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Review Article

Management of Non-Obstetric Pain during Pregnancy: A Review

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ABSTRACT

Non-Obstetric pain during pregnancy is common and multifactorial. Its management is also complex and challenging. Inadequate treatment is associated with elevated blood pressure, anxiety, depression and can also negatively affect maternal satisfaction with the pregnancy. Management of non-obstetric pain requires a multidiscipline approach due to the risk of medications to the mother, fetus, and pregnancy course.

This review aims to understand the pathophysiology and various cause of non-obstetric pain during pregnancy. Furthermore, we will explore the available evidence for prevention and management. A literature search of PubMed, MEDLINE, Science Direct, and Google Scholar was done. The search results were limited to randomized controlled trials and systemic reviews. The papers are summarized in this review.

Keywords: Non-Obstetric pain; Pregnancy; Pathophysiology; Fetus

INTRODUCTION

Non-Obstetric pain during pregnancy is common and multifactorial. It may be due to the exacerbation of the preexisting pain or the hormonal, physiological and anatomical changes during pregnancy [1,2]. Treatment and management of pain during pregnancy are complex and challenging. The risk of medications to the mother, fetus, and the course of the pregnancy requires a multidiscipline approach. Inadequate treatment is associated with elevated blood pressure, anxiety, depression and also can encourage negatively on maternal satisfaction with pregnancy [3,4].

The reasons for pain during pregnancy are mainly due to pregnancy-related changes. However, other medical and surgical conditions may cause pain such as migraine, arthritis, urolithiasis and postoperative pain. About 2% of women need some surgery during pregnancy. Acute appendicitis and acute cholecystitis are the most common surgical conditions that require surgical intervention during pregnancy [5].

PREGNANCY-RELATED CAUSES

Pregnancy-related pain is a common complaint among pregnant women. It can present as either lumbar pain or pelvic girdle pain. The average incidence is about 25% to 90%. As per the literature during their pregnancies, about 50% of pregnant women will suffer from low back pain [6,7]. Exact etiologies is poorly understood but is thought to be due to multiple mechanical and hormonal changes during pregnancy [8-12].

Musculoskeletal changes are the normal adaptations that occur during pregnancy to accommodate the growing fetus. These changes include weight gain, anterior pelvic tilt, joint laxity, abdominal muscle stretching and displacement of the center of gravity. All these changes may induce pain during pregnancy.

To accommodate the enlarging uterus stretching of the abdominal muscles can cause muscle fatigue, weakness, and separation of abdominal muscles, ultimately putting more strain on paraspinal muscles. Due to excessive stretching, they also lose their ability to perform the function of maintaining body posture [12]. Exaggeration of lumbar lordosis causes stretching of the anterior longitudinal ligament, ultimately causing an alteration in posture during pregnancy. An increase in the pelvis' anterior tilt causes increased use of hip extensor abductors and ankle plantar flexors, making them more prone to hip and back pain. Stretching of the round ligaments due to the growing fetus causes lower abdominal pain [12-14].

During pregnancy, hormonal change causes connective tissue laxity, which leads to more significant joint laxity, especially at the pelvis [13,14]. This hormone also relaxes the lumbar spine's anterior and posterior longitudinal ligaments, which causes instability and misalignment of the pelvis and spine [15]. Relaxin is a hormone that is produced by both the corpus luteum and the uterine decidua. During pregnancy, its level increases by tenfold. Many studies have been done to correlate pelvic and back pain

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with increased relaxin levels, and they have shown mixed results [15-17]. These hormonal and anatomical changes cause pain in the pelvic joints and cause generalized discomfort and pain at the entire lower back [18].

Another theory is if the pregnant lady continues to lie down in the supine position, the growing uterus compresses the vena cave, causes venous engorgement in the pelvis, which ultimately causing pelvic and back pain [18,19].

NEUROPATHIC PAIN

Nerve trapping due to physiological changes, weight gain and fluid retention are common causes of discomfort during pregnancy [2]. Stretching of the anterior abdominal wall and abdominal distension due to the growing fetus can also cause the trapping of the intercostal, lower thoracic nerves, iliohypogastric, genitofemoral and lateral cutaneous nerve of the thigh. These changes ultimately can lead to intercostal neuralgia, discomfort in the upper abdomen, and pain in the groin and labia [20,21].

The entrapment of the lateral cutaneous nerve of the thigh causing pain in the lateral thigh, known as meralgiaparaesthetica [2,20,21].

CONSEQUENCES OF PAIN DURING PREGNANCY

Pain management during pregnancy has to be safe and effective. Inadequate pain relief is detrimental to maternal and fetal well-being. Ineffective treatment of pain during pregnancy is associated with maternal hypertension, anxiety, depression, chronic pain, and preterm labour. It also can affect the developing fetus leading to the IUGR and preterm birth of the infant [22,23]. Inadequate pain relief during pregnancy also restricts the mobility of the pregnant lady, which ultimately puts her at risk for deep vein thrombosis [22,23].

MANAGEMENT DURING PREGNANCY

The management of acute pain during pregnancy is always challenging due to the developing fetus. The major fetal problems during the treatment are teratogenicity, asphyxia and preterm birth. The basic principle of acute pain management during pregnancy is the maintenance of maternal-fetal homeostasis and the avoidance of analgesics having an unsafe effect on the developing fetus. During the first trimester of pregnancy, around 50%-80% of pregnant ladies use analgesics [24,25]. During this period of organogenesis and potential teratogenic risk, many clinical trials have raised concerns. Therefore, a pain management strategy should consider fetal and maternal factors while selecting medications.

The acute pain management of the pregnant patient with any pharmaco-therapeutic intervention must be individualized. The plan must consider the pregnancy stage, risk-benefit assessment for each drug for both the mother and fetus, teratogenicity (in early pregnancy) and potential for premature labour in the latter half of pregnancy. Many pain medications are considered relatively safe during pregnancy except the period of organogenesis (weeks 4-10 of gestation), and the time was just preceding delivery [26]. Non-pharmacological treatment options should be considered, wherever possible, before shifting to analgesics. Pharmacological management of acute pain should follow the step-ladder approach.

The United States Food and Drug Administration (FDA) have developed a five-category labelling system (A through D and X) for risk assessment from medication use in pregnancy (Table 1) [27].

Table 1: The FDA-assigned pregnancy risk classification categories [27,28].

FDA Pregnancy Categories	Definition
Category A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
Category C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Category D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Category X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

FDA's five-category labelling system (A through D and X) for risk assessment presents a challenge to all health care providers as it makes risk-benefit ratio assessment difficult. 60% of all medications assigned a pregnancy category fall into category C. To overcome the criticisms of the previous labelling system, "Pregnancy and Lactation Labeling Rule" (PLLR) was developed in 2015, and the implementation of this rule occurred in several stages. It is also called as "Pregnancy and Lactation Labeling Rule" (PLLR or final rule). This rule creates a consistent format for providing information about the risks and benefits of prescription drug and biological product use during pregnancy and lactation and by females and males of reproductive potential [29,30].

ACETAMINOPHEN

Acetaminophen is the most frequently used analgesics and antipyretics in pregnancy. It is considered one of the safest drugs, but some clinical trials have recently reported its adverse effects on the fetus. It has been reported [31-33] that acetaminophen exposure during 8-14 weeks of gestation affects fetal reproductive development, causes neurodevelopmental disorders, autism, asthma, allergic disease and lower performance intelligence quotient [34-36].

U.S. Food and Drug Administration (FDA) in 2015 reviewed possible risks of pain medication use during pregnancy. It concluded that the possible connection between acetaminophen use and ADHD in children, but the weight of evidence is inconclusive. At present, there is no alternative medication for Acetaminophen. It should only be used if benefits to the mother outweigh the risk to the fetus. It remains the analgesic of choice during pregnancy, but

it should not be taken unnecessarily.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDs such as ibuprofen, naproxen, indomethacin and diclofenac are commonly used during pregnancy. They act by inhibiting the synthesis of prostaglandins [37,38]. Prostaglandins play a crucial role in both maintaining and achieving pregnancy. Research on animal models has concluded that altering prostaglandins' levels have direct effects on conception, implantation, and maintenance of pregnancy [38]. NSAIDs cross the placenta easily and have a prolonged half-life in the fetus [39,40]. Many trials have shown that NSAID use in pregnancy has been associated with increased risks of various congenital malformations, including cardiovascular defects, oral clefts, and increased risk of spontaneous abortion [39-44]. Exposure to NSAIDs after 30 weeks of gestation has also been associated with oligohydramnios, an increased risk of premature ductusarteriosus closure [39,40]. Overall, the available data are limited and conflicting. However, knowing that the use of NSAIDs has been associated with the increased risk of congenital malformations and miscarriage, there use should be avoided during early pregnancy and in the last trimester.

OPIOIDS

Opioids provide an important option to treat moderate to severe acute pain during pregnancy. The FDA has classified opioids under category C. Over the years, opioid-usage has increased drastically during pregnancy. Opioids can cross placental and blood-brain barriers with the possibility of exposure of the developing fetus. Many animal and human studies have documented their relationship with congenital malformations such as neural tube defects and gastroschisis. It is also well evident now that with growing opioids use, there is a fivefold increase in neonatal abstinence syndrome [45-48].

Jennifer et al. [49] did a systematic review to study maternal use of opioids during pregnancy and congenital malformations. They had 68 studies in this review, seventeen of these studies documented statistically significant positive associations with oral clefts and ventricular septal defects/atrial septal defects and, clubfoot. They concluded that the teratogenicity of opioids is uncertain, and when considering their use for pain control, a careful assessment of risks and benefits is necessary.

Tramadol is a synthetic centrally acting atypical opioid and is used to treat somatic, visceral pain and neuropathic pain. Its analgesic effect is mediated through its modest affinity for -opioid receptors and also through inhibiting the reuptake of noradrenaline (NA) and serotonin (5-HT). It has pharmacologically active metabolites and is excreted by the kidney. When used in pregnancy, tramadol and its metabolites are transferred over the placenta [46,50-52]. There is limited data on the use of tramadol in the pregnancy. Available date from animal and human studies is conflicting and suggests a weak teratogenic effect when used in early pregnancy and neonatal abstinence syndrome when used in third trimester [50-52]. Bengt Källén et al., [51] did a retrospective trial to study tramadol use in early pregnancy and congenital malformation risk. They advocated a weak teratogenic effect of tramadol, specifically with cardiovascular defects and pesequinovarus.

Irene et al. [53] studied 64 parturients exposed to tramadol during pregnancy; they reported pregnancy loss due to spontaneous abortion in four patients. Four newborns had a congenital malformation, syndactyly and congenital ovarian cyst.

Overall there is limited information on the use of tramadol in the pregnancy. It has been suggested to avoid its use during early pregnancy, and if exposure has occurred, the absolute risk is small, and the malformations observed are not very serious.

GABAPENTINOIDS

Gabapentinoids are widely and increasingly used to treat pain in women of childbearing potential and are currently listed as a pregnancy Category C medication. It can transfer across the placenta to the fetus. Various animal studies have shown it to be toxic to fetuses in rodents, causing delayed ossification, bone defects, urinary tract defects, including hydro nephrosis [54]. Human data on gabapentin use during pregnancy is conflicting. In a population-based study on the adverse pregnancy outcomes in women exposed to gabapentin and pregabalin [55]. Among 145243 pregnancies, 21 (0.014%) were exposed to gabapentin. Two had a spontaneous abortion, eight had a pregnancy termination, and among 11 newborns exposed to gabapentin, six were born preterm, and four were small for gestational age. Among the nine newborns exposed to gabapentin during the first trimester, two had ventricular septal defects (VSD). Their findings raised concerns over the use of gabapentin in women of childbearing age.

Fuji et al. [56] did a prospective study to determine the effect of gabapentin on pregnancy outcomes. They studied data on 223 pregnancy outcomes exposed to gabapentin vs. 223 unexposed pregnancies. The rates of major malformations were similar in both groups ($p=0.845$). There was a higher rate of preterm births ($p=0.019$) and low birth weight <2,500 g ($p=0.033$) in the gabapentin group. Among infants who were exposed to gabapentin up until delivery, 23 of 61 (38%) were admitted to either the neonatal intensive care unit or special care nursery for observation or treatment, vs. 6 of 201 (2.9%) live births in the comparison group ($p<0.001$). There were 2 cases of possible poor neonatal adaptation syndrome in neonates exposed to gabapentin close to delivery, compared with none in the comparison group. The authors suggested that though the exposure to gabapentin during pregnancy may result in some adverse events, it does not appear to increase the risk for major malformations.

In a Cochrane review 57 on Monotherapy treatment of epilepsy in pregnancy and congenital malformation outcomes in the child. 200 patients were studied with gabapentin exposure during pregnancy. The pooled incidence of major malformation was 1.47% and found no difference between the children exposed to gabapentin and either type of control group.

Regarding pregabalin, a cohort study included 1,323,432 pregnancies resulting in a live-born infant over ten years (2000-2010). They studied the risk of major congenital anomalies among the newborns to women exposed to pregabalin during the first trimester (Total 477) and compared it to newborns for women unexposed anticonvulsants [57,58]. The study findings did not prove the teratogenic effects of pregabalin [5.9% in exposed newborns compared to 3.3% in non-exposed newborns, RR 1.16 (95% CI 0.81-1.67)]. This study contradicts the result of another cohort study (2004-2013) with a smaller sample (164 exposed women vs. 656 controls). This study showed an increased risk of major congenital disabilities in the newborns for women exposed to pregabalin compared to those who were not exposed [59].

Overall available data does not support the presence of high risk

of using gabapentin and pregabalin during pregnancy. However, there are no adequate well-controlled studies to support the proper recommendation.

REGIONAL ANESTHESIA

Regional anesthesia is one of the most effective methods of analgesia during pregnancy. Selective nerve blocks and epidural analgesia has been previously reported to be effective in many painful conditions [60-62]. It has the advantage of avoiding narcotics and other analgesics side effects, especially for acute postoperative pain management. There is considerable experience with epidurals for delivery, but their use in the first and second trimester for acute pain is unusual and infrequently reported or both.

CONCLUSION

In conclusion, the management of acute pain during pregnancy is complex and multifactorial. Various drugs like NSAIDs, acetaminophen, opioids and gabapentin are being used, and the weight of evidence regarding the risks to the developing fetus and the pregnancy is inconclusive. NSAIDs should be avoided during early pregnancy and in the last trimester. Acetaminophen remains the analgesic of choice during pregnancy, although it should not be taken unnecessarily. Strong opioids do not appear to present an increased risk of fetal abnormalities; however, neonatal withdrawal and respiratory depression may be problems.

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