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Opioid Use In Pregnant Women and its Effect on the Development of Neonatal Abstinence Syndrome in Newborns

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Systematic Review: Opioid Use In Pregnant Women and its Effect on the Development of Neonatal Abstinence Syndrome (NAS) in Newborns

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Abstract

The current guidelines for chronic noncancer pain management by the American Pain Society recommends opioids as the therapeutic choice to lessen pain and/or recover physical and psychological functioning. However, misuse of opioids during pregnancy has become an alarming concern across the United States impacting the health of both the mother and newborn. Infants experiencing opioid withdrawal symptoms, also known as neonatal abstinence syndrome (NAS), are at higher morbidity risk and other long-term developmental risks that are yet to be understood. In this review, five quality studies were assessed and analyzed to make recommendations on methadone and morphine-derivative opioid use for chronic pain management in pregnant women. Methadone has proven to be an effective option for moderate to severe pain and relatively safer than other opioid choices if prescribed at a reduced dose of 30 mg daily for 7 weeks. Codeine can be selected for mild to moderate chronic pain management and should not exceed 60 mg every 4 hours for patients in the third trimester. However, it is inferior for pain relief compared to morphine, whereas methadone is comparable. Both dosing recommendations are expected to have decreased risk of NAS development compared to dosing used in literature.

1 Introduction

According to The International Association for the Study of Pain, chronic pain can be defined as pain that persists beyond normal tissue healing time, assumed to be three months, caused by a medical disease, injury, or unknown cause (1). The current American Pain Society guidelines for the management of chronic noncancer pain recommends opioid use as the best analgesic option to alleviate pain and/or improve physical and psychological functioning. Chronic noncancer pain (CNCP) includes any pain that is not related to cancer or a terminal illness, such as back pain or osteoarthritis (2). However, opioid misuse during pregnancy across the U.S. has become a fast-growing epidemic that has reached frightening peaks and led to inevitable consequences for both the mother and child. In 2012, the likelihood of infants who experienced opioid withdrawal symptoms, known as neonatal abstinence syndrome (NAS), was 5.8 per 1000 births (3). NAS is generally characterized by gastrointestinal and respiratory disturbances, autonomic and central nervous system dysfunction, and difficulties in postnatal adaptation, including sleeplessness, irritability, and seizures (4). Not to mention, exposure to mandatory opioid addiction treatments will also exacerbate the risk of developing NAS in infants (5). Not only does this place the infant at developmental risk, but severe NAS is associated with high morbidity and requires prolonged hospitalization, with additional unknown long-term effects. Furthermore, factors contributing to the development of NAS in opioid-exposed fetuses are inadequately understood. Although the connection between excessive opioid use during pregnancy and NAS has been identified, the clinical balance between therapeutic benefits of different opioid classes and safety consequences for the fetus requires further investigation. Currently, there is no standard guideline

to determine how likely different opioid prescription drugs will affect the occurrence of NAS. The only references prescribers would consider are that all opioids are classified as Pregnancy Class C and pregnant women already on opioids should consider tapering off or switching to medication-assisted therapy if the benefits of therapy change outweighs the risk (6). This makes it difficult for prescribers to make informed clinical decisions to treat severe noncancer pain or opioid dependence without knowing the therapeutic limitations of each drug and its risks to the fetus.

Our objective is to create an established guideline for opioid use in pregnant women, which provides the most therapeutic benefits for the mother and safest dose for the infant with the least risk of developing NAS. We hypothesize that the proper use of opioids can be appropriately determined in pregnant women with minimal risk of NAS development for the fetus. The rationale is recent studies have shown that the onset, duration and severity of NAS may be affected by drug type and dosing. This is a promising step in optimizing the current NAS treatment strategies.

2 Methods

To obtain relevant publications, we searched in databases such as Ovid Medline, Pubmed, and Embase. We used the following search terms: neonatal abstinence syndrome, opioid, pregnant, pregnancy, pregnant outcome, pregnant women, pregnancy complications, infant, and newborn. We limited our searches to those published in English, from January 2005 to 2017. Two reviewers examined each publication independently. Any potentially significant data cited in the references of the publications of interest were also screened for applicable data. Studies are deemed eligible if they are randomized controlled trials or retrospective/observational cohort studies assessing the effects of chronic opioid use (morphine-derivatives or methadone) in pregnant women and the risks opioids pose to the development of NAS in newborns. Studies should include the doses of opioids used, duration of therapy, past medical history, average ages of mothers, and rate of occurrence of neonatal abstinence syndrome for each opioid type. Sample size will not be limited in this review. See Figure 1 for our process of selecting eligible studies.

We captured relevant data from selected studies. Two reviewers assessed and analyzed information from retrieved articles independently. We evaluated the quality of articles based on the date of publication, description of participants, inclusion criteria, and exclusion criteria . Disagreements were resolved by consensus. Studies were evaluated based on the following criteria: 1) adult females 18-40 years age who are pregnant with or without persistent chronic pain; 2) treatment with methadone or morphine-derivatives; 3) comparator: no chronic opioid use during pregnancy; 4) statistically and clinically significant occurrences of neonatal abstinence syndrome; 5) duration of methadone or morphine-derivative use as treatment. The primary measure was the occurrence of NAS in the study population. For analysis, the therapy and type of opioid used was assessed along with the occurrence of NAS for each respective agent. We also evaluated the dose and frequency of use and the rate of NAS will be compared for each agent.

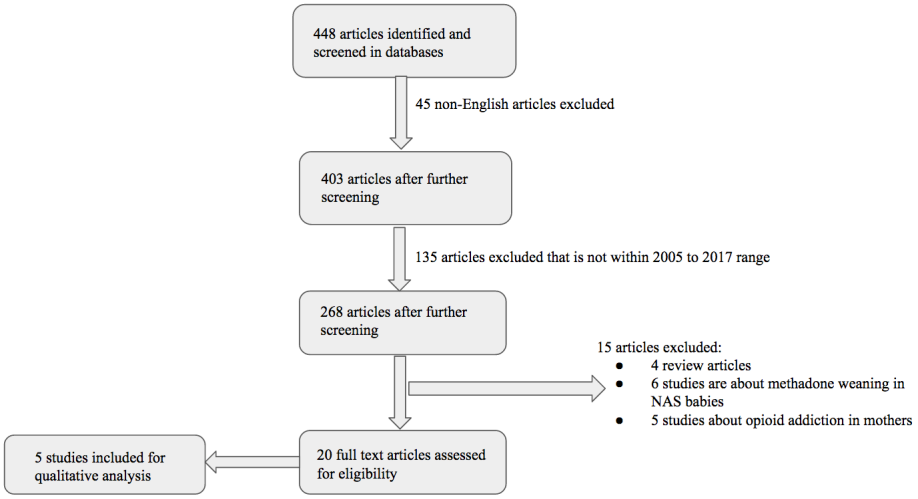

Figure 1: Study section flow diagram

3 Results

Table 1. Summary of findings evaluating the effects of opioid use for chronic pain in pregnancy

Citation	Study Design	Setting/Intervention	Patient Population	Results
Desai et. al, 2015[11]	Observational cohort study	Pregnant women filling at least one prescription opioid analgesic at any time during pregnancy. They were assessed based on: short term (<30 days), long term (>30 days), early use (first 2 trimesters), late use (3rd trimester), cumulative dose.	290,605 pregnant women who met insurance eligibility criteria between 2000 and 2007. They filled at least one prescription for an opioid analgesic during pregnancy and could potentially have additional harmful risk factors to pregnancy.	The absolute risk of NAS was greater in long term opioid users in comparison to short term users (absolute risk of 5.9 per 1000 deliveries, 95% confidence interval 5.6 to 6.2). Additionally, the researchers discovered the risk of NAS is the highest in the group of women with a history of opioid misuse or dependence (220 and 192 cases per 1000 delivers for long and short term users) compared to the group of women without risk factors (4 cases and <1 case per 1000 deliveries for long and short term users). Use of opioid during the third trimester of pregnancy showed a significant increased risk of NAS in comparison to the first two trimesters (propensity score adjusted risk ratio 1.24, 95% confidence interval 1.12 to 1.38). Absolute NAS risks is much higher in the group of pregnant women with long term use (more than 30 days) of opioids in absence of risk factors (4.2 per 1000 deliveries) compared to the short term opioid use (less than 30 days) group (0.7 per 1000 deliveries).
Jones et. al, 2005 [12]	Randomized, double-blind, double-dummy, flexible dosing, parallel-group controlled trial	Treatment with sublingual buprenorphine was compared to oral methadone using flexible dosing methods of 4-24 mg or 20-100 mg (average 60 mg) daily for an average of 7 weeks, respectively. Comprehensive drug-treatment facility that included residential and ambulatory care.	30 women were randomized to methadone and buprenorphine. Patients were between 21-40 years of age, gestational age of 16-30 weeks, DSM-IV diagnosis of opioid dependence, and self-reported recent opioid use.	Post-gestation, 45.5% of neonates required further treatment for NAS to manage their symptoms. Only the methadone treatment portion was extracted for the purpose of our review.
Nogaard M, et al., 2015[13]	Retrospective cohort study	Prenatal opioid use and its association with preterm birth, low birthweight, and NAS.	197 pregnant women exposed to methadone were identified. Women were Danish residents after the 20th week of gestation between 1997-2011. From the Danish Register of Medicinal Product Statistics, patients were identified to have used methadone from 30 days preconception to delivery.	Methadone use is associated with preterm birth (<37 weeks) in 21% of cases, low birth weight (<2500 g) in 9.3% of cases, NAS in 55% of cases, and congenital malformation in 10.4% of cases
Nezvalova-Henriksen K et al., 2011[14]	Retrospective cohort study	Outcomes of therapeutic doses of codeine use in pregnant women.	2,666 women who had history of codeine use during pregnancy were compared with 65,316 women who did not use opioids during pregnancy.	There were no significant differences identified for the congenital malformation rate (adjusted odds ratio 0.9, 95% Confidence interval 0.8-1.1) and survival rate (adjusted odds ratio 0.9, 95% confidence interval 0.6-1.5) between the codeine-treatment group and non-treated group. Codeine at any time during gestation was shown to be more likely to have a planned Cesarean delivery and postpartum hemorrhage. Other adverse effects were not seen to have significant associations.
Fischer G et al., 2006[15]	Single-site, randomized, double-blind, double-dummy study.	Patient received methadone (40-100 mg daily) or buprenorphine (8-24 mg daily) for a minimum of 3 days.	18 opioid-dependent pregnant women at 24 to 29 weeks gestation.	Only methadone therapy results were extracted from this article. Researchers found that 3 of the 14 qualifying neonates required treatment for NAS after their mothers received methadone treatment.

Figure 2: Study section flow diagram

Methadone is indicated for the continuous management of moderate to severe pain when extended analgesic therapy is required. There is high inter-patient variability in its pharmacokinetic properties, which in turn affect the relative analgesic efficacy. In a study by Gourlay et al., intravenous methadone has been shown to possess a longer duration of pain-control compared to intravenous morphine for pain. The total amount of methadone used was also significantly less compared to morphine. Furthermore, the time for first patient request for analgesia was longer compared to morphine (21 hours vs. 6 hours respectively) (7). Another retrospective study showed that the equianalgesic dose of oral morphine was significantly higher than methadone in non-pregnant adults (8). As for adverse effects, rotating from other opioids to methadone showed a reduction or elimination in laxative requirement and constipation (9). However, with methadone use there is an increased risk of QTc prolongation and cardiac arrhythmias for the mothers. It would could take up to 12 days to achieve a steady state level on a stable dose.

To compare morphine and codeine, in a study by Goldsack et al, researchers found that intramuscular morphine had significantly greater analgesic effects compared to intramuscular codeine. They enrolled 36 patients in a double-blind study and administered morphine 10 mg to half of them while the remaining received codeine 60 mg. At 1 and 2 hours post-injection, the morphine group felt significantly better pain relief compared to the codeine group ($p = 0.01$, $p = 0.005$, respectively) (10).

4 Discussion and Conclusion

According to the CNCP, the management of chronic neuropathic or nociceptive pain improved by at least 30% when managed with opioids. In multiple randomized control trials, there is also significant improvement in the patients quality of life (1). As for pregnant women, there is currently a lack of studies on the effects on long term brain development and post-NAS effects. These unanswered questions reserve opioid use only for severe pain in pregnant women that cannot be controlled by other means. Prescribers should consider that the risk of NAS is greater when opioids are taken later during gestation or for longer durations of pain management. NAS is predominantly observed when used in the last trimester (1).

Methadone use has shown to carry both benefits and risks. The longer duration of pain control and less cumulative methadone used compared to morphine make this a more attractive option than morphine. Due to the long half-life of the drug (15-60 hours), prescribers who decide to use it should be familiar with the careful titration required to prevent from unintentional overdose. It is always best to be more cautious and administer the least possible amount of drug to maintain chronic pain control. A reduction in constipation compared to other opioids would allow the patient to be more comfortable as she already has many symptoms during her pregnancy. It is also the first medication of choice used for managing opioid withdrawal in both addicted adults and neonates. Additionally, patient-specific characteristics such as renal or hepatic function and opioid tolerance can affect dose titration and regimen (2). Patients with current or history of heart disease are contraindicated from methadone use as the risk of arrhythmias and QTc prolongation would outweigh the benefits of methadone use. Due to its potential fatal cardiac effects, methadone is not recommended in patients with preexisting cardiac disease. Furthermore, due to methadones high inter-patient variability in pharmacokinetic properties, it would be difficult for a prescriber to accurately predict the analgesic efficacy in each patient. As seen in Table 1, the PROMISE trial showed that 60 mg daily of methadone use during pregnancy is correlated with a high risk of NAS treatment in neonates. Therefore, we recommend that if methadone is selected for patients at 16 to 30 weeks gestation, the prescriber should reduce the dose to no more than 30 mg daily for 7 weeks to decrease NAS occurrence and the adverse effects of inter-patient variability. This is a 50% reduction in the daily dose associated with high risk, but requires further clinical trials to confirm the significance in risk reduction. The reduced dose could potentially further reduce other pregnancy complications, such as the risks of preterm birth, low birth weight and congenital malformation.

The selection of codeine for chronic pain control will be under the condition that it is mild to moderate pain. For more severe pain, there are many more important patient characteristics to consider to optimize therapy, which can be inconvenient for both the prescriber and patient. The results of Golsack et. als study showed that the significantly better pain relief of the morphine group versus codeine group is an important factor to consider. However, as described above morphine is not without adverse effects whereas therapeutic doses of codeine did not affect the differences in rates of survival or congenital malformation. From Table 1, the significant risk of hemorrhage and Cesarean section with codeine are important factors that can be extrapolated to likelihood of NAS occurrence. From these findings, we recommend that codeine could be selected if the patient is experiencing mild to moderate pain. The analgesic effect of codeine is not sufficient for moderate to severe chronic pain control and it is not safe to titrate the dose up to achieve sufficient control and put the patient and baby at risk. If selected, the prescriber should not exceed 60 mg every 4 hours up to 360 mg daily for patients in the third trimester to reduce likelihood of the infant developing NAS.

In the Desai cohort study (Table 1), there were 1,705 identified cases of NAS among 290,605 pregnant women who filled opioid prescriptions. The increased absolute risks of NAS in long term (>30 days) opioid use in both the presence and absence of additional risk factors (alcohol or other non-opioid drug misuse, exposure to psychotropic medications, and smoking) provide clinical guidance for opioid use during pregnancy. Providers should be diligent in considering the benefits and potential risks of opioid therapy. Data suggest the timing of opioid use poses a risk of NAS development in the unborn child. Prescribers should be aware of the potential increased risk of NAS during the third trimester and reduce the use of opioids during the later stage of pregnancy if possible. During early stages of pregnancy (first and second trimesters), the NAS risk is relatively lower. In addition, prescribers should limit opioid use to short term therapies for pain management in women with no history of opioid dependence despite lower risk of NAS development. Long

term use of opioids ultimately poses a higher risk in NAS development regardless of the patients history of opioid dependence.

The strength of our paper is comparing different opioid options that have not been compared in other reviews. We created recommendations for opioid selection in the pregnant population with strong clinical data from multiple studies. Our ability to determine the safest opioid option and dosing regimen were restricted due to a lack of high quality data from randomized control trials. Most primary studies were performed in animal models but no human trials. Clinical trials and opioid experimentation in pregnant women poses a highly controversial and ethical concern, which limits the quality of the current data to retrospective and observational cohort studies. Although collecting strong data poses a challenge, it remains crucial to optimize opioid selection and dosing while maintaining the lowest risk of NAS development. For future direction, more high quality retrospective studies should be considered.

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