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Introduction

Neonatal abstinence syndrome (NAS), primarily a result of prenatal opioid use, has become an increasing problem in recent years. According to Jones and Fielder (2015), NAS most commonly occurs within 48-72 hours after birth as the neonate experiences opioid withdrawal symptoms involving “central nervous system hyperirritability and dysfunction of the autonomic nervous system, gastrointestinal tract, and respiratory system” (p. 12). Wachman and Schiff (2015) report that NAS from prenatal opioid exposure has “increased 5-fold in the U.S. since 2000,” often requiring an average of 3 weeks in the neonatal intensive care unit (p. 12). The increase in NAS has occurred alongside a growth in opioid use during pregnancy in the U.S., notably amplifying from 1.19 to 5.63 per 1000 births between 2000 and 2009 (Stover & Davis, 2015).

Opioids are often prescribed for acute pain in pregnancy, but their potential for abuse and possible threat to the fetus require providers to avoid chronic pain treatment (Yazdy, Desai, & Brogly, 2015). With the majority of opioid abuse in women occurring among those within childbearing age, it is important to understand that opioids are believed to increase the risk of birth defects and complications (Norgaard, Nielsson, & Jorgensen, 2015). Yazdy, Desai, and Brogly (2015) note that most opioids are currently classified as category C for pregnant patients, informing that a potential for harm to the fetus has been observed in animal studies, but comprehensive human studies have not been performed. However, the authors similarly reveal that oxycodone has been classified as category B, with no support for fetal harm under animal studies. Norgaard et al. (2015) reveal that it is important to consider the realization that pregnant women with opioid dependence are also more likely to follow other unhealthy lifestyle choices,

particularly noting the presence of a four-fold increase in smoking compared to the entire population of pregnant women in the U.S.

Pregnant women with opioid dependence are able to decrease the prevalence of opioid-related complications involving the fetus by opting to participate in opioid-substitution programs, which positively affect the pregnancy by decreasing the use of opioids, diminishing withdrawal, and increasing compliance (Kraft, Stover, & Davis, 2016). Methadone has been the standard of treatment for pregnant women with opioid dependence for decades, but buprenorphine was recently presented as a substitute that has become widely used (Norgaard et al, 2015). According to Kraft, Stover, and Davis (2016), buprenorphine decreases the incidence and severity of NAS greater than methadone, but methadone clinics are associated with greater additional counseling and community support, leading to lower failure rates. A study by Bell et al. (2016) reported no occurrence of fetal death or preterm delivery during the opioid detoxification process in pregnant women. The study also revealed that cases of NAS did occur among pregnant women who underwent detoxification, however, it was noted that the mothers in all of these cases had relapsed during the process.

In addition to pharmacologic treatment, Patrick (2015) proposes the importance of improving the care of NAS neonates and mothers while attempting to optimize the length of the hospital stay in order to prevent costly charges. Terplan, Kennedy-Hendricks, and Chisolm (2015) argue that punitive approaches used to reprimand pregnant women with substance abuse disorders are counterproductive because they cause women to be more reluctant to seek appropriate care. They note that it is more important to provide aid through substance dependence treatment and additional education on parenting. According to Saunders et al. (2014), the unique care required by NAS neonates and their families is best approached through

multidisciplinary care, including the necessary care after leaving the hospital. The authors note that continued research on the management of NAS infants and the long term effects on their development and behavior is essential to continue improving treatment as the incidence of NAS increases.

Definition of Terms

Neonatal abstinence syndrome – Substance withdrawal experienced by a neonate, altering the levels of neurotransmitters and resulting in “central nervous system hyperirritability, autonomic nervous system dysfunction, and gastrointestinal disturbances” (Stover & Davis, 2015, p. 562).

Opioid – “A psychoactive chemical that works by binding to opioid receptors found principally in the central nervous system and the gastrointestinal tract” often used in clinical settings for pain management (Lindsay & Burnett, 2013, p. 135).

Opioid maintenance therapy – A treatment option for pregnant women with opioid addiction that involves administration of an opioid agonist under clinical direction, which “provides a steady concentration in the maternal blood plasma and thus prevents the adverse effects of repeated withdrawal on the fetus” (Minozzi, Amato, Bellisario, Ferri, & Davoli, 2013, p. 7).

Finnegan Neonatal Abstinence Scoring Tool – A scoring system performed every 3-4 hours to assess neonates with in utero opioid exposure. The scale determines the severity of symptoms to aid in formulating a plan, which may require the use of pharmacologic therapy with elevated scores (Stover & Davis, 2015).

Addiction – A “chronic medical illness” involving using harmful substances as a result of a “psychological and physical need” (Kremer & Arora, 2015, p. 477).

Dependence – “A maladaptive pattern of substance use leading to clinically significant impairment along with tolerance and/or withdrawal following cessation of use (Park, Meltzer-Brody, & Suzuki, 2012, p. 425).

Detoxification – The acute process of completely discontinuing the use of a substance associated with dependency. The progression of the individual is often monitored by professionals to medically treat withdrawal symptoms (Bell et al., 2016).

Withdrawal syndrome – Symptoms resulting from sudden cessation of substance use. These symptoms may occur in a neonate with a mother who continuously used harmful substances prenatally (Kremer & Arora, 2015).

Literature Review

Epidemiology.

Neonatal abstinence syndrome has become an increasing concern with the current trend of opioid use in the United States. According to Hall et al. (2014), the period of time between 2000 and 2010 has experienced an increase in the number of opioid prescriptions, opioid prescription size, and associated overdose deaths. The authors specifically note that the use of opioids during pregnancy increased from 1.19 to 5.63 per 1000 births annually between 2000 and 2010. Similarly, during this same time period, the incidence of NAS increased from 1.20 to 5.63 per 1000 births annually (Gopman, 2014). The actual incidence of NAS may be higher than reported because many neonates exposed to opioids in utero do not present with symptoms of withdrawal or remain undiagnosed (Stover & Davis, 2015). In recent years, NAS has been responsible for 3% of all admissions to neonatal intensive care units in the United States, requiring a three-week length of stay and a cost of \$53,000 on average (Wachman & Schiff, 2015).

Opioid abuse originally became a major concern in pregnant women with heroin addiction, but recent trends currently show a greater concern for misuse and abuse of prescription opioid pain relievers (Jones & Fielder, 2015). Young and Martin (2012) report that a 600% increase in the number of prescriptions for opioid pain relievers was observed between 1997 and 2007, correlating with an overdose death rate greater than heroin. The authors propose that the rise of opioid pain reliever use is largely due to a “change in physician prescribing habits” (p.442). Opioids are often used by medical providers to activate receptors in the central and peripheral nervous system to provide analgesia for pregnant patients with acute pain, but

their potential for abuse and the incomplete understanding of their effect on the fetus should limit their use (Yazdy et al., 2015).

Women account for approximately 30% of the population with drug addiction, with the majority in the range of childbearing age (Wendell, 2013). A study by Martin, Longinaker, and Terplan (2015) determined that the majority of pregnant women admitted for substance abuse between 1992 and 2012 were aged 21-29, single, non-Hispanic white, unemployed, and had a minimum of a high school diploma. In general, females with drug dependency have greater rates of poverty and unemployment than the general population (Park et al., 2012). Jones et al. (2014) explain that these women are often affected by the disgrace commonly associated with opioid addiction and use during pregnancy, frequently causing them to be judged publicly. The authors note that providers must counteract this stigma to offer a beneficial relationship that can provide appropriate care to the mother and her child. Park et al. (2012) state that a majority of opioid dependent pregnant women also have coexisting psychiatric disorders, primarily including “depressive disorders, anxiety disorders, post-traumatic stress disorders, and hypomania” (p.426).

Pathophysiology.

Wendell (2013) explains that since NAS is a result of neonatal withdrawal from maternal opioid use following delivery, its risk factors encompass those of drug abuse. The author notes that these risk factors include past illicit drug addictions, alcohol and tobacco abuse, psychological disorders, physical or sexual abuse, aged early teens to late 20s, environment, access to illicit drugs, and education. Data from a study conducted by Smith, Costello, and Yonkers (2014) reveals that women with psychiatric disorders, regular tobacco use, or SSRI use

during pregnancy were twice as likely to use opioids during pregnancy. Lindsay and Burnett (2013) explain that individuals who are dependent on opioids experience tolerance to the effects of lower doses and withdrawal when the drug is not administered. The authors state that the use of heroin, a short acting opioid, results in withdrawal after 6-12 hours, while the use of methadone, a long acting opioid, results in withdrawal after 72-96 hours.

Opioid use during pregnancy, including opioid maintenance agents, are able to cross the placenta, causing pregnancy complications and withdrawal at birth when exposure is discontinued (Norgaard et al., 2015). Prenatal opioid intoxication can decrease the mother's respiratory drive leading to hypoxemia and, consequentially, acidosis in the fetus (Young & Martin, 2012). While specific permanent teratogenic effects associated with neonatal exposure to opioids have not been proven, opioid withdrawal in the infant can result in major risks of "miscarriage, placental abruption, preterm labor, and stillbirth" (Kremer & Arora, 2015, p. 474). Prenatal opioid withdrawal can cause hypertension and tachycardia in the mother resulting in reduced placental perfusion, increased metabolism of the fetus, and increased uterine contractions leading to preterm delivery (Young & Martin, 2012). While the exact mechanisms occurring in neonatal abstinence syndrome have not been completely determined, it is generally believed that symptoms partially result from altered levels of specific neurotransmitters, including norepinephrine, dopamine, and serotonin (Stover & Davis, 2015).

Since NAS is a known result of both opioid abuse and opioid maintenance therapy in pregnant women, it can be appropriately treated if providers are prepared (Terplan et al., 2015). In addition to the exposure of opioids, NAS infants are often affected by the poor lifestyles of the involved mothers. Norgaard et al. (2015) note that pregnant women enrolled in opioid maintenance programs have an incidence of cigarette use that is four times larger than the

general population. Kraft et al. (2016) specifically note that use of cigarettes, benzodiazepines, and SSRIs in combination with opioids increase the severity of NAS. In certain cases, providers must also prepare for other common complications associated with maternal intravenous illicit drug use, including hepatitis B, hepatitis C, and HIV (Shainker, Saia, & Lee-Parritz, 2012). Similarly, methadone treated pregnant women tend to have diets with decreased fiber, fruit content, vegetable content, and essential vitamins, likely due to a coinciding low socioeconomic status (Tomedi, Bogen, Hanusa, Wisner, & Bodnar, 2012). These corresponding factors of maternal opioid use can affect the development of the infant.

Prenatal Management

Opioid addiction in pregnant women must be approached as a chronic illness with those afflicted deserving appropriate treatment to prevent harm to themselves and the infant (Kremer & Arora, 2015). In addition to opioid abuse in pregnant women, NAS can also result in a less severe form as a result of opioid agonist therapy, most notably from methadone and buprenorphine maintenance programs used in treating opioid addiction in mothers (Jones & Fielder, 2015). Although the use of methadone and buprenorphine is now recognized as appropriate care for pregnant women with opioid dependency, their use has been severely underutilized in the past with only 37% of opioid abusing pregnant women being started on opioid maintenance therapy upon admission in 2012 (Yazdy et al., 2015).

Opioid maintenance therapy was initiated as a method of treating withdrawal of heroin for short periods of time and has progressed to a long term management of any opioid addiction (Kremer & Arora, 2015). Comparison studies of morphine and methadone, full receptor opioid agonists, with buprenorphine, a partial opioid receptor agonist, suggest treating opioid

dependence with a medication from the same drug class as the abused substance (Hall et al., 2016). Although methadone use during pregnancy is shown to result in less severe symptoms of NAS and a higher birth weight when compared to heroin, buprenorphine has resulted in even greater improvement (Norgaard et al., 2015). According to Schubach et al. (2016), “methadone induces stronger withdrawal symptoms in the newborn than buprenorphine” (p. 2).

Buprenorphine offers several advantages over methadone, including decreased overdose risk, drug interactions, withdrawal severity, and provider visits (Kraft et al., 2016). Infants born to mothers in opioid maintenance therapy with buprenorphine have been shown to express higher birth weights, larger head circumferences, and greater birth lengths than those exposed to methadone (Yazdy et al., 2015). Buprenorphine is also beneficial due to its ceiling effect, reducing the possibility of overdosing, which allows less frequent visits with a provider (Kremer & Arora, 2015). Overall, buprenorphine can be used in pregnant women who are more stable with their opioid dependency and do not require observed daily dosing as is necessary for methadone (Yazdy et al., 2015).

Kremer and Arora (2015) express the importance of opioid maintenance therapy in decreasing the use of high-risk narcotics, minimizing the occurrence of a relapse, reducing the number of withdrawals afflicting the fetus during pregnancy, and inducing social changes beneficial to the future of the child. Maintaining a steady low exposure to opioids through this treatment method is considered less harmful to the fetus than continued use of illicit opioids or multiple withdrawals. With the time constraint associated with pregnancy, it is best to consider the treatment plan that will cause less harm to the unborn child and the mother. Often, by the time pregnancy is detected, mothers will not have the interval necessary to completely wean off of opioids if a true dependency is present.

An alternative treatment plan to opioid maintenance therapy is medically observed withdrawal, where detoxification is managed by professionals (Stover & Davis, 2015). During extended detoxification, patients are started on an individualized dose of methadone based on their symptoms of withdrawal and slowly weaned by 20% every 1-3 days, continuing daily support and counseling (Stewart et al., 2013). Bell et al. (2016) explain that if patients undergo detoxification, the high risk of NAS can be reduced if persistent long-term follow up is appropriately completed to prevent relapse and other unhealthy behaviors. However, the authors explain that adequate detoxification and behavioral health programs are not as readily available as is necessary to implement this plan as a standard of care. Terplan et al. (2015) further note that pregnant women with opioid addiction will be unlikely to completely detoxify without relapse due to the positive effects of opioid dependence and resulting withdrawal symptoms, making it more beneficial to be assisted with observed opioid maintenance therapy. Therefore, it is not currently recommended for pregnant women with opioid dependence to undergo detoxification due to the possibility of harm to the fetus and early induction of labor (Bell et al., 2016).

Signs and Symptoms.

The effects of NAS on the gastrointestinal, respiratory, autonomic nervous system, and central nervous system result in abnormal sleeping behavior, feeding, and autonomic function (Yazdy et al., 2015). Jones and Fielder (2015) state that several of the most common symptoms that can easily be detected and warn providers of a severe case of NAS include increased muscle tone, sweating, vomiting, and tachypnea. The authors similarly note that if untreated, NAS can progress to more critical symptoms, such as seizures, that increase the mortality associated with the syndrome. Severe side effects of continued opioid use in pregnancy include “fetal death,

intrauterine growth retardation, placental abruption, postpartum hemorrhage, preeclampsia, and premature rupture of the membranes” (Kraft et al., 2016, p. 204). Several studies have also shown associations of opioid use in pregnancy with specific birth defects, including congenital heart defects, neural tube defects, clubfoot, and orofacial clefts (Yazdy et al., 2015). Jones and Fielder (2015) note that the intricacy that ensues from maternal polysubstance abuse makes identifying and grading NAS vastly difficult due to the inability to attribute the variety of effects to one specific substance.

The clinical manifestations of NAS typically occur 48-72 hours after birth but may have a delayed onset up to 4 weeks, making early identification of opioid exposed newborns of utmost importance (Jones & Fielder, 2015). Bell et al. (2016) note that it is common practice for NICU physicians to follow up with any newborn for 3-5 days if the mother states she has been using opioids during pregnancy or if a completed drug screen is positive for opioids. Wexelblatt et al. (2016) note that during a trial implementation of a standardized maternal drug testing protocol, 20% of the urine drug screens positive for opioids were identified in mothers that showed no indication of risk factors warranting a drug test under prior protocols. Thus, universal maternal drug screening can properly prepare the hospital staff for possible NAS care in cases of unknown opioid exposure status. According to Stover & Davis (2015), verification of substance abuse in pregnant women can also be obtained through drug screening of the neonate, which can identify the specific substances that were abused. They note that urine screening is easily obtainable but restricted to recent exposure, while meconium screening can detect substances exposed to the infant as early as 20 weeks gestation. Since meconium is produced during the first few days of life, it allows for an accurate and relatively quick detection of neonatal opioid exposure, which is particularly helpful among women who remain silent about their drug use during pregnancy

(Launiainen, Nupponen, Halmesmaki, & Ojanpera, 2013). However, maternal drug testing offers earlier detection of neonatal opioid exposure than newborn drug screening due to the ability to identify opioid use before birth (Wexelblatt et al., 2016).

The Finnegan scoring system is a 31 item list that is scored every 3-4 hours to determine the severity of NAS (Stover & Davis, 2015). It includes the most common symptoms of NAS, attributing numerical values to each symptom based on its level of severity (Jones & Fielder, 2015). Wachman and Schiff (2015) explain that having trained professionals observe and score infants by utilizing the Finnegan withdrawal scale is considered to be the standard practice, but it has not yet been applied universally. According to Bell et al. (2016), “if a score of ≥ 10 is obtained twice, 3 hours apart, or ≥ 12 once, then the diagnosis is made and the newborn is further treated” for NAS (p. 2). Patrick (2015) notes that although the Finnegan score has been instrumental in diagnosing the severity of withdrawal symptoms, it is highly variable between observers and has not evolved extensively since its implementation. Although it is the current standard of identifying NAS and measuring its severity, the Finnegan scoring system and its modified forms include several drawbacks, namely the high degree of training required to use it correctly and the poor inter-rater reliability (Jones & Fielder, 2015). It is also important to note that the Finnegan scoring system was designed based on a full term infant, making it less accurate when used on preterm infants (Kraft et al., 2016).

Nonpharmacological Treatment.

Nonpharmacological treatment is considered to be the primary approach to NAS and is initiated by decreasing environmental disturbances, promoting hypercaloric feeds, and encouraging interaction with the mother (Stover & Davis, 2015). Other nonpharmacologic

treatments that benefit NAS patients include physical bonding of the mother and infant, proper parent education on the process of weaning, observation and assistance with autonomic regulation, and joining community programs aimed to serve families affected by NAS (Saunders et al., 2014). According to Jones and Fielder (2015), appropriate NAS treatment is vital to reducing the duration of symptoms and preventing recurrence of NAS.

Schubach et al. (2016) explain that skin conductance, a reliable measurement of the activation of sympathetic skin nerves in response to stress and pain in newborns, appropriately reveals increased stress in newborns with NAS as compared to those that have not been exposed to opioids. Although many stress elevating factors may increase skin conductance, the authors note that the increased skin conductance in NAS infants reveal a probable correlation to distress resulting from withdrawal due to intrauterine opioid exposure. In addition to studies of new ways to measure NAS, other researchers are attempting to confirm whether normal mother behaviors must be adjusted with NAS infants. For example, Stover & Davis (2015) advocate for breastfeeding NAS infants even if the mother is being treated with opioid maintenance therapy since the levels of the medications are found to be low in breast milk. The authors state that breastfeeding promotes maternal involvement and has been associated with less severe NAS symptoms.

Saunders et al. (2014) established a standard NAS protocol involving numerous medical specialties to be utilized during a study to determine its usefulness in improving NAS treatment. The implementation of the protocol saw a decrease in length of hospitalization, reduction in the use of adjunctive therapy, and improved weaning efficacy, providing evidence for the benefits of establishing a standardized treatment protocol that involves communication between all necessary professions. Kraft et al. (2016) note that creating a standardized treatment protocol

with multidisciplinary focus has been shown to be of greater importance than attempting to discover the ideal medication.

Patrick (2015) proposes the importance of implementing the following three objectives in a standardized treatment plan: focus on providing safe and effective care based on the needs of the infant and mother; aid the general population by providing substance abuse treatment programs and adopting better opioid prescribing practices; and reduce the cost of care by decreasing the length of hospitalization. Providers must recognize the importance of utilizing social services and opioid maintenance programs, understanding that criminalizing opioid addiction may be unproductive (Kremer & Arora, 2015). Terplan et al. (2015) explain that bringing punitive action against mothers for substance use during pregnancy by considering the action a form of child abuse is counterproductive because it prevents women from pursuing the appropriate obstetrical care and substance abuse treatment. The authors propose focusing on treating substance abuse with opioid maintenance therapy and utilizing social services instead.

Pharmacological Treatment.

Treatment of newborns with NAS includes supportive and pharmacological management, depending on the severity of NAS determined by the Finnegan withdrawal score (Schubach et al., 2016). Hall et al. (2014) state that although the majority of NAS treatment plans involve the weaning of a specific opioid, the optimal agent for treatment of NAS has not been established nationally. In many cases, hospitals have a preferred primary medication to initiate NAS treatment but still lack standardized dosing and weaning protocols between the numerous providers (Wachman & Schiff, 2015). Overall, there is no national standard for first-line

medication, threshold to begin treatment, rate of dose acceleration, rate of weaning, or conditions for adjunctive therapy (Hall et al, 2016).

Although morphine offers a more adaptable dosing schedule based on symptom severity due to its shorter half-life, methadone has been shown to decrease the number of days required for opioid treatment and is able to be less frequently dosed in severe cases based on its longer half-life (Wachman & Schiff, 2015). Buprenorphine, a partial opioid receptor agonist, offers new advantages, “including ceiling effect for respiratory depression, limited risk for outpatient misuse, longer half-life compared with morphine, and less cardiovascular effects” (Hall et al., 2016, p. 39). However, methadone and buprenorphine may result in defects in the neurodevelopment of the infant due to the inclusion of ethanol as a preservative in some preparations (Wachman & Schiff, 2015). Overall, the recent use of buprenorphine in NAS treatment has resulted in a decrease in opioid exposure and length of hospitalization when compared to methadone (Hall et al, 2016).

Dosing of opioids used to treat NAS is determined by the infant’s weight and severity of NAS based on the Finnegan score (Stover & Davis, 2015). Although weight based dosing is often utilized in neonates to prevent overdose and harmful side effects, symptom-based dosing may be more appropriate for treatment of NAS due to the relative greater exposure of opioids in smaller infants (Jones & Fielder, 2015). Weaning of opioids by 10% at regular intervals can be initiated once the symptoms of NAS have been stable under treatment for 24-48 hours (Stover & Davis, 2015). Although the exact steps in treatment are not nationally recognized, data from a study conducted by Hall et al. (2014) concluded that the greatest reduction in opioid exposure and length of hospital stay for newborns was observed when a standardized protocol was followed extensively, regardless of the opioid of choice between morphine and methadone. The

study concludes that a strict weaning protocol with a defined starting dose is more important than choosing a particular opioid when considering the significance of decreasing the amount of total opioid exposure and cost to the family.

Hall et al. (2014) note that additional therapies often utilized include comforting the neonate, decreasing sensory stimuli, and implementing the use of a sedative, most commonly phenobarbital. Infant exposure to multiple substances in utero often require more intensive treatment with adjunctive therapy (Wachman & Schiff, 2015). While no standardized approach exists in response to the failure of a first-line agent, phenobarbital and clonidine are often used as adjunctive therapy to decrease the duration of treatment and hospitalization for NAS infants (Jones & Fielder, 2015). Kraft et al. (2016) state that phenobarbital, a barbiturate, enhances the efficacy of NAS treatment with initial opioid therapy in cases of multiple substance exposure due to its general depressive effect on the central nervous system and ability to increase metabolism of drugs by cytochrome P450. However, Jones and Fielder (2015) note that phenobarbital has been observed to cause cognitive deficits in children. Furthermore, in a study conducted by Hall et al. (2016), there was no difference observed in the treatment course length of either methadone or buprenorphine when phenobarbital was added as adjunctive therapy. Clonidine, a central alpha agonist similarly used in adjunctive therapy, decreases the sympathetic tone in NAS infants but induces side effects of hypotension and rebound hypertension (Kraft et al., 2016).

Post-Hospital Care.

Previous practices of allowing continued outpatient weaning of opioids in NAS treatment have been replaced with completion of weaning during hospitalization due to the higher rates of success when the process is continuously monitored by readily available providers (Saunders et

al., 2014). Wachman and Schiff (2015) note that outpatient opioid treatment with methadone has been initiated in many instances, decreasing the cost and length of hospitalization, but it requires intensive cooperation between the family and the provider to appropriately monitor NAS symptoms and opioid dosing. Although allowing patients to be discharged from the hospital and continue with outpatient treatment of methadone can decrease the length of stay and cost to the family, it will result in a longer total treatment length of opioids (Kraft et al., 2016).

Various forms of outpatient management for both pharmacologic and nonpharmacologic needs exist. Some programs offer mothers of NAS infants an opportunity to learn parenting skills directed at the necessary extra care that must be given to infants affected by NAS (Terplan et al., 2015). These types of services are a necessary addition to long term care of NAS infants, but they are often scarce in many areas of the United States. Outpatient care, especially if involving pharmacological treatment, requires an evaluation of the home environment and access to care to determine if the family will be able to continue optimal treatment with absolute compliance (Kraft et al., 2016).

Long Term Effects.

Although the use of legal substances, such as tobacco and alcohol, during pregnancy are known to be responsible for fetal demise and developmental disabilities, the isolated long term effects of opioids are not completely clear (Terplan et al., 2015). It is generally believed that NAS may play a role in long term negative neurodevelopmental outcomes, including the development of attention deficit hyperactivity disorder and developmental delay (Saunders et al., 2014). While a few studies have attempted to assess the long term effects observed in infants exposed to opioids in utero, no clear connections have been deduced due to the inability to

differentiate long term NAS effects from environmental effects (Bell et al., 2016). Polysubstance abuse involving opioids during pregnancy has been associated with a decreased brain size, cognitive problems, and behavioral issues, but the long term effects of each individual substance requires further research (Stover & Davis, 2015). Hall et al. (2016) explain that future studies on the neurodevelopment of NAS infants treated with opioid agents are necessary to optimize current treatment protocols.

Future Direction.

Stover and Davis (2015) note that many areas of NAS still require future research, specifically the method of decreasing opioid use in pregnant women, improving opioid maintenance therapy programs, and understanding long term effects of NAS. Due to the lack of a current universal treatment protocol for NAS, future clinical trials are a promising aid in the goal to establish a standardized practice. Although many hospitals currently have a most commonly used opioid agent in treating NAS, more studies are needed to determine which medication is the most appropriate option for first line therapy (Wachman & Schiff, 2015). Future standardized protocols for treatment of NAS must be developed in order to quickly identify initial signs of NAS, accurately monitor for severity of symptoms, follow an appropriate opioid dosing and weaning schedule, provide all accessible therapeutic interventions, and decrease length of hospitalization (Saunders et al., 2014).

Jones and Fielder (2015) note the importance of future studies identifying the relative efficacy of morphine, methadone, and buprenorphine to determine the appropriate patient population that would benefit most from each agent. Wachman and Schiff (2015) propose that a single opioid agent will not be the most appropriate treatment in all cases as the agent exposed to

the neonate in utero often determines which medication will be the most efficient at treating withdrawal symptoms. Once a medication has been selected for use as treatment, the initial dosing will also vary for each individual as the maximum relief from withdrawal is associated with the specific characteristics of the prenatal exposure to opioids (Jones, et al., 2012).

As new studies will likely demonstrate the most appropriate treatment plans, current researchers are discovering other methods of altering the way in which NAS is approached. Schubach et al. (2016) suggests utilizing skin conductance in the future to compare the level of stress of NAS infants associated with the different treatment options. This approach may provide a better understanding of which treatment protocol more accurately manages levels of stress and pain associated with withdrawal in newborns. Hall et al. (2014) further emphasize the importance of investing in community programs to support mothers with NAS infants and those currently at risk. Future studies on the genetics of NAS will help to individualize treatment protocols utilizing an ideal medication and dose for an NAS infant based on the genetic factors (Kraft et al., 2016). Jones and Fielder (2015) express the necessity of developing a screening tool to be used consistently by trained professionals to identify early signs of NAS in all infants, not solely those with known maternal substance use. This method would differ from the Finnegan scoring system through its simplicity, allowing it to be a broad screening tool applied by a greater number of employees instead of an arduous instrument designed for specific cases.

Conclusion

Neonatal abstinence syndrome continues to be a growing concern due to the increasing prevalence of the syndrome and a greater understanding of the negative outcomes for the newborns. Often a result of prenatal opioid use, NAS can be more difficult to manage if addicted mothers do not follow correct protocols during the pregnancy. Although universal protocol for medication choice and dosing have not yet been established, opioid dependent pregnant women are advised to begin opioid maintenance therapy, replacing their substance abuse. It is imperative to screen regularly for opioid dependence in pregnant women with questionnaires or drug testing if consent is obtained. Patients must be educated on the outcome of opioid use during pregnancy in order to understand the necessity of initiating and continuing treatment. Providers must create a welcoming environment for patients to accurately disclose any current substance abuse and make it known that the primary concern is the health of the neonate.

With proper preparation, NAS can be well managed in the hospital setting. Patients who have been properly following up with their providers to manage opioid maintenance therapy will benefit from the hospital staff being adequately prepared for the NAS infant before its birth. With timely notification, the healthcare professionals can formulate a plan to treat the common complications that are likely to arise. Cases of unreported prenatal opioid use require correct use of the Finnegan scoring scale in order to diagnose NAS and initiate appropriate treatment. If NAS is not identified during hospitalization, infants are at risk of developing complications after discharge when professional care is not present. Thus, it is essential to perform thorough examinations and proper screening in all infants, even if they have not been reported for opioid exposure in utero.

Further research on NAS is necessary to develop improved identification and treatment of the syndrome. Implementation of a universal protocol may benefit the outcome of NAS, but one has yet to be established. There is a great call for researchers to identify the most effective treatment plan for individualized cases. In addition to accumulating information through research, providers can improve NAS outcomes through patient education. Informing patients about the need to follow up regularly with a healthcare provider is an essential practice. Continued care after mothers and NAS affected newborns are discharged is necessary to diminish relapses and long term complications. As the knowledge base concerning NAS grows, future management of the syndrome will continue to improve.

References

- Bell, J., Towers, C. V., Hennessy, M. D., Heitzman, C., Smith, B., & Chattin, K. (2016).
 Detoxification from opiate drugs during pregnancy. *American Journal of Obstetrics and Gynecology*. doi:10.1016/j.ajog.2016.03.015
- Gopman, S. (2014). Prenatal and postpartum care of women with substance use disorders. *Obstetrics and Gynecology Clinics of North America*, 41, 213-228.
- Hall, E. S., Isemann, B. T., Wexelblatt, S. L., Meinzen-Derr, J., Wiles, J. R., Harvey, S., & Akinbi, H. T. (2016). A cohort comparison of buprenorphine versus methadone treatment for neonatal abstinence syndrome. *Journal of Pediatrics*, 170, 39-44.
 doi:10.1016/j.jpeds.2015.11.039
- Hall, E. S., Wexelblatt, S. L., Crowley, M., Grow, J. L., Jasin, L. R., Klebanoff, M. A., . . . Walsh, M. C. (2014). A multicenter cohort study of treatments and hospital outcomes in neonatal abstinence syndrome. *Pediatrics*, 134(2), 527-534. doi:10.1542/peds.2013-4036
- Jones, H. E., Deppen, K., Hudak, M. L., Leffert, L., McClelland, C., Sahin, L., . . . Creanga, A. A. (2014). Clinical care for opioid-using pregnant and postpartum women: The role of obstetric providers. *American Journal of Obstetrics & Gynecology*, 210(4), 302-310.
- Jones, H. E., & Fielder, A. (2015). Neonatal abstinence syndrome: Historical perspective, current focus, future directions. *Preventive Medicine*, 80, 12-17.
 doi:10.1016/j.ypmed.2015.07.017
- Jones, H. E., Fischer, G., Heil, S. H., Kaltenbach, K., Martin, P. R., Coyle, M. G., . . . Arria, A. M. (2012). Maternal opioid treatment: Human experimental research (MOTHER) – Approach, issues, and lessons learned. *Addiction*, 107(1), 28-35. doi:10.1111/j.1360-0443.2012.04036.x

- Kraft, W. K., Stover, M. W., & Davis, J. M. (2016). Neonatal abstinence syndrome: Pharmacologic strategies for the mother and infant. *Seminars in Perinatology*, 40(3), 203-12. doi:10.1053/j.semperi.2015.12.007
- Kremer, M. E., & Arora, K. S. (2015). Clinical, ethical, and legal considerations in pregnant women with opioid abuse. *Obstetrics and Gynecology*, 126(3), 474-8. doi:10.1097/AOG.0000000000000991
- Launiainen, T., Nupponen, I., Halmesmaki, E., & Ojanpera, I. (2013). Meconium drug testing reveals maternal misuse of medicinal opioids among addicted mothers. *Drug Testing and Analysis*, 5, 529-533.
- Lindsay, M. K., & Burnett, E. (2013). The use of narcotics and street drugs during pregnancy. *Clinical Obstetrics & Gynecology*, 56(1), 133-141.
- Martin, C. E., Longinaker, N., Terplan, M. (2015). Recent trends in treatment admissions for prescription opioid abuse during pregnancy. *Journal of Substance Abuse Treatment*, 48(1). 37-42. doi:10.1016/j.jsat.2014.07.007
- Minozzi, S., Amato, L., Bellisario, C., Ferri, M., & Davoli, M. (2013). Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database of Systematic Reviews*, 12, 1-23. doi:10.1002/14651858.pub3
- Norgaard, M., Nielsson, M. S., & Heide-Jorgensen, U. (2015). Birth and neonatal outcomes following opioid use in pregnancy: A Danish population-based study. *Substance Abuse: Research and Treatment*, 9(2), 5-11. doi:10.4137/SART.S23547
- Park, E. M., Meltzer-Brody, S., & Suzuki, J. (2012). Evaluation and management of opioid dependence in pregnancy. *Psychosomatics*, 53(5), 424-432.
- Patrick, S.W. (2015). The triple aim for neonatal abstinence syndrome. *Journal of Pediatrics*,

167(6), 1189-91. doi:10.1016/j.jpeds.2015.09.047

- Saunders, C., King, T., Smith, S., Buchheit, J., Cook, K., Edds, J., & Mefford, L. (2014). Neonatal abstinence syndrome: Evaluating the effectiveness of an evidence-based multidisciplinary care approach. *Journal of Perinatal & Neonatal Nursing*, 28(3), 232-240. doi:10.1097/JPN.0000000000000049
- Schubach, N. E., Mehler, K., Roth, B., Korsch, E., Laux, R., Singer, D., ... Hunseler, C. (2016). Skin conductance in neonates suffering from abstinence syndrome and unexposed newborns. *European Journal of Pediatrics*. doi:10.1007/s00431-016-2716-8
- Shanker, S. A., Saia, K., & Lee-Parritz, A. (2012). Opioid addiction in pregnancy. *Obstetrical and Gynecological Survey*, 67(12), 817-825.
- Smith, M. V., Costello, D., Yonkers, K. A. (2015). Clinical correlates of prescription opioid analgesic use in pregnancy. *Maternal and Child Health Journal*, 19. 548-556. doi:10.1007/s10995-014-1536-6
- Stewart, R. D., Nelson, D. B., Adhikari, E. H., McIntire, D. D., Roberts, S. W., ... Sheffield, J. S. (2013). The obstetrical and neonatal impact of maternal opioid detoxification in pregnancy. *American Journal of Obstetrics & Gynecology*, 209(267), e1-5. doi:10.1016/j.ajog.2013.05.026
- Stover, M. W., & Davis, J. M. (2015). Opioids in pregnancy and neonatal abstinence syndrome. *Seminars in Perinatology*, 39(7), 561-5. doi:10.1053/j.semperi.2015.08.013
- Terplan, M., Kennedy-Hendricks, A., & Chisolm, M. S. (2015). Prenatal substance use: Exploring assumptions of maternal unfitness. *Substance Abuse: Research and Treatment*, 9(2), 1-4. doi:10.4137/SART.S23328
- Tomedi, L. E., Bogen, D. L., Hanusa, B. H., Wisner, K. L., & Bodnar, L. M. (2012). A pilot

study of the nutritional status of opiate-using pregnant women on methadone maintenance therapy. *Substance Use & Misuse*, 47, 286-295.

doi:10.3109/10826084.2011.635324

Wachman, E. M., & Schiff, D. M. (2015). Bringing attention to a need for a standardized treatment and weaning protocol for neonatal abstinence syndrome. *Translational Pediatrics*, 5(1), 12-15. doi:10.3978/j.issn.2224-4336.2015.12.03

Wexelblatt, S. L., Ward, Laura P., Torok, K., Tisdale, E., Meinzen-Derr, J. K., & Greenberg, J. M. (2015). Universal maternal drug testing in a high-prevalence region of prescription opiate abuse. *Journal of Pediatrics*, 166(3), 582-586.

Yazdy, M. M., Desai, R. J., & Brogly, S. B. (2015). Prescription opioids in pregnancy and birth outcomes: A review of the literature. *Journal of Pediatric Genetics*, 4(2), 56-70.

doi:10.1055/s-0035-1556740

Young, J. L., & Martin, P. R. (2012). Treatment of opioid dependence in the setting of pregnancy. *Psychiatric Clinics of North America*, 35(2), 441-460.

doi:10.1016/j.psc.2012.03.008

Abstract

Objective. The purpose of this literature review is to disclose the current problem of neonatal abstinence syndrome and propagate appropriate strategies by determining the epidemiology, pathophysiology, risk factors, signs and symptoms, diagnosis, management, prevention, and future objectives for NAS.

Method. PubMed and JSTOR were predominately used as the online databases for the research. The search terms used in the online databases include neonatal abstinence syndrome, opioids, pregnancy, methadone, buprenorphine, management, outcomes, and treatment.

Results. Articles were obtained discussing the rising prevalence of NAS, current prenatal management recommendations, methods of diagnosing the syndrome, various treatment options, and goals for future research.

Conclusion. NAS has experienced an increase in incidence associated with the higher rates of opioid use. Opioid maintenance therapy during pregnancy is the recommended approach to decrease the number of withdrawals the fetus experiences. After delivery, initiating and slowly weaning an opioid agonist is considered first line treatment for an NAS infant, but no universal protocol has been established. The topic of NAS continues to be an area of active research to further refine treatment.

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