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Opioid Abuse in Pregnancy: A Systematic Review

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Author Note

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Abstract

Prenatal opioid abuse is a serious public health concern and linked with numerous health consequences for both mothers and children. Despite research describing negative outcomes of drug use during pregnancy, it is still a prevalent problem in the United States, with researchers finding that women are at highest risk for substance abuse during their reproductive years. Opioid abuse during pregnancy is common, including opioids such as hydrocodone, oxycodone, morphine, and heroin. Use of these drugs results in both short and long term side effects for the mother and child. Therefore, the prevalence of this problem should not be underestimated. It is important for nurses to understand this problem and promote health in populations of women, specifically of reproductive age, and children with the use of evidence-based practice. The purpose of this review is to describe and critically analyze evidence about outcomes of prenatal illicit opioid abuse in pregnant women and treatment methods utilized in an attempt to increase the likelihood of favorable outcomes. This will be done by completing a literature review consisting of professional academic sources published within the past ten years.

Introduction

When pregnant women abuse prescriptive and non-prescriptive drugs, the women and their babies are adversely affected in both the short and long term (Behnke & Smith, 2013). Women who abuse drugs such as opioids can experience a variety of side effects such as cardiovascular and respiratory complications, neurologic disruption and pregnancy complications. Additionally, the fetuses experience many of the side effects and can have developmental and birth complications from the effects of the drug use by the mother (Behnke & Smith, 2013). When neonates are born with drug

addictions, they can experience serious complications including Sudden Infant Death Syndrome (SIDS), Neonatal Abstinence Syndrome (NAS), and respiratory distress or failure (Minnes, Lang & Singer, 2011). There may also be long-term developmental, behavioral and cognitive anomalies associated with the mother's drug use that occurred over the course of the pregnancy. Specifically in Ohio, data collected between 2004 to 2014 demonstrated that 9,498 infants were hospitalized postpartum for NAS (Ohio Department of Health, 2014). In 2014 alone, there were 1,875 NAS admissions equating to approximately 5 admissions per day. In 2004, the prevalence of infants born with NAS was 14 in 10,000 live births. That number grew nearly 10 times to 134 per 10,000 live births in 2014 (Ohio Department of Health, 2104). The most common complications associated with the NAS babies were respiratory complications, low birth weights, feeding difficulties and seizures (Ohio Department of Health, 2014). These health complications put a burden on hospitals and the Ohio healthcare system each year. Over the course of one year, the treatment of NAS babies contributed over \$105 million in costs with the average hospital stay of an NAS babies being 14 days. In NAS infants versus non-NAS infants, the inpatient costs were approximately 4 times higher and the length of stay was approximately 4 times longer (Ohio Department of Health, 2014).

This problem is relevant to nursing practice because it demonstrates the ever-growing need for education, support, guidance, and health promotion related to drug abuse, especially for women of the childbearing age. Nurses are the forefront of health promotion and it is important that patient education is evidence-based. It is important that nurses and other health care providers screen for drug abuse during prenatal health

visits and provide resources for prompt treatment to reduce the potential harm on the fetus. The purpose of this systematic review is to identify, describe, and critically appraise the evidence of outcomes in babies and children whose mothers were addicted to opioids during pregnancy. The review answers the following PICOT questions: In children, what are short and long-term outcomes when pregnant women abuse opioids and what treatment methods can be utilized to improve outcomes?

Methods

The methods used to identify and select publications answering the PICOT question are described in this section. These publications are reviewed in the next section of the paper. This literature consisted of primary academic and research-based sources.. The literature search included scientific journals, research studies, and research articles published within the last ten years. Search key terms included: pregnant, mother, unborn, drugs, abuse, opioids, infant, neonatal, heroin, neonatal abstinence syndrome and addiction. Databases included Akron Electronic journals, Cinahl, PubMed, and Medline Plus. The criteria for journal selection included date published, key words included, relevance to topic and validity of publication. Therefore, retention of publications was made to assure the quality of the evidence, allowing for a greater reliance on collection of studies. A comprehensive, detailed search was completed to include all major relevant research. Selector bias was avoided by including research from various publications that take different stances on the topic and reported differences in findings.

Review of Literature

The following review of literature attempts to demonstrate and discuss the effects of drug use during pregnancy based on current studies published in academic journals

between 2007 to 2017. These journals were acquired through internet searches utilizing a multitude of databases. There was a wide range of sample sizes ranging from 26-138,000+. Due to the massive differences in sample sizes, it was evident that the limitations of some studies were much more vast versus others. Limited results and conclusions for smaller sample sizes was noted . Additionally, polysubstance abuse was a factor included in some of the studies, which may have impacted the results of those studies. Precautions were taken to include only the information that was directly linked to opioid abuse and not polysubstance abuse.

Researchers have found that prenatal drug abuse results in many outcomes in infants, including physiological, emotional, cognitive, and psychosocial effects. We will discuss these ramifications in depth throughout this review of literature. The main limitation with research in the domain of opioid use is that much of the information is self-reported, which can cause research to be inaccurate if participants under-report or falsify information. Additionally, information gathered in a study published in the *Journal of Pregnancy* (2014) explained that women who are addicted to opioids likely suffer from multiple comorbidities including depression and anxiety (Whiteman et al., 2014). Maternal comorbidities in combination with opioid use may influence the neonates outcomes more substantially versus opioid abuse alone but this has not been specifically studied or identified in research and thus, is a limitation that must be taken into account. Also, it is important to recognize that the demographic of opioid users is very diverse. It has shifted from inner city, low-income population to a more socioeconomically and demographically varied population, which includes pregnant women (McQueen & Murphy, 2016). Opioid exposure is particularly problematic not

only because of its high prevalence but because of the need for pharmacotherapy to mitigate withdrawal signs (Wiles et al., 2014).

The effects of opioid use during pregnancy propose the most direct threat to infant mortality. Opioid use is directly related to respiratory dysfunction, toxemia, third trimester bleeding and infant mortality. Exposure to these substances increases neonatal abstinence syndrome. NAS will be discussed in detail later on in this paper. However, neonates may have many congenital abnormalities and neurobehavioral effects such as decreased arousal, and poor quality of movement (Wong et al., 2011). Maternal hypertension and intrauterine growth restriction are also some antenatal concerns (Wong et al., 2011). Opioid abuse leads to many negative effects on the fetus. This can include higher rates of prematurity and growth retardation resulting in small for gestational age babies, deficits in behavior, attention and cognition, neonatal morbidity and mortality, and Neonatal Abstinence Syndrome (McQueen et al., 2015).

OPIOID ACTION

In order to better understand the mechanism in which opioids affect the fetus, it is important to note the specific action in which opioids act on the mother. When opioids are introduced into the body, there are a variety of functions that become altered due to the mechanism of action the opioid has. The basic mechanism of opioid action in the brain involves the mu-opioid receptors, or primary opioid receptors (Keough & Fantasia, 2017). These receptors are responsible for aiding in regulation of emotional and pain responses in addition to pleasure and well-being (Keough & Fantasia, 2017). More importantly, the mu-opioid receptors in the brain stem regulate respiration and when

over-stimulated, can result in respiratory depression and death (Keough & Fantasia, 2017).

In regards to the reproductive system of the body, opioids inhibit Gonadotropin Releasing Hormone (GnRH), thus impacting the peripheral reproductive tissues (Böttcher, Seeber, Leyendecker, & Wildt, 2017). More specifically, the granulosa cell of the ovarian follicle, the oocyte, and the human endometrium in combination with follicular maturation and embryo implantation can be adversely affected (Böttcher, Seeber, Leyendecker, & Wildt, 2017). It should be noted that an increase in endogenous opioids within the body triggered by stress, starvation or anorexia nervosa have been shown to cause a decrease in the circulating levels of FSH and LH within the body (Böttcher, Seeber, Leyendecker, & Wildt, 2017). Absence of these hormones can lead to a failure of follicular maturation and anovulation (Böttcher, Seeber, Leyendecker, & Wildt, 2017). Research on mice exposed to opioid substances demonstrated various adverse effects on embryo development and implantation, derailing normal implantation and delaying the stages of embryonic development (Böttcher, Seeber, Leyendecker, & Wildt, 2017). By better understanding the mechanism of action in which opioids act on the mother, specifically in regards to the pleasure and respiratory responses, it can be better understood how these substances act on the fetal brain and body. The substances have a far greater effect on the fetal brain versus the mother's brain due to the immaturity and vulnerability of the fetus during the essential perinatal developmental period. It is important to note that opioids have a rapid rate of transplacental passage, less than 60 minutes, and withdrawal symptoms will occur for the mother and fetus 6-48hrs after the last usage (Bhuvanewar, Chang, Epseain & Stern, 2008).

NAS

Neonatal abstinence syndrome, also known as NAS is an essential concept to consider when assessing an infant. NAS is a serious postnatal withdrawal syndrome that occurs primarily in opioid exposed infants. NAS is a combination of maternal and neonatal factors this includes the opioid dose, frequency and timing before delivery, maternal pharmacokinetics (PK), placental metabolism, concurrent medications, and neonatal PK and pharmacogenomics (Wiles et al., 2014). It is comprised of a collection of symptoms in newborns including central nervous system irritability (tremors, increased muscle tone, high-pitched crying, and seizures), gastrointestinal dysfunction (feeding difficulties), and temperature instability (Ko et al., 2016). Although there have been other substances linked with NAS, it is most commonly accredited to in utero opioid exposure. (Ko et al., 2016). In simplest terms, NAS is the withdrawal newborns experience after birth due to the substances taken by the mother during the course of pregnancy (Witt. et al., 2017). Neonatal Abstinence Syndrome is often associated with excessive medical expenditures and has become a costly medical condition in the United States due to the rising rates of infants requiring hospitalization from this condition (Desai et al., 2015). Additionally, it was noted that a mother who abuses opioids for a long-term time frame versus those who used during the third trimester were at an equal risk for the infant developing symptoms of NAS (Desai et al., 2015). NAS is not something that is isolated solely to infancy. There are many long-term outcomes that can affect the child due to the neurological damage that can occur in utero.

NEONATAL OUTCOMES

Studies researching substance abuse during pregnancy have demonstrated a variety of both immediate short-term and long-term effects in infants. Short-term medical issues that can arise during the newborn period immediately following delivery can have a range of manifestations including small birth weight, withdrawal symptoms, congenital anomalies, and neurobehavioral problems (Behnke & Smith, 2013). Fetuses that face drug exposure in utero can experience intrauterine growth restriction and decreased birth weight (Behnke & Smith, 2013). Withdrawal is typically observed shortly after birth for infants exposed to opiates in the form of Neonatal Abstinence Syndrome (NAS). Common neurobehavioral problems observed during the newborn period include impaired orientation, abnormalities with muscle tone (hyper- or hypotonicity), poor habituation, very low or high levels of arousal, NAS, poor movement quality and, increased stress (Behnke & Smith, 2013). It has been found that the use of illicit substances during pregnancy, impacts brain function and the development of higher-order cortical areas (Thompson, Levitt, & Stanwood, 2009). A diagnosis of NAS has been strongly associated with a poor school performance (Terplan et al., 2017). Research has also been found that it often leads to children having additional educational needs due to cognitive deficits related to delayed and inhibited brain development (Thompson et al., 2009).

It has been shown that mothers who use while pregnant can cause their children to suffer from long-term effects regarding behavior and language, as well (Behnke, & Smith, 2013). It is evident children with NAS will require longer hospitalization at birth than unexposed infants. They will also need supportive care involving pharmacologic

interventions such as the use of morphine in addition to nonpharmacologic interventions. Research has shown that children with a history of NAS were more likely than unexposed children to be readmitted to the hospital during the first five years of life (Witt. et al., 2017). After eliminating other risk factors, such as maternal age, maternal education, gestational age and intrapartum smoking status, the increased risk of readmission associated with NAS exposure persisted (Witt. et al., 2017). Reasons for hospitalization can include infectious diseases, diseases of the nervous system, respiratory system, digestive system, skin and subcutaneous tissue, infections and cellulitis and additional perinatal conditions (Witt. et al., 2017). For neonates exposed to methadone treatment while in utero, common “long-term” findings include altered motor development and motor patterns as discovered by observation (Logan, Brown, & Hayes, 2013). Motor deficits, specifically motor-rigidity and dysregulated motor patterns in combination with decreased activity, can impact infants as they grow, as observed in multiple studies, leading to social developmental issues, shorter attention spans and lack of social responsivity (Logan et al., 2013).

Additionally, it was noted that the toddlers had poor social engagement (Logan et al., 2013). The most frequent long-term diagnoses for children born from drug-abusing mothers were ADHD and depression, both heavily impacting educational and social experiences (Herranz, Vílchez, Ledo, Sierra, 2014). It is likely that the ADHD diagnosis stems from not only altered brain activity but also other neurocognitive deficits including auditory dysfunction and poor visual-motor integration (Logan et al., 2013).

When taking into account all of these factors, it can be noted that achievement and learning will likely be affected long-term. A study published by the American

Academy of Pediatrics (2017) outlined the long-term academic deficits associated with NAS. This study was able to demonstrate that children diagnosed with NAS at birth are associated with poorer performance in standardized curriculum (Oei et al., 2017). These learning deficits can be noted as early as 3rd grade, in regards to standardized educational examinations, when directly compared with non-NAS children of the same demographic background (Oei et al., 2017). Comparisons of first year high school freshman scores to scores of normal children in grades 5 and 7 demonstrate significant delays in learning in NAS diagnosed children, despite the gaps in age (Oei et al., 2017). This becomes extremely concerning because the link between poor education and adverse socioeconomic outcomes later in adult life is evident.

Additionally, the environment children are raised in impacts their development. Affected children may grow up in an unsafe and unstable environment and other socioeconomic consequences of maternal substance may play a role in their development (Witt. et al., 2017). Research across all drug categories states that regardless of the specific drug-related exposure in utero, environment postpartum has a great effect on development for parental users who do not receive treatment for their abuse. According to research done by Logan, Brown, and Hayes, “The current view is that environmental risk factors conspire with prenatal exposures to promote epigenetic changes in gene expression and methylation patterns that have both immediate and long-term implications related to developmental programming” (p. 2) Environment in combination with social considerations can be a key determinant in predicting outcomes for neonates exposed to opioids in utero.

TREATMENT MEASURES

In regards to treatment methods for mothers who are opiate-dependent, there are a multitude of options that can aid in the weaning process. Prompt treatment and intervention can contribute to more favorable outcomes for the neonate. If left untreated, neonatal outcomes are far more unfavorable with outcomes including preterm labor, fetal growth restriction, abruptio placentae, and intrauterine passage of meconium (Keough & Fantasia, 2017). There are two notable treatments that are used to aid in the withdrawal from opioids: methadone and buprenorphine. According to research published in the *Journal of Substance Abuse Treatment* (2017), methadone treatment (MAT-M) is considered the “first-line” treatment for women suffering with Opioid Use Disorder (OUD) (Wilder, Hosta & Winhusen, 2017). Methadone is a Schedule II and is strictly regulated through state laws and regulations (Keough & Fantasia, 2017). When used to treat opiate withdrawal for pregnant women, treatment is available through doctors or advanced practice nurses that work in hospitals or methadone-specific clinics (Keough & Fantasia, 2017). If women are treated appropriately with methadone throughout their pregnancy and refrain from use of any illicit opioids, the infant will likely have more favorable outcomes. It should be noted that even if the mother does go through the proper treatment, there is still an extremely high chance (~94%) that the infant will have some type of opioid withdrawal symptoms (Keough & Fantasia, 2017). This may not be to the extremes of NAS. Specific dosages must be titrated and closely monitored by the prescribing physician to ensure adequate treatment of withdrawal signs and symptoms (Keough & Fantasia, 2017). Factors that can impact the success of the treatment are dependent upon many factors with the most important factor being duration of treatment.

The longer duration treatment plans have shown to be more successful and is associated with more favorable fetal outcomes (Wilder, Hosta & Winhusen, 2017).

Buprenorphine is a Schedule III medication and does act on similar receptors to opioids, the mu opioid receptors, but additionally acts on the kappa receptors as an antagonist (Keough & Fantasia, 2017). This medication also must be prescribed and administered by a physician who has undergone specific training and credentialing in regards to the proper use of it (Keough & Fantasia, 2017). Unlike methadone, this medication is able to be administered in an office and does not have to be controlled through state-regulated clinics or hospital settings (Keough & Fantasia, 2017).

Buprenorphine treatment may be chosen over methadone treatment because there are fewer drug interactions, office visits only have to be scheduled monthly rather than daily, there is a decreased potential for severe withdrawal side effects in the neonate and there is a decreased risk of abuse and overdose (Keough & Fantasia, 2017). Additionally, there is a decreased cost associated with Buprenorphine, which is likely to be a significant factor when considering the populations in which opiate abuse is more common (Keough & Fantasia, 2017).

SOCIAL IMPLICATIONS

State laws regarding drug abuse during pregnancy vary on types of treatment and penalties associated with use (Stone, 2015). Care for these women becomes challenging because oftentimes, there are disagreements between health care providers and legal experts on penalties and treatment for these mothers and that can impact the care they receive (Angelotta C., Weiss, Angelotta J., & Friedman 2016). The general consensus regarding the standard of care is that mothers who know they will be charged with child

abuse for endangering the life of their child from using illicit drugs are far less likely to seek out substance abuse treatment and prenatal care versus their non-using counterparts (Angelotta et al., 2016). Substance abusing mothers can face a variety of barriers when seeking prenatal care and substance abuse treatment, all while worrying about the potential of losing their child postpartum. Barriers for treatment can be both physical and psychosocial in nature. More commonly, mothers fear the psychosocial barriers more than anything else due to the punishment aspect that can accompany them (Stone, 2015). Common psychosocial barriers include fear of detection, denial of pregnancy, and social isolation (Stone, 2015). Common physical barriers include lack of access to treatment and avoidance of medical care (Stone, 2015)

Research also states that workers in the legal system, specifically those that deal with opioid addiction in pregnant mothers, need education regarding alternative therapies like medication-assisted treatment (MAT) versus criminalization and hard withdrawal to improve outcomes and the standard of care (Angelotta et al., 2016). Threats of punishment adversely affect mothers from seeking out treatments and have the potential to increase the harms done to the fetus versus those mothers who have the option to receive MAT as a “matter of policy” to treat opioid substance abuse disorders (Angelotta et al., 2016).

It is also a common trend to see that the stigma and fear associated with criminal penalties becomes a barrier to women who want to receive prenatal and substance abuse treatment (Thompson et al., 2009). Due to the various federal and state laws in place to keep children safe from substance abuse, hospitals are mandated to test anyone they suspect to be using drugs (Stone, 2015). Additionally, any child born that seems to be

suffering from withdrawal symptoms must be tested and CPS must be notified (Stone, 2015). These laws were developed from the Keeping Children Safe Act of 2003, which further added requirements for drug testing as outlined by the Child Abuse and Treatment Act (Stone, 2015). Furthermore, researchers have concluded that health care professionals and social workers must be more upfront about treatment options, specifically methadone treatment programs, if they want to see decreases in untreated substance abuse cases. Research suggests that early methadone treatment can help mothers to keep custody of their children so long as they have follow up with their case manager and adhere to their treatment plans. Though methadone treatment is not widely accepted by the medical community, it has been shown to improve infant and maternal outcomes (Vucinovic, Roje, Vučinović, Capkun, Bucat, & Banović, 2008). As nurses we must consider the management of patients who use opioids. Therefore in 2016, the CDC released the Guideline for Prescribing Opioids for Chronic Pain. This guideline has been implemented, providing strategies to address the opioid epidemic. The guidelines consisted of three recommendations: 1) consider nonopioid pharmacologic therapy for chronic pain management, 2) discuss family planning and how long-term opioid use might affect future pregnancies before initiating opioid therapy in reproductive-aged women, and 3) prescribe the lowest effective dose when opioids are started (Ko et al., 2016)

Critical Findings and Gap Identification

Based on the information that was gathered through the research articles included in this review, it is important to note that many of the articles found limited data in regards to long-term outcomes. There is information readily available outlining and

discussing the immediate signs and symptoms of Neonatal Abstinence Syndrome spanning approximately 10 weeks postpartum but limited information is available after that timeframe. Additionally, it should be noted that many of the studies were limited due to the underreporting or misreporting of opioid use. Some participants in the studies were polysubstance abusers, which may have impacted the study results but oftentimes, this was taken into account for each individual study. Of all the studies and research used, everything that was included was considered to be valid information. Little information was found in the studies that was not valid and if found, was intentionally not included in the review. Information regarding polysubstance abuse was intentionally out as to not impact the results of the opioid-focused review. The studies often contained data gathered from the state based upon urine samples and specific signs and symptoms of NAS upon birth. Additionally, some information was gathered through surveys that were administered during office visits. Because of the nature of this substance abuse disorder and the population that often most associated with it, there was a limited amount of information gathered regarding prenatal care and thus, this could not be included in the study. It can be concluded that there is a lacking of information and research regarding the topic of prenatal opioid abuse and outcomes. It is recommended that more measures be taken to educate the public about this epidemic so that accurate information regarding resources is available for those who suffer from this substance abuse disorder.

Care recommendations could include more comprehensive screening methods and techniques to identify those at a greater risk for opioid abuse or for those who are already experiencing the substance abuse disorder. These could take form in physical self-administered surveys or through healthcare provider-assisted screenings. Additionally,

information regarding resources for those who need treatment and access to treatment centers needs to become more available. Government funding and policies should be guided by the current research, which explains the need for better access to treatment centers and clinics. Training for healthcare providers should also be more accessible so that providers are able to meet the increasing needs of the affected population.

Conclusion

Prenatal substance abuse is a significant problem. The public and healthcare professionals need to be educated and made aware of the issue. It is pertinent to public health, due to the fact it results in detrimental maternal and neonatal outcomes. There are multiple factors that play a role in the severity of the outcome included, drug exposure, prenatal care, comorbidities, mental health, socioeconomic factors, and support systems available. These all contribute to the negative outcomes experienced by the infant.

Timeline

Throughout the course of fall 2017 we have been collaborating on this project to complete it at an earlier due date than originally projected. Emily Seburnia will be graduating at the end of the Fall 2017 semester. Therefore, we have been working diligently and efficiently to complete this paper before the end of the Fall 2017 semester. Although the project will be completed, Colleen Fearon will still be enrolled in senior honors project independent study during spring 2018 semester with approval from the Honors College, Dr. Graor, and Don Canary. During the spring 2018 semester, the primary objective of our work is to present the project at a research and educational event. Our primary sponsor is Debra Horning. Our readers for this project are Michelle Zelko and Sherri Hartman.

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