Review Article

Management of cancer pain in pregnancy: can opioids be used?

Esther W. Nafula[1], John Weru[2*], Sriram Yennurajalingam[3*]

[1]Palliative Care Unit, Kenyatta National Hospital, Nairobi, Kenya; [2]Department of Haematology Oncology, Aga Khan University Hospital, Nairobi, Kenya; [3]Department of Palliative Care Rehabilitation, and Integrative Medicine, University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Contributions: (I) Conception and design: S Yennurajalingam; (II) Administrative support: J Weru, S Yennurajalingam; (III) Provision of study materials or patients: EW Nafula; (IV) Collection and assembly of data: EW Nafula; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to this work.

Correspondence to: Sriram Yennurajalingam, MD, MS, FAAHPM. Professor of Medicine, Department of Palliative Care Rehabilitation, and Integrative Medicine, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd. #1414, Houston, TX 77030, USA. Email: syennu@mdanderson.org.

Abstract: Cancer in pregnancy is less common, however its frequency is increasing due to delayed onset of childbearing. Pregnant patients with cancer can experience high frequency of moderate to severe cancer pain. It can be challenging to manage cancer pain due to the complexity with assessment and treatment as many of the analgesics are avoided. There exists limited research and few guidelines by national and international organizations to guide effective opioid management among pregnant women or pregnant woman with cancer pain. Pregnant patients with cancer need to be managed by interdisciplinary team with multimodal analgesia including opioids, adjuvants, non-pharmacological interventions for optimal care of these patient and later the neonate. Opioids such as morphine may be considered for the management of severe cancer pain during pregnancy. It is important to prescribe the lowest effective dose and quantity of opioids after taking into consideration the risk/benefit to patient-infant dyad. Neonatal abstinence syndrome should be anticipated after delivery and carefully managed in intensive care, if possible. Further research is needed. In this review article we describe the challenges of managing cancer pain in pregnant woman and the current approach of opioids management for cancer pain in these patients using a case report.

Keywords: Cancer pain; uncontrolled pain; pregnancy; opioids; morphine

Submitted Jan 18, 2023. Accepted for publication May 29, 2023. Published online Jun 05, 2023.
doi: 10.21037/apm-23-74
View this article at: https://dx.doi.org/10.21037/apm-23-74

Introduction

Cancer in pregnancy is relatively rare occurrence of one per 1,000 pregnancies annually (1-5). This data may be an underestimation due to challenges involved in cancer diagnosis during pregnancy as well as limited data from low and middle income countries (LMICs) (6). The rates of malignancies in pregnancy are expected to increase in the coming years due to delayed onset of childbearing and better methods to diagnose (1,7). The most common malignancies reported in pregnancy include melanoma, breast cancer, cervical cancer, lymphomas and leukemia (8,9).

Many pregnant women experience pain with some having chronic pain prior to pregnancy (10-12). Cancer pain is one of the most distressing symptoms in patients with cancer (13). The frequency and impact of cancer pain is not clear in pregnant cancer patients, however, would likely have similar negative impact as other cancer patients especially in their quality of life including its impact on symptoms such as anxiety, depression, and enjoyment of life, and in some patients the anticipation of pain is so distressing that they fear the pain more than death itself (2,10,14). The use of opioids during pregnancy has been on rise. In a recent Quebec Pregnancy Cohort study evaluating the prevalence and duration of prescribed opioid use during pregnancy [1998–2015], 4.7% pregnancies were exposed

to opioids (15). There is no evidence-based treatment guidelines for management of cancer pain in pregnancy as well as limited expertise in pain management for these patients (10,16-20). Many pain management teams decline to manage pregnant women for pain and refer them back to the obstetricians (10,21). Currently, there are limited studies on pain management in pregnancy due to the lack of ethical approval to conduct studies among pregnant subjects who are considered a vulnerable population (22,23). Existing studies are mainly literature reviews and many focus on pharmacological approaches to pain management rather than a broader scope of how to approach pain syndromes in pregnancy (10,24).

Therefore, in this review article we describe the challenges of managing cancer pain in pregnant woman and the current approach of opioids management for cancer pain in these patients using a case report.

Case description

The patient was a 33-year-old female with a diagnosis of metastatic embryonal rhabdomyosarcoma for a period of 8 months prior to referral to palliative care consultation (PC). She had metastasis to the lungs and liver. She was also a primigravida at 23 weeks of gestation. She initially presented to PC with a 6-month history of a progressive thigh mass with a fungating wound. She had over 60 days' history of pain on the left thigh which she rated as 10 on the 0/10 numerical pain scale (0= no pain, and 10= worst possible pain). The pain was dull in nature, non-radiating, associated with sensation of pins and needles. It was worse at night and during wound dressings. In addition to pain, she had 30-day history of associated dyspnea on exertion that was progressively worsening with time. At the time of referral to palliative care service she rated her symptoms on Edmonton Symptom Assessment Scale (ESAS) (25) as 10/10 for pain, 8/10 for fatigue, 9/10 for depression, 9/10 for anxiety, 6/10 for dyspnea, 10/10 for feeling of wellbeing and 10/10 for sleep. At the time of the initial PC she was treated with acetaminophen 1 g every 8 hours for the management of pain.

Prior to the diagnosis of the rhabdomyosarcoma, she had been attending her ante-natal clinics, and did not report to have any comorbidities. She had been married for 2 years. Her husband worked as a casual laborer while she was a homemaker. They lived in one of the largest slums in Nairobi, Kenya and they had social insurance.

On examination during the review by the palliative care team, her vital signs were within normal range. Her Eastern Cooperative Oncology Group score was 3. Local examination revealed a large fungating wound that was friable and bleeding easily. On examination she had normal breath sounds with no crepitations nor rhonchi. On abdominal examination she had a fundal height of 20 weeks.

Baseline investigations were done including a total blood count, renal function tests, liver function tests. These tests were normal except for a normocytic normochromic anemia with a hemoglobin level of 7.0 g/dL. An abdominal/pelvic ultrasound revealed normal intrauterine gestation at 22 weeks. A shielded high resolution computed tomography scan chest revealed multiple modular lesions more on left side with bilateral small pleural effusions.

Histology from a biopsy of the thigh mass revealed an undifferentiated embryonal rhabdomyosarcoma. The patient's goals of care were pain relief and treatment of illness with a hope of carrying pregnancy to term despite obstetricians recommending termination of pregnancy.

At the initial consultation visit the PC team commenced morphine syrup, immediate release orally at 10 mg every 4 hours with double the dose at night. She continued on oral acetaminophen and amitriptyline 25 mg was added at night. An additional oral morphine dose was also recommended 30 minutes prior to wound dressing. After 72 hours on these interventions, she reported improvement in symptoms on the ESAS as follows 3/10 for pain, 5/10 for fatigue, 6/10 for depression, 6/10 for anxiety, 4/10 for dyspnea, 5/10 for feeling of wellbeing and 3/10 for sleep resulting in improvement in distress in patient and their family. The oncology team was able to go ahead with cancer treatment plan due to improved symptoms. She was started on the first cycle of chemotherapy with vincristine, actinomycin D, cyclophosphamide (VAC) and then discharged home. After discharge, patient did not follow up with the PC team. At home, the patient's condition worsened, and she underwent an emergency caesarian delivery. At birth, the neonate had a birth weight of 900 g and was born at 28 weeks. She was managed for 4 months in the neonatal unit. During the stay at the neonatal intensive care unit (ICU), she was started on morphine after delivery that was weaned off over time. The neonate was discharged home after attaining a weight of 1.8 kg. The patient however succumbed to her illness 1 week after delivery.

Cancer in pregnancy

Many signs and symptoms of cancer overlap with

physiological changes that occur in pregnancy and are often missed during routine clinic visits. Therefore, pregnant women with cancer report that their symptoms were mistaken for those of pregnancy and diagnosis is often delayed (1). Making a diagnosis and staging of cancer in pregnancy is also challenging (1,8). There are valid concerns about exposure to the fetus to ionizing radiation, radiological contrasts, surgical or anesthetic procedures leading to further delays in investigating suspicious symptoms (26). Intrauterine exposure to ionizing radiation, whether for diagnosis or treatment is associated with teratogenicity, growth retardation, intellectual disability or death (27). Non-radioactive imaging modalities such as magnetic resonance imaging or ultrasound are favored in pregnancy but are not often the best in cancer diagnosis or staging (28). Gadolinium which is a routinely used imaging contrast cross the placental barrier and has been found to be teratogenic in animal studies. It is therefore not recommended in imaging for pregnant women (1). Serum tumor markers are not very useful in monitoring treatment for pregnant women. They lack specificity as some of them such as cancer antigen 125 (CA125), cancer antigen 15-3 (CA15-3) and alpha fetoprotein (AFP) levels are increased in pregnancy (1).

Cancer treatment is very difficult during pregnancy as many options pose great risks to the fetus (1). Concerns about exposure of the fetus to anesthetic agents makes surgeon hesitant to offer interventions during pregnancy (28). Radiotherapy is not routinely recommended since high doses are often needed for cancer treatment (1,8). High doses are lethal to the fetus and radiotherapy is often deferred until after delivery (1).

Most chemotherapeutic agents have low molecular weight and can cross the placental barrier. Exposure to chemotherapy in the first 2 weeks of pregnancy causes spontaneous abortions. Nearly all chemotherapeutic agents have found to be teratogenic in animal studies (1). Major congenital anomalies are expected when chemotherapy is administered in the first trimester. Studies have found chemotherapy to be relatively safer in the second and third trimesters (1).

Cancer pain in pregnancy

Chronic pain in pregnancy is common with the most reported cases being of migraines, lower back pain, delivery associated pains and cancer pain (in pregnant women with cancer) (10). Chronic, severe pain that is not adequately treated is associated with hypertension, anxiety, and depression—none of which is conducive to a healthy pregnancy (29). Chronic pain in pregnancy is hard to manage due to limited data on reproductive safety of many pharmacological agents except acetaminophen (23). Many existing guidelines on pain management are also focused on cancer pain management and chronic non-cancer pain but none for cancer pain in pregnancy (10). There is generally lack of guidelines on treatment of cancer pain in pregnancy and the complex physiologic and pharmacologic changes in pregnancy make it difficult to manage pain (30).

Pregnant women with cancer pain experience "total pain" just like other cancer patients. "Total pain" is a phenomenon first described by Dr. Cecily Saunders in the 1960s. Pain is not just physical but also has an emotional aspect to it. Pain is thought to be an interplay of psychological, cognitive, social, spiritual and cultural factors (31). Pain management in palliative care, therefore not only focuses on the physical aspects of pain but on the other domains of illness as well.

Physiologic changes in pregnancy influence choice of analgesia. Many of these changes alter drug absorption. Gastro-intestinal motility is often slowed and can lead to delayed onset of controlled release medication (22,30). Orally administered drugs may have increased absorption due to prolonged gastric emptying while emesis and esophageal reflux reduce absorption of orally administered medication (30).

Some medication such as opioids cross the placental barrier and some metabolites bind to fetal proteins (32). The drugs are sometimes metabolized to active compounds that affect the fetus (32). Opioid exposure to the fetus has been associated with neonatal abstinence syndrome (NAS) where the neonates have an opioid withdrawal syndrome after birth (23,30,32,33). Many studies that have been done on opioid safety in pregnancy have been among women using methadone to treat heroin addiction (22,30,32). In a recent Quebec Pregnancy Cohort study, codeine is the most prescribed opioid (70%). Other frequently used opioids during pregnancy were hydromorphone, morphine, tramadol, methadone, and oxycodone (15,34). Buprenorphine and methadone have been used to treat addiction even among pregnant women (35). Methadone is an effective opioid analgesic but use in pregnancy remains only for cases of addiction to heroin or opioids (30,32). It has been used in few cases to manage pain in pregnancy. Methadone when used as an analgesic was found to have less intrauterine growth retardation but more neonatal morbidity and preterm births compared

to women with opioid use disorder (10). Some pregnant women have had opioids prescribed for pain management though it is not a common practice (23). A population-based study was conducted in Sweden between 2007 and 2013 where multiple observational design studies were done to evaluate the consequences of prescribed opioids in the prenatal period (23). This study found that infants exposed to prescription opioids at any time of pregnancy were at increased risk of pre-term births with higher risks to those exposed in multiple trimesters. Therefore, fetal exposure remains the highest concern with use of opioid analgesics in managing pain in pregnancy (23,30,32,36).

The World Health Organization and cancer organizations has recommended the use of morphine for managing severe cancer pain and it has proven effective over many decades. Many patients with cancer pain suffer from severe pain that needs round the clock medication with morphine syrup being the mainstay analgesic for LMICs (16). Opioids remain the mainstay for management of severe pain in pregnancy in many conditions including cancer and painful crises associated with sickle cell disease (37). However, the current opioid crisis has made severe pain management in pregnancy using opioids a challenging endeavor (38).

The Canadian guidelines for opioid use in pregnancy have recommended that opioids should be tapered and discontinued in pregnancy or prescribed at the lowest possible effective dose; codeine should be avoided in the post-partum period and can only be used for up to 4 days; women should be managed by perinatologists; women with opioid use disorder should be referred for appropriate management (10,24,39).

Cancer pain management in pregnancy

Pain assessment

Pain should be assessed holistically with a focus not just on the physical but the other aspects of pain—psychological, social, and spiritual. Obstetric assessment is important to determine the pregnancy history, physical examination, pre-existing chronic pain and illnesses, current treatments, and pregnancy viability.

Oncologic assessment should be carried out to determine the definitive diagnosis, immunohistochemistry, proposed treatment, side effects of proposed treatment on the pregnant woman and the fetus. A birth plan should be discussed between the pain management, obstetric and oncology team. Where possible, pregnancy should be carried to term and the infant managed for any consequences of oncologic or pain management such as NAS.

Assessment of non-medical opioid use and opioid use disorder

Prior to opioid prescription, all pregnant women should be assessed for pre-existing use of alcohol, illicit drugs, and non-prescription opioids. The risk for addiction, overdose and abuse of prescription medications should be determined and the necessary support should be provided.

Establish treatment goals

Discuss and plan with the patient their goals of pain treatment with patient family in collaboration with the oncologist, obstetrician, and interdisciplinary team. Set realistic objectives and help the patient to understand the treatment choice, possible side effects and overall pain management plan. The patient should understand that the choice of analgesia is meant to minimize in-utero exposure while maximizing obstetrical and fetal health. The goal of pain management is not only to improve the quality of life of the pregnant patient but also to prolong the gestational period.

Opioids for pain management

Opioids are appropriately indicated in acute pain (17). For women, including pregnant women, with an opioid use disorder, opioid agonist pharmacotherapy is the recommended therapy (18,40). For chronic pain, practice goals include strategies to avoid or minimize the use of opioids for pain management, highlighting alternative pain therapies such as nonpharmacologic (e.g., exercise, physical therapy, behavioral approaches) and nonopioid pharmacologic treatments (21,22,41).

Common opioids (*Table 1*) that may be used to treat cancer pain include morphine, fentanyl, hydromorphone, hydrocodone, oxycodone, codeine, and tramadol as they are relatively safe at low doses (22,29). In pregnant woman with opioid use disorder, use of methadone or buprenorphine are safe and can reduce the risk of pregnancy complications (18,42). These opioids allow the mother-to-be to focus on prenatal care and her opioid use disorder treatment and recovery program.

The safety of opioids has been evaluated in several observational studies, case control studies. However,

Table 1 Opioids use in pregnant woman with cancer

Opioid	Mechanism/initial dose (route) and onset, duration	Pregnancies related changes in pharmacology	Fetal effects	Comments
Morphine	Phenanthrene, μ agonist/5–15 mg (PO), 30 min, 4 h; 2–3 mg (IV), 4 h	Dose reduction should be considered as compared to non-pregnant cancer patients as pregnancy results in increased bioavailability of morphine due to change in absorption, reduced protein binding, and increased in hepatic enzyme activity	Category C*; prenatal fetal exposure of opioids is associated with NAS. NAS is a set of drug withdrawal symptoms that can affect the central nervous system, gastrointestinal and respiratory systems in the newborn	Renal dysfunction results in accumulation of morphine-3-glucuronide can cause neurotoxicity American Academy of Pediatrics classifies morphine as usually compatible with breastfeeding
Hydromorphone	Phenanthrene, μ agonist/1–3 mg (PO), 30 min, 4 h; 0.5–1.5 mg (IV), 4 h	Same as morphine	Same as morphine; Category C*	Renal dysfunction results in accumulation of hydromorphine-3-glucuronide can cause neurotoxicity Breast feeding in lactating woman on hydromorphone is safe
Oxycodone	Phenanthrene, μ agonist/5–10 mg (PO), 30 min, 3–4 h	Same as morphine	Same as morphine; Category C*	–
Oxymorphone	μ agonist/5–10 mg (PO), 30 min, 4 h	Same as morphine	Same as morphine; Category C*	–
Hydrocodone	μ agonist/5–10 mg (PO), 30 min, 3–4 h	Same as morphine	Same as morphine; Category C*	–
Tramadol	4-phenyl-piperidine analogue of codeine, μ agonist, inhibits reuptake of norepinephrine and serotonin/50 mg (PO), 30 min, 4 h	Same as morphine	Same as morphine; Category C*	–
Codeine	Phenanthrene, same as morphine/Category C*; 30–60 mg (PO), 30 min, 3 h	Same as morphine Metabolized to morphine by P50 enzyme cytochrome CYP 2D6 Risk for post-partum hemorrhage	Same as morphine; Category C*	Increased risk of nausea in ultra-rapid metabolizer
Fentanyl	Phenylpiperidine, same as morphine/Category C*; 12–25 μg (TD), 48–72 h Transdermal preparation: dose reduction would be necessary as compared to non- pregnant patients due to increased absorption subcutaneously and decrease in maternal albumin	Same as morphine	Same as morphine; Category C*	Due to low bioavailability, some literature suggests fentanyl has fetal NAS lowest among opioids and hence relatively safe
Methadone	Diphenyl heptane, opioid agonist, NMDA receptor antagonist, weak serotonin reuptake inhibitor/2.5–10 mg (PO), >8 h; 2.5–5 mg (IV)	Same as morphine	Same as morphine; Category C*	QT-prolongation—especially with other QT-prolonging drugs Challenging conversion
Buprenorphine	Partial μ agonist making overdose less likely in pregnant woman with opioid use disorder/2–4 mg (SL). Transdermal preparation/5–7.5 μg/h, 7 days: dose reduction would be necessary as compared to non-pregnant patients due to increased absorption subcutaneously	Same as morphine	Same as morphine; Category C*	Use of buprenorphine and methadone may have higher safety for pregnant cancer patients with history of opioid use disorder

*, short-term use. FDA classification system for fetal risk Category C: teratogenic or embryocidal risk indicated in animal studies, but controlled studies in women have not been done or there are no controlled studies in animals or humans. Opioid abuse as well as use of chronic opioids during pregnancy is associated with NAS. Chronic, high dose is associated with FDA Category D designation (positive evidence of fetal risk but use in pregnant woman is acceptable since the maternal benefit outweighs the risk to the fetus). Breast feeding for cancer patients may be generally safe similar to non-cancer lactating women. However always monitor for respiratory depression. FDA, Food and Drug Administration; IV, intravenous; NAS, neonatal abstinence syndrome; NMDA, N-methyl-D-aspartate; PO, oral; SL, sublingual; TD, transdermal.

prenatal, fetal safety of opioid exposure during pregnancy is not fully understood because clinical trials typically exclude pregnant woman due to ethical reasons (22,29). There are no published studies in specifically for cancer pain in pregnant woman (32,43). The main concerns of opioid use during pregnancy include poor fetal growth, preterm birth, birth defects, and NAS (32). An association between first trimester use of codeine and congenital abnormalities has been found in some studies but not in others (44,45). A study from first nations population in northwestern Ontario found association between preterm births and maternal oxycodone use (46). In US Collaborative Perinatal Project found no increased teratogenic effects with the use of morphine in pregnant woman (n=448) (47). Similarly, in a Michigan Medicaid study found no significant increased risk of major birth defects with the use of opioids such as hydrocodone, oxycodone or codeine in the first trimester, NAS after birth in neonates is common in opioid exposed pregnant woman (32,48). In a population based National Birth Defects Prevention Study, of the 17,499 mothers with birth defects, 454 (2.6%) reported opioid use. There was a positive association between maternal opioid use and congenital heart disease, spina-bifida or gastroschisis in infants (46).

Therefore, due to the limited studies on the safety of use of opioid in pregnancy and need to effectively manage severe cancer pain, it may be important to prescribe the lowest effective dose and quantity of opioids after taking into consideration the risk/benefit to patient-infant dyad. Infants born to woman who used opioids for pain should be monitored for NAS by a pediatric provider (21). Pregnancy should not be a reason to avoid treating acute pain because of concern for opioid misuse or NAS (21,49). In pregnant women with opioid use disorder, opioid use is recommended to avoid risk for relapse, withdrawal, and worse outcomes (18). Breast feeding should be encouraged in woman on stable doses of opioid agonist (18).

Like the management of patients with chronic pain with opioids, management for cancer pain in pregnant women can be more complex and challenging, especially in Kenya or other LMICs. These challenges can be many but as seen in our patient in the case report it may be the consequences of limited monitoring due to lack of or limited follow up especially due to natural calamities such as coronavirus disease 2019 (COVID-19) pandemic. This also further complicates the gestational care and increases the risk for NAS. Further studies are needed to develop strategies to avoid these important challenges in use of opioids in pregnancy especially in LMICs.

Adjuvant analgesics

Acetaminophen has been found to be safe in all stages in the pregnancy at standard doses without increase in the risk for congenital defects and other major outcomes. Low-dose aspirin is relatively safe. Aspirin may potentially inhibit platelet function and may contribute to maternal and fetal bleeding. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, ketorolac are safe in first trimester but should be avoided in the third trimester as its use is associated with increased risk of premature ductal closure and bleeding (21,50,51).

Nonpharmacological management

Nonpharmacological management for pain is frequently considered in pregnant women. The non-pharmacological interventions which were studied include cognitive behavioral therapy (CBT), biofeedback, mind body practices such as yoga, meditation, mindfulness stress reduction practices (52-54), acupuncture (55-57), exercise and physical therapy (58,59), massage (60,61), hydrotherapy (62,63), osteopathic and spinal manipulation, transcutaneous nerve stimulation (64-67). Caution should be taken to ensure these procedures do not affect the stimulation of cervix or uterus. The strength of evidence regards to use for cancer pain is unclear as there are no published studies using these interventions for cancer pain in pregnant woman.

Cognitive behavioral therapy

CBT is an effective, non-pharmacological treatment for chronic pain (68). CBT aims to improve the coping skills of the patients via pain education, relaxation, activity pacing, cognitive restructuring, self-care, interpersonal skills (patient-clinician communication). There are limited or no studies of effectiveness of chronic management in pregnant woman especially those with cancer pain. A recent preliminary study found that 8-week CBT intervention with shared decision-making improved average prescription opioid morphine equivalent dose, prescription opioid misuse, worst pain ratings, and pain interference in general activity and at work among pregnant women misusing prescription opioids (69).

Physical activity

In systematic review describing the effects of physical

activity (exercise) is to treat pain in pregnancy found all studies showed significant reduction of pain levels among intervention participants at postintervention, thereby suggesting a positive effect of the reported interventions on alleviation of pregnancy-related pain, including low back pain and lumbopelvic pain (70). Prior studies found that moderate-intensity exercise from early to late pregnancy is not associated with preterm delivery and it does not affect the birth weight of the newborn (71,72).

Yoga is a multimodal physical activity intervention which involves stretching, core strengthening, balance training, mindfulness, acceptance, and self-compassion. It is one of the frequent complementary and alternative medicine (CAM) interventions in pregnant women (73). There are limited controlled studies showing effectiveness of yoga for chronic pain in pregnancy despite its efficacy in general population (74-76).

Acupuncture an important CAM intervention which involves inserting fine needles into acupoints along the meridian (77). Prior studies found that acupuncture significantly improved pain, functional status and quality of life in women during the pregnancy (56,77). No observable severe adverse influences on the newborns. Further studies are required (78). Detailed review of non-pharmacological management is beyond the scope of this article.

Neonatal abstinence syndrome

For patients with cancer during pregnancy on opioids for cancer pain, it is essential to develop a management plan for delivery and neonatal care with the obstetricians and neonatologists. Pain management must continue during labor and in the post-natal period. NAS is a drug withdrawal syndrome that opioid exposed neonates experience shortly after birth (79,80). NAS often presents with neurological, gastrointestinal or autonomic symptoms (81). Neurological symptoms include tremors, irritability, increased muscle tone, frequent yawning, sneezing or seizures. Gastrointestinal dysfunction presents with feeding difficulties, vomiting, uncoordinated sucking, vomiting, diarrhea and poor weight gain. Autonomic symptoms include diaphoresis, nasal stiffness, fever, and temperature instability. The neonates must be managed for NAS in the acute neonatal ICU (80). Several scoring systems have been developed to guide treatment of NAS (82-84). Management of NAS involves non-pharmacological care (85), as well as pharmacological therapy (49,80,86-88). Non-pharmacological interventions may include environmental modifications such as reducing stimulation (85,89). First-line pharmacological treatment is morphine (80,90). Other opioids that have been used for NAS include methadone and buprenorphine (80,88,89). Adjunctive pharmacologic agents are required for infants who fail to respond to the first-line medication. Common adjunctive therapies include phenobarbital and clonidine (80,89).

Conclusions

Pregnant patients with cancer pain need comprehensive assessment that involves an interdisciplinary team to determine the characteristics of pain, factors related to pain including symptoms such as depression; viability of pregnancy; cancer treatment plan; delivery plan, and postnatal care for the neonate who may develop NAS. Pregnant patients with cancer pain need to be managed by multi-disciplinary team for optimal care of the patient-infant dyad during pregnancy, and after birth. Nonpharmacological strategies should always be considered first if possible. Multimodal analgesia including opioids such as morphine may be considered. NAS should be anticipated after delivery and carefully managed in intensive care, if possible. There is a need for further research in pain management in pregnancy.

Acknowledgments

Funding: None.

Footnote

Peer Review File: Available at https://apm.amegroups.com/article/view/10.21037/apm-23-74/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-23-74/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Hepner A, Negrini D, Hase EA, et al. Cancer During Pregnancy: The Oncologist Overview. World J Oncol 2019;10:28-34.
2. Stensheim H, Møller B, van Dijk T, et al. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. J Clin Oncol 2009;27:45-51.
3. Wolters V, Heimovaara J, Maggen C, et al. Management of pregnancy in women with cancer. Int J Gynecol Cancer 2021;31:314-22.
4. Dalmartello M, Negri E, La Vecchia C, et al. Frequency of Pregnancy-Associated Cancer: A Systematic Review of Population-Based Studies. Cancers (Basel) 2020;12:1356.
5. Skrzypczyk-Ostaszewicz A, Rubach M. Gynaecological cancers coexisting with pregnancy - a literature review. Contemp Oncol (Pozn) 2016;20:193-8.
6. Pavlidis NA. Coexistence of pregnancy and malignancy. Oncologist 2002;7:279-87.
7. Amant F, Verheecke M, Wlodarska I, et al. Presymptomatic Identification of Cancers in Pregnant Women During Noninvasive Prenatal Testing. JAMA Oncol 2015;1:814-9.
8. Kalampokas E, Vlahos N, Kalampokas T, et al. Common Malignancies During Pregnancy: A Comprehensive Review. Cancer Diagn Progn 2021;1:103-9.
9. Van Calsteren K, Heyns L, De Smet F, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. J Clin Oncol 2010;28:683-9.
10. Ray-Griffith SL, Wendel MP, Stowe ZN, et al. Chronic pain during pregnancy: a review of the literature. Int J Womens Health 2018;10:153-64.
11. Interrante JD, Scroggs SLP, Hogue CJ, et al. Prescription opioid use during pregnancy and risk for preterm birth or term low birthweight. J Opioid Manag 2021;17:215-25.
12. Corsi DJ, Hsu H, Fell DB, et al. Association of Maternal Opioid Use in Pregnancy With Adverse Perinatal Outcomes in Ontario, Canada, From 2012 to 2018. JAMA Netw Open 2020;3:e208256.
13. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, et al. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. J Pain Symptom Manage 2016;51:1070-1090.e9.
14. Cleeland CS. The impact of pain on the patient with cancer. Cancer 1984;54:2635-41.
15. Zhao JP, Berthod C, Sheehy O, et al. Prevalence and duration of prescribed opioid use during pregnancy: a cohort study from the Quebec Pregnancy Cohort. BMC Pregnancy Childbirth 2021;21:800.
16. Paice JA, Bohlke K, Barton D, et al. Use of Opioids for Adults With Pain From Cancer or Cancer Treatment: ASCO Guideline. J Clin Oncol 2023;41:914-30.
17. Dowell D, Ragan KR, Jones CM, et al. CDC Clinical Practice Guideline for Prescribing Opioids for Pain - United States, 2022. MMWR Recomm Rep 2022;71:1-95.
18. Committee on Obstetric Practice ASoAM. Opioid Use and Opioid Use Disorder in Pregnancy 2017. Available online: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/08/opioid-use-and-opioid-use-disorder-in-pregnancy
19. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. J Addict Med 2015;9:358-67.
20. Medicine ASoA. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Treatment of Opioid Use Disorder [cited 2020]. Available online: https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline
21. Shah S, Banh ET, Koury K, et al. Pain Management in Pregnancy: Multimodal Approaches. Pain Res Treat 2015;2015:987483.
22. Black E, Khor KE, Kennedy D, et al. Medication Use and Pain Management in Pregnancy: A Critical Review. Pain Pract 2019;19:875-99.
23. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 2015;162:276-86.
24. Busse JW, Craigie S, Juurlink DN, et al. Guideline for opioid therapy and chronic noncancer pain. CMAJ 2017;189:E659-66.
25. Bruera E, Kuehn N, Miller MJ, et al. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 1991;7:6-9.
26. de Haan J, Vandecaveye V, Han SN, et al. Difficulties with

diagnosis of malignancies in pregnancy. Best Pract Res Clin Obstet Gynaecol 2016;33:19-32.
27. Streffer C, Shore R, Konermann G, et al. Biological effects after prenatal irradiation (embryo and fetus). A report of the International Commission on Radiological Protection. Ann ICRP 2003;33:5-206.
28. Andersson TM, Johansson AL, Fredriksson I, et al. Cancer during pregnancy and the postpartum period: A population-based study. Cancer 2015;121:2072-7.
29. Babb M, Koren G, Einarson A. Treating pain during pregnancy. Can Fam Physician 2010;56:25, 27.
30. Wunsch MJ, Stanard V, Schnoll SH. Treatment of pain in pregnancy. Clin J Pain 2003;19:148-55.
31. Gomes-Ferraz CA, Rezende G, Fagundes AA, et al. Assessment of total pain in people in oncologic palliative care: integrative literature review. Palliat Care Soc Pract 2022;16:26323524221125244.
32. Yazdy MM, Desai RJ, Brogly SB. Prescription Opioids in Pregnancy and Birth Outcomes: A Review of the Literature. J Pediatr Genet 2015;4:56-70.
33. Reddy UM, Davis JM, Ren Z, et al. Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes: Executive Summary of a Joint Workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation. Obstet Gynecol 2017;130:10-28.
34. Esposito DB, Huybrechts KF, Werler MM, et al. Characteristics of Prescription Opioid Analgesics in Pregnancy and Risk of Neonatal Opioid Withdrawal Syndrome in Newborns. JAMA Netw Open 2022;5:e2228588.
35. Meyer MC, Johnston AM, Crocker AM, et al. Methadone and buprenorphine for opioid dependence during pregnancy: a retrospective cohort study. J Addict Med 2015;9:81-6.
36. Wang X, Wang Y, Tang B, et al. Opioid exposure during pregnancy and the risk of congenital malformation: a meta-analysis of cohort studies. BMC Pregnancy Childbirth 2022;22:401.
37. Krčevski Škvarč N, Morlion B, Vowles KE, et al. European clinical practice recommendations on opioids for chronic noncancer pain - Part 2: Special situations. Eur J Pain 2021;25:969-85.
38. Fiat F, Merghes PE, Scurtu AD, et al. The Main Changes in Pregnancy-Therapeutic Approach to Musculoskeletal Pain. Medicina (Kaunas) 2022;58:1115.
39. Kahan M, Wilson L, Mailis-Gagnon A, et al. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 2: special populations. Can Fam Physician 2011;57:1269-76, e419-28.
40. Zipursky J, Juurlink DN. Opioid use in pregnancy: An emerging health crisis. Obstet Med 2021;14:211-9.
41. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. JAMA 2018;320:2448-60.
42. Minozzi S, Amato L, Jahanfar S, et al. Maintenance agonist treatments for opiate-dependent pregnant women. Cochrane Database Syst Rev 2020;11:CD006318.
43. Stanhope TJ, Gill LA, Rose C. Chronic opioid use during pregnancy: maternal and fetal implications. Clin Perinatol 2013;40:337-50.
44. Broussard CS, Rasmussen SA, Reefhuis J, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011;204:314.e1-11.
45. Nezvalová-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. Eur J Clin Pharmacol 2011;67:1253-61.
46. Kelly L, Dooley J, Cromarty H, et al. Narcotic-exposed neonates in a First Nations population in northwestern Ontario: incidence and implications. Can Fam Physician 2011;57:e441-7.
47. Klebanoff MA. The Collaborative Perinatal Project: a 50-year retrospective. Paediatr Perinat Epidemiol 2009;23:2-8.
48. Desai RJ, Hernandez-Diaz S, Bateman BT, et al. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. Obstet Gynecol 2014;123:997-1002.
49. Zankl A, Martin J, Davey JG, et al. Opioid treatment for opioid withdrawal in newborn infants. Cochrane Database Syst Rev 2021;7:CD002059.
50. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA recommends avoiding use of NSAIDs in pregnancy at 20 weeks or later because they can result in low amniotic fluid: NSAIDs may cause rare kidney problems in unborn babies. Published October 15, 2020. Available online: https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-avoiding-use-nsaids-pregnancy-20-weeks-or-later-because-they-can-result-low-amniotic#:~:text=NSAIDs%20are%20commonly%20used%20to,low%20levels%20of%20this%20fluid (accessed on June 1, 2023).

51. Bloor M, Paech M. Nonsteroidal anti-inflammatory drugs during pregnancy and the initiation of lactation. Anesth Analg 2013;116:1063-75.
52. Dhillon A, Sparkes E, Duarte RV. Mindfulness-Based Interventions During Pregnancy: a Systematic Review and Meta-analysis. Mindfulness (N Y) 2017;8:1421-37.
53. Babbar S, Oyarzabal AJ, Oyarzabal EA. Meditation and Mindfulness in Pregnancy and Postpartum: A Review of the Evidence. Clin Obstet Gynecol 2021;64:661-82.
54. Schell LK, Monsef I, Wöckel A, et al. Mindfulness-based stress reduction for women diagnosed with breast cancer. Cochrane Database Syst Rev 2019;3:CD011518.
55. Soliday E, Betts D. Treating Pain in Pregnancy with Acupuncture: Observational Study Results from a Free Clinic in New Zealand. J Acupunct Meridian Stud 2018;11:25-30.
56. Yang J, Wang Y, Xu J, et al. Acupuncture for low back and/or pelvic pain during pregnancy: a systematic review and meta-analysis of randomised controlled trials. BMJ Open 2022;12:e056878.
57. Fang J, Balica A. Acupuncture as Treatment for Pelvic Girdle Pain in Pregnancy: A Literature Review [A282]. Obstetrics & Gynecology 2022;139:81S.
58. Stuge B, Hilde G, Vøllestad N. Physical therapy for pregnancy-related low back and pelvic pain: a systematic review. Acta Obstet Gynecol Scand 2003;82:983-90.
59. Kinser PA, Pauli J, Jallo N, et al. Physical Activity and Yoga-Based Approaches for Pregnancy-Related Low Back and Pelvic Pain. J Obstet Gynecol Neonatal Nurs 2017;46:334-46.
60. Mueller SM, Grunwald M. Effects, Side Effects and Contraindications of Relaxation Massage during Pregnancy: A Systematic Review of Randomized Controlled Trials. J Clin Med 2021;10:3485.
61. Field T, Figueiredo B, Hernandez-Reif M, et al. Massage therapy reduces pain in pregnant women, alleviates prenatal depression in both parents and improves their relationships. J Bodyw Mov Ther 2008;12:146-50.
62. Carrascosa MDC, Navas A, Artigues C, et al. Effect of aerobic water exercise during pregnancy on epidural use and pain: A multi-centre, randomised, controlled trial. Midwifery 2021;103:103105.
63. Peng MS, Wang R, Wang YZ, et al. Efficacy of Therapeutic Aquatic Exercise vs Physical Therapy Modalities for Patients With Chronic Low Back Pain: A Randomized Clinical Trial. JAMA Netw Open 2022;5:e2142069.
64. Pennick VE, Young G. Interventions for preventing and treating pelvic and back pain in pregnancy. Cochrane Database Syst Rev 2007;(2):CD001139.
65. Close C, Sinclair M, Liddle SD, et al. A systematic review investigating the effectiveness of Complementary and Alternative Medicine (CAM) for the management of low back and/or pelvic pain (LBPP) in pregnancy. J Adv Nurs 2014;70:1702-16.
66. Keskin EA, Onur O, Keskin HL, et al. Transcutaneous electrical nerve stimulation improves low back pain during pregnancy. Gynecol Obstet Invest 2012;74:76-83.
67. Koukoulithras I Sr, Stamouli A, Kolokotsios S, et al. The Effectiveness of Non-Pharmaceutical Interventions Upon Pregnancy-Related Low Back Pain: A Systematic Review and Meta-Analysis. Cureus 2021;13:e13011.
68. Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. Pain 1999;80:1-13.
69. Shapiro M, Sujan AC, Guille C. A Clinical Trial of a Program for Pain Management and Opioid Reduction During Pregnancy. Reprod Sci 2022;29:606-13.
70. Chan CWH, Au Yeung E, Law BMH. Effectiveness of Physical Activity Interventions on Pregnancy-Related Outcomes among Pregnant Women: A Systematic Review. Int J Environ Res Public Health 2019;16:1840.
71. Barakat R, Pelaez M, Montejo R, et al. Exercise throughout pregnancy does not cause preterm delivery: a randomized, controlled trial. J Phys Act Health 2014;11:1012-7.
72. Haakstad LA, Bø K. Exercise in pregnant women and birth weight: a randomized controlled trial. BMC Pregnancy Childbirth 2011;11:66.
73. Holden SC, Gardiner P, Birdee G, et al. Complementary and Alternative Medicine Use Among Women During Pregnancy and Childbearing Years. Birth 2015;42:261-9.
74. Holden SC, Manor B, Zhou J, et al. Prenatal Yoga for Back Pain, Balance, and Maternal Wellness: A Randomized, Controlled Pilot Study. Glob Adv Health Med 2019;8:2164956119870984.
75. Jeter PE, Nkodo AF, Moonaz SH, et al. A systematic review of yoga for balance in a healthy population. J Altern Complement Med 2014;20:221-32.
76. Martins RF, Pinto e Silva JL. Treatment of pregnancy-related lumbar and pelvic girdle pain by the yoga method: a randomized controlled study. J Altern Complement Med 2014;20:24-31.
77. Elden H, Fagevik-Olsen M, Ostgaard HC, et al. Acupuncture as an adjunct to standard treatment for

pelvic girdle pain in pregnant women: randomised double-blinded controlled trial comparing acupuncture with non-penetrating sham acupuncture. BJOG 2008;115:1655-68.
78. Maia LB, Amarante LG, Vitorino DFM, et al. Effectiveness of conservative therapy on pain, disability and quality of life for low back pain in pregnancy: A systematic review of randomized controlled trials. Braz J Phys Ther 2021;25:676-87.
79. Jansson LM, Patrick SW. Neonatal Abstinence Syndrome. Pediatr Clin North Am 2019;66:353-67.
80. Patrick SW, Barfield WD, Poindexter BB, et al. Neonatal Opioid Withdrawal Syndrome. Pediatrics 2020;146:e2020029074.
81. Hudak ML, Tan RC; , et al. Neonatal drug withdrawal. Pediatrics 2012;129:e540-60.
82. Finnegan LP, Kron RE, Connaughton JF, et al. Assessment and treatment of abstinence in the infant of the drug-dependent mother. Int J Clin Pharmacol Biopharm 1975;12:19-32.
83. Sarkar S, Donn SM. Management of neonatal abstinence syndrome in neonatal intensive care units: a national survey. J Perinatol 2006;26:15-7.
84. Grossman MR, Lipshaw MJ, Osborn RR, et al. A Novel Approach to Assessing Infants With Neonatal Abstinence Syndrome. Hosp Pediatr 2018;8:1-6.
85. Velez M, Jansson LM. The opioid dependent mother and newborn dyad: nonpharmacologic care. J Addict Med 2008;2:113-20.
86. McPherson C. Pharmacotherapy for Neonatal Abstinence Syndrome: Choosing the Right Opioid or No Opioid at All. Neonatal Netw 2016;35:314-20.
87. Frazier LM, Bobby LE, Gawronski KM. Emerging therapies for the treatment of neonatal abstinence syndrome. J Matern Fetal Neonatal Med 2022;35:987-95.
88. Cook CE, Fantasia HC. Interventions for the Treatment of Neonatal Abstinence Syndrome. Nurs Womens Health 2019;23:357-65.
89. Mangat AK, Schmölzer GM, Kraft WK. Pharmacological and non-pharmacological treatments for the Neonatal Abstinence Syndrome (NAS). Semin Fetal Neonatal Med 2019;24:133-41.
90. Tolia VN, Patrick SW, Bennett MM, et al. Increasing incidence of the neonatal abstinence syndrome in US neonatal ICUs. N Engl J Med 2015;372:2118-26.

Cite this article as: Nafula EW, Weru J, Yennurajalingam S. Management of cancer pain in pregnancy: can opioids be used? Ann Palliat Med 2023;12(5):925-935. doi: 10.21037/apm-23-74

