37]. Benzodiazepines are not recommended in pregnancy due to risk of congenital defects and neonatal withdrawal symptoms.

Opioids include morphine-like agonists and synthetic opioid analogues. Studies of therapeutic dose use in pregnancy have not been associated with congenital defects [33]. In general, a multimodal approach to pain management aims to maximize the positive aspects of treatment while limiting associated side effects. As many side effects are related to opioid use, minimizing opioid use is advised. Patients should also be screened for history of and risk factors for opioid misuse. Please see Chap. 7 for additional information regarding opioid use in pregnancy.

An additional drug route of administration to consider is topical. Both over-the-counter and prescription anesthetic, NSAID, and combination therapies are available. Compound topical medication can combine local anesthetics, muscle relaxants, and neuropathic pain medication. Topical NSAIDs are considered a safer route of administration with lower systemic absorption. Therefore, the topical form is considered safe for use in the first and second trimesters of pregnancy [35].

The risks and benefits of incorporating pharmaceutical use for treatment of musculoskeletal pain in pregnancy should be considered. Combining medications with different mechanism of action yields potential of synergistic effect with a lower total dose of medication and less side effects. Similarly, blending pharmaceutical and non-pharmaceutical approaches can reduce the use of medication [38].

6.3.1.1 Injections

In addition to oral medications, injections can be an effective tool for focal pain relief. Injections most often involve a corticosteroid mixed with local anesthetic. A single dose of corticosteroid given for CTS in the third trimester is considered a safe option if needed [39], and a meta-analysis did not find any significant fetal risk with corticosteroid use [40]. There have not been any teratogenic effects reported from local anesthetic use in pregnancy [38]. Common problems during pregnancy in which an injection can be helpful are carpal tunnel syndrome, sacroiliac joint (SIJ) pain, and trochanteric bursitis. Ultrasound guidance can improve accuracy of injection site. If cortisone injection is being considered, it is recommended to collaborate with the patient's ob-gyn or midwife in developing the treatment plan.

If the source of pain is primarily muscular, such as a muscle spasm of the neck, upper back, or paraspinal areas, a trigger point injection of local anesthetic at the point of maximum tenderness can be quite effective. This is a safe modality and can be repeated as a series of procedures to alleviate muscle spasm and myofascial pain. Similarly, dry needling technique is a modality offered by physical therapists with certification for this procedure. The safe use of "nerve blocks" is more fully explored in Chap. 5 within this text.

6.3.2 Non-pharmaceutical

There are many non-pharmacologic strategies for managing musculoskeletal pain in pregnancy. Patients should be educated on these options to allow for a customized treatment plan (Fig. 6.5).

6.3.2.1 Bracing

There are several types of braces that can be used to alleviate pain in pregnancy. If the patient is complaining of low back pain and reports pain subsides when she supports her abdomen with her hands or supportive clothing, then an abdominal support binder is the best option. However, if the patient presents with pelvic girdle pain and feels the SIJ or pubic bones "slipping" or "rubbing" during ambulation, then a sacroiliac belt will provide relief. If the primary symptom is vaginal pressure or perineal swelling, then the V-2 supporter is very helpful.

As pelvic girdle pain is in-part related to joint laxity in pregnancy, a pelvic belt can aid with lumbopelvic stability [41]. Round ligament pain is a common component of pelvic pain, and sudden stretch of the ligaments can aggravate this problem. To reduce the risk of sudden stretch, it is recommended to avoid extended periods of sitting or standing and to transition slowly from one position to another. Use of a maternity support belt to prevent the overstretching of these ligaments is more effective at alleviating round ligament pain versus stretching exercises. A recent study assessed the use of pelvic belts for treatment of pelvic girdle pain in pregnancy. The findings supported decreased pain, improved sensation of support, and improved tolerance for daily activities and walking [41]. Use of an abdominal binder can also alleviate pressure over the LFCN in treating meralgia paresthetica. Given the safety and positive study results of this intervention, it is a beneficial tool

Fig. 6.5 Distribution of pelvic forces in pregnancy. © Kim Bogart. Illustration commissioned for the book *Holistic Pain Management in Pregnancy*. Ed. Theresa Mallick-Searle, Springer Nature 2022

to consider for treatment of pain and promotion of improved activity. Please see the resource section below (Box 6.2) for specific types of bracing options.

6.3.2.2 Manual Therapies

In addition to bracing, manual therapies are a beneficial tool for treatment of pregnancy-related low back and pelvic girdle pain. These modalities can be provided by a physical therapist or a Doctor of Osteopathic Medicine (D.O.). Manual therapies combine a variety of techniques such as joint manipulation and soft tissue mobilization. A systematic review and meta-analysis showed moderate-quality evidence of positive findings for this non-pharmacologic modality. Manual therapies and massage are good options for reducing muscle tension in the lumbopelvic and lower extremity regions [1]. PFPTs can also offer muscle energy techniques [42]. These are safe and effective options for treating sacroiliac joint dysfunction while pregnant since they are gentle manual therapy techniques that are very effective at treating joint restrictions without using a full thrust manipulation [42].

These can be alternated and used in combination with other treatments. It is important to note a sacroiliac belt will be more effective if the pelvis is aligned by a PFPT prior to fitting the brace. If the patient is fitted with a belt prior to being in proper alignment, symptoms may be exacerbated. Often used in conjunction with manual and muscle energy therapies, ice and heat application are simple, effective modalities for musculoskeletal pain.

6.3.2.3 Neuropathies

Most cases of CTS in pregnancy resolve in the postpartum period, and conservative treatment usually controls symptoms adequately. Interestingly, a study comparing

pregnant and nonpregnant women with CTS found that pregnant women recovered at least three times faster compared to nonpregnant individuals [28]. Neutral wrist splints offload compression of the median nerve when worn at night and ergonomic adjustments can be helpful [30]. A wrist orthosis is easily accessible over the counter and prevents wrist flexion while sleeping. If symptoms are not improving, physical or occupational therapy may be of benefit for therapeutic stretching. Cortisone injection is reasonable for more severe or persistent cases. Surgery is not typically recommended for pregnancy-associated CTS, though referral to an upper limb specialist is indicated if symptoms do not resolve postpartum. For persistent symptoms, especially grip weakness and decreased coordination, injection and/or surgical intervention should be considered [28].

A conservative approach is also recommended for meralgia paresthetica in pregnancy. First-line treatment is avoidance of tight garments around the inguinal canal area and hip flexor stretches. Additional modalities include physical therapy, Kinesio tape application, dry needling, and lateral femoral cutaneous injection [27].

6.3.3 Behavioral Management Therapies

Behavioral strategies combine physical movement with cognitive practice and are a key component of multimodal pain management. Yoga, Pilates, and relaxation techniques have all been shown to reduce pain during pregnancy.

A 2014 study assessed the effect of a Hatha yoga as a behavioral intervention for pregnancy-related lumbar and pelvic girdle pain [43]. The findings supported yoga as an effective modality for reducing pain severity compared to postural education. As yoga integrates breathing techniques, meditation, and movement, pain may be alleviated through both physical and psychologic pathways [43]. Yoga is well-accepted for pregnancy and is recommended as a safe form of exercise by ACOG. Patients can choose to attend in-person yoga classes or utilize video sessions for guidance, as modifications to yoga poses may be needed. As referenced previously, pregnant women should be educated on avoiding long periods of time on their back due to risk of supine hypotension syndrome. It is also recommended that the patient takes yoga from an instructor who is trained in the pre-/postnatal population, as this type of yoga is different than traditional yoga.

In her book *The Joy of Movement*, Dr. Kelly McGonigal draws connections between synchronized movement and pain tolerance. Studies of dancers moving in unison, even with seated gestures, showed improved pain tolerance compared to groups moving together but not in unison [44, 45]. McGonigal discusses concepts of *collective joy* and *synchrony*, describing the added benefit of physical movement in a group such as an exercise class. Applying these sensations to a yoga class, she describes:

> The breath becomes the beat that drives the flow of poses, and the sound of the group inhaling and exhaling in unison provides a satisfying sensory feedback.

While many convenient online exercise options are available, these findings support participating in a group experience. Similarly, Pilates is also a good option for pregnancy-related musculoskeletal pain. Pilates is an exercise technique that

emphasizes core stabilization, posture, breathing, and flexibility [46]. Evidence supports a correlation between gluteus medius weakness and low back pain in pregnancy [3]. Abdominal muscles become stretched and weaker as the uterus grows, and the lumbar musculature takes on increased stress to compensate [2]. Therefore, core strengthening has the potential to address these factors. Exercises that strengthen the gluteal muscles also improve stability for hip abduction and extension [1].

Given the focus on lumbopelvic stability, a 2018 study showed pregnant women who practiced Pilates weekly for 8 weeks reported significantly less pain compared to standard exercise [46]. Both yoga and Pilates are recommended as behavioral options for management of pregnancy-associated lumbar and pelvic pain. As discussed previously, pregnant women should be mindful of the risk of supine hypotension syndrome and modify exercises as needed.

Additional behavioral strategies include acupuncture, massage, and relaxation techniques. Systematic review of interventions for lumbar and pelvic pain in pregnancy found low-level evidence but with positive outcomes for these interventions [47]. As safe and noninvasive modalities, they are reasonable options to consider for pregnancy-associated pain. Relaxation techniques specifically are accessible and can complement other pain management tools. Patients may find it beneficial to track activity level and pain to identify patterns of aggravating/alleviating factors and pain level. For example, limiting length of time standing and modifying clothing to avoid tight garments can decrease meralgia paresthetica symptoms.

6.3.4 Physical Therapy

> Pelvic floor physical therapy *(PFPT)* is an evidence-based, low-risk, and minimally invasive intervention, and women's healthcare providers can counsel women about the role that PFPT may play in the prevention, treatment, and/or management of pelvic floor dysfunction.—Samantha Lawson CNM, WHNP-BC Ashley Sacks PT, DPT [48]

A PFPT can be integral to treatment of musculoskeletal pain in pregnancy. The therapist uses a multimodal approach, combining education of body mechanics, instruction of individual exercises, and use of manual therapies to align joints and treat soft tissue.

6.3.4.1 What Does a Typical Pelvic Physical Therapy Treatment Session Look like (Box 6.1)?

PFPT treatment is tailored to the woman's status, pregnant or postpartum. During pregnancy, therapists focus on treating pain with the use of manual skills such as massage, gentle joint mobilization, or muscle energy techniques. These techniques are used to align joints and to release areas of muscle tension [42].

Pelvic PTs educate patients on proper posture, body mechanics, and positioning to ease discomfort. Recommendation of various braces and support belts is often included as well (see Box 6.1 for a list of brace options). Therapists provide instruction on individualized core stability exercises, as well as stretches to target

muscles that have tightened in response to body changes during pregnancy. Specific symptoms of incontinence (urinary or fecal), pelvic organ prolapse, or vulvar varicosities can be addressed by a pelvic physical therapist. The notion of "It's just part of pregnancy and will go away once the baby is delivered" is outdated. Clinicians and women should be informed there is a profession dedicated to rehabilitation of the pelvic floor. In addition to addressing specific pelvic symptoms and pain, pelvic therapists educate women how to prepare their body for labor and delivery with the use of perineal massage, squatting, and breathing techniques. These prenatal treatment sessions not only relieve the patient's discomfort and prepare her for a healthy labor and delivery, but they also help establish a relationship with the therapist. The patient can then feel comfortable returning to PT after her birth to address any pelvic floor or abdominal conditions that may arise.

Treatment can also be of benefit in the postpartum period. Although not common in the United States, some pelvic physical therapists offer telehealth during the early postpartum period to identify pain or positioning issues that can be addressed prior to the standard 6-week postpartum evaluation. The physical therapist can provide instruction on correct posture and body mechanics during childcare activities to prevent back injury. Gentle Kegel exercises may be recommended to improve blood flow and healing to the perineal region.

During this early phase, a home visit may be warranted to see the patient in person and address any incontinence or pain issues. Home visits and telehealth are good options if the woman does not feel comfortable leaving the home or separating from her newborn baby. In France, every woman is offered perineal rehab after they give birth [18]. Once the patient is cleared by her ob-gyn or midwife for an internal pelvic exam, the PT will perform this evaluation to assess muscle integrity/strength, perineal scar tissue, pelvic organ prolapse, and any pain that the patient may have. Symptoms such as incontinence, pain with intercourse, and diastasis recti of the abdominal muscles are common issues treated. If the patient had a cesarean section, this scar will be evaluated, with instruction on scar massage/management provided. It is standard to include screening for postpartum depression, and referrals to outside resources are provided as necessary.

Box 6.1: Pubic and Sacroiliac Pain: Common PT Treatment Plan

Education of symmetrical movement with transfers [20–22].

Performance of isometric exercises [20–22].

Utilization of a sacroiliac belt (www.serola.com is a good resource) [41].

Limitation of long strides with gait, taking steps one at a time, avoiding single leg stance.

Muscle energy techniques to equalize muscles on either side of the joint [42].

Gentle joint mobilization to align the joint [42].

Instruction of stabilization exercises to create a home exercise program [42, 48].

6.3.4.2 Prehabilitation

The process of prehabilitation has been utilized in recent years within the orthopedic specialty. This concept involves enhancing one's functional capacity through exercise prior to external stressors, to both better tolerate the physical stress and improve recovery time [49]. The prehab approach can also be applied to pregnancy with goals of decreased pain, improved stamina, and optimal postpartum recovery. Women should be encouraged to establish an exercise routine prior to pregnancy to improve general fitness and reduce the risk of developing musculoskeletal pain. Indeed, a recent study showed pregnant women with higher self-reported physical fitness had decreased lumbar and sciatic pain, lower generalized pain, and reduced pain disability [50]. In addition, an early focus on exercise and nutrition is relevant to the high rate of overweight and obesity in the United States [1]. It is well-documented that lack of physical activity causes loss of muscle strength, decreased bone density, reduced flexibility, and increased risk of chronic health disorders [49]. As previously described, working with physical therapy can be a valuable part of prehabilitation. It is advantageous to consult with a PFPT who specializes in women's health to determine the safest exercises that minimize strain of the abdominals and pelvic floor.

Exercise is safe, accessible, and can be performed in a variety of environments with minimal equipment [8]. There have been variations in findings regarding exercise and pelvic girdle pain. One study with a large sample size showed prepregnancy exercise reduced the risk of pelvic girdle pain [51], where meta-analysis did not find an effect of exercise during pregnancy on pelvic pain [16]. Likewise, systematic review has shown low-quality evidence for a relationship between exercise and reduction of pregnancy-associated low back pain, though some moderate-quality evidence for exercise improving disability and lowering sick leave [47]. Given the multiple health benefits and safety profile, therapeutic exercise and physical therapy should be recommended to women in the prenatal period [16] and incorporated with pregnancy education. The safest forms of exercise in pregnancy as recommended by ACOG are walking, swimming and water exercise, stationary biking, and modified yoga and Pilates.

6.3.4.3 Swimming

Both swimming and aquatic exercise are excellent options for physical activity during pregnancy. Water exercise offloads joints and muscular forces while providing a natural resistance for low-impact activity [52]. Additional benefits include swelling/edema reduction and ease of modifying effort as needed. Community and fitness centers are good resources for water aerobics classes. In addition to organized classes, water exercise can be practiced independently. One study assessed the effects of an unsupervised water exercise intervention, AquaMama, that utilized a program developed by the Danish Rheumatism Associated [53]. The study showed good compliance with a reduction in back pain. An exercise session included four swimming laps (100 meters) as a warm-up, followed by the six AquaMama exercises, cooling

down with another four laps. The six exercises were completed as a set of two sets and required aqua equipment: two foam dumbbells, a swim belt, and a kickboard [53].

Short video clips of each AquaMama exercise are available as a resource at: www.youtube.com/watch?v=F2uWMmtDD2w&list=PL10D1C9FDEF43F91F

Water exercise and hydrotherapy have been utilized for medical treatment and promotion of healing for centuries. Whether or not aqua equipment is not available, water walking, swimming, and movement can improve aerobic conditioning in pregnancy while reducing joint load [52].

6.4 Practical Resources – Box 6.2

Box 6.2 Multimodal Treatment Toolbox

Behavioral	Relaxation techniques [47] Exercise [16] Physical therapy/ prehabilitation Yoga and Pilates [46] Manual therapy [1, 42] Ice/heat application	Prenatal water exercise online videos (first, second, and third trimester): https://www.youtube.com/playlist?list=PLH4wIFcXUPgtmd2pEgZndrWSWnjQasU_8 Prenatal yoga: https://youtu.be/0cKnStmV1dI
Pharmacologic	Acetaminophen [33] Cyclobenzaprine [35, 37] Focal injection [38, 40] Topical NSAID [35]	
Pelvic floor PT [18–22]	www.aptapelvichealth.org – click on Find a PT www.hermanwallace.com – click on Find a Practitioner Contact local hospital(s) rehabilitation department and inquire about physical therapists with specialized training in pelvic floor rehabilitation	Online search terms: Pelvic Physical Therapists, Women's Health Physical Therapists, or Pelvic Floor Rehabilitation Programs
Bracing [41]	hpms.com/CMO-Mother-To-Be-Maternity-Support-p/sct-0055-x.htm www.bellybandit.com www.babybellyband.com	www.serola.net – Sacroiliac belt www.cmtmedical.com – V2-support Department stores – girdle

6.5 Clinical Considerations

Optimal treatment of musculoskeletal issues in pregnancy involves partnering with patients when discussing diagnoses and developing a plan of care. Treatment recommendations should be individualized and use a multimodal approach. Patients are more likely to adhere to recommendations if they participate in developing the plan and goal setting. Through educating patients and involving them in the plan of care, fears of a structural source of pain can be alleviated [1]. Self-management skills include empowering patients to manage a condition through problem solving, resources, and shared decision-making.

A helpful goal setting strategy when working with patients is the acronym SMART. This tool for defining and attaining goals has been applied to chronic disease self-management [54] and can also be used to facilitate goal setting during pregnancy. The acronym stands for specific, measurable, achievable, relevant, and time-based. This is a practical approach that clinicians can implement with patients to develop action plans for behaviors that can both prevent and reduce pain during pregnancy. As component of SMART goal setting can be a written exercise prescription or action plan.

In addition to assessing for current musculoskeletal symptoms, it is important to gather a history of prior orthopedic issues. For example, a patient with history of scoliosis, rheumatoid arthritis, or spasticity may have special considerations during pregnancy and delivery. If a patient is not responding to conservative measures or exam findings are concerning, referral to an orthopedic or physiatrist specialist should be made.

6.6 Case Study: 34-Year-Old Pregnant Client with Pubic Pain at 31 Weeks of Gestation

The following case illustrates the benefits of pelvic floor therapy evaluation and treatment for musculoskeletal pain in pregnancy.

Background Symphysis pubis dysfunction (SPD) is defined as a collection of signs and symptoms of pain in the anterior portion of the pelvis that may cause radiating pain to the perineum or upper thigh. This pain is often associated with pregnancy and can be quite debilitating. Due to the hormonal changes in pregnancy which cause relaxation of connective tissue and joints, pelvic instability may occur. In severe cases, it can even lead to a partial or full pubic symphysis rupture. Research on the latest treatments for SPD, however, is still quite limited.

Case Description A 34-year-old pregnant patient presented to pelvic physical therapy at 31 weeks of gestation with complaints of 8/10 left-sided pubic pain after performing a lower extremity adduction movement on her Pilates reformer. She reported a history of extreme joint flexibility throughout her body. She also reported constipation, difficulty emptying her bladder fully, migraines, and occasional low back pain. She denied any other pain aside from the sharp left pubic pain.

Objective assessment revealed good posture (despite a slight scoliosis), with the exception of bilateral midfoot pronation. She also had extreme myofascial tension throughout the back and lower extremities. Her left pubic bone presented higher than the right in both standing and supine positions. As she did not have a high-risk pregnancy or activity restrictions, a gentle pelvic floor muscle exam was performed. This revealed normal reflexes but significantly low muscle tone at all three layers of the pelvic floor. It was noted the patient had difficulty relaxing her pelvic floor muscles after a contraction. The patient was very tender to palpation on the inferior aspect of her left pubic bone as well as on bilateral sides of the urethra. Several trigger points were found in the sphincter urethrae muscle and the left pubococcygeus muscle.

For treatment, the patient was instructed in symmetry of movement to decrease strain on the pubic symphysis and an isometric adductor exercise to build strength. She was encouraged to wear a sacroiliac belt when active to stabilize her pelvis.

On the subsequent visit, the patient reported 5/10 left pubic pain and feeling less "down" about her situation. Upon exam, the left pubic bone was only slightly higher than the right. A muscle energy technique was performed to align the pubic bones, a leg pull technique was performed on the left, and myofascial release techniques were performed to the left adductors. The patient was instructed in a home exercise program (HEP), which consisted of an isometric adductor exercise and a core stabilization exercise. She was also educated on how to coordinate diaphragmatic breathing with pelvic floor muscle relaxation to facilitate fully emptying her bladder during voids. She continued to wear a sacroiliac belt.

During the next two PT visits, the patient's pubic pain averaged 4–5/10 when she was active, despite the interventions provided. Further internal pelvic assessment revealed trigger points in the pubococcygeus and sphincter urethrae muscles at their attachment site posterior to the left pubic bone. After internal myofascial release techniques were performed in this region, the patient reported significant pain relief and was able to walk with little to no pubic pain. The pubic bones were now fully aligned, and the patient better tolerated her SI belt. The therapist continued to progress her strengthening program using safe stabilization techniques in side-lying, quadruped, and standing. Exercises in supine were avoided due to risk of supine hypotension syndrome. Two of the exercises were a clamshell exercise (hip external

rotation) in side-lying and a wall sit (with a ball squeeze) to facilitate hip and thigh strengthening. At 36 weeks of gestation, the patient was instructed in perineal massage and diaphragmatic breathing exercises to prepare her pelvic floor for delivery. Six days prior to her due date, she delivered her baby vaginally and endured a grade 2 perineal tear, which healed well by her 6-week postpartum visit.

The patient returned to PT at 8 weeks postpartum. Over the span of 6 visits, the therapist addressed pubic and low back pain, perineal scar restrictions, and pain with intercourse. The patient denied any issues of incontinence after delivery but had occasional constipation, which was addressed. She responded very well to the manual therapy techniques, stabilization exercises, education on nutrition and behavior modification, and instruction on proper body mechanics during childcare activities. Upon discharge from PT, her pubic pain was resolved unless walking a long distance without her sacroiliac belt. The patient was very compliant with her HEP. She demonstrated good posture and body mechanics when caring for her infant, as well as good nutrition/behavior habits for bowel function. Her motivation and consistency with a HEP were integral to meeting her therapy goals.

Due to her positive outcome, the patient resumed pelvic PT before and after the birth of her second child 2 years later. She had a favorable outcome and is an advocate for women to receive pelvic floor PT during the prenatal and postpartum phases of pregnancy.

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Migraine in Pregnancy

7

Theresa Mallick-Searle and Maureen Moriarty

7.1 Occurrence/Incidence

Primary headache defined as migraine, tension-type headache, cluster headache, and other trigeminal autonomic cephalgias occurs in 10–17% of pregnancies [1, 2]. Ninety percent of those with one of the aforementioned primary headaches, presenting to primary care, is diagnosed with migraine. Although many women with migraine report avoiding pregnancy due to fear of worsening attacks [3], over half experience a marked improvement with reduced frequency and intensity during attacks. Improvement often begins during the first trimester and continues as the pregnancy progresses. Less than 10%, of those diagnosed with migraine prior to pregnancy, report an increased headache frequency or intensity during gestation [4]. For some women, migraine can worsen during the first trimester. A drop or big change in estrogen level can sometimes trigger a migraine attack, and there can be some drastic changes in estrogen early in pregnancy. Changes in hormone levels may off and improves in the second and third trimesters [5, 6]. Migraine attacks may start with pregnancy. Episodes without aura may begin in 1–10% of pregnant women. The onset of migraine with aura, with a pathophysiology believed related to endothelial reactivity linked to estrogen fluctuation, has an incidence of 11–14% [7]. Accurate diagnostic recognition is essential in managing migraine with and without aura during pregnancy. Another primary headache seen commonly in

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pregnancy is tension-type headache (TTH). Reported incidence of TTH in pregnancy is as high as 26% of headaches in pregnancy [8]. TTH would be expected to improve during gestation as female hormones modulate serotonin and endorphins, which are involved in TTH pathophysiology [9].

A common question is if having migraine increases your risk of complications during pregnancy. Clinicians must be knowledgeable and monitor patients for changes in their chronic migraine, especially during pregnancy, but currently there is no data to suggest that a migraine attack that occurs during pregnancy is harmful to maternal or fetal health. However, in people who have migraine, there is a higher risk of other medical issues, such as preeclampsia, hypertension, and possibly blood clotting disorders [10, 11], so monitoring for these disorders is an important part of perinatal care.

Management of secondary headache in pregnancy generally targets the underlying disorder, and, thus, is not the focus of this chapter. It is however important for the clinician to be able to differentiate between a primary and secondary headache, to be able to refer or initiate workup of urgent, such in the case of refractory hypertension, preeclampsia, intercranial hemorrhage, and tumor.

7.2 Diagnosis

Understanding the difference between primary and secondary headaches is fundamental. Primary headaches are those headaches where the headache disorder is the disease; in contrast, secondary headaches are a symptom of another underlying diagnosis, as in the example of a secondary headache because of increased intracranial pressure related to a tumor [12]. The International Classification of Headache Disorders-3 (ICHD-3) establishes guidelines in diagnosing migraine with and without aura [13]. These criteria are listed in Box 7.1a and 7.1b. These criteria, while useful and essential in clinical research, may be cumbersome for busy primary care clinicians. The ID Migraine Tool [14] is a reliable and valid alternative for screening. Composed of the following three questions, the tool may be completed by patients alone or during clinical interview.

- Has a headache limited your activities for a day or more in the last 3 months?
- Are you nauseated or sick to your stomach when you have a headache?
- Does light bother you when you have a headache?

This is a rapid reliable method for diagnosing migraine in a primary care setting. If two of the three questions are answered affirmatively, there is a 93% likelihood the patient has migraine.

A large majority of the secondary headaches seen in pregnancy and the puerperium are caused by vascular disorders, in particular conditions associated with gestational hypertension [15, 16]. Clinical findings that require additional workup, referral, and consultation include the following.

Box 7.1a: International Classification of Headache Disorders-3 Migraine Diagnostic Criteria [13]

Migraine without aura

Recurrent headache disorder manifesting in attacks lasting 4–72 h. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe pain intensity
    4. Aggravation by or causing avoidance of routine physical activity (walking or climbing stairs)
D. During headache at least one of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

Box 7.1b: International Classification of Headache Disorders-3 Migraine Diagnostic Criteria [13]

Migraine with aura

Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory, or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C.
B. One or more of the following fully reversible aura symptoms:
    1. Visual
    2. Sensory
    3. Speech and/or language
    4. Motor
    5. Brainstem
    6. Retinal
C. At least three of the following six characteristics:
    1. At least one aura symptom spreads gradually over ≥5 min
    2. Two or more aura symptoms occur in succession

3. Each individual aura symptom lasts 5–60 min (when, for example, three symptoms occur during an aura, the acceptable maximal duration is 3 × 60 min. Motor symptoms may last up to 72 h)
4. At least one aura symptom is unilateral (aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.)
5. At least one aura symptom is positive (scintillations and pins and needles are positive symptoms of aura.)
6. The aura is accompanied, or followed within 60 min, by headache.

D. Not better accounted for by another ICHD-3 diagnosis.

Box 7.2 Red Flags in Clinical History or Neurologic Examination Requiring Further Evaluation [7, 17]

Clinical symptoms

- Sudden onset (thunderclap headache).
- Progressive, worsening.
- Change from prior headache type.
- Refractory to treatment.
- Worsening with valsalva maneuver, straining, coughing, or sneezing.
- Worsens with posture (sitting or standing).

Examination or laboratory findings

- Papilledema.
- Peripheral edema.
- Hypertension.
- Focal neurologic findings (numbness, weakness).
- Fever.
- Seizure.

7.3 Treatment

The optimal therapeutic approach for the management of primary headaches during pregnancy and lactation should be to consider non-pharmacological therapies first. It is important to initiate treatment timely, as an untreated migraine can lead to stress, sleep loss, depression, and poor nutritional intake, all of which can harm both the mother and the infant, leading to unfavorable outcomes. If non-pharmacological therapies are ineffective, a well-considered decision on the use of medicine should be taken, taking into account all of the advantages and potential risks.

7.4 Pharmaceutical

Acute and preventative medication treatment guidelines in adults with migraine with and without aura are well established (see Tables 7.1 and 7.2). Before applying these medication guidelines in pregnancy, potential maternal and fetal risk should be considered (Table 7.3). We have addressed many of the pregnancy considerations for commonly used pharmaceuticals for both TTH and migraine in Chap. 2.

Additional medications for migraine treatment and prevention, not currently recommended in pregnancy, but have established pregnancy registries (see Chap. 2), are onabotulinumtoxinA (Botox) and calcitonin gene-related peptide monoclonal antibody antagonists (CGRP mABs) [20].

7.5 Symptomatic/Acute Treatment in Pregnancy

Acetaminophen is considered the safest option to treat acute pain during pregnancy and breastfeeding [7]. Caffeine at moderate intake of caffeine seems safe for mother and child when breastfeeding [21]. NSAIDs (see Chap. 2). Considerable data is available on the use of sumatriptan in pregnancy. Due to its small molecular weight, sumatriptan can pass through the placenta [22]. However, the transfer is slow and passive, so that only about 15% of maternal dose reach the fetus after 4 h [23]. A few large pregnancy registries covering more than 3000 pregnancies have retrospectively reviewed the use of other triptans, in particular rizatriptan, zolmitriptan, and eletriptan [7]. Acute migraine medications (including triptans, NSAIDs, acetaminophen, caffeine) should not be used on a daily basis, to reduce the risk of medication overuse headache [24].

Supplements for migraine (also see Chap. 4 for supplement recommendations during pregnancy):

- Magnesium at recommended doses (up to 350 mg daily) can be used during pregnancy and lactation [25].
- Coenzyme Q10 appears safe during pregnancy [26, 27].
- Melatonin has not been shown to have harmful effect during pregnancy [28].
- High-dose riboflavin, feverfew, and butterbur should be AVOIDED during pregnancy [26, 29].

7.6 Preventative Treatments in Pregnancy

Beta-blockers metoprolol and propranolol are the first-line agents recommended needed from migraine prophylaxis in pregnancy and breastfeeding [7, 30].

OnabotulinumtoxinA (Botox) has been used as a preventative treatment for chronic migraine since 2010. Given the tremendous benefit that patients receive with this treatment, and as many of the patients studied were women of childbearing age, the question was raised about the safety and efficacy of continuing treatment during pregnancy. Many studies, including reporting from the Allergan pregnancy

Table 7.1 Acute migraine treatments recommended by American Headache Society (AHS) [18]

Level A	Level B	Level C	Level U	Other
Analgesics Acetaminophen 1000 mg (for non-incapacitating attacks)	*Antiemetics* • Chlorpromazine IV 12.5 mg • Droperidol IV 2.75 mg • Metroclopramide IV 10 mg • Prochlorperazine IV/IM 10 mg, PR 25 mg	*Antiepileptics* Valproate IV 400–1000 mg	*NSAIDs* Celecoxib 400 mg	*Level B negative, Other* Octreotide SC 1000 mcg
Ergots DHE: nasal spray 2 mg, pulmonary inhaler 1 mg	*Ergots* • DHE: IV/IM/SC 1 mg • Ergotamine/caffeine 1/100 mg	*Ergots* Ergotamine 1–2 mg	*Others* • Lidocaine IV • Hydrocortisone IV 50 mg	*Level C negative, Antiemetics* • Chlorpromazine IM 1 mg/kg • Granisetron IV 40–80 mcg/kg
NSAIDs • ASA 500 mg • Diclofenac 50, 100 mg • Ibuprofen 200, 400 mg • Naproxen 500, 550 mg	*NSAIDs* • Flurbiprofen 100 mg • Ketoprofen 100 mg • Ketorolac IV/IM 30–60 mg	*NSAIDs* Phenazone 1000 mg		*NSAIDs* Ketorolac • Tromethamine nasal spray
Opioids Butorphanol nasal spray 1 mg		*Opioids* • Butorphanol IM 2 mg • Codeine 30 mg oral • Meperidine IM 75 mg • Methadone IM 10 mg • Tramadol IV 100 mg		*Analgesics* Acetaminophen IV 1000 mg

(continued)

Table 7.1 (continued)

Level A	Level B	Level C	Level U	Other
Triptans Sumatriptan, zolmitriptan, Rizatriptan, rizatriptan, etc.	*Others* • $MgSO_4$ IV (migraine w/ aura) 1–2 g • Isometheptene 65 mg	*Steroid* Dexamethasone IV 4–16 mg		
Combinations • Acetaminophen/aspirin/ caffeine 500/500/130 mg • Sumatriptan/naproxen 85/500 mg	*Combinations* • Codeine/acetaminophen 25/400 mg • Tramadol/acetaminophen 75/650 mg	*Others* • Butalbital 50 mg • Lidocaine intranasal *Combinations* • Butalbital/acetaminophen/ caffeine/codeine 50/325/40/30 mg • Butalbital/acetaminophen/ caffeine 50/325/40 mg		

Table 7.2 Preventative migraine treatments recommended by American Headache Society (AHS) [19][a]

Level A	Level B	Level C	Level U
Antiepileptics • Divalproex • Valproate • Topiramate	*Antidepressants* • Amitriptyline • Venlafaxine	*ACE inhibitors* Lisinopril	*Antidepressants* Fluoxetine
Beta-blockers • Metoprolol • Propranolol • Timolol	*Beta-blockers* • Atenolol • Nadolol	*ARBs* • Candesartan • Clonidine • α-Agonists	*Calcium-channel blockers* • Verapamil • Nifedipine
Triptans Frovatriptan	*Triptans* • Naratriptan • Zolmitriptan	*Antiepileptics* Carbamazepine	*Antiepileptics* Gabapentin
		Beta-blockers • Nebivolol • Pindolol	

[a]Not a complete list

Table 7.3 Commonly used acute and preventative medications for migraine (adapted partially from Burch R. Headache in Pregnancy and the Puerperium. Neurol Clin. 2019;37: 31–51.). Also see Chap. 2 for greater detail

Medication	Use	Safety	Hale's lactation risk rating
Acetaminophen	Acute	No increased risk of teratogenic effects	Compatible
NSAIDs	Acute	Use restricted to second trimester	Ibuprofen = compatible; diclofenac = probably compatible
Triptans	Acute	No increased risk of major congenital malformations. Evidence best for sumatriptan, naratriptan, rizatriptan. Conflicting studies about possible increase risk of premature birth	No data, probably compatible. Eletriptan is likely to have lowest concentration in breast milk. Avoid long acting triptans
Ondansetron	Acute; nausea	No increased risk of congenital malformations	Probably compatible. Evidence is lacking
Prednisone	Rescue	Increased risk of cleft lip/palate, low birth weight Risks increase with chronic versus episodic use. Benefit versus risk assessment strongly advised	Probably compatible
Lidocaine	Acute/rescue	Limited data, existing studies show no increase in congenital malformations. Intranasal formulation presumed to have a better safety profile to systemic [33]	Probably compatible
Propranolol	Preventative	Considered first-line option in pregnancy and breastfeeding. Potential side effects of intrauterine growth retardation, premature birth described in some studies [26, 29]	

registry [31], have shown no evidence of teratogenic effects on the fetus. Botulinum toxin is a large molecule and, when injected intramuscularly in recommended doses, is not expected to enter systemic circulation [32]. Therefore, onabotulinumtoxinA is unlikely to cross the placenta. Although not recommended to use during pregnancy or lactation, many clinicians have been encouraged by the long-term safety data and, in the right patient, have supported clinical use as a migraine preventative in patients that have established efficacy with treatment before pregnancy and when the benefits outweigh the potential risks.

Gabapentin, although not found to be highly effective as a migraine preventative, level U on the AHS list of preventative migraine medications [19], still might prove to be effective in some patients. Gabapentin has been seen as relatively safe in pregnancy and lactation (see Chap. 2).

7.7 Non-pharmaceutical

First and foremost, non-pharmacological treatment should start with education by a knowledgeable clinician about migraine management, about incidence of disease impact on pregnancy. This will instill confidence and reduce stress about the unknown in this patient population. We already established earlier in this chapter that many women with migraine report avoiding pregnancy due to fear of worsening attacks [3]. Secondly, as with migraine prevention in the setting of non-pregnancy, women should be counseled about the importance of trigger identification, modification, and avoidance. Triggers like sleep deprivation, skipping meals, dehydration, and emotional stress should be avoided. A balanced lifestyle with attention for physical activity and regular eating and sleeping habits is recommended. Acupuncture and behavioral therapies like biofeedback and yoga have been shown to be beneficial [26, 27, 34]. Also see Chaps. 5 and 10 for addition information.

Injection therapies have shown benefit in acute and chronic migraine treatment [35, 36]. The use of peripheral nerve blocks in regions of the greater, lesser, and third occipital, auricular temporal, and supratrochlear and supraorbital nerves proved effective in stopping a severe migraine or at times decreasing the frequency and intensity of recurrent headache [36]. In pregnancy, nerve blocks and trigger point injections should be administered with only lidocaine. Bupivacaine crosses the placenta and may induce fetal bradycardia and cardiotoxicity. Use is avoided during pregnancy [7, 37]. Also see Chap. 9 for additional information on nerve blocks.

7.7.1 Noninvasive Neuromodulation

Bhola 2015 reported in a prospective single-group study, using magnetic stimulation experienced resolution of their acute migraine, that three patients who received transcranial magnetic stimulation experienced resolution of their acute migraine-related symptoms [38].

Also see Chap. 9 for additional information on neuromodulation.

7.8 Clinical/Nursing Considerations

- Why you should discuss medication safety before pregnancy?
  A large percentage of pregnancies are unexpected or unplanned, and the majority of our patients at the headache clinic are women of childbearing potential.
- Study shows fears about pregnancy with migraine are common.
  The good news is we do have treatment options that can be effective during pregnancy; it's just a matter of talking to your healthcare provider about it and making sure they feel comfortable using different treatment options, whether it be for the prevention of migraine or for migraine attacks themselves. Allowing an open dialogue about patient's fears is therapeutic.
- How to plan for pregnancy when you have migraine?
  Planning for pregnancy includes learning which migraine treatments are safe during pregnancy and which lifestyle measures can help. Providing resources and reassurance is key.

7.9 Case Study

Twenty-seven-year-old female patient diagnosed with menstrual migraines in her teens, that became chronic around 3 years ago. She is now coming to your clinic every 3 months for onabotulinumtoxinA (Botox) injections via the PREEMPT paradigm for chronic migraine prevention and uses one of the new CRRP antagonist medications one to two times a month for acute migraine episodes. She informs you that she missed her last period and thinks that she maybe pregnant and is concerned how a pregnancy will affect her migraines. She and her husband are pleased about having a baby.

Plan:

- Educate her about what is known about reduction in migraine symptoms during pregnancy in many females, but you will monitor her symptoms and provide treatment options for possible worsening migraines.
- Tell her that you recommend stopping the Botox injections for now.
- Prescribe sumatriptan for acute migraine flares; stop the CRRP antagonist medication.
- Reinforce avoidance of triggers, behavioral management strategies, mindfulness, meditation, and diet.
- Offer to try propranolol if her migraines get worse during this time.

7.10 Summary

Headache is a common complaint, especially among women. As a result, it's not unexpected that it's a common occurrence in pregnant women. The majority of headaches in pregnancy are caused by primary headaches such as migraine and

tension headache. In the second and third trimesters of pregnancy, most women discover that their headaches disappear or significantly improve, probably due to a decrease in reproductive hormonal changes.

However, approximately 10% of women have an exacerbation of symptoms, and most women soon return to their prepregnancy migraine pattern after delivery. Because of the risk of certain drugs to the fetus and the fact that medications may be transferred in various degrees in a mother's milk, pregnancy and lactation might complicate therapy options for women with migraine.

Acetaminophen use in pregnancy is safe, and NSAIDs such as ibuprofen can be prescribed for short-term use in the first trimester. There are increasing safety data on triptans to treat migraine in pregnancy, and sumatriptan may be used to treat acute migraine attacks also while breastfeeding. Options in prescription preventive medications are limited, and it may be best to consider lifestyle changes and behavioral treatment for stress management. When preventive pharmaceutical treatment is needed for migraine, metoprolol and propranolol are the first choice followed by amitriptyline. Although still not widely recommended, safety data looks very good for onabotulinumtoxinA (PREEMPT) in pregnancy [31]. The new CGRP Abx all also has robust pregnancy registries, and hopefully some preliminary information will be forth coming.

7.11 Resources

- Hale's Medications and Mothers Milk 2021: https://www.halesmeds.comUpdated regularly, available as an online subscription and Published: Springer Publishing Company.
- Pregnancy registries are generally sponsored by interested organizations (pharmaceutical companies, academic institutions, government sponsored), ongoing for a finite period, and often listed on the U.S. FDA website: https://www.fda.gov/science-research/womens-health-research/pregnancy-registries Also see Chap. 2.
- American Headache Society: Pregnancy and Lactation – Migraine Management Toolbox https://americanheadachesociety.org/wp-content/uploads/2018/05/Pregnancy_and_Lactation_Toolbox.pdf

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Fibromyalgia/Generalized Body Pain during Pregnancy

8

Theresa Mallick-Searle

8.1 Occurrence/Prevalence

Studies suggest that the prevalence of Fibromyalgia syndrome (FMS) in pregnancy is on the rise [1]. FMS is the term used to include other frequently co-occurring diagnosis associated with FM, including migraine, sleep dysregulation, irritable bowel, pelvic pain, and depression [2]. This in part could be related to a better recognition of the disorder due to improved diagnosis and greater clinician/provider recognition. There also may be a subset of women with a genetic predisposition to FM, and the inciting event of disease expression could be the stress of pregnancy. The global prevalence of fibromyalgia, in 26 studies worldwide, is 2.7% [3]. That is over 200 million lives lived with FM and has an incidence ration of 5:1 female to male. The actual rate of FM in pregnant women is unknown; however, one study references the rate at 0.06% of expectant mothers [1].

The incidence of chronic rheumatological disorders in pregnancy was felt to be so significant that in 2021, the European League Against Rheumatism called for a for a core data set of recommendations for pregnancy registries in rheumatology [4]. Fibromyalgia has been diagnosed in 5–20% of patients with rheumatoid arthritis, spondyloarthritis, Sjogren's syndrome, and psoriatic arthritis [5]. A task force was created, whose purpose is to stimulate and facilitate multinational collaborations that aim to increase the knowledge about pregnancy course and safety of treatment in women with chronic rheumatological disorders during pregnancy [4].

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8.2 Diagnosis

The diagnosis of fibromyalgia may be made before pregnancy; often the diagnosis is made in women during their third and fourth decade of life. According to the US Department of Health and Human Services, Office on Women's Health, the average age range at which fibromyalgia is diagnosed is 35–45 years old [6]. With a preexisting diagnosis of FM, preemptive planning for pain and symptom management should be part of family planning, as the effective management of FM during pregnancy is a vital part of a healthy pregnancy. A recent, large population study looking at maternal and neonatal outcomes among a cohort of women with FM, evaluation of over 12 million births, concluded that FM is a high-risk pregnancy condition with adverse maternal and newborn outcomes [1]. The authors of this study identified an increased risk of gestational diabetes, placental abruption, and premature rupture of membranes in women with FM, as well as a commonality of pregnant women with a diagnosis of FM and obesity, substance use, and older age [1]. Another study which evaluated pregnancy outcomes in patients with FMS, looking at 112 women with FMS compared with controls, concluded that FMS is an independent risk factor for restricted intrauterine fetal growth [7].

If the diagnosis of FM is made during a woman's pregnancy, the diagnostic criteria are the same as in individuals who are not pregnant. The diagnosis of fibromyalgia is challenging because the differential diagnosis can be large, given the commonality of clinically presenting symptoms and overlapping conditions. Most important is to rule on other metabolic, infectious, neurologic disorders that can present with symptoms similar to FM. Once the differential of metabolic, infectious, possibly neurologic disorders are ruled out, the treatment with regard to pain and symptom management is similar even if the diagnosis is made in parallel to other coexisting rheumatological or musculoskeletal pain disorders. Although there continues to be discussion about the best way to characterize and diagnosis fibromyalgia [8], the current prevailing diagnostic criteria used in clinical practice and research is the American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. The criteria is as follows, a score on the widespread pain index scale (WPI) of ≥ 7 and a score on the symptom severity scale (SS) of ≥ 5, or a WPI between 3 and6 and SS ≥ 9 [9, 10] (Fig. 8.1).

8.3 Treatments

Management of fibromyalgia pain and symptomology is vital during pregnancy, and if the diagnosis is made early, creating a preemptive/preventative treatment plan is valuable to help reduce symptom flares. A study looking at pregnancy outcome in patients with fibromyalgia syndrome, undertaken by Zioni and colleagues, concluded that FMS is an independent risk factor for intrauterine growth restriction and associated with lower rates of preterm deliveries [11]. Although the conclusions of this review are questionable, it highlights the importance of establishing a preemptive treatment approach and will also reduce anxiety in both patient and provider, as well

New Clinical Fibromyalgia Diagnostic Criteria - Part 1.

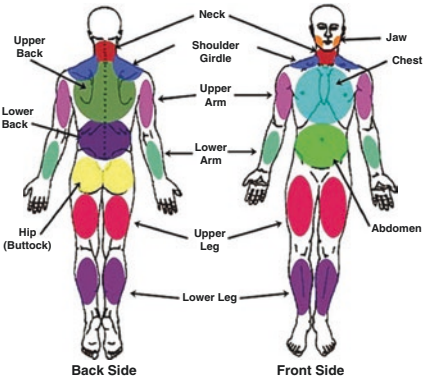
To answer the following questions, patients should take into consideration

- how you felt the **past week.**
- while taking your current therapies and treatments, and
- exclude your pain or symptoms from other known illnesses such as arthritis, Lupus, Sjogren's, etc.

Determining Your Widespread Pain Index (WPI)
The WPI Index score from Part 1 is between 0 and 19.

Check each area you have felt pain in over the past week.

- ☐ Shoulder girdle, left
- ☐ Shoulder girdle, right
- ☐ Upper arm, left
- ☐ Upper arm, right
- ☐ Lower arm, left
- ☐ Lower arm, right
- ☐ Hip (buttock) left
- ☐ Hip (buttock) right
- ☐ Upper leg left
- ☐ Upper leg right
- ☐ Lower leg left
- ☐ Lower leg right
- ☐ Jaw left
- ☐ Jaw right
- ☐ Chest
- ☐ Abdomen
- ☐ Neck
- ☐ Upper back
- ☐ Lower back
- ☐ None of these areas



Count up the number of areas checked and enter your Wildespread Pain Index or WPI score here_____.

Symptom Severity Score (SS score) - Part 2a.

Indicate your level of symptom severity over the past week using the following scale.

Fatigue

- ☐ 0 = No problem
- ☐ 1 = Slight or mild problems; generally mild or intermittent
- ☐ 2 = Moderate; considerable problems; often present and/or at a moderate level
- ☐ 3 = Severe: pervasive, continuous, life disturbing problems

Waking unrefreshed

- ☐ 0 = No problem
- ☐ 1 = Slight or mild problems; generally mild or intermittent
- ☐ 2 = Moderate; considerable problems; often present and/or at a moderate level
- ☐ 3 = Severe: pervasive, continuous, life disturbing problems

Cognitive symptoms

- ☐ 0 = No problem
- ☐ 1 = Slight or mild problems; generally mild or intermittent
- ☐ 2 = Moderate; considerable problems; often present and/or at a moderate level
- ☐ 3 = Severe: pervasive, continuous, life disturbing problems

Tally your score for Part 2a (not the number of checkmarks) and enter it here _____.

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Fig. 8.1 Clinical fibromyalgia diagnostic criteria. Adapted with permission from: Fibromyalgia Network

as to improve outcomes of a healthy pregnancy and birth. Once all the preemptive preparation is done (identifying patients at risk, optimizing available therapies, providing education), a plan should be established through joint decision-making between patient and clinician using the best available evidence and treatment risk assessment

available. Clinicians should be up-to-date on what evidence-based treatments are available, identify other healthcare provider collaborators in the community, and create an open two-way, ongoing dialogue with the patient. Treatment during the course of pregnancy must be multimodal and interdisciplinary for best outcomes. We will discuss the use of pharmaceutical and non-pharmaceutical therapies below.

8.4 Pharmaceutical

Options listed for you in this section are the general recommendations for treatment not in pregnancy. For considerations of pharmacotherapies in pregnancy, please review Chap. 2.

Any recommendations about the use of pharmaceuticals during pregnancy should be done in direct consultation with the woman's treating clinician. Currently in the United States, there are three Food and Drug Administration (FDA)-approved pharmaceuticals for FM (duloxetine, pregabalin, milnacipran). As of this writing, these three medications are not approved for FMS in Europe, Middle East, and Africa (EMEA). A recent review article looking at published case reports, FDA adverse events reporting system databases, pharmaceutical pregnancy registries, and other publish literature, evaluated the proposed perinatal safety of these three agents. The author's conclusions were that duloxetine and pregabalin should only be given to pregnant women diagnosed with severe forms of FMS, after weighing the benefits and risks [12]. In the five case reports reviewed of in utero exposure to duloxetine, no congenital malformations were recorded; however, there is a risk of *prenatal antidepressant exposure syndrome* [13]. As of this writing, the perinatal safety of milnacipran, no data have been published on pregnancy outcomes following gestational exposure to milnacipran. However, the Savella Pregnancy Registry designed to monitor pregnancies exposed to milnacipran is active (see Resources (Sect. 8.9)) and listed on https://clinicaltrials.gov/ct2/show/NCT01026077. Estimated completion date for this study is June 2023. This is an observational, exposure-registration, and follow-up registry designed primarily to estimate the prevalence of major congenital anomalies and secondarily to estimate the prevalence of recognized spontaneous abortions, stillbirths, induced abortions, minor congenital anomalies, and any serious adverse pregnancy outcomes among pregnancies exposed to Savella as well as adverse outcomes observed during the first year of life in offspring's born from these exposed pregnancies. The use of LDN for FM/FMS is growing in popularity [14–16].

Please see (Chap. 2) for considerations of LND in pregnancy. Kim and Fishman published an article in 2020 looking at *Low-Dose Naltrexone for Chronic Pain: Update and Systemic Review*. One of the clinical conditions evaluated was FM. They concluded that "Low-dose naltrexone (LDN) has shown promise to reduce symptoms related to chronic pain conditions such as fibromyalgia, inflammatory bowel conditions, and multiple sclerosis. The mechanism of LDN appears to be modulation of neuro-inflammation, specifically, the modulation of the glial cells and release of inflammatory chemicals in the central nervous system" [16]. The use of over-the-counter analgesics (acetaminophen and NSAIDs), along with topical analgesics, is addressed in Chap. 2.

The health of the microbiome and fibromyalgia is an evolving area of research [17–19]. Preliminary research has identified alterations in the constituents of the gut microbiome in patients with FM, compared with controls. While research is still in the preliminary stages of understanding the role of the gut microbiome in chronic pain and specifically FM, the goal in future research is to elicit a better mechanistic understanding of FM, for the development of objective diagnostic aids and potentially for new therapeutic modalities. Although nutraceutical/supplements/probiotics to regulate the microbiome are considered complementary therapies, I am mentioning them here (under the heading of pharmaceutical) to clearly differentiate from non-pharmaceutical therapies. Please see Chap. 4 for more discussion on the use of probiotics/nutrition to regulate the microbiome in pregnancy.

8.5 Non-pharmaceutical

Non-pharmacological therapies over time have been the mainstay for management of chronic FM/FMS symptoms [8, 20, 21].

Adapted from: 2017 EULAR revised recommendations for the management of fibromyalgia – overview of results from selected systematic reviews of non-pharmacological; complementary and alternative medicine and therapy trials (Table 8.1) [20].

Table 8.1 Non-pharmacological treatments for fibromyalgia

Treatment	Overall quality of trial(s) reviewed	Strength of recommendation	Safety and comments
Acupuncture [22] Acupressure	Moderate	Recommend for all patients	One in six people who had acupuncture and one in three controls reported adverse events. Such events were minor and lasted less than 1 day. No serious adverse events were reported in any trials [20]. Also see Chap. 10
Biofeedback [23]	Poor		Only two trials reported adverse event data. 4% of patients in one trial receiving EMG biofeedback reported stress. And 74% of patients in another, receiving EEG biofeedback reported a variety of side effects, including headache, fatigue, and sleep problems [20]

(continued)

Table 8.1 (continued)

Treatment	Overall quality of trial(s) reviewed	Strength of recommendation	Safety and comments
Cognitive behavioral therapy (CBT) [24]	Low	Should be considered for those with mood disorder or unhelpful coping strategies. In clinical studies, CBT was effective at producing modest, long-term reductions in pain, disability, and improving mood	The assessment of safety in most studies was insufficient. Two studies reported dropout due to worsening of comorbid mental disorders. However, CBT is generally considered safe [20]
Exercise [25]	Moderate	Recommend for all patients	Although patients may initially notice a deterioration in symptoms, exercise is generally considered safe, especially when practiced under supervision [20]
Hypnotherapy [26]	Good	Recommend improving pain, fatigue, quality of life	Adverse events were not reported in any of the trials [20]
Massage	Low to moderate		No adverse events were reported in any of the trials
Meditative movement [27]	Moderate	Recommendations in relation to meditative movement therapies (which improved sleep, fatigue, and quality of life	Although no serious adverse events were reported, six participants (3.1%) withdrew from the trials because of adverse events (increase of pain; muscle inflammation; chlorine hypersensitivity) the review authors concluded that the acceptance and safety of all types of meditative movement therapies were high [20]
Mindfulness/ mind-body therapy [28]	Low	Recommendations in relation to mind-body therapies which improved pain and quality of life	
Multicomponent therapy [29]	Moderate		No adverse events were reported in any of the trials [20]
Other guided imagery	Good		Adverse effects not reported [20]
Other homeopathy	Low to moderate		No information provided on safety [20]

Table 8.1 (continued)

Treatment	Overall quality of trial(s) reviewed	Strength of recommendation	Safety and comments
Nutrition/ supplements	N/a		See Chap. 4 for considerations in pregnancy
Transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS)	N/a	The application of tDCS to the motor cortex is the only intervention shown to decrease pain in the short and medium term in patients with FM. The application of both interventions showed improvements in pressure pain threshold, catastrophizing, and quality of life when applied to the motor cortex and in fatigue when applied to the dorsolateral prefrontal cortex [30]	See Chap. 9 for considerations in pregnancy
Green light therapy	Low (few clinical trials) one animal study in the literature [31]; recent abstract presented in 2021 at International Anesthesia Research Society [32]	From limited data reported, treatment with green light therapy when compared to differed wavelengths appears to be beneficial for reducing pain symptoms in subjects tested	Noninvasive, nonsystemic. Even though no outcomes have been reported in pregnancy seems to be a very low risk to fetus

8.6 Nursing/Clinical Considerations

- A successful patient-provider relationship requires establishing an effective method of communication [33, 34]. This is particularly important with this patient population for compliance. Many patients with FM have been victims of stigmatization and even been seen by healthcare providers (HCPs) as drug-seeking and noncompliant.
- The CDC recommends that individuals with FM join a self-management education class to learn to manage symptoms to improve quality of life. Alternatively, education can come from the patient's HCP for reinforcement and monitoring of patients' comprehension and education received [35].
- Importance of focused, guided exercise for pain reduction, sleep and fatigue improvement, and stamina improvement [20, 36] should be a focused priority. HCPs can help with education, resources for care, and follow-up.

- Both patients and HCPs value the interprofessional team (nutritionist, PT, psychologist, peer support group) approach to care. Other key aspects included the benefits of the group, exercise, and the positive focus of the program [37]. The patient's primary HCP is instrumental in coordinating the interprofessional team.

8.7 Case Study

32-year-old female patient diagnosed with several conditions, including fibromyalgia, irritable bowel, anxiety, and depression. She is an established patient and come to you to discuss family planning, as her husband and she have been considering starting a family. She is concerned about the medications that she is currently taking and how this will affect her fetus; also she is concerned about the effects that a pregnancy may have on her FM and chronic pain.

The patient is currently using tramadol as needed for pain and occasional lorazepam for sleep. She has a body mass index (BMI) of 27 (overweight) and does not report a regular exercise regime.

Plan:

- Have her keep a weekly food diary and consider referral to nutritionist.
- Counsel about exercise and microbiome.
- Wean tramadol; counsel about use of benzodiazepines for sleep (consider melatonin) and alternatives to opioids. If an opioid is needed, consider a non-synthetic opioid.

8.8 Summary

Fibromyalgia (FM) is a rheumatologic disorder marked by chronic, widespread pain and associated comorbid conditions, and studies suggest that the prevalence of FMS in pregnancy is on the rise. With a preexisting diagnosis or newly diagnosed fibromyalgia, preemptive planning for pain and symptom management should be part of family planning, as the effective management of FM during pregnancy is a vital part of a healthy pregnancy. Treatment during the course of pregnancy must be multimodal and interdisciplinary for best outcomes and should start with an open dialogue with and education to the patient. There are many evidenced-based pharmacological and non-pharmacological treatments that can be employed during pregnancy. Clinicians need to be educated about what is available and partner with the patient for compliance and best healthcare outcomes.

8.9 Resources

- The American College of Rheumatology has compiled this list to give you a starting point for your own additional research. The ACR does not endorse or maintain these websites and is not responsible for any information or claims

provided on them. It is always best to talk with your rheumatologist for more information and before making any decisions about your care. https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Fibromyalgia

- National Fibromyalgia Association: https://fmaware.net/
- National Fibromyalgia and Chronic Pain Association: https://fibroandpain.org/
- **FDA List of Pregnancy Exposure Registries**: https://www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries
- **FDA Pregnancy Registries**: https://www.fda.gov/science-research/womens-health-research/pregnancy-registries
- **Cymbalta Pregnancy Registry** – Syneos Health.
  Website: http://www.cymbaltapregnancyregistry.com
  Phone: 866-814-6975
- **Antiepileptic Drug Pregnancy Registry** – Massachusetts General Hospital.
  Website: http://www.aedpregnancyregistry.org
  Phone: 1-888-233-2334
- **National Pregnancy Registry for Antidepressants** – Center for Women's Mental Health at Massachusetts General Hospital.
  Website: https://womensmentalhealth.org/research/pregnancyregistry
  Phone: 1-866-961-2388
- **The Savella Pregnancy Registry (SPR)** – Syneos Health.https://clinicaltrials.gov/ct2/show/NCT01026077
  Savella Pregnancy Registry associate 877-643-3010
  pregnancyregistries@syneoshealth.com

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Use of Nerve Blocks and Neuromodulation in Pregnancy

9

Theresa Mallick-Searle

Injection therapies typically attempt to target the presumed source of the pain (e.g., sacroiliac joint injection for SI joint pain; occipital nerve block for occipital neuralgia) while minimizing the need for pharmacotherapies that may expose the patient to systemic side effects [1–3]. The goals of injection therapies include reducing pain and improving mobility/function, while reducing possible systemic side effects of pharmacotherapies that could cause sedation, gastrointestinal distress, and altered cognition and could possibly be teratogenic to the fetus. When coupled with focused physical therapy (see Chap. 6), the outcomes of injection therapies may be improved.

The consideration of injection therapies should include an accurate diagnosis to the potential source of the pain, patient willingness, appropriate expectations, an understanding of the risks and complications, and, if necessary, the ability to refer to a clinician experienced to perform the procedure.

The use of neuromodulation devices in pregnancy remains controversial, as there have been very few studies done in safety of such devices. In 2019 a study was published by Camporeze and associates, looking at a review of the literature on indications, complications, and results in pain control using spinal cord stimulation (SCS). Their findings were, "Based on the literature and author's experience, the evaluation of SCS effects during pregnancy of patients affected by neuropathic pain syndromes is still initial and controversial" [4]. Of the studies evaluated, 72% of patients were affected by complex regional pain syndrome (CRPS), 25% failed back pain syndrome (FBSS), and 4% with neuritis. During the prenatal and postnatal period, the absence of complications was shown in 70% (n = 22/32) and 94% (n = 30/32) of pregnancies, respectively. In the prenatal period, the intrauterine growth restriction (IUGR) was shown in 3% (n = 1/32), hardware malfunction in 3% (n = 1/32), systemic arterial hypertension (HAS) in 9% (n = 3/32), abortion in

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9% (n = 3/32), and gestational diabetes (DMG) in 6% (n = 2/32) of pregnancies. The outcome analysis showed maternal and neonate healthy in 100% (n = 32/32) and 88% (n = 28/33) of pregnancies, respectively. Regarding the obstetric and nontechnical complications during the SCS, the authors summarized ten complications: three cases of miscarriages and HAS, two cases of DMG, as well as one description of IUGR and foot drop each. The cases of patients affected by HAS, miscarriages, and DMG presented previous obstetric and clinical history of these complications such that they are not suggestive of secondary complications during SCS.

The use of neuromodulation can be through either permanent or temporary placement of a stimulation electrode either in the epidural space or percutaneously near a peripheral nerve (such as with an occipital nerve stimulator for occipital neuralgia), along with the generator unit [5–8].

There are also several external neuromodulation devices available, mostly only approved at this time for primary headaches and facial pain (see Table 9.1). None of these devices has regulatory approval to be used during pregnancy, as the clinical studies showing safety and efficacy are lacking.

Carpal tunnel syndrome (CTS) and meralgia paresthetica (MP) are two common neuropathies complicating pregnancy. Each of these disorders can be treated safely during pregnancy [9]. A 2011 study of 20 pregnant women with electrophysiologically diagnosed CTS showed promise for combined steroid and lidocaine injections. Patients were injected under the carpal tunnel with 4 mg dexamethasone and 0.5% lidocaine [10]. A 1-time subcuticular injection of dexamethasone in the third trimester is considered safe in pregnancy [11]. Lateral femoral cutaneous nerve blocks using a combination of lidocaine and corticosteroids are also often used in the treatment of MP. A 2000 study found that the majority (80%) of their patients' symptoms remitted in the first week after injection [12], although the evidence is lacking in pregnancy. A large meta-analysis from 2000 did not find that corticosteroid therapy posed a major teratogenic risk and concluded that there was no statistical difference in the rate of major abnormalities between pregnant women treated with corticosteroids and pregnant controls [13].

Primary headaches (migraine, tension-type, cluster) are common during pregnancy and can create major treatment challenges for obstetric providers [14]. A retrospective chart review using peripheral nerve blocks for the treatment of refractory migraine in parturients was published by Govindappagari and associates [15]. They found that 51.8% of the study participants received nerve blocks as a treatment for status migrainous and 48.1% as a short-term prophylactic therapy for an exacerbation of high-frequency episodic or chronic migraine with escalation in attack frequency or severity. Eighteen injections included the greater occipital, auriculotemporal, supraorbital, and supratrochlear nerve blocks. Six featured greater occipital nerve blocks alone. Patients were treated with lidocaine (70.3%), bupivacaine (14.8%), or both drugs (11.1%). When

Table 9.1 Types of external neuromodulation devices

Type	Proposed mechanism of action	Painful condition(s) used for	Safety in pregnancy
External trigeminal nerve stimulator (e-TNS)	The supraorbital nerve is a branch of the first division of the trigeminal nerve. Transcutaneous supraorbital nerve stimulation has been developed as a potential treatment for headache [23]	Acute migraine treatment [23]; prevention chronic migraine [24]	Unknown/ indeterminant
Vagus nerve stimulator (VNS)	The vagus nerve is a mixed motor and sensory nerve that is important in controlling autonomic responses; it projects to several higher centers that are important in pain regulation [25]	Migraine prevention [26] and acute treatment [27]; cluster headaches prevention/acute treatment [28]	Unknown/ indeterminant
Transmagnetic (TMS)	Patients with migraine are thought to have a state of brain hyperexcitability, and this has been shown in transcranial magnetic stimulation studies. This hyperexcitable cortex leads to a lowered threshold for cortical spreading depression, a wave of depolarization of neural membranes. In studies, single-pulse transcranial magnetic stimulation inhibits cortical spreading depression [29]	Acute migraine treatment [29]	Unknown/ indeterminant
Distal transcutaneous electrical stimulator (wearable, smartphone-controlled neurostimulation device)	State-of-the-art technology, including various neuromodulation and neuroscience advancements. The device's innovative design produces a patented waveform that is delivered to C-fiber nerves, which trigger a pain-reducing mechanism of analgesics in the brain stem [30]	Acute migraine treatment [30]	Unknown/ indeterminant
Transcutaneous electrical nerve stimulation (TENS)	Low-intensity, non-noxious TENS paranesthesia (conventional TENS) relieves pain by a segmental mechanism. Higher-intensity TENS increases the likelihood of activating extra segmental descending pain inhibitory pathways and diffuse noxious inhibitory controls via counterirritant effects. TENS will also cause peripheral blockade of afferent impulses that have arisen from a peripheral structure [31]	Nociceptive, neuropathic acute pain [31–33]	Unknown/ indeterminant

evaluating patient delivery outcomes, 38.4% of patients delivered at >37 weeks' gestation, 23.0% at >35 weeks, and 15.3% were preterm at 29 weeks for pre-eclampsia. No patients had any serious immediate or procedure-related adverse events. The authors concluded that in parturients with refractory migraine, therapeutic peripheral nerve blocks may be an effective option when other treatment modalities have failed to offer relief. However, a larger randomized controlled trial is needed to verify these findings and to evaluate delivery and neonatal outcomes.

Low back pain (LBP) is commonly experienced during pregnancy, affecting approximately 50% of pregnant women, and is associated with significant morbidity in pregnancy and postpartum patients [16–18]. There is limited evidence on neuraxial blockade in the peripartum period for analgesia. Sehmbi and associates published a systematic review of the role of neuraxial analgesia to treat low back pain in pregnancy [16]. They found three case reports describing the injection of steroids into the epidural space (ESI) to relieve LBP and radicular pain; but all patients eventually required operative intervention due to the recurrence or progression of neurological symptoms. Ultrasound-guided injection of local anesthetic and steroid into the symphysis pubis joint in a pregnant patient to relieve severe symphysis pubis pain was also reported. Additionally, there were two reports of injections into the SI joint in pregnancy with good analgesic response. They found weak evidence for the analgesic and surgery-delaying effect of ESI in pregnant patients with LBP, which is consistent with observations in nonpregnant patients. Although a single dose of epidural steroid appears to be of low risk to the fetus, it is recommended that ESI be reserved for patients with new onset of signs or severe symptoms of lumbar nerve root compression. Finally, they reported that in pregnant patients with history of LBP, spinal deformities or previous spinal surgery are associated with higher rates of complications and failures.

Comlek looked at a retrospective review of ultrasound-guided interventions during pregnancy for lumbosacral pain unresponsive to conservative treatment [19]. In this study, 20 women in the second trimester of pregnancy with lumbosacral pain developed during pregnancy unresponsive to conservative treatments who underwent the following ultrasound-guided pain interventions were included: sacroiliac joint, caudal epidural, interlaminar epidural, and trigger point injections. All patients were followed up until early postnatal period. All but one patient achieved satisfactory pain control throughout the pregnancy with a single injection, which was maintained thereafter until early postnatal period. In Comlek's conclusions it was felt that injections used for effective interventional pain management in nonpregnant populations seem to represent an effective and safe method also for pregnant women

when performed under ultrasound guidance, with rapid onset and enduring duration of action until the time of delivery.

Finally, a review of the literature revealed a few case reports of nerve blocks during pregnancy:

- A Case Report of Paravertebral Block: A Safe Alternative for Microdiscectomy in a Pregnant Patient. A 31-year-old woman with multiple (triplets) pregnancy, in her first trimester. The magnetic resonance imaging revealed a diffuse disk herniation with caudal migration at fifth lumbar vertebra–first sacral vertebra level causing marked extradural compression. She was treated with an ultrasound-guided, modified bilateral paravertebral block, safely with a total of 15 mL of 0.5% bupivacaine, and favorable outcomes [20].
- Erector spinae plane (ESP) block as rescue analgesia in gestational week 16. A 42-year-old woman was referred to our pain clinic with pain in her neck and left arm, associated with episodes of stabbing pain with burning symptoms in the lateral aspect of her left shoulder and the interscapular area. An ultrasound-guided ESP block was placed using 20 mL of a mixture containing plain lidocaine 0.5% and bupivacaine 0.25% with 40 mg triamcinolone. Assessing by means of response to cold, dermatomal spread from C5 to T3 was revealed. The patient had a positive response to treatment at 2 and 8 weeks after the procedure, describing a global reduction in pain of 85% proximally (cervical and scapular area) and 50% distally (forearm) at 2 weeks and 90% reduction of both symptoms at 8 weeks [21].
- Recurrent anterior cutaneous nerve entrapment syndrome (ACNES) in three consecutive pregnancies. 31-year-old G2P1001 woman at a 30-week gestation presented with a recurrence of pinpoint right upper abdominal wall pain, similar pain experienced during her earlier pregnancies. She underwent an ultrasound-guided rectus sheath nerve block at 30 weeks with complete and immediate relief for the remainder of the pregnancy [22].

As a clinician caring for women during pregnancy with pain complaints that you feel may be amenable to injection therapies that you are unable to provide, it is important to know who is in your community experienced and educated to care for these patients (Table 9.2).

- Training/certification in interventional pain management.
  - American Board of Interventional Pain Physicians: https://abipp.org/
- Training/certification in obstetric anesthesia: 12 months of fellowship training in an ACGME-accredited subspecialty program.

Table 9.2 Common injection therapies

Type	Painful condition(s) used for	Guidance needed	Safety in pregnancy
Epidural	Back pain, with/without radiculopathy	Fluoroscopy	The effect of radiation on the fetus has been derived primarily from animal studies and human exposures to diagnostic and therapeutic radiation as well as atomic bomb exposure. Pregnancy poses special considerations regarding radiation exposure. Therefore, decisions to expose the mother must include need for the procedure, consideration of other modalities to evaluate the condition, knowledge of maternal and fetal dosage, and fetal gestational age [34] Case reports using ultrasound guidance in severe cases of lumbar radiculopathy, attempting a caudal epidural approach, have been shown to be efficacious [35, 36]
Trigger point injection	Myofascial pain	Ultrasound or landmarks	**(see below)***
SI joint injection	Focal low back pain	Fluoroscopy or ultrasound	**Ditto**
Peripheral joint injection	Focal joint pain	Ultrasound or landmarks	**Ditto**
Selective nerve blocks (occipital, trigeminal, other)	Migraine, occipital neuralgia, trigeminal neuralgia	Ultrasound or landmarks	**Ditto**
Piriformis muscle injection	Piriformis syndrome	Ultrasound	**Ditto**
Median nerve block	Carpal tunnel syndrome	Ultrasound or landmarks	**Ditto**
Lateral femoral cutaneous nerve block	Meralgia Paresthetica	Ultrasound or landmarks	**Ditto**
Botox injections via PREEMPT	Chronic migraine prevention	Landmarks	24-year retrospective review of the Allergan safety database shows that the prevalence of fetal defects in onabotulinumtoxinA-exposed mothers before/during pregnancy (2.7%) is comparable with background rates in the general population. Pregnancy outcome monitoring in onabotulinumtoxinA-exposed women continues [40] A 29-year retrospective analysis of safety in onabotulinumtoxinA-exposed mothers demonstrated that prevalence rates of abnormal birth outcomes were within/below those reported in the general population, with no new safety signals identified [41].

*The use of injection therapies, like the use of pharmacotherapies, needs to be weighed with the potential benefits versus the risks during pregnancy. Decision-making must be as a collaborative effort between patient and clinician. The clinician must be able to explain the risks to the patient using the currently available evidence. The use of various injections for discrete pain conditions has been shown to be effective. The use of small amounts of corticosteroid and local anesthetic injected peripherally has been shown in various studies to be non-teratogenic [9–22, 35–39].

9.1 Summary

Although the literature is slim regarding safety, it seems that the use of a single injection of local anesthetic and steroid in pregnant patient's refractory to other therapies seems to be effective and relatively safe. The use of neuromodulation devices, invasive procedures in particular, need further studies before recommended use.

The use of injection therapies, like the use of pharmacotherapies, need to be weighed with the potential benefits versus the risks during pregnancy. Decision-making must be as a collaborative effort between patient and clinician. The clinician must be able to explain the risks to the patient using the currently available evidence. The use of various injections for discrete pain conditions have been shown to be effective. The use of small amounts of corticosteroid and local anesthetic injected peripherally has been shown in various studies to be non- teratogenic.

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Complementary Treatments in Pregnancy

10

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Complementary alternative medicine (CAM) therapies used for pain management during pregnancy have been studied and generally considered safe [1–6]. A large retrospective cohort study looking at over 20,000 pregnant females in Korea evaluated the safe use of acupuncture during pregnancy (adjusted for maternal age, history of high-risk pregnancy, multiple pregnancy) comparing incidence of full-term delivery, preterm delivery, and stillbirth by pregnancy duration and among the high-risk and multiple pregnancy groups. The authors found no significant difference in delivery outcomes (preterm delivery and stillbirth) observed between confirmed pregnancies in the acupuncture and control groups. Therefore, concluding that in pregnancy, acupuncture therapy may be a safe therapeutic modality for relieving discomfort without an adverse delivery outcome [7].

A systematic review looking at the safety of acupuncture in pregnancy was published by Park and associates in 2013. Of 105 included studies, detailed adverse effects (AEs) were reported only in 25 studies represented by 27 articles (25.7%). AEs evaluated as certain, probable, or possible in the causality assessments were all mild/moderate in severity, with needling pain being the most frequent. Severe AEs or deaths were few and all considered unlikely to have been caused by acupuncture. Total AE incidence was 1.9%, and the incidence of AEs evaluated as certainly, probably, or possibly causally related to acupuncture was 1.3%. The authors concluded that acupuncture during pregnancy appears to be associated with few AEs when correctly applied. The estimated incidence of AEs associated with acupuncture in pregnant women was 193 per 10, 000 acupuncture sessions. In general, commonly reported mild AEs associated with acupuncture include bleeding or hematoma, pain, and tiredness or drowsiness [8].

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Controversies continue to exist over "forbidden points in pregnancy" [9]. Although controversial, many acupuncturists will avoid points that stimulate the cervix and uterus, as they can induce labor [10]. If recommending a pregnant patient for acupuncture, it is advised to find an acupuncturist who has experience with pregnancy.

Numerous studies have shown the efficacy of acupuncture at various stages of pregnancy [3, 5]. Kvorning and colleagues looked at 72 pregnant women reporting pelvic or low-back pain. Participants were randomized during pregnancy weeks 24–37 to an acupuncture group ($n = 37$) or to a control group ($n = 35$) at three maternity wards in southern Sweden. During the study period, VAS scorings of pain intensity decreased over time in 60% of patients in the acupuncture group and in 14% of those in the control group. At the end of the study period, 43% of the acupuncture patients were less bothered than initially by pain during activity compared with 9% of control patients. The authors concluded that acupuncture relieves low-back and pelvic pain without serious adverse effects in late pregnancy [11].

Another notable study evaluating the efficacy of acupuncture during pregnancy was conducted by Jorge Vas and colleagues. This was a 4-group, multicenter, randomized controlled trial conducted at 18 public primary care centers in three regions in Spain, with the participation of 220 pregnant women at 24–36 weeks of gestation, aged 18 years or more, diagnosed with pregnancy-related low-back and pelvic girdle pain and who had not previously received ear acupuncture. Participants were randomly assigned (1:1:1:1) to receive standard obstetric care plus two sessions (over 2 weeks) of verum ear acupuncture, or nonspecific ear acupuncture, or placebo ear acupuncture, or standard obstetric care alone, and pain was assessed at set time points. With respect to baseline values, the reduction in pain intensity among the verum ear acupuncture group vs standard obstetric care was significantly greater, both at 2 weeks and 3 months. The authors concluded that after 2 weeks of treatment, ear acupuncture applied by midwives and associated with standard obstetric care significantly reduces lumbar and pelvic pain in pregnant women, improves quality of life, and reduces functional disability [12].

Accumulated bodies of evidence that acupuncture is beneficial in various conditions have enhanced understandings to the mechanisms of acupuncture treatment. However, there is still no conclusive evidence in acupuncture clinical studies [13]. Modern research into acupuncture suggests that there are both central and peripheral mechanisms affected in pain modulation [14].

Acupressure as an independent treatment for pain in pregnancy lacks the studies to demonstrate efficacy and generally gets studied along with acupuncture. It can be assumed that, as the science of acupressure focuses on similar mechanisms as with acupuncture, the evidence of safety seen in acupuncture applies. Unfortunately, as the delivery is much different, the same inference to efficacy cannot be made. A review of the literature, using keywords of acupressure and pregnancy in "PubMed" shows articles related to acupressure use nausea and vomiting in early pregnancy [15, 16].

A Cochrane Database review looking at "Acupuncture or acupressure for induction of labour" published in 2017 reported two findings of acupressure as an independent treatment [17].

> Acupressure versus sham control: There was no evidence of benefit from acupressure in reducing caesarean sections compared to control (RR, 0.94, 95% CI 0.68 to 1.30, two trials, 239 women, moderate-quality evidence). There was no evidence of a clear benefit in reduced oxytocin augmentation, instrumental vaginal birth, meconium-stained liquor, time from trial intervention to birth of the baby, and spontaneous vaginal birth.
>
> Acupressure versus usual care: There was no evidence of benefit from acupressure in reducing caesarean sections compared to usual care (RR 1.02, 95% CI 0.68 to 1.53, two trials, 151 women, moderate-quality evidence). There was no evidence of a clear benefit in reduced epidural analgesia, Apgar score < 7 at 5 minutes, admission to neonatal intensive care, time from trial intervention to birth of the baby, use of other induction methods, and spontaneous vaginal birth.

One review published in 2017 looked at the combined use of acupuncture and acupressure during labor. The study by Schlaeger and colleagues focused on a review of the current literature that has addressed the effects of acupuncture and acupressure on intrapartum events. Overall, they found that although there was inconsistency in the available literature looking at the use of acupressure alone in pregnancy, many of the studies that have been conducted examining both acupuncture and acupressure used large samples and have overall found positive effects for both acupuncture and acupressure [18]. A similar finding was reported by Levettt and associates in their review, *Acupuncture and acupressure for pain management in labour and birth: a critical narrative review of current systematic review evidence* [19].

An even lesser-studied CAM therapy for pain in pregnancy is aroma therapy. The use of essential oils has been studied as an adjuvant treatment for health and wellness [20] and as a neuroprotective [21], but little is known about the full applicability in pregnancy. Smith and colleagues authored a Cochrane Database review on *Aromatherapy for pain management in labour* in 2011. They found that of the two trials (535 women) in the review, the trials found no difference in pain outcomes to make recommendations for its utility. Conclusions were that further research is needed before recommendations can be made for clinical practice [22]. Equally, there were no reported AEs to council against the use of aroma therapy as an adjuvant treatment in pregnancy for pain and symptom management. So, if this is a strategy that has been utilized by the patient before pregnancy, then could be safely continued during pregnancy. Additionally, aroma therapy could be introduced for the first time as an adjuvant for pain and symptom management during pregnancy.

Essential oils are thought to increase the output of the body's own sedative, stimulant, and relaxing substances. The oils may be massaged into the skin or inhaled by using a steam infusion or burner. Aromatherapy is increasing in popularity among midwives and nurses [23]. The most common application of aromatherapy during labor is by massage, bath, or inhalation, and two oils commonly used include lavender and frankincense [24]. Other essential oils used during labor and delivery include eucalyptus, jasmine, roman chamomile (pain), clary sage (increase contractions), lemon (elevated mood), mandarin, nerdi, ylang-ylang (relaxation), and rose (anxiety) [25, 26].

Table 10.1 CAM therapies

Therapy	1st trimester	2nd trimester	3rd trimester	Labor
Acupuncture [7, 8]	Safe	Safe (avoid points that may stimulate uterus and cervix) [9, 10]	Safe (avoid points that may stimulate uterus and cervix) [9, 10]	Safe
Acupressure [19]	Assumed safe	Assumed safe	Assumed safe	Assumed safe
Aroma therapy [22]	Assumed safe	Assumed safe	Assumed safe	Assumed safe
Hydrotherapy/ aqua therapy [23]	Use with caution (avoid hot tubes)	Use with caution (avoid hot tubes)	Use with caution (avoid hot tubes)	Use with caution (birthing pool)
Chiropractic care [23]	Use with caution (pressure off abdomen)	Safe	Use with caution (avoid lying on back)	Not studied

10.1 Summary

There have been several large-scale surveys which indicate that 48% of all women of childbearing age currently use at least one CAM therapy (Table 10.1) for health-related conditions [27]. A 2010 systematic review on CAM use during pregnancy cited a broad prevalence ranging from 1% to 87% [1]. Concerns over drug use during pregnancy have helped increase the use and recommendations of other non-pharmacological treatments. Among them, acupuncture is increasingly practiced in pregnant women. Often the use of acupuncture and acupressure is seen as complementary, with acupuncture being the most studied. Acupuncture, especially when performed by an acupuncturist experienced with pregnancy, has been seen as safe and effective in all stages of pregnancy. There are of course AEs to any intervention and should be considered in those at highest risk (history of high-risk pregnancy, multiple births, miscarriages). The use of aroma therapy, although poorly studied, does not appear to pose undue risk to a woman during pregnancy, especially if currently using aroma therapy preconception for health and wellness.

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Conclusion

Pregnancy may be one of the most transitional periods in a woman's life. For many women it is a time of joy and anticipation, but for some it may be associated with anxiety and fear, confusion, and uncertainty. This can be the case when the pregnant female has a history of chronic pain. There is a lot that healthcare professionals can do to assist the pregnant female during this time to allay fears and support emotional well-being and physical health.

Although healthcare professionals want the best possible outcomes for their patients, at times we may not be tooled with the knowledge and confidence to meet all the needs of their pregnant patients; this can be especially true when it comes to the management of pain during pregnancy. Pain management in pregnancy is uniquely challenging because clinical decision-making must account for the pregnant female and the developing fetus. There are many treatment approaches/considerations available, but there continues to be a lack of urgency placed on education when it comes to the management of pain in pregnancy. There also continues to be a need for research into safety and best practice.

I hope that this book has lent insights to traditional and some new treatment approaches that reinforce the excellent care you are providing and has given you some new tools. Ultimately becoming familiar with the resources and latest evidence available to manage this unique patient population for the best possible outcomes will help the healthcare professional to feel empowered and confident to celebrate the joy of pregnancy and childbirth with our patients.

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