FACTORS ASSOCIATED WITH THE INCIDENCE AND SEVERITY OF NEONATAL ABSTINENCE SYNDROME IN INFANTS BORN TO OPIOID DEPENDENT MOTHERS

Lisa Anne Scott

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Doctoral Committee

Susan M. Rawl, PhD, RN, FAAHB, FAAN , Chair

Carol Shieh, DNSc, MPH, RNC-OB, FAAN

July 13, 2018

Cynthia Stone, DrPH, MSN, RN

Joan Duwve, MD, MPH

DEDICATION

This body of work is loving dedicated to my mother, Evelyn Kelley Fath.

Life begins at the end of your comfort zone.

-Neale Donald Walsch

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FACTORS ASSOCIATED WITH THE INCIDENCE AND SEVERITY OF NEONATAL ABSTINENCE SYNDROME IN INFANTS BORN TO OPIOID DEPENDENT MOTHERS

Neonatal abstinence syndrome (NAS), the constellation of withdrawal symptoms experienced by neonates exposed to opioids prenatally, is an epidemic affecting an estimated 23,580 infants each year with an annual cost of $720 million. The purpose of this study was to examine factors associated with the incidence and severity of NAS as measured by the need for initiation of neonatal medication, peak medication dose, hospital length of stay (LOS), and hospital costs among newborns born to opioid-dependent mothers. A retrospective review of medical records was conducted with two convenience samples: 204 infants born to mothers who used opioids during pregnancy; and 121 of these infants who required treatment with morphine to control symptoms of NAS. Data from April 2011 to September 2017 were collected from medical records of a large Midwestern hospital. Exploratory analysis and descriptive statistics were performed.

Associations between independent variables and outcomes were examined using correlations, chi-square, t-tests, analyses of variance, and linear regression. Of the 204 neonates who were exposed to opioids prenatally, 121 (59%) developed symptoms of NAS requiring treatment with morphine. Neonates requiring morphine had significantly higher gestational ages than those who did not (37.7 vs 36.4 weeks; $p = < .001$) and their mothers were present at the neonates' bedside a lower proportion of their total hospital

stay (mean = 0.5684 of days vs 0.7384 of days; $p = < .001$). Compared to maternal use of buprenorphine, maternal methadone use was associated with higher peak morphine doses needed to control the neonate's withdrawal symptoms (0.089 mg/kg versus 0.054 mg/kg; $p = .023$), and with longer hospital length of stay when compared to maternal use of buprenorphine and other opioid analgesics (34.2 vs. 20.8 vs. 22.5 days, respectively; p=0.02). Higher visitation time from the primary caregiver was correlated with lower hospital LOS (r = -0.421; $p = < .001$). Future research is needed to examine these relationships prospectively in a larger and more diverse sample. An effective response to the epidemics of opioid use during pregnancy and the incidence of NAS requires ongoing coordinated research and intervention in clinical care, public health, and health policy.

Susan Rawl, PhD, RN, FAAHB, FAAN, Chair

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LIST OF ABBREVIATIONS

AAP	American Academy of Pediatrics
ACOG	American College of Obstetricians and Gynecologists
IOM	Institute of Medicine
FIMR	Fetal Infant Mortality Review
LOS	Length of Stay
MAT	Medication Assisted Treatment
NAS	Neonatal Abstinence Syndrome
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NGA	National Governor's Association
OUD	Opioid Use Disorder
SAMHSA	Substance Abuse and Mental Health Services Administration
SUD	Substance Abuse Disorder

CHAPTER ONE

Background and Significance

The Opioid Epidemic and Its Impact on Maternal Child Health

The use of opioids in the United States, both prescription and illicit, has increased significantly in the past 10 years (Ailes et al., 2015). There were several policy and regulatory factors which contributed to this increase. Relaxing of the restrictions on laws regulating prescribing of opioids for the treatment of chronic non-cancer pain which occurred in the 1990s, resulted in an increase in opioid prescriptions (Edlund et al., 2014; Hansen, Noe, & Racz, 2014; Kuehn, 2007; Volkow, McLellan, Cotto, Karitanom, & Weiss, 2011; Vowles et al., 2015). In 2000, the Joint Commission on the Accreditation of Health Care Organizations (JCAHO) introduced new pain management guidelines and encouraged providers to be aware of the patient's right to effective pain relief (Olsen, Daumit, & Ford, 2006; Phillips, 2000a; Vowles et al., 2015). As a result, the use of opioids for managing both acute and chronic pain was encouraged.

Other factors that contributed to increased opioid prescribing include aggressive marketing by the pharmaceutical industry, promotion of opioids to and by physicians for chronic pain management, and reports in medical and lay literature that the dangers of opioid use were exaggerated (Manchikanti, Helm, Janata, Pampati, & Grider, 2012; Phillips, 2000b; Vowles et al., 2015). This increase in opioid use has created a public health crisis with serious and fatal consequences including higher rates of opioid overdose, opioid dependence disorder, and blood-related infectious diseases (CDC, 2011; SAMHSA, 2014).

In 2008, drug overdoses in the United States were responsible for 36,450 deaths (Jones, Mack, & Paulozzi, 2013). In 2016, the total number of drug overdose deaths rose to over 63,600 in the United States (Seth, Scholl, Rudd, & Bacon, 2018). From 2015 to 2016, deaths increased across all drug categories examined. The largest increases involved cocaine (52.4%) and synthetic opioids (100 %) (Seth et al., 2018). The rate of drug overdose deaths reported involving synthetic opioids (such as fentanyl) doubled from 2015 to 2016 (Hedegaard, 2017). The overall rate of reported drug overdose deaths increased from 6.1 per 100,000 in 1999 to 19.8 in 2016 (Hedegaard, 2017). The rate of increase varied during this time increasing by 10% per year from 1999 to 2006, then by 3% per year from 2006 to 2014, and up by 18% per year from 2014 to 2016 (Hedegaard, 2017; Seth et al., 2018). The rate of overdose deaths reported has continued to increase in all categories of opioids; synthetic, natural and semi-synthetic, and heroin and across all demographics, states, and urbanization levels (Hedegaard, 2017; Seth et al., 2018).

In 2011, the Drug Abuse Warning Network (DAWN) estimated that about 2.5 million emergency department (ED) visits resulted from medical emergencies involving drug misuse or abuse, the equivalent of 790 ED visits per 100,000 population. Between 2004 and 2011, the annual overall number of ED visits attributable to drug misuse or abuse rose steadily each year for a total increase of 52 percent, or about 844,000 visits (SAMHSA, 2011).

The rate of infectious disease, such as HIV and Hepatitis-C, also increased with the growth of injectable opioid use (Grigoryan et al., 2009). Researchers estimate approximately 3.5 to 3.9 million persons in the general population of the United States have chronic hepatitis C infections (Degenhardt et al., 2016; Han et al., 2017). Among

patients with hepatitis C, 53% have a history of illicit drug use (Aceijas & Rhodes, 2007). The hepatitis C positivity rate among people who inject drugs is estimated to be as high 80-90% (Amon et al., 2008; Lavanchy, 2009; Smith, Combellick, Jordan, & Hagan, 2015). Local infections such as abscesses and cellulitis are also extremely common among persons misusing intravenous drugs (Del Giudice, 2004). A small town in rural Indiana experienced one of the most notable infectious disease outbreaks associated with opioid addiction. Austin, Indiana (population 4,200) in rural Scott County made national news in March, 2015, after reporting 185 cases of HIV related to sharing of hypodermic needles and the widespread use of the synthetic opioid, Opana ER (Conrad et al., 2015; Ungar, 2015).

Opioid medications are obtained in two ways, through prescription or through illicit sources. These two avenues can be inter-related because as the number of prescriptions increase, drugs available for diversion to illicit use also increase (Compton & Volkow, 2006; Manchikanti, 2012). Chronic use of opioids and subsequent physical dependence leads to misuse or addiction in an estimated 14-35% of people who use opioids regardless of whether opioids were introduced through prescription or illicit use (Compton & Volkow, 2006; Couto, Romney, Leider, Sharma, & Goldfarb, 2009; Manchikanti, 2010; Vowles et al., 2015).

Treatment of Opioid Use Disorder in the General Population

Opioid Use Disorder (OUD) is classified by the Institute of Medicine (IOM) and the National Institutes of Health (NIH) as a chronic medical disorder. OUD is defined in the DSM V as a problematic pattern of opioid use which leads to clinically significant impairment or distress and involving behaviors such as taking larger amounts than

intended, unsuccessful efforts to control opioid use, cravings or strong desire to use opioids, use of opioids interfering with role obligations, a great deal of time spent in activities necessary to obtain the opioid, taking opioids to relieve or avoid withdrawal symptoms, and recurrent opioid use in situations in which it is physically hazardous (Hasin et al., 2016).

Guidelines for effective treatment of OUD recommend medication-assisted treatment (MAT). MAT is the use of FDA-approved medications, in combination with counseling and behavioral therapies, to provide a "whole-patient" approach to the treatment of substance use disorders (Kampman & Jarvis, 2015; SAMHSA, 2015; Soyka et al., 2011; Volkow, Frieden, Hyde, & Cha, 2014). The FDA has approved several different medications to treat opioid use disorder. A common misconception associated with MAT is that it simply substitutes one drug for another. However, the purpose of these medications is to relieve withdrawal symptoms and restore chemical imbalances in the body. Research on treatment efficacy has shown that when provided at the proper dose, medications used in MAT do not adversely affect the individual's intelligence, mental capability, or physical function. Methadone, buprenorphine and naltrexone are medications which are recommended in MAT programs (SAMHSA, 2015).

The history of identifying affordable and effective care and integrating this care model into public health policy began more than 40 years ago. In the early 1970s, under the leadership of Dr. Jerome Jaffe, director of the Special Action Office for Drug Abuse Prevention in the Executive Office of the White House, methadone maintenance programs, the most common MAT, became a major public health initiative to treat opioid addiction. Jaffe's office oversaw the creation of a nationwide, publicly-funded system of

treatment programs for opioid addiction (Center for Substance Abuse Treatment, 2005). The goal of these treatment programs was to move from addiction to maintenance to abstinence from all opioid drugs. This is usually achieved by a gradual weaning of the treatment medication (Kampman & Jarvis, 2015; Stotts, Dodrill, & Kosten, 2009). The treatment methods proven to be most effective for opioid addiction are often expensive and labor intensive in the short term. The extended length of treatment and need for quality support and supervision of patients can be difficult to accomplish due to funding shortages and difficulty ensuring treatment quality and proper oversight (Kolodny et al., 2015; Lobmaier, Gossop, Waal, & Bramness, 2010).

Methadone continues to be used today, but other medications have been added in the effective treatment of OUD. Buprenorphine is another approved medication used to treat OUD. It is a partial opioid agonist. It has antagonistic properties as well which prevents euphoric effects. These qualities decrease abuse potential, increase safety, and cause fewer and less severe withdrawal symptoms with weaning and discontinuation (Gordon & Krumm, 2013; Lobmaier et al., 2010). It is being used increasingly as MAT, in part because it requires less supervision. Some studies indicate there may be concerns about retention in buprenorphine therapy, continued use of illicit drugs during treatment, and increased subsequent treatment needs (Bell, Trinh, Butler, Randall, & Rubin, 2009; Burns et al., 2015; Fiellin et al., 2008; Mattick & Hall, 1998)). These issues may be resolved by adjusting the dosing regimen, as retention in a fixed dose program at a higher dose, rather than a flexible dose regime, is comparable to methadone for retention in the treatment program and suppression of illicit opioid use. (Mattick, Breen, Kimber, & Davoli, 2014).

There are four possible levels of care recommended for OUD which have varying levels of reimbursement provided by Medicaid and private insurers. Current available treatment for OUD includes short term (30 day) inpatient and outpatient abstinence-based programs; however, brief or extended period detoxification therapy has been shown to be less effective in the treatment of opioid addiction as compared to treatment and stabilization with MAT (Kampman & Jarvis, 2015; Sigmon et al., 2012; Stotts et al., 2009). The addition of medication therapy serves a purpose in both biological and behavioral aspects of addiction, controlling symptoms of withdrawal with long-acting opioid agonist or partial agonist taken orally once daily and continuing a daily routine associated with drug administration (Bellg et al., 2004; Volkow, Frieden, Hyde, & Cha, 2014). To better control the current nationwide problem of increasing opioid addiction, the IOM and NIH recommended relaxing the strict regulation of MAT and expansion of availability of treatment (Rudd, 2016; Volkow et al., 2014).

Access to effective evidence-based treatment for OUD is often difficult to obtain. The current state of available services is inadequate in quality and quantity (Grogan et al., 2016; Martin, Longinaker, & Terplan, 2015a; Stein et al., 2015; White House, 2016). Substance use disorder (SUD) is categorized as a chronic illness with the need for ongoing treatment and relapse prevention (Han, Compton, Jones, & Cai, 2015; Kampman & Jarvis, 2015). However, reimbursement for SUD has always been less than payment for other chronic diseases in both private and public health insurance plans (Andrews et al., 2015; Grogan et al., 2016). Addiction, and other substance-related disorders, are misunderstood and stigmatized conditions leading to policies which produce an

inadequate benefit structure, and restrictions on access to affordable and effective care (Andrews et al., 2015; Grogan et al., 2016; McLellan & Woodworth, 2014).

Substance use disorder has never been viewed, treated, or insured like other illnesses. Many private insurance plans have never included addiction treatment in their coverage and most of addiction treatment financing has come from government sources, such as State Block grants and the Veteran's Administration, with only a small portion from private insurance (McCabe, Cranford, & West, 2008; McLellan, Lewis, O'Brien, & Kleber, 2000). The Affordable Care Act does provide for a public health approach requiring health insurers to cover, and healthcare organizations to provide, prevention, screening and brief interventions for the full spectrum of substance use disorders, not just for the most severe (McLellan & Woodworth, 2014).

It important to note there are wide disparities between US states in both coverage and availability for substance use disorder treatment. Many states do not cover all levels of care required for effective treatment which limits providers' ability to make optimal choices for treatment (Grogan et al., 2016). Researchers conducted a recent survey on the increasing need for OUD treatment and the number of providers (Jones, Campopiano, Baldwin, & McCance-Katz, 2015). They found the number of available services and providers continues to be deficient despite a marked increase in licensed providers between 2003 and 2012. The growth of providers did not keep pace with the increase in patients affected by OUD, leaving an estimated gap of nearly 1 million people nationally. The researchers' findings demonstrate significant variation between states in treatment need and capacity, but with a majority of states still having higher rates of treatment need than treatment capacity (Jones et al, 2015).

Special Considerations for Treatment in Women

Studies indicate women and men differ in both their substance abuse etiology and their access to addiction treatment (Greenfield et al., 2007; Hayes et al., 2011; CDC, 2009; Tuchman, 2010; Winklbaur et al., 2008). Although men and women demonstrate similar rates of misuse of opioids, gender differences are found in their risk factors for misuse of prescription opioids (Jamison, Butler, Budman, Edwards, & Wasan, 2010). Women with opioid use disorder have different demographic, social, and health profiles than men with OUD. Women are more likely than men to report their first exposure to opioids was physician prescribed pain medications (52% versus 38%) (Bawor et al., 2014; McHugh, Nielsen, & Weiss, 2015). Women are more likely than men to have experienced adverse childhood experiences such as childhood physical and sexual abuse (Jamison et al., 2010). Women who develop substance use disorders more frequently have antecedent comorbidities of major depression and other mental health disorders than men (Helmbrecht & Thiagarajah, 2008; Jamison et al., 2010)). Women are also more likely to have physical health problems, family history of mental illness, and greater childcare responsibilities (Bawor et al., 2014). Substance abuse treatment services that are gender-specific and tailored to the common barriers and facilitators described by women could enhance their entry into treatment (Grella, 2008; Tuchman, 2010). Very few programs offer specialized services for women and additional research is needed on the comparative effectiveness of programs of this type (Greenfield, Back, Lawson, & Brady, 2010; Messina, Grella, Cartier, & Torres, 2010).

Opioid Use during Pregnancy

Pregnant women who misuse opioids present unique and concerning health risks to both themselves and their unborn children. The incidence of pregnancy complications, such as premature labor, poor fetal growth during pregnancy, complications at delivery, and infant and fetal loss is higher among women with OUD compared to the general population (Pinto et al., 2010); (Ordean, Kahan, Graves, Abrahams, & Kim, 2015). Women who use all types of illicit drugs have a preterm birth rate of 25% compared to 9.6 % in the general population (Goel, Beasley, Rajkumar, & Banerjee, 2011; March of Dimes, 2015). The incidence of poor fetal growth or low birth weight (LBW) is significantly higher among women who use or misuse opioids during pregnancy than pregnant women in a control group (31% among women with OUD versus 5-8% in the general population) (Pinto et al., 2010). Mother's use of opioids in pregnancy is also associated with complications during labor and delivery such as postpartum hemorrhage (OR 3.02), and operative or wound complications (OR 4.85) and for the infant metabolic acidosis with an increased risk of umbilical arterial pH less than 7.0 (OR 2.65) (Losso, Friedman, & Whitten, 2017).

A mother's use of opioids not only increases complications during pregnancy and delivery but also is associated with complications after birth such as inadequate maternal-infant bonding, insecure infant attachment, and lack of maternal responsiveness to infant cues (Keegan, Parva, Finnegan, Gerson, & Belden, 2010; Mirick & Steenrod, 2016). Complications such as re-hospitalization of the infant, abuse, and neglect, and sudden unexplained infant death are also increased with maternal opioid use (Foulkes, 2015;

Friedman, Heneghan, & Rosenthal, 2009b; Nørgaard, Nielsson, & Heide-Jørgensen, 2015).

Substance use has been cited as one of the most common reasons to not seek adequate prenatal care (Friedman, Heneghan, & Rosenthal, 2009a; Phillippi, 2009). Inadequate or late prenatal care is often associated with a history of illicit substance use (Goettler & Tschudin, 2014). Barriers that inhibit pregnant women who use opioids from seeking prenatal care include fear that their substance use will be discovered, fear of losing custody of their child or child protective services involvement, stigma attached to use of drugs during pregnancy, lack of access to needed treatment and mental health programs, and lack of family or partner support (Ordean et al., 2015; Ordean & Kahan, 2011; Stone, 2015a). In a qualitative study of 36 women examining help-seeking behaviors, results indicate many women who used drugs during pregnancy did seek prenatal care but identified barriers which prevented follow through, such as fear of punitive actions from health care providers, or social service agencies. Other barriers identified included lack of access to substance abuse treatment programs and unsupportive partners (Jessup, Humphreys, Brindis, & Lee, 2003).

Women who use opioids have a complex set of needs related to pregnancy care, including SUD treatment, behavioral evaluation and treatment, and social support which are frequently not being met by the conventional prenatal care system (Jones & Kaltenbach, 2013; Scott, Shieh, Umoren, & Conard, 2017; Winklbaur-Hausknost et al., 2013). Early and comprehensive prenatal care are known to be crucial factors in improving pregnancy outcomes (Heaman, Newburn-Cook, Green, Elliott, & Helewa, 2008; Hoyert, Mathews, Menacker, Strobino, & Guyer, 2006; Partridge, Balayla,

Holcroft, & Abenhaim, 2012). This is true for all women, including those using opioids, if the programs properly address the many specific needs of this population. Women with OUD have higher rates of co-morbidities such as psychiatric illness, trauma, and prior abuse and need treatment for these integrated into a comprehensive approach for prenatal care (Haug, Duffy, & McCaul, 2014). Pregnancy may serve as a sentinel event that motivates all mothers with substance use or misuse issues to modify their behavior in the interest of improved outcomes for their infants as well as themselves (Goettler & Tschudin, 2014).

Treatment of Opioid Use Disorder during Pregnancy

Pregnancy adds another layer of complexity to treating women with OUD (McLellan & Woodworth, 2014). Programs that provide comprehensive and coordinated treatment involving prenatal care, SUD services, behavioral health, and social support provide more complete treatment and achieve more consistent participation. Recent reviews of the literature examining prenatal care models used for women with substance use disorders indicated that a collaborative approach in a high-risk specialty clinic using a standard protocol for care may decrease stigma, improve attendance, and improve outcomes for both mothers with OUD and their infants (Goettler & Tschudin, 2014; Lewis, Wu, Prasad, & Locke, 2017; Milligan et al., 2010; Tarasoff, Milligan, Le, Usher, & Urbanoski, 2018). Women enrolled in programs integrating maternity care and treatment for SUD have improved outcomes such as attending more prenatal visits and less use of illicit drugs at the time of birth (Goler, Armstrong, Taillac, & Osejo, 2008; Jones et al., 2008; Jones, O'Grady, & Tuten, 2011). However prenatal clients with OUD often do not receive either adequate prenatal care or comprehensive OUD treatment

services (Goettler & Tschudin, 2014; Goler et al., 2012). There is a shortage of OUD treatment providers willing and able to accept pregnant women (Grella, 2008; Jackson & Shannon, 2012b). The lack of available services causes resistance among obstetrical care providers to screen adequately for substance misuse during prenatal care when they are unable to facilitate proper referrals in light of a positive drug screen (ACOG, 2013).

Possible barriers and facilitators to seeking OUD treatment during pregnancy have been explored. Qualitative researchers examined the possible facilitators and barriers in pregnant women with opioid dependence and found they were often denied access to residential treatment programs because their situation was found to be "too complex" (Jessup et al., 2003). Pregnancy can be a barrier to selection of appropriate treatment regimes, as drug dependence in pregnancy is attached to additional stigma and requires provision of additional health care services that some treatment programs do not feel they can provide (Jackson & Shannon, 2012a, 2012b; Jessup et al., 2003; Martin, Longinaker, & Terplan, 2015b). The enabling factors that cause women to seek treatment for SUD include the desire to retain child custody and their concern for fetal and child well-being. Researchers found that a punitive approach toward the mother with threats and warnings is not a motivating factor and causes additional barriers to seeking care by generating distrust and therapeutic ambivalence between the mother and health care providers (Jackson & Shannon, 2012b; Jessup et al., 2003).

Women's negative prenatal care-seeking experiences, fear of discovery, and stigma limit utilization of services (Chandler et al., 2013; Stone, 2015a). If opioid use during pregnancy was promptly identified through early prenatal care and appropriate screening, many medical and social complications of perinatal opioid use could be

prevented for both the women and their children. Negative prenatal care experiences will also influence care-seeking behaviors in future pregnancies, and potentially also with seeking needed behavioral health services and SUD treatment, increasing the risk of future morbidity related to maternal opioid use (Jessup et al., 2003; Stone, 2015a).

Opioid-Related Neonatal Abstinence Syndrome

Neonatal Abstinence Syndrome (NAS), also known as neonatal drug withdrawal, is a condition characterized by a group of symptoms that occur in a newborn (infant less than 4 weeks of age) exposed to opioids via the placenta during gestation (Jansson, Velez, & Harrow, 2009; Jansson, 2012). Opioids cross the placenta and can cause dependency and subsequent withdrawal symptoms in newborns (McQueen, Murphy-Oikonen, & Desaulniers, 2015). Maternal prenatal substance use of opioids places the infant at risk for developing opioid-related NAS (Murphy-Oikonen, Montelpare, Southon, Bertoldo, & Persichino, 2010). Symptoms of NAS include tremors, sleeplessness, irritability, high-pitched cry, excoriated skin, excessive sucking, poor feeding, diarrhea, sneezing, vomiting, and seizures (Nelson, 2013).

NAS was first recognized as a public health problem and named as a syndrome in the 1970s (Finnegan & MacNew, 1974). At that time there was a national problem of heroin addiction (Berridge & Mars, 2004; Kolodny et al., 2015). Biological research conducted in the 1970s focused on newborn infant's reaction to prenatal heroin exposure, as well as reactions to methadone that was utilized in treatment of heroin addiction (Zelson, Lee, & Casalino, 1973). NAS is broadly defined with the essential attributes of 1) opioid drug discontinuation 2) followed by appearance of specific physical withdrawal symptoms related to gastrointestinal, metabolic, and neurological systems (Finnegan,

Connaughton, Kron, & Emich, 1975; Hodding, Jann, & Ackerman, 1980; Kocherlakota, 2014; Lall, 2008).

The literature on NAS provides a general consensus for specific criteria used to identify the syndrome, such as prenatal exposure to opioids and the constellation of symptoms. There are two variations in the use of the term NAS, the first, which is the focus of this study, is related to prenatal substance exposure. The second is acquired dependence from analgesia and sedation provided during neonatal medical treatment. Iatrogenic opioid and benzodiazepine dependence may require medication to control symptoms and prolong hospital stays (Hudak & Tan, 2012) however, the two types are best examined separately because of the variations in context, etiology, biology, and social implications. In this study, newborns with iatrogenic NAS will not be included.

The increasing incidence of NAS and related expenses has become a major public health concern. Between 2000 and 2009, the national incidence of NAS increased from 1.2 per 1000 live births to 3.4 per 1000 births (Patrick et al., 2012). During the same time, prenatal opioid use increased 1.19 per 1000 births to 5.63 per 1000 (Patrick, Davis, Lehmann, & Cooper, 2015). The reason for this increase in maternal opioid use is varied and includes many of the same factors described in the general population, such as an increase in general opioid prescribing (Volkow, McLellan, Cotto, Karithanonom, & Weiss, 2011), steadily increasing use of illicit narcotics (Hayes & Brown, 2012), and mothers in opioid use disorder programs with opioid medication substitution (McCabe et al., 2008). These circumstances make opioid-related NAS the most significant problem in prenatal substance exposure.

Between 55% and 95% of infants prenatally exposed to opioids will experience symptoms of NAS severe enough to require treatment with medication, such as morphine solution (MacMullen, Dulsk, & Blobaum, 2014). Medication is needed by many infants with NAS due to potential life-threatening complications of seizures, poor oral feeding, and dehydration. Weaning from these opioid medications is often a protracted process requiring slow incremental weaning of medication. This process leads to extended NICU stays, disruption of family attachment, and altered developmental experience for these newborns (Logan, Brown, & Hayes, 2013; Welle-Strand, Skurtveit, Jones, et al., 2013).

Neonatal abstinence syndrome is responsible for a significant and growing portion of the financial resources utilized in neonatal care. Rates of admission to NICU for diagnosis of NAS increased from 7 per 1000 admissions in 2004 to 27 per 1000 in 2013 (Tolia et al., 2015). Length of hospital stay for NAS infants range from 7 to 42 days, creating substantial social and economic costs. The percentage of total NICU days attributable to NAS patients increased from 0.6% to 4% between 2000 and 2009 (Tolia et al., 2015). The total cost of treatment of NAS in the US has risen from approximately $190 million in 2000 to $720 million in 2009 (Patrick et al., 2012). In 2009, the estimated number of newborns with NAS was 13,539 or approximately one infant born every 39 minutes in the United States with symptoms of drug withdrawal (Patrick, Davis, Lehman, & Cooper, 2015).

Infants diagnosed with NAS are more often insured by Medicaid as compared to other births (81.5% vs 46.4%; $p < 0.001$) (Patrick et al., 2015). Over 73% of NAS births in 2004 and 82.0% of NAS births in 2014 were insured by Medicaid (Winkelman, Villapiano, Kozhimannil, Davis, & Patrick, 2018). Among infants insured by Medicaid,

the incidence of NAS rose to 14.4 per 1000 births in 2014 (Winkelman et al., 2018). The estimated total hospital costs for NAS births insured by Medicaid was $462 million in 2014 (Winkelman et al., 2018). The increased burden on public resources is a concern for health care providers, policymakers, and elected officials and has increased attention and urgency in developing clinical care and health policies, which will reduce the incidence of maternal opioid use, reduce the occurrence of NAS, and decrease related costs (GAO, 2015; Warren, Miller, Traylor, Bauer, & Patrick, 2015).

Identifying Infants at Risk for NAS

Agreement on the most effective methods for identifying infants at risk for NAS is difficult to achieve because of the many biological and psychosocial factors that potentially act as mediators and moderators (Hall et al., 2014; L. M. Jansson & Velez, 2011). Components include universal screening of mothers during prenatal care to ascertain exposure to opioids and obtaining a thorough history to determine the infant's potential risk factors.

Identification of risk for NAS begins with identifying opioid use during pregnancy. Intrauterine exposure to opioids is the essential component which places a neonate at risk for developing NAS, but the severity and length of treatment can vary significantly, even between infants exposed to the same opioid (Abrahams, Chase, Desmoulin, Roukema, & Uddin, 2012; Lind et al., 2015; Murphy-Oikonen et al., 2010). Current guidelines from the American Academy of Obstetrics and Gynecology (ACOG) recommend screening all pregnant women for opioid use disorder by history (ACOG, 2013). Universal screening is felt to decrease stigma associated with selected or risk-based screening (Hotham, Ali, White, Sullivan, & Robinson, 2013; Seib et al., 2012). The

addition of urine drug testing can be used to detect or confirm suspected substance use but must be done only with the patient's consent and according to state laws (ACOG, 2013).

Identification of opioid use in pregnancy is important for other reasons besides predicting risk of NAS. It facilitates the mother's entry into appropriate services, addiction treatment and behavioral therapy if needed, and facilitates preparation for parenting and management of neonate (WHO, 2014). Prenatal care provides a unique entry point to coordinate services for addiction therapy and behavioral health because of additional maternal motivation of protecting fetal well-being. Additional needed services can be incorporated into routine prenatal care and specialized treatment coordinated throughout pregnancy and into the postpartum period (Jones et al., 2014).

Toxicology screening of the neonate at birth is another strategy for identifying infants at risk. Toxicology screening in not intrusive; it can be done with urine, meconium, or umbilical cord tissue samples. Screening at birth augments maternal screening and increases the likelihood of attaining accurate information regarding substance exposure of the infant (Murphy-Oikonen et al., 2010).

Assessing Severity of NAS and Need for Treatment

Two areas of neonatal abstinence care, assessment of symptoms, screening, and neonatal medication treatment guidelines have achieved improved consistency in the past decade through meta-analysis, integrative review, and the subsequent development of consensus and expert opinion-based clinical guidelines. Professional guidelines have been developed in assessing severity of symptoms and need for treatment. The American Academy of Pediatrics (AAP) published formal practice guidelines first in 1993 (AAP,

1993) and then revised recommendations in 2012 (Hudak & Tan, 2012). The committee's report included information on the scope of the problem, clinical presentation, and recommendations for identification and treatment of opioid withdrawal. Key recommendations for use in clinical practice included the use of valid and reliable screening tools to guide treatment (Hudak & Tan, 2012; AAP, 2012).

Various diagnostic tests of the neonate can be utilized to detect the presence of opioids or other illicit drugs including blood sampling, urine drug screen, umbilical cord tissue sample, and meconium drug testing. Unfortunately, all these diagnostic tests have limitations in their ability to help identify NAS. Toxicology screening can be negative in the presence of exposure and exposure alone does not guarantee development of the symptoms of NAS (Kuschel, Austerberry, Cornwell, Couch, & Rowley, 2004). Standardized instruments are necessary for assessing the severity of NAS symptoms and guiding treatment with an opioid substitute, as well as non-pharmacologic comfort measures (Ebner et al., 2007; Murphy-Oikonen et al., 2010). Choosing a valid and reliable measure, training staff adequately, and monitoring consistency of measurement are important considerations when establishing a screening method (Jensen, 2014; Retskin & Wright, 2014). NAS is comprised of constellation of opioid withdrawal signs that involve multiple body systems, CNS, gastrointestinal, and metabolic/autonomic (Bio, Siu, & Poon, 2011). Comprehensive screening tools should reflect symptoms related to each of these systems and provide a basis of uniform, objective criteria for the assessment and treatment of the neonate (Finnegan, 2010).

The first published scoring instrument for severity of NAS was developed by Loretta Finnegan and associates in the 1970s, in response to the increasing use of heroin

and subsequent identification of neonatal drug withdrawal (Finnegan, Kron, Connaughton, & Emich, 1975). The term neonatal abstinence syndrome was first defined by Dr. Finnegan and used exclusively to refer to infants exposed prenatally to heroin (Finnegan & MacNew, 1974). A scoring system was developed as a clinical and investigative tool. The score was designed to monitor opioid exposed infants in a more comprehensive and objective manner than clinical judgement alone (Finnegan, Kron, et al., 1975). The tool was also used to evaluate the efficacy of different treatments and the progression of withdrawal symptoms before, during, and after therapy. The Modified Finnegan Scoring Tool has become the gold standard and is widely used in clinical care. It had a high inter-rater reliability coefficient of 0.82 when initially developed (Finnegan, 1976; Finnegan, Connaughton, Kron, & Emich, 1975). The instrument's use over a long period of time has provided an opportunity for modification and improvement, as well as increased familiarity and consistency among providers (Kocherlakota, 2014; Kron, Finnegan, Kaplan, Litt, & Phoenix, 1975).

The Lipsitz score is also used in some clinical settings (Lejeune, Simmat-Durand, Gourarier, & Aubisson, 2006; Lipsitz, 1975). It covers symptoms in multiple areas but has fewer items than the Finnegan scale and so is felt to be easier to use (Colombini et al., 2008). The decreased number of scoring items does decrease the time involved and ease of use, however issues with consistency among raters has brought questions of reliability with the instrument (O'Grady, Hopewell, & White, 2009).

There are several instruments currently in development with testing at individual clinical sites, but no other tools widely used. The subjectivity of the current instruments is controversial and some advocate using objective measures alone, such as adequate oral

feeding and weight gain (Hunseler, Bruckle, Roth, & Kribs, 2013). An instrument using an additional objective measure of sucking quality, measured by an electronic pacifier that provides data on strength, consistency, and length of sucking burst, is a novel approach (Kron, Litt, Phoenix, & Finnegan, 1976). Although the addition of more objective measurement will likely improve consistency of scoring between caregivers, the equipment necessary is not commonly available in clinical settings (Bagley, Wachman, Holland, & Brogly, 2014).

Unfortunately, the sensitivity and specificity of current objective instruments of assessment of withdrawal intensity are only slightly more reliable when compared to subjective clinical judgment (Bagley et al., 2014). The most common difficulties reported with their use by clinical staff, are the need for detailed and consistent training and regular continuing education and updates to insure inter-rater reliability (Zahorodny et al., 1998).

Another limitation to current tools is their focus on behaviors of the newborn in the first few days of life. During prolonged hospitalizations for treatment, tools become developmentally obsolete for older neonates. Clinicians often use untested variations, such as dropping items from the tool that are no longer developmentally appropriate, such as sleeping three hours between feeding, or weighting gastrointestinal symptom items more heavily in their treatment and weaning decisions (Retskin & Wright, 2014). Some facilities report switching to a basic pediatric pain assessment tool rather than an instrument specific to NAS (D'Apolito, 2014).

In clinical practice there is a high degree of variability in assessment of NAS symptoms that range from use of published abstinence tools to inconsistent clinical

assessment strategies (Bagley, Wachman, Holland, & Brogly, 2014). Infants are typically scored every 3-4 hours with feedings and decisions on increasing and weaning medication are based on these scores. Treatment decisions based on these scoring strategies make this a crucial area for improvement to reduce length of stay. The American Academy of Pediatrics (AAP) recommends use of a standardized tool such as the gold-standard modified Finnegan abstinence assessment for evaluation of NAS (AAP, 2012). They also recommend an ongoing inter-observer reliability program to improved consistency and quality.

Guidelines for Treatment of NAS

Infants who experience clinically significant symptoms, as identified by a standardized screening tool, should be treated with appropriate pharmacotherapy. The amount and type of medication which best controls symptoms and reduces length of stay has been the primary research question in several studies (Bagley et al., 2014; Jones & Fielder, 2015). National recommendations to guide practice and treatment have been developed by professional organizations (AAP, 2012; SAMSHA, 2014). These guidelines, and the increased use of institutional protocols, have improved consistency in medication regimes, but there remains a great deal of variability in practice. There are still many questions and inconsistencies surrounding choice of opioid, dosing schedule, and weaning protocols (Jensen, 2014).

The most efficacious treatment for NAS cannot be easily determined, because of the lack of sufficient controlled studies comparing medications (Ebner et al., 2007). Recent reviews and meta-analysis warn there is a lack of high-quality evidence to support specific treatments. Current guidelines are based on expert opinion and clinical consensus

and recommend the use of an opioid to control symptoms (Osborn & Cole, 2010; Kuschel, 2007).

Initial treatment protocols for NAS favored sedation with a medication such as phenobarbital and these sedatives are still used, particularly when infants are exposed to multiple substances in utero (Osborn & Cole, 2005). The increased number of infants diagnosed with NAS brought increased experience for care providers in caring for these infants and problem areas were identified with this approach. First, sedative medications controlled CNS symptoms only and had no effect on metabolic/autonomic, or gastrointestinal effects of opioid withdrawal. Also, it was difficult to be certain these sedative medications were even effectively managing the CNS symptoms since infants cannot describe their experience. Medications other than opioids could potentially be masking, but not controlling, discomfort (Osborn, & Cole, 2010). In addition, collaboration with adult addiction specialists confirmed these potential problems based on their experiences with patients who were able to communicate directly about the experience and side effects of various agents used for MAT (Greenfield et al., 2007). Using an opioid medication for neonatal treatment was also found to decrease symptoms and shorten length of hospitalization when compared to phenobarbital (Ebner et al., 2007). In their 2012 consensus statement on opioid exposed neonates, the AAP confirmed opioid medications as the recommended pharmacotherapy for NAS (AAP, 2012; Osborn et al., 2010).

For NAS there are several possible choices for opioid medication: methadone, tincture of opium, oral morphine preparations, and buprenorphine are the recommended treatment options. Methadone is the most common choice for opioid therapy in adults and

also has been utilized for treatment of NAS. Methadone has the advantage of over three decades of patient use and testing for opioid dependence (Cleary et al., 2013; Inturrisi, Colburn, Kaiko, Houde, & Foley, 1987; Mattick et al., 2014; Mattick & Hall, 1998). It is known to be effective in adults, has low patient drop-out rates when used in OUD therapy, and its pharmacokinetics have been well-studied. However, there are several limitations to its use in infants with NAS. The long half-life of methadone, 26 hours in neonates, make timely dose adjustments and weaning difficult. This long half-life may also contribute to dose stacking and drug accumulation in the infant (Hudak & Tan, 2012; Madden et al., 1977).

Morphine-containing, tincture of opium provided the first alternative to methadone. Tincture of opium has been used safely and effectively in neonates for the treatment of NAS (Ebner et al., 2007; Sarkar & Donn, 2005; Lifshitz, Gavrilov, Galil, & Landau, 2001). Tincture of opium was the drug recommended for NAS by the AAP in their 1998 position statement (AAP, 1998). It was preferred to other available opioid preparations at that time because it contained less alcohol and other potentially harmful additives (Bio et al., 2011). There are some concerns about the formulation of tincture of opium. It is a combination medication with other alkaloid components (such as alcohol), which have effects and the alkaloid content is not standardized, so there is a question of the consistency and amount of active substance per dose.

Another alternative for neonatal opioid medication is oral morphine solution. Oral morphine solution is a feasible option with no questionable additives or alcohol (Jackson, Ting, McKay, Galea, & Skeoch, 2004). It has been shown to be effective in controlling central nervous system/ autonomic and gastrointestinal symptoms in comparisons to

phenobarbital and methadone without excessive sedation (Bada et al., 2015; Hudak & Tan, 2012; Kokotajlo, Robinson, & Presti, 2013). The half-life of morphine solution in a neonate is 6-8 hours, allowing for flexibility with dosing amount and frequency if indicated by NAS scoring tools (Bio et al., 2011; Colombini et al., 2008). In a comparison of tincture or opium and morphine solution, researchers showed similar Finnegan scores and length of stay between the two medications, with improved weight gain in the morphine group (Langenfeld et al., 2005).

Buprenorphine recently has been investigated as an option for treatment of NAS. Its use in the treatment of adults with opioid dependence has increased significantly in the past few years. It has desirable properties in addiction treatment, as it is long acting and has pharmacokinetics properties which are abuse deterrents. Buprenorphine is a partial mu opioid receptor agonist/antagonist, which binds to the mu opioid receptor with high affinity but has low intrinsic activity resulting in milder analgesia and euphoria, and it also blocks the binding of other mu agonists such as morphine (Brogly, Saia, Walley, Du, & Sebastiani, 2012; Metz et al., 2011). Buprenorphine is beginning to be examined as an alternative treatment for NAS. A randomized, open-label, control study of buprenorphine for the treatment of NAS was done comparing the agent to standard treatment with tincture of opium (Kraft et al., 2008). Dosing decisions for both groups were made by a standardized and reliable instrument (modified Finnegan scoring system). The infants assigned to the buprenorphine group had a shorter length of treatment and a shorter hospital stay (Kraft et al., 2008). The clinical group involved in the study has continued to use buprenorphine for treatment of NAS on their units and has further revised their

clinical guidelines and dosing based on continued experience with the medication (Kraft et al., 2011; Kraft & van den Anker, 2012).

Adjunctive therapy with phenobarbital and clonidine may be used with opioid medication for NAS, particularly when there is a maternal history of polysubstance use (Bio et al., 2011). Clonidine is used in pain management for adults and children, both as a primary medication and an adjunct with an opioid (Cox & Pappagallo, 2001). Clonidine also is used in combination with an opioid substitute to treat withdrawal symptoms in older children and adults (Cox & Pappagallo, 2001). Researchers compared addition of clonidine with standard therapy of an opioid and found reduced length of treatment and reduced peak doses of opioid were needed (Agthe et al., 2009). In a case study review of neonates treated with clonidine as a primary agent for opioid withdrawal infants had Finnegan scores < 8 (mean 6) and length of treatment average at 6.4 days. However, this study is limited in generalizability to all NAS patients, as the subjects were mostly preterm neonates with a mean gestational age of 30.1 weeks (range 24 to 40) and eleven of fourteen were iatrogenic exposure from treatment in the intensive care unit with a fentanyl drip. Only three infants were born to mothers who used opioids throughout pregnancy (Leikin et al., 2009). Both decreased gestational age and exposure to opioids after birth are known to decrease severity of NAS symptoms and length of treatment. The lack of current information is reflected in the AAP Committee on Drugs statement which recommends that larger clinical trials and additional pharmacologic data are needed before the routine use of clonidine can be recommended for treatment of NAS (AAP, 2012).

Phenobarbital, although decreased in use as a primary treatment, is still recommended as an adjunct therapy, particularly in infants exposed to maternal polysubstance use. A meta-analysis of phenobarbital use in NAS from the Cochrane group found reduced length of stay, reduced treatment failure and decreased NAS scores on standardized measures when compared to supportive care or opioid use alone (Osborn et al., 2005). The group does recommend further studies on safety and efficacy, as well as investigation of possible long-term effects of use on infants' developmental outcomes (Osborn et al., 2005).

Non-pharmacological Treatment Strategies of NAS

Recently several studies examined non-pharmacologic treatments such as acupuncture, acupressure, and rocking beds, as well as other non-opioid medications, for treatment of NAS but thorough discussion of these interventions is beyond the scope of review undertaken for this project (Boucher, 2017; Cox & Pappagallo, 2001; D'Apolito, 1999; Hall et al., 2014).

Currently in the United States, the most common model for environment of care in NAS patients is transfer to a neonatal intensive care unit (NICU) for observation and treatment. Kaiser Family Foundation estimates the cost per day of all diagnoses for inpatient care including physician billing, hospital costs, and ancillary services to be $2212 for the US and $ 2240 for the state of Indiana (http://kff.org/other/state-indicator/expenses-per-inpatient-day). In contrast, the average cost for a NICU stay for all diagnoses is about $10,000 (Phibbs, Williams, & Phibbs, 1981).

The hospital in which the data for study of maternal, infant, and environmental factors affecting medication use and length of hospital stay was conducted has a 26-bed

NICU and a 15-bed pediatric inpatient unit. A survey of case management records for the facility over the past six years, using cases identified for this study indicated an average cost for infants with a diagnosis of NAS of $4238 per day when cared for in the NICU. Daily costs for infants transferred to the inpatient pediatric unit for weaning of medication after initial treatment in NICU was lower at $2852. The charge for newborn nursery/ post-partum days was much lower at about $750 per day. The excessive cost of inpatient care makes reducing length of stay a priority, even 2-6 days results in a significant cost savings. There are other potential deleterious factors related to transfer of the newborn to the NICU such as separation from mother, difficulty maintaining breastfeeding, and interruption of maternal infant bonding (Brenneman & Price, 2014).

There are significant gaps in knowledge concerning many factors that may aggravate or ameliorate the illness course of infants with NAS. There are several factors, other than choice of medication substitution and weaning protocol, which have been identified in literature as possible contributors to the onset and severity of symptoms of NAS and subsequently to length of stay and hospital cost. These are typically not the focus of the study but mentioned as possible confounding factors and have received minimal attention. These factors include maternal history and demographics, exposure to other drugs, maternal tobacco use, feeding method, social support, family involvement, non-pharmacologic treatment measures, and experience of caregivers.

A more thorough examination of such non-pharmacologic factors could direct future research and facilitate development of more innovative and effective interventions related to care delivery for NAS patients. Maternal and infant screening and clinical care guidelines that have potential to decrease infant illness, decrease medication needs, limit

inpatient hospital stay, and costs are priorities for this population. The purpose of this study was to examine several of these factors which may be associated with severity of NAS, as measured by need for medication treatment and peak medication dose, length of hospital stay, and hospital cost in infants exposed to opioids prenatally.

A retrospective review of electronic and paper medical records was conducted with a convenience sample of 204 infants born to mothers who used opioids during pregnancy and 121 infants who then received medication treatment with morphine solution for symptoms of NAS from April 2011 to September 2017 at a large Midwestern hospital. Exploratory analysis and descriptive statistics were performed using IBM-SPSS statistical software package. Associations were analyzed related to the independent variables and the outcomes of interest.

Purpose and Aims

The purpose of this study was to examine factors associated with severity of NAS as measured by the outcome variables of use of neonatal medication (yes/no), peak medication dose (morphine solution in mg/), hospital length of stay (LOS), and calculated total hospital costs among newborns born to opioid-dependent mothers. Specific aims are to:

Aim 1. Identify what proportion of all infants prenatally exposed to opioids will develop symptoms that require initiation of neonatal medication to control symptoms during their first week of life.

Aim 2. Identify what maternal, infant, and environmental factors are associated with initiation of neonatal medication for treatment of NAS.

Aim 3. Among infants who receive medication, examine maternal factors (e.g. age, parity, race, reason for opioid use, type of opioid used during pregnancy, tobacco use) that are associated with level of peak morphine dose, hospital stay length of stay and hospital cost.

Aim 4. Among infants who receive medication, examine infant factors (e.g. gestational age, birthweight, and sex) that are associated level of peak morphine dose, hospital length of stay, and hospital costs.

Aim 5. Among infants who receive medication, examine environmental factors (e.g. type of inpatient unit, type of feeding method: breastmilk/formula, presence of primary caregiver, and use of non-pharmacologic interventions) that are associated with level of peak morphine dose, hospital length of stay, and hospital costs.

Conceptual Framework

Based on the review of literature a conceptual model was developed to reflect possible factors associated with the immediate outcomes of initiation of neonatal medication, hospital length of stay, and hospital costs. Research which formed the basis for the current care model for post-partum mothers and normal newborns was guided by attachment theory (Bretherton, 1992). More recently, regulation theory (Schore, 2001; Schore & Schore, 2008) was developed based on attachment theory. It is a more detailed examination of the neurobehavioral reactions developed during attachment. Regulation Theory examines potential causes of the positive effects observed from secure attachment and positive interaction. The theory has been utilized in other infants who experience prolonged separation due to admission in the NICU, such as premature infants (Weber, Harrison, & Steward, 2012). Many concerns related to infant behavior and development

that are felt to be improved by close maternal contact, such as improved feeding, infant emotional stability, and improved sleep, are closely related to the symptoms of NAS patients. Neurobehavioral and biochemical reactions facilitated by secure attachment influence the development of the infant's mood regulation and coping capacity (Schore, 2001). Influences of secure attachment on structural development of the right brain, dopamine release, endogenous opiate release, and sensory control (Schore, 2001) provide a mechanism for amelioration of many NAS symptoms. A comprehensive illustration of the model is contained in **Appendix B**. **Figure 1** below illustrates the factors that were addressed in this study.

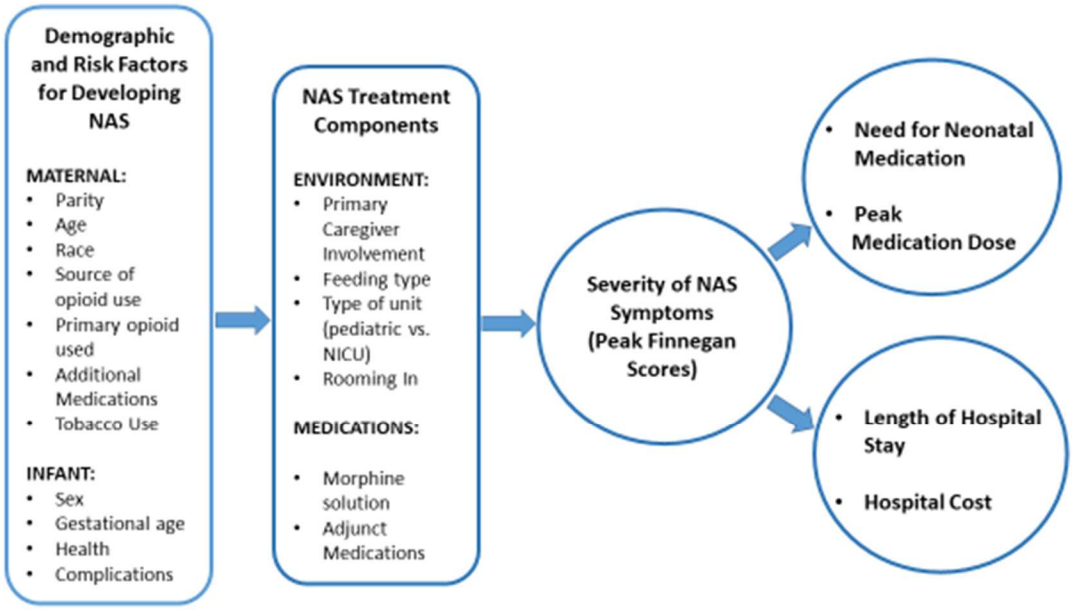

Figure 1: NAS Conceptual Model

Review of Literature: Factors that Affect the Severity of Neonatal Abstinence Syndrome

The increasing incidence and cost of neonatal abstinence syndrome (NAS) make it imperative to develop evidence-based practice guidelines for assessment and care of these neonates. An evaluation of current literature for best practice of management of neonates with NAS was undertaken which focused on three areas: identification of neonates at risk for developing NAS, valid and reliable instruments for assessing severity of symptoms and determining need for treatment, and guidelines for effective treatment. This study will concentrate on factors that may affect the development and severity of symptoms and environment of treatment components that may affect the severity of NAS and hospital course. Several key factors in each of these categories that are included in the complete conceptual model will not be examined in this study because either it is not possible to retrieve adequate information from the medical record to evaluate the factor, or there is not enough variability among the patient sample. These factors will be discussed briefly in each of the sections to illustrate their importance in future research.

Potential mediators that may contribute to the exposed infant's risk of developing clinically significant symptoms of withdrawal are also important in assessing risk. The relationship of these factors to outcomes is not well explored but they are often discussed as an incidental finding in studies with a primary research question that focus on medication regimens for the mother or the infant (Johnson, Jones, & Fischer, 2003; Jones et al., 2012; Kaltenbach et al., 2012). These influencing factors can be distributed in three categories: maternal, infant, and environmental. Maternal factors include issues related to mother's current drug use, such specific opioid drugs used, prescription of illicit use, use

of other prescription or illicit drug outside the opioid family, and use of tobacco. Infant factors examined are gender, birthweight, and gestational age.

Potential moderators of NAS severity related to potential treatment are the medication choices and environment of treatment factors that may influence the amount and severity of symptoms. Environment of treatment factors include non-pharmacologic treatments, such as swaddling, sleep promotion, use of rocking beds, location and atmosphere of treatment. The course of NAS can also be impacted by healthcare provider characteristics, such as inter-observer reliability in the NAS scoring and experience and training. A care environment of rooming-in with mother as compared to transfer to a neonatal intensive care unit, choice of breastmilk feeding, and infant care by a consistent family or primary caretaker involvement also are potential factors that influence the severity of NAS. Other pharmacologic treatment components include choice of medication for the neonate and use of adjunct medication to control symptoms when the primary medication is not sufficient.

Maternal Factors

The maternal factors examined in this study were: 1) source of opioid use 2) primary type of opioid used 3) use of other drugs/ medications 4) Tobacco use.

The largest portion of current research on these potential mediators involves maternal factors. These include comparisons of outcomes with different drugs chosen for maternal MAT (Jones, Kaltenbach, Heil, Stine, Coyle, Arria, O'Grady, et al., 2010; Patel et al., 2013; Welle-Strand, Skurtveit, Jansson, Bakstad, Bjarko, et al., 2013; Wiegand et al., 2015) and the influence of exposure to other drugs, such as selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines (Jansson et al., 2012; Wachman, 2011)

(Cleary et al., 2012; McQueen et al., 2015). Maternal tobacco use has also been mentioned as a potential risk factor for NAS (Chisolm et al., 2011; Jones et al., 2013).

Recommended prenatal treatment for the women with opioid addiction is medication-assisted treatment (MAT) with an opioid replacement (ACOG, 2012). This provides consistency in fetal medication exposure, better compliance with prenatal care, and MAT is more effective in preventing relapse than abstinence treatment programs as it addresses both biologic and behavioral aspects of withdrawal (Baker, Japuntich, Hogle, McCarthy, & Curtin, 2006). Methadone is currently the recommended drug of choice for maternal MAT (Kraft & van den Anker, 2012).

Recently, additional drugs have become available for medication maintenance therapy (buprenorphine and buprenorphine+ naloxone) (Winklbaur et al., 2008). Three studies compared buprenorphine (BMT) versus methadone (MMT) for maternal MAT (Jones, Kaltenbach, Heil, Stine, Coyle, Arria, O'Grady, et al., 2010; Welle-Strand, Skurtveit, Jansson, Bakstad, Bjarko, et al., 2013; Wiegand et al., 2015). One study compared buprenorphine versus non-buprenorphine opiate substitution, or non-opiates (Patel et al., 2013). All four studies found improved short-term perinatal outcomes such as increased GA, birthweight, and OFC with BMT. Two studies (Jones, Kaltenbach, Heil, Stine, Coyle, Arria, O'Grady, et al., 2010; Wiegand et al., 2015) also found significantly lower length of stay for the BMT exposed infants. In one study, treatment for neonates was completed as outpatients so length of stay was known but there was significant missing data for length of treatment (Patel et al., 2013). Maximum morphine doses were higher in the non-buprenorphine group in this study. There was no difference in need for medication treatment or peak NAS scores in three of the studies. However, Wiegand

(2015) did show a decreased incidence of NAS diagnosis and need for treatment. Three study designs were retrospective chart review but the study by Jones et al (2010) was a blinded randomized controlled study assigning women to MMT or BMT. An aspect worth consideration in this study was a higher maternal dropout rate that was statistically significant in the BMT group (33% versus 18% in MMT; P <.02) (Jones, Kaltenbach, Heil, Stine, Coyle, Arria, O'Grady, et al., 2010).

Benzodiazepines are often prescribed as an adjunct therapy for opioid use disorder to limit increases in opioid dose. Illicit use of benzodiazepines is also common both with persons using illicit opioids and also with clients in treatment for OUD (Winklbaur et al., 2008). Mothers who have used benzodiazepines during pregnancy have an increased rate of preterm birth, low birthweight, and hypoglycemia (Wikner, Stiller, Bergman, Asker, & Källén, 2007). Neonates exposed to benzodiazepines prenatally have associated withdrawal symptoms which overlap opioid withdrawal symptoms, such as increased muscle tone, jitteriness, and poor feeding (Wikner et al., 2007; Winklbaur et al., 2008).

Four studies provided information on the influence of exposure to other drugs, such as selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines. In all these studies, the population included was mothers in treatment with methadone. Two studies found that both benzodiazepines and SSRIs increased length of stay in infants with NAS (Cleary et al., 2012; Wachman, 2011). Two studies utilized categories for drug exposure. Forty-nine women were categorized into three groups: methadone and poly drug use; methadone only; or non-methadone treatment (Jansson et al., 2012). Infants exposed to other drugs, that included benzodiazepines, barbiturates, and cocaine, had an increased

incidence of NAS requiring medication treatment, however there was no difference in length of treatment. In another study, four groups were used; methadone only, methadone and other substances, a single non-methadone drug exposure (that included 95% other opioid and 5% non-opioid drugs), and polysubstance non-methadone (McQueen et al., 2015). A retrospective chart review was conducted that obtained 137 eligible infants. In both methadone groups, the need for treatment was higher and the length of stay longer. The methadone and polysubstance group had the longest length of stay. The number of different drugs included in the polysubstance group (10 classifications) was diverse with very small numbers in some categories. Researchers in a study comparing mothers who were concomitantly taking antidepressants and MAT with buprenorphine found the time to resolution of NAS symptoms was significantly longer in infants exposed to both buprenorphine and antidepressants when compared to those exposed to buprenorphine alone (129.8 h versus 70.2 h, $p = 0.042$) (O'Connor, O'Brien, Alto, & Wong, 2016).

It is difficult to compare tobacco effects because concomitant tobacco use is so high in addiction disorders. Cigarette smoking is reported in as much as 95% of mothers in addiction treatment (Jones et al., 2013). Researchers in two studies found an association between increased amounts of tobacco consumption and increased need for medication treatment for NAS (Chisolm et al., 2011; Jones et al., 2013). These studies included 119 and 131 subjects respectively. The remaining study which included 23 participants did not indicate relationship between increased tobacco consumption and need for treatment (O'Connor et al., 2011). All researchers mentioned an increase in adverse perinatal outcomes such as low birthweight among tobacco exposed infants.

Researchers explored incidence of NAS with maternal prescription opioid use, as opposed to illicit use (Desai et al., 2015). They used a broad review technique, which examined opioid prescriptions from Medicaid data. They concluded overall prescription opioid use was associated with a minimal risk of NAS. The design of the study limited the usefulness of this conclusion. The population included all women who filled an opioid prescription at any time during pregnancy. Infants in the groups that would be suspected of being at risk for NAS, women using prescription opioids late in pregnancy or using opioids long term (greater than 30 days) showed an increased risk for NAS.

Mothers included in this study had a variety of sources for opioid use. Some were on prescribed analgesics, some were in outpatient MAT treatment with an opioid substitute, and others were taking illicit opioids. Another possibility for prenatal opioid exposure which will not be explored is a rapid detoxification program, rather than maintenance on MAT throughout pregnancy. The possibility of rapid weaning of opioid use during pregnancy is an area of increased attention because this approach has the possibility of greatly decreasing the incidence of NAS and subsequently the cost of care (Haabrekke, Slinning, Walhovd, Wentzel-Larsen, & Moe, 2014; Stewart et al., 2013). However, the utilization of a rapid detoxification program during pregnancy is controversial. The crucial issues cited are safety of the infant without adequate means for assessing fetal well-being during rapid weaning and high incidence of potential relapse to illicit substances for the mother (Unger & Fischer, 2012; Ward, Hall, & Mattick, 1999).

The other potential maternal factors influencing severity of NAS for which there was inadequate information available in the medical record include the impact of maternal drug dose or cumulative exposure (Cleary et al., 2012; de Castro et al., 2011;

Jones et al., 2014; O'Connor et al., 2011; Seligman et al., 2010), use of prescription as compared to illicit opioids (Desai et al., 2015), and maternal treatment with rapid detoxification as compared to maintenance MAT throughout pregnancy (Haabrekke et al., 2014; Stewart et al., 2013).

Infant Factors

The infant factors examined in this study were: 1) Sex 2) Gestational age 3) Birthweight and 4) Other Health Complications.

Gestational age is frequently discussed as a factor based on anecdotal evidence and clinical experience. Preterm infants do not exhibit the same incidence or symptoms of opioid withdrawal (Dabek, Poeschl, Englert, & Ruef, 2013; Liu, Jones, Murray, Cook, & Nanan, 2010). Different physiological responses to opioids are observed in premature animals and humans (Dysart, Hsieh, Kaltenbach, & Greenspan, 2007). This may be due to metabolism, as the systems responsible for opioid metabolism in the liver are immature in a preterm infant. Another possible cause is the length and amount of exposure is decreased when an infant of an opioid dependent woman is born prior to term (de Castro et al., 2011). Differences in placental transfer also are seen closer to term with increasing amounts of opioid transfer occurring in the third trimester (Dysart et al., 2007). Researchers in a large multi-center study examined the influence of several perinatal factors including gestational age (Liu et al., 2010). Records of 232 infants exposed prenatally to methadone were analyzed by logistic regression to identify risk factors for NAS requiring treatment. Results confirmed risk was lower for younger gestational ages (Liu et al., 2010).

The effect of birthweight is often included when researchers are examining multiple maternal and infant characteristics that may influence severity of NAS. Researchers found birth weight was helpful in predicting incidence of NAS (Liu et al., 2010). Birthweight is also associated with increased risk of NAS which requires medication. A secondary analysis of a large placebo controlled RCT made comparisons about many factors, including birthweight. Researchers concluded increased infant weight was associated with increased NAS scores and greater risk of medication treatment. (Kaltenbach et al., 2012).

Several researchers have examined the influence of gender (O'Connor, O'Brien, & Alto, 2013; Holbrook & Kaltenbach, 2010; Jansson, Dipietro, Elko, & Velez, 2010; Unger et al., 2011). There is some evidence of gender related differences in opioid receptors in both animals and humans. There are indications of both quantitative and qualitative differences in opioid effects for males and females (Bawor et al., 2014). These changes are apparent in both therapeutic reaction and side effects (Dahan, Kest, Waxman, & Sarton, 2008). In a secondary analysis of data from the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study, researchers evaluated data from 131 infants who were born to mothers maintained on either buprenorphine or methadone for MAT in pregnancy (Unger et al., 2011). They compared differences between males and females in perinatal outcomes, such as gestational age (GA), birthweight, head circumference, birth mode, and Apgar scores. They also examined NAS outcomes such as peak NAS score, peak morphine dose, and duration of treatment. They found differences in birthweight and OFC with males having increased birthweight and head circumference; this is consistent with typical fetal and neonatal growth patterns. They

found no difference in any of the NAS related outcomes (Jones et al., 2012; Welle-Strand, Skurtveit, Jones, et al., 2013).

Jansson (2010) found support for the possibility of sex differences in relation to markers of changes in vagal tone and course of NAS. There were 65 infants included in the study. Findings showed males had increased peak NAS scores, there was no difference in incidence of treatment but there was increased duration of treatment and hospital stay in male infants. The study was controlled for potential confounding variable of maternal methadone dose. There was no discussion of correlation for other factors, which might affect morphine dose and length of stay such as birthweight, gestational age, and Apgar score. There was no discussion of relationship of GA, but all infants are described as term or > 37 weeks. These factors were compared in treated versus untreated infants but treated male versus treated female was not described (Jansson et al., 2010).

O'Connor also compared male versus female outcomes in mothers maintained on buprenorphine during pregnancy (O'Connor et al., 2013). The study included 90 infants. They found an increase in peak NAS score and an increase with number of males treated with medication. No difference in length of stay was found but infant medication used was phenobarbital and infants were discharged prior to weaning off medication. This treatment approach is somewhat unusual as current guidelines recommend treatment with medication of exposure. However, the author cited an unusually high rate of multi-drug exposure as their reason for using phenobarbital as the first line medication. The average GA was 37 weeks, but the range was not specified. Length of treatment also was increased with maternal toxicology screen positive for benzodiazepines, increased infant birthweight, and higher maternal methadone dose.

In the current study, information was also collected on the infant's other diagnoses or health complications during the initial inpatient stay. These factors could be confounding factors that influence length of stay and hospital cost (Berry, Shah, Brouillette, & Hellmann, 2008; Pritham, Paul, & Hayes, 2012). Other complications which may extend hospitalization include prematurity, congenital anomalies, and respiratory distress syndrome.

NAS Treatment Components

The institution of a standardized protocol for identification and treatment of NAS is recommended and is associated with a decreased LOS (Lucas & Knobel, 2012; Murphy-Oikonen, Montelpare, Bertoldo, Southon, & Persichino, 2012; Stephen W Patrick et al., 2016). The clinical facility for this study uses standard screening and treatment guidelines for infants diagnosed with NAS. These guidelines include a standard screening tool (the modified Finnegan), the use of neonatal morphine solution as the primary medication, an algorithm to direct weaning of medication, and the use of adjunct medications of either clonidine or phenobarbital. However, the use of consistent guidelines reduces the variability related to these factors in the study sample so NAS screening tools, selection of primary medication, dosing and weaning of opioid medication, routine non-pharmacologic treatments, and healthcare provider characteristics, such as experience and training could not be examined in this study. Information was collected on the use of adjunct medications, clonidine and phenobarbital, to assist in controlling symptoms as these can reflect severity of symptoms since they are recommended when symptoms are not well controlled using morphine solution.

Environmental Factors

The environmental factors examined in this study were: 1) Breastmilk feeding 2) Primary caregiver involvement 3) Location/ Inpatient unit of care (using neonatal intensive care unit versus mother infant or pediatric unit).

There were eight articles reviewed which apply to the category of environmental factors. The potential impact of breastfeeding as a possible confounding variable in severity of NAS and in treatment outcomes was discussed in three articles (O'Connor, Collett, Alto, & O'Brien, 2013; Welle-Strand, Skurtveit, Jansson, Bakstad, Bjarko, et al., 2013; Isemann, Meinzen-Derr, & Akinbi, 2011). One study detailed effects of the implementation of standardized clinical guidelines. In four studies, researchers examined location of care; rooming-in versus transfer to a neonatal intensive care unit, or inpatient versus outpatient weaning of medication (Abrahams et al., 2007' Backes et al., 2012; Hunseler et al., 2013; Metz et al., 2011).

Several studies have explored the impact of feeding method and type and describe decreased NAS scores and reduced need for medication treatment in infants who were breastfed, as compared to bottle-fed, or combination of breast and bottle, and in infants fed breastmilk. Findings in two studies indicated a shorter duration of medication therapy in breastmilk fed infants (Isemann et al., 2011; Welle-Strand, Skurtveit, Jansson, Bakstad, Bjarko, et al., 2013). Breastfeeding was associated with reduced odds of requiring neonatal medication (OR 0.55, 95% CI 0.34-0.88) in a study of 450 neonates prenatally exposed to methadone (Dryden, Young, Hepburn, & Mactier, 2009). Infants who were predominately breastfed had statistically significant lower mean NAS scores as measured by a modified Finnegan scale ($p < 0.0001$) when compared to infants who were

combination fed or predominately formula fed (McQueen, Murphy-Oikonen, Gerlach, & Montelpare, 2011). The use of breastmilk versus formula, regardless of feeding method may also affect NAS severity as measured by Finnegan scores and need for medication treatment. In a retrospective chart review of 190 drug-dependent mother and infant pairs, breast milk intake was associated with reduced neonatal abstinence syndrome severity, regardless of the gestation age of the neonate and the type of prenatal drug exposure (Abdel-Latif et al., 2006).

Current research indicates one factor which may ameliorate the severity of NAS and decrease the need for medication is a consistent primary caregiver, or maternal-newborn couplet care, rather than separation of mother and newborn (Hodgson & Abrahams, 2012; Hunseler et al., 2013). Most newborns treated for NAS are separated from their mother shortly after birth and cared for in a separate neonatal intensive care unit, potentially increasing length of stay, limiting maternal involvement, and affecting maternal attachment (Bagley et al., 2014). The problem with this care model is two-fold, mothers are not prepared to participate in care and the arrangement discourages participation. The separation further alters the developmental environment of the newborn during a critical period. Maintaining a traditional maternity care model of rooming-in for mothers and infants dependent on opioids with the mother or primary caregiver providing the majority of infant's care may decrease severity of NAS and length of stay, as well as provide additional benefits to the family for bonding and early infant development (Abrahams et al., 2007; Bagley et al., 2014; Dumas et al., 2013; Hodgson & Abrahams, 2012; McKnight et al., 2015; Metz et al., 2011; Norr, Roberts, & Freese, 1989; O'Connor, Vietze, Sherrod, Sandler, & Altemeier Iii, 1980). For the current

study, information about primary caregiver involvement was limited. The number of days the mother or caregiver visits is recorded in the infant's chart. The percentage of days the mother or primary caregiver was present at the infant's bedside during the entire hospital stay was used as a proxy for primary caregiver involvement.

In this study, we had an opportunity to compare outcomes for neonates with NAS who were cared for in the NICU and those who were cared for on the pediatric ward. Infants are initially transferred to the NICU, but some are subsequently transferred to the pediatric ward for weaning off medication and eventual discharge. The customary practice of transferring infants to a neonatal intensive care unit is receiving increased attention recently and several researchers have examined alternative approaches (Grossman et al., 2017; Holmes et al., 2016; Loudin et al., 2017; Metz et al., 2011). These include continuing in a traditional post-partum and newborn model of rooming-in on the maternity ward or a transfer to an alternative inpatient ward, either a pediatric ward, or a specialty unit specifically for infants diagnosed with NAS. Outcomes such as need for medication, length of medication treatment, and hospital LOS may be affected by differences in location of care (Grossman et al., 2017). In one study of 287 methadone-exposed infants who were admitted from post-partum unit to a pediatric ward, rather than transferred to NICU, LOS decreased from 22.4 to 5.9 days. Infants treated with morphine decreased from 98% to 14% and costs decreased from $44 824 to $10 289 ($p < .01$). No infants were readmitted for treatment of NAS and no other adverse outcomes were reported (Grossman et al., 2017).

One clinical facility created a specialized therapeutic unit for NAS patients. The environment was designed to address the needs of NAS patients including low-light, low

noise, parent involvement was encouraged, and specially trained staff and volunteers with expertise in therapeutic and support techniques were used for these neonates. A retrospective chart review identified 1023 infants with prenatal exposure to drugs as confirmed by cord tissue sample and comparisons were made between infants cared for in the NICU and those cared for in the diagnosis specific specialty unit. The creation of the new unit reduced the average daily census in the NICU, but there was no significant difference in LOS between the two groups (median stay 24 days NICU; 26 days specialty unit). There was a significant cost reduction with median cost in NICU of $90,601 and specialty unit $17,688 ($p < 0.0001$) (Loudin et al., 2017).

An environment of care model not explored in this study was the possibility of outpatient weaning of MAT. This is of interest due to potential of cost savings. Concerns about safety and medication diversion have resulted in the prevalence of inpatient weaning models. Researchers who were able to compare these two care models found that infants treated as outpatients had a longer length of treatment but a shorter length of stay. There were significantly lower hospital costs in the outpatient group (Backes et al., 2012). Although this is a critical area for future research, there are several potential problems that warrant caution. Increased length of treatment does translate to increased exposure time to methadone. Long term outcomes for the infant, such as adverse behavioral and developmental effects may be associated with cumulative methadone exposure. The other concern is screening and proper patient selection of candidates for outpatient weaning is very important. This model of care requires dependable attendance at follow-up visits which can be very challenging among the patient population with of

substance abuse disorder. Proper screening and support to navigate barriers is essential in this model of care delivery.

Summary of Literature

There has been considerable progress over the past decade on consistent recognition and appropriate medication substitution treatment for NAS. NAS is a complex problem that is multi-factorial and there are many potential influences that need to be examined to improve care and outcomes. Despite the growing scope of the problem of neonatal opioid exposure and ongoing research, there are still gaps in knowledge concerning mediating factors and the optimal treatment strategy for infants with NAS. There has been a substantial amount of research in recent years concerning which medications are best used to treat NAS and what weaning protocol should be followed although this has not lead to consistency of treatment between centers and regions (AAP, 2012; Asti, Magers, Keels, Wispe, & McClead, 2015; Kelly, Knoppert, & Koren, 2015; Kokotajlo et al., 2013).

There are gaps in current knowledge concerning risk factors for developing symptoms of NAS, proper identification and screening, and best practices in clinical care. Further exploration of potential mediators such as maternal history and demographics, exposure to other drugs, maternal tobacco use, feeding method, social support, and family involvement, have potential to help with early identification, and perhaps even prevention of clinically significant NAS requiring medication treatment. Further study in the areas of environment of care, non-pharmacologic treatment measures, moving primary care responsibilities back to parents or a primary caregiver, and strategies to insure adequate experience and preparation of health care providers all have potential to guide the

development of innovative and effective care delivery in NAS patients and to shorten inpatient hospitalization and decrease hospital costs.

Operational Definitions of Variables in the Conceptual Model

The variables measured in this study were maternal characteristics (maternal opioid use: medication used for MAT and/or other opioid use, use of other drugs, tobacco use), infant characteristics (sex, birthweight, gestational age, health complications), environment of treatment components (primary care giver involvement, location of treatment, and health care providers) and outcome variables of initiation and peak dose of neonatal morphine solution, hospital length of stay, and cost of hospital stay. The variables examined in this study are also defined and described in the table in Appendix C. The table includes operational definitions and the source used to obtain the data.

Outcome Variables. Outcome variables to be examined in this study are: 1) the incidence and severity of NAS as measured by the initiation of neonatal opioid medication, 2) peak total daily dose of neonatal opioid medication, 3) hospital LOS, and 4) hospital cost of stay. The measures used for need for neonatal medication were the initiation of medication (yes/no) and the peak dosage (in milligrams per kilogram and in total milligrams). Peak Finnegan scores were also collected as the clinical guidelines utilized at the facility recommend the use of Finnegan scores as a means to quantify severity of NAS symptoms and guide the initiation and weaning of medication. Hospital LOS is also affected by the Finnegan scores since recommendations for weaning of medication and when to discontinue medication are based on Finnegan scores. Hospital LOS was collected in days from the electronic and paper chart records. Hospital costs were collected from the case management review reports used for hospital billing. Information

contained total dollar amount billed by hospital. It does not include medical provider billing. Actual cost was only obtained for 35% of patients. A more complete estimate of cost for the entire sample was obtained using information supplied by the hospital administration and case management on the average cost per day for infants with the diagnosis of NAS. Estimates were provided for individual units of care (newborn nursery, neonatal intensive care unit, and pediatrics), but were de-identified and could not be connected to individual infants.

Intrauterine Opioid Exposure and Neonatal Abstinence Syndrome. The operational definition for intrauterine drug exposure was an ICD-9 code of 760.7 (substance affecting newborn via the placenta) or ICD-10 codes of 099.320 (drug use complicating pregnancy) and P04.4 (newborn affected by maternal drug use) and intrauterine exposure to opioids confirmed by medical record review finding maternal or infant positive toxicology screen for opioids (urine, meconium, or umbilical cord) or opioid use confirmed by maternal report. The operational definition for NAS was an ICD-9 code of 779.5 (neonatal drug withdrawal) or ICD-10 of P96.1 (neonatal abstinence syndrome neonatal drug withdrawal with symptoms) and medical record review confirming a modified Finnegan score of greater than eight or initiation of neonatal opioid medication for treatment of withdrawal symptoms.

Peak Score Modified Finnegan Scale. The modified Finnegan scale has been the most common measure of presence and severity of NAS symptoms since 1974 (Finnegan, Connaughton, Jr., et al., 1975). The tool is an observation scale dividing symptoms in three broad categories of neurological, metabolic, and gastrointestinal. It has been widely tested and utilized in practice (Orlando, 2014; Retskin & Wright, 2014; Sarkar & Donn,

2006). The tool is used exclusively in the designated clinical sites for assessment of NAS, as well as to guide treatment decisions about neonatal MAT use and weaning. Information on the Finnegan score collected included peak score, and day of life of peak score.

Maternal Characteristics. Opioid medications used by the mother during pregnancy collected by mother's report on prenatal history and hospital admission history, and by toxicology screen (maternal urine, infant urine, infant meconium, infant cord tissue). Type of opioid medication used and dose in milligrams recorded from prenatal records or mother's report. Other drugs used by the mother during pregnancy with information collected in the same ways. Tobacco use by the mother collected by mother's report and by prenatal records.

Infant Characteristics. Infant sex (male, female, indeterminate), birthweight (in kilograms), and gestational age (in weeks) was collected from electronic and paper chart birth records. The presence of other health complications which may be associated with increased hospital length of stay and hospital cost, such as prematurity, feeding disorders, genetic syndromes, and congenital anomalies was also collected.

Treatment Components-Medication. The need for neonatal opioid medication is largely determined by the modified Finnegan Scale. The need for treatment of withdrawal with an opioid medication (morphine solution) is directed by established clinical guidelines utilized throughout the medical group for initiation of treatment. Clinical guidelines for the medical group recommend initiation of neonatal medication treatment with morphine for two consecutive Finnegan scores of greater than eight, three scores of greater than eight in a 12-hour period, or one score greater than or equal to 13. The peak of dose of

morphine solution parameter was measured in three ways, in milligrams per kilogram per dose as per dose variation occur between patients based on infant weight, and as total dose medication of medication in milligrams per dose and per day, as this can impact weaning time and length of stay. Ultimately the dose in milligrams per kilogram was used in the analysis for an accurate comparison of doses among infants of different weights. The highest Finnegan score recorded during the hospitalization was also collected as a reflection of severity of symptoms. There were clinical guidelines for beginning adjunct medications such as clonidine and phenobarbital, if symptoms of NAS were not well controlled with morphine solution. The use of adjunct medication was collected by occurrence and type.

The health care provider group in the clinical facility used for this study has standardized clinical guidelines for assessment of treatment of NAS. The guidelines recommend morphine solution as the primary medication for neonatal treatment. Information about neonatal opioid medication use was collected including time to initiation of medication due to Finnegan scores in treatment range (two consecutive scores greater than 8 or one score greater than 13), peak dose of medication in milligrams per kilogram and total milligrams per day, date and time morphine solution was discontinued, any adjunctive medication in addition to morphine solution, time initiated and time discontinued. Adjunct medications were measured as yes and no, as there are standard doses for these medications and they are not adjusted.

Caregiver Involvement. Primary caregiver involvement data was collected from an observational log which is currently a standard part of charting in this patient population at the current clinical site. The bedside nurse records if the mother or primary caregiver is at the infant's bedside at the time of assessment and care. The measurements of total number of days the caregiver was recorded as at the bedside was collected. The number of visit days was then divided by the total hospital LOS to obtain the percentage of the hospital days when the primary caregiver was recorded at the infant's bedside as a way to quantify caregiver involvement.

Feeding Method. The feeding method and type was collected from the EMR and available paper records. It is unclear whether the potential benefits of breastfeeding are related to opioid medication excreted in breastmilk or to the physical closeness and involvement with a primary caregiver which the act of breastfeeding encourages. The intention for this variable was to collect both method (direct breast vs bottle) and type (breast milk vs formula), however available medical record data did not contain sufficient information on feeding method, so only type of feeding was included. Feedings were categorized in three ways: exclusive breastmilk feeding, exclusive formula feeding, and combination of breastmilk and formula feeding.

Unit of Care: Neonatal Intensive Care Unit and Inpatient Pediatric Unit. The hospital unit of care (NICU and pediatric ward) in total number of days, was extracted from electronic medical record. The location of care may be important for several reasons. The unit of care may facilitate primary caregiver involvement as the design of the units and the facilities differ. The pediatric unit is designed to accommodate parents with larger rooms, sleeping couches in every room, increased privacy, and bathroom facilities. There

may be other factors which affect hospital LOS and hospital cost as well, such as different nursing/ ancillary staff and staffing patterns.

Due to possible variation in clinical guideline adherence between individual providers which may affect the outcome variables of hospital LOS and hospital cost, the attending provider of record was also collected in days from progress notes in the EMR and from provider schedules. Additional details for conceptual and operational definitions of variables are included in **Appendix C**. The results of this study will be reported in chapter four.

Summary

Neonatal abstinence syndrome is a complex and challenging clinical and public health issue which will require a multi-pronged collaborative approach to improve outcomes. Multiple factors have contributed to the incidence and severity including social determinants of health, health policy and management, and clinical care for both women and infants. Research and interventions which go beyond identification and clinical care of the infant exposed to opioids prenatally have the potential for the greatest impact. Two additional complementary studies are included in this dissertation; one which explored the experience of the mothers with opioid use disorder (OUD), pregnancy, and fetal and infant loss (Chapter 2) and a second original study which assessed the United States public health and policy response to the increasing use of opioids during pregnancy (Chapter 3).

Collaborative research which includes representatives from the disciplines of behavioral health, maternal child health, health policy and management, and law enforcement will be able to thoroughly examine the many aspects of the problem of

increasing opioid use. Assessment of the individual experiences of women with opioid use disorder, development of health policies for prevention and treatment of opioid dependence disorder, and clinical research to support clinical decision-making for mother and infant are all required to adequately address the current problem of maternal opioid use during pregnancy and neonatal abstinence syndrome.

CHAPTER TWO: Care Experiences of Women Who Used Opioids and Experienced Fetal or Infant Loss

Introduction

Use of prescription and illicit opioids in the United States has increased significantly in the past 10 years (Ailes et al., 2015; Patrick, Kaplan, Passarella, Davis, & Lorch, 2014; Tolia et al., 2015). This increase has created a public health crisis of increased opioid dependence and addiction, drug overdose, and corresponding infectious disease (Degenhardt & Hall, 2012; Jones, Mack, & Paulozzi, 2013; Paulozzi, 2006; Roy et al., 2011). Opioid dependence during pregnancy presents unique perinatal health risks for women and their infants, including intrauterine fetal demise, low birthweight, preterm labor, and fetal and infant loss (Goettler & Tschudin, 2011; Pinto et al., 2010; Whiteman et al., 2014). Women who use opioids during pregnancy have complex needs, including addiction therapy, behavioral evaluation and treatment, and social support that are frequently not available through conventional prenatal care approaches (Jones et al., 2013; Jones & Kaltenbach, 2013; Winklbaur, Kopf, Ebner, Jung, Thau, & Fischer, 2008). Although coordinated care is critical for these women, little is known about care needs from the women's perspectives. The purpose of our qualitative study was to explore care experiences of women who used opioids throughout pregnancy and experienced fetal or infant loss.

Literature Review

Needs for Prenatal and Drug Treatment Care

From 2000 to 2009, the prevalence of opioid use in the prenatal period increased five-fold from 1.2 to 5.6 per 1,000 live births (Patrick, Davis, Lehmann, & Cooper,

2015). Compared to the general population, women who use opioids have higher rates of preterm birth (25% vs. 9.6%), low birth weight (31% vs. 5-8%), and intrauterine growth restriction (30% vs. 8% (Pinto et al., 2010). In response to the rapid increase in the use and abuse of opioids, the federal government passed the Protecting Our Infants Act of 2015. This legislation directed agencies to develop strategies to prevent and treat opioid use during pregnancy and neonatal abstinence syndrome (NAS) by assessing the comprehensive health care needs of women who use opioids during pregnancy and the long-term consequences of prenatal opioid exposure on infants (Miller et al., 2016; Ruble, 2016). The American College of Obstetricians and Gynecologists (ACOG, 2012) has developed policy statements and clinical care recommendations to improve prenatal care, substance abuse treatment availability and accessibility, and reduce NAS. Prenatal care for women who use opioids includes assessment of substance use history; referral to tertiary obstetric services or drug treatment specialists; opioid substitution therapy during antenatal, birth, and postpartum stages; and management of relapse (Abrahams, Chase, Desmoulin, Roukema, & Uddin, 2012; Arunogiri, Foo, Frei, & Lubman, 2013; Winklbaur et al., 2008).

Opioid use remains one of the most common reasons why women do not seek early prenatal care (Friedman, Heneghan, & Rosenthal, 2009; Schempf & Strobino, 2009). The stigma attached to the use of drugs during pregnancy could be a barrier. Public discourse and media attention have focused on the dangers of fetal exposure without considering the history of each woman (Kennedy-Hendricks, McGinty, & Barry, 2016). Also, the complex physical, psychological, and social needs of this population make it difficult to design appropriate, comprehensive, and coordinated care. Women

who use opioids during pregnancy are at higher risk for perinatal complications and require high-risk pregnancy services. They have additional needs for substance abuse treatment, chronic pain treatment, behavioral health services, and social support. Attitudes of care providers toward pregnant women who use opioids may also deter the women from seeking care. Goodman and Wolff (2013) found that 46% to 95% of physicians believed that drug or alcohol use during pregnancy is a form of child abuse and favored compulsory treatment for the women. However, drug treatment, such as opioid substitution therapy (OST), may not always be viewed by the women as helpful. Chandler et al. (2013) found that some women perceived OST as a barrier to normal family life because substitute drugs (e.g., methadone) gave them "a kind of fuzzy feeling" and drug treatment required frequent trips to care centers and disclosure of their drug histories to more people. As suggested by Jones et al. (2008) advancing an evidence-based approach to optimal care for women with opioid use is possible only when we know more about the needs of opioid-dependent pregnant women.

Transition to Motherhood: Care and Support for Women Who Use Opioids

In the Transitions Framework, Meleis (2000) described pregnancy, childbirth, and parenthood as lifespan transition and emphasized that a healthy transition enables an individual to feel connected, to better interact with others, and develop confidence and coping strategies. While many women easily transition to motherhood, women who use opioids may be challenged in this transition by difficulty in developing the maternal-infant relationship, custody loss, or death of the infant. Prenatal opioid use was associated with insecurity in attachment to the infant, re-hospitalization, and child abuse and neglect (Foulkes, 2015; Friedman et al., 2009; Patrick & Wu, 2015; Terplan, Kennedy-

Hendricks, & Chisolm, 2015; Worcel, Furrer, Green, Burrus, & Finigan, 2008). Mothers who use drugs may be less sensitive to infant cues and have inadequate infant care knowledge and skills. Removing an infant from a mother who uses opioids and placing the infant in a different family environment is often done to offer protection to the infant (Smith, Johnson, Pears, Fisher, & DeGarmo, 2007; Young, Boles, & Otero, 2007). However, this course of action could be viewed by the mother as punitive and can be detrimental to the mother's recovery and treatment compliance (Krans & Patrick, 2016; Ordean, Kahan, Graves, Abrahams, & Kim, 2015; Stone, 2015; Worcel, 2008). Nevertheless, loss of parental rights or custody is common for mothers who use drugs and constitutes an involuntary loss which can cause a grief response with persistent anger and could result in the need to blame others to minimize the consequences attributable to substance abuse and allow the mother to manage guilt and maintain her maternal identity (Sykes, 2011; Wells, 2011).

Another type of loss experienced by mothers who use opioids is perinatal or infant death. Women who abuse substances are 3-4 times more likely to experience fetal or infant death than the general population (King-Hele et al., 2009). Potential complications of opioid use that increase these risks are intrauterine growth restriction, premature labor, placental abruption, and sudden unexplained infant death (Jones, H. 2013a; Whiteman, 2014). Research on the perinatal or infant death experiences of mothers who use opioids is limited. Fetal and infant loss or death was described as a painful and traumatic experience for all mothers during their transitions to motherhood (Gaudet, 2010; Kersting, 2012; Rubin, 1985; Rubin & Malkinson, 2001). Mothers with such loss experience numbness, yearning, disorientation and despair (Badenhorst, &

Hughes, 2007; Bennett, 2005). Unresolved grief reactions may contribute to initial addiction or relapse of substance abuse, and addiction can also hinder the resolution of the grieving process in subsequent losses (Denny, 1984; Smith, 2009).

Substance use is a potential complication of the grief experience as bereaved mothers have as much as a two-fold increase in the need for hospitalization due to substance use over mothers who have not experienced a loss (Li, Laursen, Precht, Olsen, & Mortensen, 2005; Zuckoff et al., 2006). Some mothers seek to maintain relationships with their deceased children by carrying photographs and observing anniversaries; others may withhold emotional attachment in subsequent pregnancies until the perceived threat of loss is resolved (Lewis, 2006). Even though rates of perinatal loss are increased with maternal opioid use and the number of women who use opioids during pregnancy is increasing, there is little information in current literature about the unique aspects of these mothers' experiences. Our study, which was based on Fetal and Infant Mortality Review (FIMR) maternal interviews, was designed to explore the care experiences of women who used prescribed or illicit opioids during pregnancy and had fetal or infant loss.

Methods

Design

We conducted a thematic analysis (Sandelowski, 2000; Vaismoradi, 2013) of qualitative maternal interview data from a FIMR program in a Midwest County Department of Public Health in the United States. Our study was approved by the Institutional Review Board of Indiana University. Only de-identified FIMR data were used and were stored in a password protected drive used specifically for research data.

Participants

Inclusion criteria required participants to be age 18 or older with known histories of prenatal opioid use and fetal or infant losses. Between the years 2007 and 2012, the local FIMR program reviewed a total of 381 infant mortality cases; 194 (51%) of the mothers participated in interviews. In the same period, 26 adult mothers experienced a fetal or infant loss and were also identified as opioid users (prescribed or illicit). Of the 26 women, 11 (42.3%) participated in a semi-structured telephone or in-person maternal. Data from the 11 interviews were analyzed in this study. Interviews were conducted 3.5 – 10 months after the death (average = 5.2 months). Nine participants were interviewed by five months after infant death).

Data Collection

The 11 interviews were conducted by four FIMR program nurses who received the National FIMR Maternal Interview Training on how to conduct an interview, comply with public health and safety codes, and handle difficult encounters. Interview questions asked of each participant focused on their thoughts and perceptions of the care they and their infants received and their experiences throughout the pregnancy and loss (See **Table 1** for FIMR suggested questions). Interviewers took detailed written notes during the interviews. Audio or video recordings were not used in the interviews because of the sensitive nature of the subject. The interview notes were typed and saved in a FIMR database.

Table 1

Fetal Infant Mortality Review (FIMR) Case Study Suggested Questions

Perinatal Events	Prenatal, Labor, and Delivery	Infant's Death
Questions	Please tell me about the last few days of your pregnancy, your labor, and when your baby was born. How satisfied were you with the prenatal care you received?	How was your baby's death explained to you? What is your understanding of your baby's death? Share what happened after your baby's death.

Data Analysis

Coding and thematic analysis were conducted in three phases using the thematic analysis process described by Vaismoradi (2013). The first author is a neonatal nurse practitioner and a Ph.D. student with experience in treating infants with NAS. The second author is a prenatal health behavior researcher with experience in qualitative data analysis. In the first phase, to familiarize ourselves with the data, the first two authors read interview documents several times along with abstracted medical, obstetric, and infant data. The second phase of data analysis consisted of organizing data, including generating initial codes, searching for themes, and reviewing and naming themes. Interview data were initially organized based on the experience of pregnancy, birth, and postpartum periods (including care of the newborn), and infant care (up to 1 year). First, the two authors coded interviews independently; codes with similar meaning were grouped into themes within each perinatal stage. Then, we met in person to resolve coding and theme naming discrepancies. In the third phase of analysis, two additional

authors reviewed codes and themes: a neonatologist with experience in qualitative research and the FIMR process and the coordinator of the local FIMR program. These two team members verified whether they could follow the analysis processes (dependability) and commented on whether the themes in each stage were meaningful to individuals in clinical and public health practice (transferability). Discrepancies in this phase were resolved by group discussion via email. Data saturation was reached in each theme.

Results

Participants

The sample consisted of 11 participants (**Table 2**). The participants ranged in age from 18 to 36 years. Most were White (n = 8), single (n = 9), and with less than high school educations (n = 7). Nine participants used opioids exclusively, and two reported or tested positive for polysubstance abuse. Four participants used prescription opioids for chronic pain, one participant was in a drug rehabilitation program using methadone, and five participants used opioids illicitly. Three deaths occurred before birth (intrauterine fetal demise), three during the neonatal period (first month after birth), and the remaining five in infancy (one month to one year after birth). Six deaths were related to prematurity or congenital/genetic abnormalities, and five were caused by sudden unexpected death, pneumonia, placental abruption, or unknown causes.

Table 2

Demographics, Drug Use History, and Obstetric History for Study Participants (N = 11)

Variables	N (%)	Variables	N (%)
Age (years) Mean (SD)	25 (7.27)	Number of Pregnancies	
Range: 18 - 36		Mean (SD)	3.45 (1.97)
		Range: 1 - 6	
Ethnicity		First Pregnancy	
African American	3 (18)	No	10 (77)
White	8 (72)	Yes	3 (23)
Education		Timing of Perinatal/Infant Death	
Less than high school	7 (64)		
High school	2 (18)	Fetal stage	3 (27)
Master/PhD	2 (18)	Neonatal stage	3 (27)
		Infant stage	5 (45)
Marital Status		This Pregnancy Planned	
Married	2 (18)	No	4(36)
Single	9 (82)	Yes	3 (27)
		Unknown	4 (36)

Tobacco Use		Health Insurance	
Yes	8 (73)	Medicaid	9 (82)
No	2 (18)	Private	1 (9)
Unknown	1 (9)	None	1 (9)
		Reasons for Fetal/Infant Death	
Maternal Opioid Use		Prematurity	4 (36)
Prescription	6 (55)	Congenital Anomalies	1 (9)
Illicit	5 (45)	SUIDS/ Suffocation/Apnea	2 (18)
		Genetic Syndrome	1 (9)
		Pneumonia	1 (9)
		IUFD (abruption)	1 (9)
		Unknown	1 (9)

Note. IUDF: intrauterine fetal demise; SUIDS: sudden unexpected infant death.

Themes

Five themes were identified that represented the experiences of participants. The themes were: frustration and anger related to not being heard, feeling minimalized, being overwhelmed with attempts to process and understand medical complications and outcomes, profound sense of grief and coping with loss, need to understand why and make difficult decisions, placing blame and guilt over death.

Frustration and anger related to not being heard, feeling minimalized

Many participants voiced their frustration that care providers did not listen to their concerns during pregnancy or the infant's illness. They wanted care providers to value their input and experiences. They also wanted care providers to "listen to" and "pay attention to" them:

"My baby could have been saved if my prenatal doctor would've listened to me and paid attention to me." "I think if they looked more into what I was going through my loss could have been prevented."

"I took her to the clinic multiple times…and the doctors kept saying she was fine and not to worry about it. Then in May, I took her to get her shots and the next thing I know she's dead."

Some participants stated that providers did not ask what they wanted regarding their infant's care. Some participants felt they knew something was wrong, but care providers did not listen to their concerns: "I knew something was wrong. They never listened to me. They were all against me, and never asked what I wanted." "If my prenatal doctor would've listened to me and paid attention to my extremely high blood pressure; took my son… when I begged her to because I had pre-eclampsia and my son's heartbeat was only 118."

Some participants felt "upset" because they were not adequately informed about complications and medical treatment. They were not allowed to fully participate in care decisions. If explanations were offered, they did not facilitate the participant's understanding. The lack of information and communication frustrated the participants

and contributed to their feelings of being ignored and marginalized in making care decisions:

"Everything was going okay, not great, but okay. Then one day they told me that they removed the breathing tube, without my permission. He didn't like it, and they had to put it back in. When they put it back in, they punctured a lung and messed everything up. We had no idea what was going on, and all of sudden they handed me my son and said he was dead. I called the father, he was driving home from work, and I told him I was holding our dead baby. We had no idea what happened. I was so upset. I needed to get out of there."

Being overwhelmed with attempts to process and understand medical complications and outcomes

Some participants had preexisting medical problems (e.g., hypertension, obesity, sexually transmitted infection, hypothyroidism, sickle cell trait) and pregnancy complications, such as vaginal bleeding, placental insufficiency, or chorioamnionitis. Some participants also reported behavioral health issues such as bipolar disorder, anxiety, depression, and schizophrenia. These medical and behavioral comorbidities added complexity to their prenatal care and often required referrals. "I went from jail to the mental hospital, and they put me on a medication called Lurasidone that killed my baby. With my other children, I wasn't taking no medication, and nothing like that happened." "My OB saw me while I was in the hospital and decided to transfer me to another hospital because they didn't know what else to do. I had two blood transfusions, and they stopped the magnesium."

It was sometimes difficult for participants to identify physical signs of complications such as preterm labor. Some were seen and evaluated and sent home. As a result, they did not know whether they were actually in labor when the pain recurred. “I was having pains in my side and didn’t realize I was having contractions until I got to the hospital.” “I stayed home until the pain became unbearable and then went back to the hospital.”

Other complications during pregnancy were also common in the participants. Thoughts about hemorrhage, placental problems, and pregnancy-induced hypertension worried some mothers and increased their anxiety levels. The participants reported being anxious about their treatment, being transferred to another hospital, being told of the need for a cesarean birth, and uncertainty of the baby’s survival. “She was born two weeks before that time she could live. Her heart and lungs were underdeveloped. They said she might make it and might not.” “I went to the hospital and was bleeding everywhere. Pool of blood. They said my daughter swallowed it.”

Profound sense of grief and coping with loss

Participants struggled to deal with grief. They expressed “how lost I feel about losing him” and “this is a very hard thing to go through.” Some participants wished “there was something you can do” to bring back their infants. Others thanked God for having other children who were alive. “Do you know how hard it is to deal with this after having him inside you all these months and then touching his hands and feet? This has been the worst 5 months of my life.” “That is a very hard thing to go through, and you still wish there was something you could do.” “…just how lost I feel about losing him and how lost I am without him! I just thank God for my other sons.”

Participants talked about the support they received during the experience with grief. Some expressed appreciation for bereavement services, such as booklets on bereavement, molds of handprints and footprints, or photographs. Others experienced frustration and disappointment because they did not receive enough support or resources. Participants also expressed receiving various degrees of professional bereavement support. Some had begun counseling with a psychiatrist or were considering grief support groups. "Everyone at the hospital was excellent. They made molds [of my baby's hands and feet]. I was worried that I couldn't afford to bury her, so they let me talk to the trustee."

"I am seeing [a] psychiatrist right now for my grief. I think it is helping. I am not ready to talk to people about it in a group or talk to other people. It's just too hard, and I am not ready."

Some participants had difficulty managing their grief and others actively made plans for closure through a "memorial service" for their baby, spirituality, and family support. They sought validation for their feelings of grief and loss but sometimes felt pushed by family and friends to move on. "We had a memorial service for him and buried him at the cemetery…We are doing okay with the loss; we have a lot of family."

"Can I ask you something? People tell me the more I talk about her, or keep wanting to celebrate her birthday; I will never get over her …Do you think it is okay to celebrate her birthday?"

Need to understand why and make difficult decisions

Participants expressed that they were adept at recognizing changes in their infant's health status (e.g., coughing and throwing up or not breathing) particularly after

hospital discharge. They sought medical attention and explanations. However, there were times some participants had to make difficult decision about care and treatment. “My baby did good at first. When he was 3 and half or 4 months old I noticed he couldn’t open his hand or sit up straight.” “I took her to the hospital and clinic multiple times because she was coughing and throwing up.” “I called out for someone to call 911 and started CPR, but it was already too late.” “His father and I decided to take him off the machine.”

Participants wanted to understand and make sense of their infant’s death. Knowing how and why their infant died seemed to offer them a “closure.” Knowing the cause of infant death was also important for them to understand implications for future children. They also wanted reassurance that their care, as a parent, and the health care provided was sufficient as “they did what they could for her [infant].” “Well, at least now we have closure. I wish someone had told us sooner; we have been going nuts not knowing.” “Now I know he did die because of sleep apnea.” “They said she had a tube defect and it was an encephalocele, and she couldn’t live.” “I don’t remember the name of the condition he had, but the doctors said it was genetic.”

Placing blame and guilt over death

Participants responded to infant death with two reactions. Some blamed health care providers because “they are responsible for her [infant] death.” Others blamed themselves for the infant’s death and believed that if they had done something to help the baby, the death would not have occurred. “I believe the OB doctors should be checked out. My baby could have been saved …” “I wanted to sue the hospital and clinic because they are responsible for her death.”

At times, pressure from family and friends precipitated feelings of self-blame and guilt. Occasionally, participants turned the blame to themselves and searched for how they might have prevented the death. “If we had used the monitor he might be alive. I wish we had kept on using the machine anyway.” “When I woke up, I knew something was wrong. I freaked out. So I told everyone she dies in her crib. But she was in bed with me. I tell everyone I know, see with a baby, everyone- not to sleep with their baby.” “All my friends and family thought I killed my baby. They kept saying I smothered her and stuff. My mom was real angry, but she was also crying.”

Discussion

Our results indicate that women who used opioids and experienced infant/fetal loss had complex needs which were often unmet. Of note, participants in our study repeatedly voiced concerns about not being heard, being ignored, and being undervalued. These concerns may be related to the stigma of addiction; however, it is also likely that they may have been exacerbated by participants’ anxiety about their high-risk conditions and frequent urgent medical treatments. The perception that their feelings were minimalized could also reflect their frustration and helplessness over the deaths of their infants. In previous studies on addiction, women expressed feelings of stigmatization from family, friends, society, and health care providers (Chandler et al., 2013; Earnshaw, Smith, & Copenhaver, 2013; McGinty, Goldman, Pescosolido, & Barry, 2015). If allowed to develop, these perceptions of stigma can create a lack of trust in individual health care providers and the health care system and serve as barriers to accessing care (Casper & Arbour, 2013; Winklbaur et al., 2008).

Many participants in our study had difficulty understanding why devastating medical complications occurred for them and their infants and often felt the

communication from health care providers was inadequate, incomplete, or difficult to understand. This problem of incomplete understanding may be caused partially by the stress and uncertainty of the situation itself, but also may reflect a lack of communication skills among health care providers (Pozzo, Brusati, & Cetin, 2010). Several previous studies conducted with patient populations facing high stress and complex medical situations, such as cancer or high-risk pregnancy, have indicated the need for standard protocols and practice in delivering bad news (Pozzo et al., 2010). In the context of maternal opioid users experiencing fetal and infant complications, providers could also be helped in their regular communication by training on how to deal with the mothers' emotional reactions and the mother's need to be well informed. Communication would be enhanced if health care providers created illustrations and provided information in clear and simple terms. Mothers who report satisfaction with the information they receive are better prepared to take action and make good decisions (Makary, 2015).

Dealing with grief, guilt, and blame was an ongoing process for participants from the first time infant complications were identified through the infant's death and months later. Although every mother grieves in her own way, lack of support may prolong grief (Badenhorst, 2007; Cacciatore, Schnebly, & Froen, 2009; Kersting & Wagner, 2012). Moreover, the perinatal loss can be a trigger for addiction relapse (Smith, 2009). Bereavement support can help mothers with fetal/infant loss acknowledge their feelings of guilt over blame and the added burden of stigmatizing addiction (Bennett, Litz, Lee, & Maguen, 2005; Murphy, Shevlin, & Elklit, 2014).

Anger and blame towards others, or self is a typical reaction after a perinatal loss, particularly when mothers feel unsupported or uninformed (Badenhorst, 2007; McCright,

2008; Cacciatore, Frøen, & Killian, 2013). Providers need to recognize that grief may be expressed in many ways, including blaming others. Blame is a normal aspect of grief in perinatal loss and many mothers blame themselves for their loss which may be a barrier to resolution of grief (Cacciatore, 2013). However, our participants turned blame toward themselves with less frequency than in general perinatal grief studies (Badenhurst, 2007; Kersting, 2012)). Blaming others may represent an abnormal grief reaction related to the need to minimize implications of substance use. Regardless of the reason, providing support and counseling is essential.

Limitations

The use of secondary data analysis provided only a narrow window into the care experience of the mothers. The FIMR interview was constructed for a specific purpose of identifying multiple maternal and infant healthcare, social, and community service issues. We were unable to clarify participants' care experience with additional interview questions. We were also unable to explore specific care experiences regarding methadone use or other drug treatment during pregnancy. The interviews were not recorded on audio or visual media. Although extensive written notes were completed based on the FIMR protocols, written notes might not have captured all information given by each interviewed mother. The range of time between the loss and the interview (3.5 to 10 months) is also a possible limitation. Grief is an individual experience and mothers interviewed soon after their infant's death may report a very different experience than those interviewed several months later. Unique perspectives related to opioid use and dependence may also affect the grief experience.

The secondary data analysis also prevented us from conducting member checks. Member checks reviewing the themes identified with the participants would have helped validate our findings. Our study was limited to a small number of women in one local FIMR program. Further study is needed to determine whether findings our similar with other similar women.

Implications for Practice

Our findings indicate that health care providers need to partner with women who use opioids designing care and making treatment decisions that acknowledge their needs, perceptions, and satisfaction are important (Wolf, Lehman, Quinlin, Zullo, & Hoffman, 2008). Such a partnership fosters respect, shared decision making, and a caring environment where mothers who use opioids concerns can be addressed. This partnership focus also encourages care providers to be sensitive to the needs of these women to help reduce the perception of stigmatization and increase the perception of being valued.

The need for health care provider education and training in effective and sensitive communication is evident from this study. The participants' perception was that caregivers who did not listen to them, minimized their feelings, and were unsupportive, contributed to their pain, guilt, and bereavement experience. Projecting acceptance, accessibility, and readiness to listen is essential, as well as providing understandable medical information about the care provided and procedures performed (Fleischer, Berg, Zimmermann, Wüste, & Behrens, 2009). It is important to understand communication is bidirectional and the patient's interpretation of the message may be very different than the nurse's intended message (Kourkouta & Papathanasiou, 2014). It is also necessary to

continually assess the mother's knowledge and confirm understanding of health information given.

Comprehensive multidisciplinary care models may provide opportunities for care providers from different disciplines to develop coordinated care plans for opioid-using mothers and their infants, as well as to enhance communication among care providers. Continuing education programs or conferences could emphasize multidisciplinary aspects of care for the mothers with opioid use.

Bereavement support and counseling is particularly important for the mothers who use opioids and experience perinatal or infant death. Such support and counseling may need to be long-term in order to resolve the mothers' reactions of guilt, anger, and blame. There is a need to improve patient-provider communication and to address both individual and systems failures which may lead to poor outcomes through formal review processes such as FIMR and Child Death Review programs.

Recommendations for Future Research

Further exploration of this topic could best be accomplished with a phenomenology approach using open-ended interviews. This would provide a richer and more complete description of the participants' experience. More focused exploration divided by the timeframe of the loss (fetal, neonatal, or infant) may also aid in theory development, as well further defining guidelines for effective practice.

Conclusions

The rapid increase in opioid use among pregnant women has led federal agencies to demand more research to determine best practice for caring for affected women and infants. We examined the care experiences of women who used opioids throughout

pregnancy and experienced fetal or infant loss. Five themes were identified: not being heard, or feeling minimalized, being overwhelmed with attempts to process and understand medical complications and outcomes, a profound sense of grief and coping with loss, a need to understand why and make difficult decisions, a need to place blame and assign guilt over death. The study findings suggest interdisciplinary team care, partnership in decisions, provider training for skillful communication, and emotional support for mothers with opioid use and pregnancy or infant loss. These findings have been published prior to their presentation here (Scott, Shieh, Umoren, & Conard, 2017). A release of copyright is included (**Appendix A**).

In thoroughly addressing the needs of mothers who use opioids during pregnancy and their newborn infants, a collaborative effort with families affected, healthcare providers, public health providers, and policymakers is vital. Policy decisions inform and reflect public opinion concerning mothers who use opioids during pregnancy. Gaps in research, availability of treatment, and coordination of services are closely related to health care policy decisions. The priorities set for legislation, public health policy, and funding of opioid use disorder treatment and prevention determine availability and reimbursement for treatment and ancillary services. An examination of current US state policies and services related to opioid use in pregnancy and NAS is an essential step in developing viable plans for optimal care of women and infants.

CHAPTER THREE: Survey of US States' Policies Regarding Maternal Opioid Use and Neonatal Abstinence Syndrome

Introduction

Opioid abuse and misuse among pregnant women have reached epidemic proportions and has influenced maternal child health policy at the federal, state, and local levels. The number of women taking opioids during pregnancy increased five-fold between 2000 and 2009 (1.2 per 1000 live births to 5.6 per 1000) (Patrick, Davis, Lehmann, & Cooper, 2015). Much of this increase is related to prescription opioid use and abuse. Between 1992 and 2012, the proportion of pregnant women admitted for substance abuse treatment that reported a history of prescription opioid abuse increased from 2% to 28% (Krans & Patrick, 2016). The rapid increase in the incidence of this problem, as well as the accompanying economic and societal costs, has attracted attention and research focus by many health care professionals and policymakers. It is essential that health care policy be informed by research and evidence-based guidelines which support optimal outcomes for both pregnant women and their infants.

Background and Significance

In 2015, the Government Accountability Office (GAO) published "Prenatal Drug Use and Newborn Health," a report that discussed current gaps in research and programs related to services for mothers during pregnancy and services for their infants after birth. Research gaps focused on treatment of opioid use during pregnancy and the long-term effects of prenatal opioid exposure on children. The lack of available treatment programs for both pregnant women and newborns with neonatal abstinence syndrome (NAS) was identified as a service gap. Other gaps included a lack of guidance for and coordination

among behavioral health providers, prenatal care providers, public health professionals, and policymakers in their efforts to address prenatal opioid use or NAS. Experts also noted that the most effective treatment options were hindered by difficulties in identifying and retaining pregnant women with substance use disorders for research. Recruitment to studies is hampered by women's reluctance to participate in such studies due to fear of criminal charges or other repercussions from discovery (GAO, 2015; Poland, Dombrowski, Ager, & Sokol, 1993; Stone, 2015).

The purpose of this study was to examine current US state policies and services related to opioid use in pregnancy and NAS, specifically, how these policies have evolved recently related to the increased population of opioid use disorder and how well current policies align with the federal and state objectives for women and infants outlined in the *Protecting Our Infants Act of 2015* and in the National Governor's Association (NGA) statement on *Priorities for Addressing the Nation's Opioid Crisis* (NGA, 2016) .

Conceptual Framework

The concepts of substance misuse and addiction have been approached from many different perspectives, all have contributed to understanding the causes, consequences, and potential development of effective interventions. However, all the approaches have some shortcomings in offering a comprehensive explanation for the behavior and success or failure of existing treatment models. Several broad categories of theory can be identified, individual susceptibility, addictive stimuli, motivational constructs, socioeconomic and environmental factors, bio-psychological factors, and pharmacokinetics (Köpetz, Lejuez, Wiers, & Kruglanski, 2013; West, 2001). Interesting approaches related to behavioral economics (Worley, Shoptaw, Bickel, & Ling, 2015)

and attachment theory (Flores, 2006) blend biological, motivational, and behavioral factors. The number of theories and conceptual models developed to describe substance use disorder illustrate the difficulty in developing a comprehensive theory to explain human behavior.

Kovac (2012) attempts to integrate the many different theoretical frameworks by emphasizing these different approaches are not mutually exclusive, but rather complementary. The multi-sourced model of addiction (Kovac, 2013) acknowledges the complexity and synergy that exists between various explanations. This model focuses on the individual, but emphasizes the influence of pre-disposition, actions/choices, neurobiology, social, historical, and cultural context, and neurobiology (see **Figure 2**). This model does not favor a sole mechanism or a simple interactive effect but instead describes factors, which concurrently act to form a forceful behavioral pattern (Kovac, 2013).

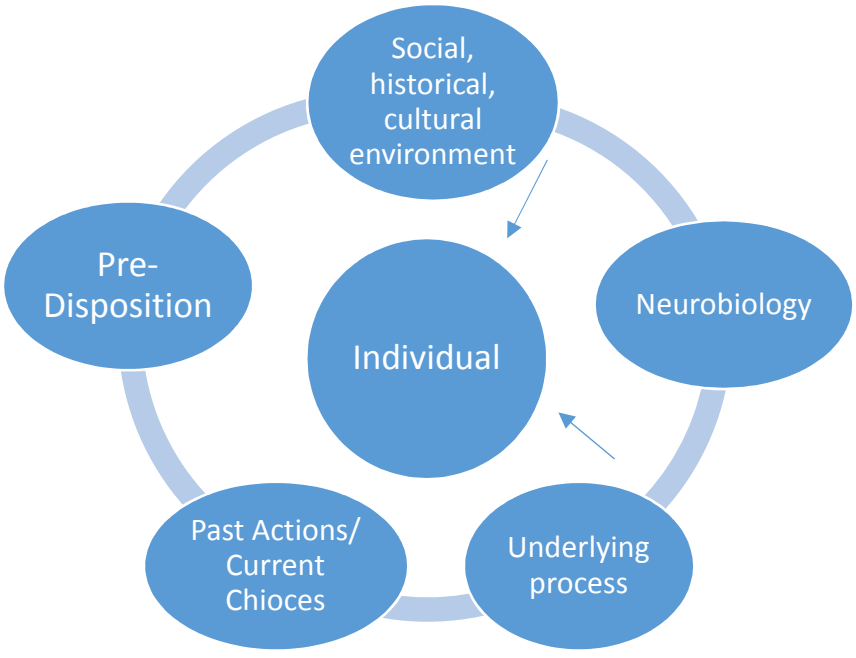

Figure 2: Kovac (2012) A Multi-sourced Model of Addiction

Research Aims

- Assess U.S. state legislatures current response to the public health and economic issue of increases in opioid use disorder and its impact on pregnant women and infants as reported by survey respondents.
- Assess the impact of federal and state policy objectives *(Protecting Our Infants Act of 2015* and NGA priorities statement*)* and professional guidelines concerning opioid use disorder in pregnancy on public health and legislative initiatives as reported by survey respondents.

Review of Literature

The rising incidence of opioid use disorder during pregnancy and the subsequent escalation of NAS, and its related expense, have brought increasing attention by health care providers, policymakers, and payers. Professional organizations, such as the American College of Obstetricians and Gynecologist (ACOG), the American Academy of pediatrics (AAP) and the American Society for Addiction Medicine (ASAM) have published guidelines or position statements concerning the treatment of substance abuse in pregnancy and NAS (Hudak & Tan, 2012; Kampman & Jarvis, 2015; Krans & Patrick, 2016). Through the *Protecting Our Infants Act of 2015* (S.799/H.R.1462) (Congress, 2016), the federal government has described objectives for establishing and disseminating best practice strategies and recommendations for diagnosis and treatment of NAS (White House, 2016). State priorities have been described by the National Association of Governors (NGA) concerning prevention and treatment of opioid use disorder (Desai, Hernandez-Diaz, Bateman, & Huybrechts, 2014). Private and public healthcare payers are also developing strategies to mitigate their costs and limit patient exposure to potentially addictive opioid medications (Katz et al., 2013).

The *Protecting Our Infants Act of 2015* (Public Law 114-91/S.799/H.R.1462) is an ambitious directive which outlines priorities for research, education, and treatment. This bill requires the Department of Health and Human Services (HHS) to review current initiatives related to prenatal opioid use and NAS and develop a strategy to address gaps in research as well as gaps and duplication in programs. It directs the HHS to conduct a study and develop recommendations for preventing and treating prenatal opioid use disorders, including the effects of those disorders on infants. The bill also details the essential components of the HHS report on maternal opioid use and NAS, such as an assessment of existing research, best practice recommendation for treatment of women, an evaluation of the barriers to treatment for women, and recommendations on prevention of opioid use disorder in women. Further research is also recommended on the effects of prenatal opioid use on infants. In addition, this bill would require the Centers for Disease Control and Prevention (CDC) to expand data collection and surveillance activities and would require the Agency for Healthcare Research and Quality (AHRQ) to study and recommend treatments for prenatal opioid abuse and NAS (Senate, 2016). The Congressional Budget Office estimates the cost of implementing H.R. 1462 would be about $27 million over the 2016-2020 period (2016). No funding has yet been appropriated for the bill.

The recent NGA statement addresses opioid use and abuse as a public health crisis and describes states priorities. Priorities can include preventing and identifying addiction, developing best practice guidelines for addiction treatment services, increasing access to treatment programs, and eliminating regulations on Medicaid funding which

restrict reimbursement for inpatient treatment for substance abuse and mental illness (NGA, 2016).

Some previous surveys have been conducted to assess state policies and practices concerning opioid use disorder in pregnancy. A survey of policies regarding substance use in pregnancy was conducted to assess the impact of decreased federal oversight and the transfer of budget and regulatory control to the states which occurred in 1994 (Chavkin, Breitbart, Elman, & Wise, 1998). Their survey of substance abuse directors and child protective services showed an increase between 1992 and 1995 in mandatory drug testing of pregnant women and neonates (2% to 12%; .05% to 7%), increased mandatory reporting of positive maternal toxicology screens (2% to 17%), and an increase in criminal prosecution of drug using women (45% to 71%). There was also a trend toward mandating or prioritizing drug treatment services for pregnant women (24% of states). They found a general delay between the development of policy and the establishment of related services. There were gaps identified in policy, such as mandated treatment but lack of availability of services and eligibility for reimbursement (Chavkin et al., 1998).

Another survey examining state policies concerned mandatory reporting of substance abuse during pregnancy and it found twenty states had laws requiring health care providers to report perinatal substance use to child protective authorities, and four states required reporting only when a health care provider thought child maltreatment was involved. Only about 50% of states with a mandatory reporting law had a provision facilitating substance use disorder treatment in the perinatal period (Jarlenski et al., 2017).

In 2004, a review was published summarizing policy research findings in substance abuse during pregnancy (Lester, Andreozzi, & Appiah, 2004). Policy is usually shaped by elected officials so is dependent on social context and public perception. There are two competing discussions involving attitudes about maternal substance use which have shaped public perception and consequently informed policy. One approach is to view drug abuse as a mental health or medial illness. This leads to policies which emphasize treatment and prevention strategies. The competing approach is punitive and views pregnant women who misuse drugs as criminals who are placing their infants at risk. These perceptions both agree on the necessity of appropriate treatment, but many other points related to the formation of policy, such as the origin and clinical approach to treatment, women's autonomy, the legal status of the fetus, and the usefulness of punitive measures are in conflict between the two groups (Lester et al., 2004).

State policy around perinatal substance abuse is shaped through two objectives; the state has a concern for the welfare of its citizens, and then the overall cost to the state (medical care, child protective services, public assistance and foster care are some of the state budget areas impacted by opioid use disorder in pregnancy) (Bishop et al., 2017). State approaches include prosecutorial strategies with a variety of potential charges for the pregnant substance user (child abuse, delivery of controlled substances to a minor, manslaughter) (Flavin & Paltrow, 2010). At the time of this review, three states mandated universal screening of pregnant women for substance use, fifteen (30%) mandated reporting prenatal substance abuse as child abuse and more than 25% of states (13) had passed laws that define mother's substance use as child abuse (Lester et al., 2004). Fifteen states provided treatment programs or coordination of services and four states

gave priority access for addiction treatment services to pregnant women (Lester et al., 2004).

This study will evaluate the impact of published federal and state objectives and professional organizations' guidelines on current state programs and policies for pregnant women with opioid use disorder and infants with NAS. Our study was approved by the Institutional Review Board of Indiana University. Data were stored in a password protected drive used specifically for research data.

Methods

Sample

Participants were a convenience sample of 145 representatives from individual U.S. state's departments of child welfare/ child and family services and representatives of state health departments in the divisions of substance abuse and mental health. The sampling frame and contact information was obtained from departmental contact listing from the Child Welfare Information Gateway, SAMHSA's state profiles on substance abuse services, and individual states.gov websites and later by a respondent's referral to the National Association of State Alcohol and Drug Abuse Directors. Participants were invited to participate by email contact with link to the electronic survey. They initially contacted by email and were assured of confidentiality and given an opportunity to decline to participate in the study.

Design and Materials

The design was a non-experimental descriptive study using an electronic survey with telephone follow-up for non-respondents. A 19-question survey instrument with a total of 54 discrete answers and two items with free text was developed. The survey was formatted in REDcap and grouped on seven sequential screens to minimize transmission time. This also allowed questions to be displayed completely and prevented the need for participants to scroll through pages. A pilot study to assess clarity and accessibility was conducted with five volunteer respondents who work in similar positions as the designated participants, within state child protective services or as health care social workers. The survey was revised to address any technical issues or ambiguity noted by the pilot volunteers.

Procedure

The survey link and a brief email introduction describing the goals of the survey and allowing participants to decline to participate by responding to the email was sent to the selected agency representatives. The survey link remained open for two months, during which time reminders and telephone contacts were also being sent. No response to the email implied consent as stated in the letter. If no response was received within six weeks of the email with two reminder emails sent at two week intervals, a telephone contact was attempted to offer the individual the opportunity to complete the survey via telephone conversation, in this way individuals with technical or user problems could still participate reducing potential nonresponse error. Early returns of the survey were scrutinized for any patterns of missed responses, skipped questions, or technical difficulties. Corrections of these problems was addressed in follow-up reminder surveys

to avoid an unnecessary number of non-respondents or increased measurement error due to technical issues.

The initial survey was sent with a unique individual identifier and could not be forwarded to closely control and identify respondents. This proved too cumbersome for respondents, as it required contacting the study team by email or telephone to refer the survey to co-workers who they felt could provide more complete information. In subsequent electronic mailings, a public link was included and allowed recipients to forward the survey.

Responses to surveys completed online, were downloaded into an electronic database spreadsheet (Excel) per REDCap. Responses to surveys conducted by telephone were manually entered into the database. There were a total of 145 survey invitations sent electronically. Total responses online and by telephone were 52 for 36%. There were a total of 30 surveys completed online, three returned as emails directly to the researcher, and 19 completed by follow up telephone interview for a total of 52 respondents representing 39 states for 78% of states represented. Individual questions on two surveys were ultimately dropped from the analysis due to inconsistencies in answers between two respondents from the same state.

Data Analysis

The data were first reviewed to find and delete incomplete and duplicate responses. The two open-ended questions were analyzed with a qualitative descriptive approach. The researcher conducted a thematic analysis (Sandelowski, 2010; Vaismoradi, 2013) of the two items requiring free text. Coding and thematic analysis were conducted using the thematic analysis process described by Vaismoradi (2013). The data analysis

consisted of organizing data, including generating initial codes, searching for themes, and reviewing and naming themes. Descriptive statistics and relative frequency statistics was calculated on the ordinal data using REDCap and the SPSS statistical package (IBM 2016).

Results

Respondents' Information and Demographics

Of the 52 respondents, 31% were from children and family services and 46% were from behavioral health/ substance use/ addiction services and 23% chose other. Professional credentials included social workers 13.5%, nurses 13.5%, psychologists 2%, physicians 6%, and other 65%. The years of experience reported were 48% with > 5 years, 23% with 3-4 years, 27% 1-2 years and 2% with less than 1 year. A summary of respondents' information can be found in **Table 3**.

Table 3

Respondents Demographic Information

Sample Composition	**N (%)**				
Position	Children/ Family Services	Behavioral Health	Other		
	16 (31)	24 (46)	12 (23)		
Credentials	Social Worker	Nurse	Physician	Psychologist	Other
	7 (13.5)	7 (13.5)	3 (6)	1(2)	34 (65)
Years of Experience	< 1 years	1-2 years	3-4 years	+5 years	
	1 (2)	43 (27)	12 (23)	25 (48)	

Screening and Services

All participating states indicated they were responding in some way to the public health and economic impact of increases in opioid use disorder. These actions included a combination of public health initiatives, surveillance, and clinical treatment. Of individual respondents, 22% indicated universal toxicology screening of pregnant women was recommended or required in their state. Twenty-five percent of respondents indicated screening of infants was required in their state. Thirty-nine per cent of the states responding indicated their state required mandatory reporting of positive screen in pregnant women to child protective services. Seventy percent indicated their state required mandatory reporting of positive screen in newborn infants to child protective services, 7% to the state department of health, no states required or recommended reporting to law enforcement. A positive maternal or infant toxicology was categorized as child abuse or neglect in 34% of the states. Twenty percent indicted their state has criminally prosecuted women for using illicit drugs during pregnancy some of the time, 80% responded their state never utilizes criminal prosecution for abuse, neglect or other charges.

Enrollment in treatment services was mandatory in cases of positive toxicology screen during pregnancy most of the time in 24% of those responding, 47% indicated women were required to participate in treatment some of the time, and in 20% treatment was never mandatory. Only 10 % of respondents felt availability of treatment services was always adequate in their state, 47% felt service availability was sometimes adequate, 24% responded most of the time, and 20% felt services were never adequate.

Treatment services, including medication assisted treatment with an opioid substitute was covered by state Medicaid programs and was always available according to 60% of respondents, 24% felt it was available most of the time, and 16% reported it was covered some of the time. Some additional services for pregnant women with opioid dependence were offered in 96% of states. Only 4% reported their state never offered additional services or prioritized pregnant women for opioid dependence programs. Forty-four percent reported additional services were available some of the time, 20% most of the time, and 32% always available. These additional services included prioritizing pregnant women for available treatment, additional funding which waived fees and co-pays, social support services including transportation and childcare, and coordinated services which combined prenatal care, behavioral health, and opioid dependence treatment.

Routine developmental follow up for infants exposed to opioids during pregnancy was provided by 34 % of respondents' states some of the time, 42% most of the time, 14% always, and 10% responded developmental services were never available.

Policy Changes and Funding

The exact impact of federal and state policy objectives (Protecting Our Infants Act of 2015 and NGA priorities statement) and professional organizations' guidelines on public health and legislative initiatives is difficult to assess. There are many instances where recent state policy changes, and plans align with recommendations from these documents. Eighty per cent of states had recently increased funding or added additional programs for opioid use disorder. These included changes in general programs for opioid dependence, as well as some which specifically targeted pregnant women and infants.

Focus areas for treatment for the general population included additional funding for detoxification services or medication assisted treatment services, expanded Medicaid coverage for treatment services, and liberalizing licensure practices for narcotic treatment programs. Other priority areas included establishing care coordination positions within the state and counties, expanded services to rural areas through primary care engagement in treatment, additional oversight and tracking of prescribing practices, and increased availability of naloxone for overdose treatment.

Prevention, early intervention, and public health education were also mentioned as new areas with enhanced programs. Specifically, for women and children, recent enhancement of programs included increasing targeted outreach programs to engage women earlier in care, expansion of high-risk pregnancy services to include opioid dependence and increasing availability of drug rehabilitation and behavioral health treatment within obstetric services. Some states also reported establishing care coordination services for pregnant women to include opioid dependence treatment and behavioral health, and implementing specialized program designed to reduce the severity of neonatal abstinence syndrome.

Respondents indicated recent increases in funding or plans for increasing funding or adding additional programs in 62% of the states. Some of these included increased access to naloxone, increased funding for medication assisted treatment programs, expanding to primary care-based programs with advanced providers in rural areas, expanding residential services, and enhancing community-based recovery support. Increasing education and prevention efforts was also mentioned including education to providers on safe opioid prescribing, as well as public education on safe use of opioids

and early identification of dependence. Most respondents indicated a general initiative to continue to enhance, expand, and integrate recovery support and services. Some respondents mentioned their planning is dependent on the future of the patient protection and affordable care act (ACA) which will determine available funding for OUD both at the federal and state level. A summary of the multiple-choice responses can be found in **Table 4**. A summary of the themes identified in the narrative responses can be found in **Table 5**.

Table 4

Summary of Multiple Choice Question Responses

Question	**All of the Time**	**Most of the time**	**Most of the time**	**Never**
Does your state criminally prosecute mothers for illicit drug use during pregnancy?	0%	0%	20%	80%
Is the availability of addiction treatment services adequate in your state?	10%	24%	47%	20%
In your state, is participation in treatment mandatory in cases of positive toxicology screen during pregnancy?	0%	24%	47%	20%
Does your state provide Medicaid coverage for opioid use disorder (OUD) treatment?	60%	24%	16%	0%
Does your state offer additional services which facilitate OUD treatment during pregnancy?	32%	20%	44%	0%
Does your state provide developmental follow up services for infants exposed to opioids during pregnancy?	14%	42%	34%	10%

Table 5

Qualitative Analysis: Current and Future Plans for Treatment of Opioid Use Disorder

Themes	Representative Quotes
Increased availability of medication assisted treatment	*Allows all medication approved by FDA to be used in licensed narcotic treatment programs* *More liberal licensing for suboxone providers (PCP)* *Expansion of the number of OTPs and OBOTs with tripling of number of people in treatment*
Education and regulation of safe prescribing practices	*Recent laws passed affect prescription of opioids* *Clinical practice measures for safer opioid prescribing*
Increased availability of naloxone	*Naloxone standing orders* *increased Narcan availability to the pubic*
Increasing services in rural areas	*Pilot of expansion of MAT services in rural areas using advanced practice nurses* *Through grant funding office-based narcotic treatment programs will be available in rural xxxv (state)* *DBHS is looking at recruiting MAT providers in rural areas*
Increased availability of services for pregnant women & families	*Increasing targeted outreach services to engage women earlier in care* *Increasing the availability of intervention and treatment services for pregnant women* *Development of NAS peer recovery support specialists*

	Addition of Family Task Force
	Pilot treatment programs for mothers with children
Increased funding & reimbursement for treatment services	*Obtained additional federal funds for medication assisted treatment*
	Additional funding related to opioid treatment
	Increase in funding for all SUD services
Addition of funding and availability for residential treatment	*Funding for and certification of recovery housing*
	Approval of Medicaid waiver to pay for residential services
	Include coverage for adult residential and partial hospitalization programs
Plans for education and prevention programs	*Increase education and prevention efforts*
	Implement programs for the prevention … of opioid misuse
	Developed clinical guidelines to assist providers in care of pregnant women and infants

Discussion

This survey captures an interesting moment in time when policymakers and their constituents seem united in the opinion that opioid use disorder is a public health crisis and deserves attention and funding. Although there are many potential models related to SUD, each of these approaches has shortcomings. The multi-sourced model of addiction emphasizes the complexity of this problem and illustrates that a single strategy will not be sufficient to adequately address all the contributing factors (Kovac, 2013). A multi-pronged approach which considers neurobiology, individuals, underlying issues, and social, historical, cultural and environment factors will have the greatest impact. The

trend toward interdisciplinary problem solving by planning committees and task forces indicates states are recognizing the importance of a diverse and comprehensive plan to address maternal opioid use and NAS.

There is evidence in the survey results of continuing conflict in the United States on the view of substance use disorder as a criminal act or public health issue, with 20% indicating prosecution of maternal substance abuse is sometimes pursued. These punitive responses continue in some areas even though they have been shown to be costly and ineffective (Kovac, 2013; Paltrow & Flavin, 2013). This attitude may be driven by policymakers' constituents who continue to see substance abuse as a criminal and moral issue, rather than as a chronic disease. However, respondents indicate policy and program changes in recent years emphasize the public health approach, addressing first safety, with increased naloxone availability and screening to identify those in need of treatment and second, increasing availability of effective treatment and funding the cost of treatment.

Many states have undertaken needs assessments and research reviews, looking to evidence to assist in shaping their future policy and funding. There is a trend toward increases in testing and reporting, but many individuals feel their state lacks adequate services for referral to treatment once substance abuse has been identified. Many states are examining unique methods for addressing this in a safe and timely fashion, such as moving medication-assisted treatment to primary care and expanding licensure to PCPs and nurse practitioners. Several states reported they next hope to examine education and prevention. Although substance abuse is viewed as a chronic disease by the public health community, public opinion continues to be mixed with conflicts apparent in some

policies which reflect the continued view of substance use as a moral issue (Angelotta, Weiss, Angelotta, & Friedman, 2016). It is important to address these attitudes as they inhibit both the individual and public from an effective response. For the individual, continued social stigma associated with substance use and marginalization inhibits their use of resources and help-seeking. For public health policy, the attitude will continue to interfere with the development and funding of substance use programs which are innovative and effective. Public health-oriented approaches with demonstrated effectiveness and which are widely available are essential for progress toward the state and federal goals related to opioid use disorder.

Limitations

There are several limitations to this study, the first of which is the representativeness of the sample. Self-directed sampling was utilized, soliciting particular representatives assigned as state contacts for both SAMHSA and the Child Welfare Gateway who the researchers felt might increase the likelihood they were interested and informed on the particular topic of the survey. Choosing potential participants from a public list presents several problems, the contact list may not be accurate and up to date, and the recipient may not be familiar with the topic areas. The demographic information was limited because the survey did not allow a free text answer for the question concerning professional credentials. Most of our respondents (65%) recorded “other”. The telephone interviews indicate many of the respondents in this category may be information, or public relations professionals, but the online survey was not constructed to obtain complete information in this area.

The decision to allow a public link and forwarding increased the number of respondents but credentials, identifying information, and demographic information were then entirely by self-report and may be inaccurate, and in some cases were missing making it difficult to determine exactly who participated. Response bias is always a concern for survey research and there may be an imbalance of respondents who viewed their state response to opioid use disorder in either an overly positive or negative way. Respondents also may not feel comfortable providing answers that present themselves, or their state, in an unfavorable manner.

The survey was sent to at least two and sometimes three representatives from the same state to increase the likelihood of obtaining information from a higher percentage of states. More than one response was received from some states and in some instances different answers were recorded from the same state. In two instances one respondent had left a question blank and another had answered. In these cases, the answers were used in the analysis. Two respondents had conflicting answers within the same state and those survey questions were dropped from the analysis. The ability to reach respondents is one challenge of surveys. Lack of accessibility to an online survey is a threat and there was a significant technical issue with one electronic follow up mailing, the personal link was not working correctly, and some participants could not access the survey. One respondent was kind enough to email and notify the researcher of the problem with the survey and provided an explanation of the technical difficulties, this technical issue may have discouraged and frustrated some potential respondents.

Some of the survey question answer options may have been unclear and led to variations in data because respondents may be have interpreted them differently. For

example, the answer option "some of the time" may represent different amounts to different respondents. There were also respondents who requested a response of "not applicable", although we had purposively not included this as an option as we felt it was not an appropriate answer. However, another available option such as "unsure", or "I do not know" may have been an accurate alternative option.

The survey also represents a very limited snapshot of time for this problem. Opioid use disorder is an area which is currently receiving tremendous attention by public health officials, policymakers, and the public. Opinions, from all of these groups, are very fluid and can change on even a daily basis. There may be significant changes in plans for policies and services, even during the relatively brief time of survey collection and data analysis. There is also a predictable lag between development of policy and the offering of program services, so responses concerning plans or policy may not reflect actual availability of services.

Conclusions

Overwhelmingly, states have recently initiated new programs and the majority of states continue to plan for additional services for opioid dependency prevention and treatment. Potential problems were identified between the development of policy and the delivery of program services related to these policies, such as allocating funding and availability of OUD treatment providers and facilities. Although the recognition of the scope and severity of the problem was slow, the progression from policy statements to program implementation has been accomplished in a timely manner in many states. The responses indicate a trend toward expanding services, acknowledging evidence-based care, improving treatment for pregnant women, and for the general population with

opioid use disorder. Although many states have not addressed gender-related issues, including responsibility for children, increased need for social support and services, and greater incidence of comorbidities such as behavioral health issues, most have expanded services for pregnant women and heightened standards of care.

Most public health programs recently enacted focus on short-term harm reduction which is an appropriate initial response, but these need to be followed by evidenced-based long-term approaches to treating and preventing opioid use disorder and NAS. There are several maternal, infant, and environmental factors that have been identified in literature as possible contributors to the incidence and severity of symptoms of NAS, and subsequently to use of neonatal medication, length of stay, and hospital cost. Additional research studies examining the effects of these factors can guide both policy recommendations and clinical care.

CHAPTER FOUR: Factors Associated with the Need for Neonatal Medication Among Infants Born to Opioid Dependent Mothers

Introduction

Neonatal abstinence syndrome (NAS), the constellation of withdrawal symptoms experienced by neonates exposed to opioids prenatally, is a growing health problem affecting an estimated 23,580 infants per year (Ko, 2016) with an estimated cost of $720 million annually (Patrick et al., 2012). The number of women taking opioids during pregnancy increased five-fold between 2000 and 2009 (1.2 per 1000 live births to 5.6 per 1000) (Patrick & Wu, 2015). Between 55% and 95% of infants prenatally exposed to opioids will experience serious physical manifestations of withdrawal requiring treatment with medication to control their symptoms (MacMullen, Dulski, & Blobaum, 2014). NAS is a complex problem with many potential contributing factors and complex clinical practices related to screening, treatment, and appropriate follow-up which have not been adequately explored. There are significant gaps in knowledge concerning many factors that may aggravate or ameliorate the illness course of infants with NAS.

There are several factors that have been identified in literature as possible contributors to the onset and severity of symptoms of NAS and subsequently to use of neonatal medication, length of stay, and hospital cost. These are typically not the primary focus of most studies but are mentioned as possible confounding factors and have received minimal attention. These factors include maternal opioid use history (Desai et al., 2015; Jones et al., 2010; Patel et al., 2013; Welle-Strand, Skurtveit, Jones, et al., 2013), exposure to other drugs (Cleary et al., 2013; Jansson et al., 2012; McQueen, Murphy-Oikonen, & Desaulniers, 2015,(Wikner et al., 2007; Winklbaur et al., 2008)),

maternal tobacco use (Chisolm et al., 2011; Jones et al., 2013), feeding method (Isemann, Meinzen-Derr, & Akinbi, 2011; McQueen, Murphy-Oikonen, Gerlach, & Montelpare, 2011; O'Connor, Collett, Alto, & O'Brien, 2013; Welle-Strand, Skurtveit, Jansson, et al., 2013), family or primary caregiver involvement (Abrahams et al., 2007; Bagley, Wachman, Holland, & Brogly, 2014; Dumas et al., 2013; Hodgson & Abrahams, 2012), location of care (Grossman et al., 2017; Holmes et al., 2016; Loudin et al., 2017; Metz et al., 2011), non-pharmacologic/comfort measures (Maguire, 2014), and healthcare provider experience and use of standardized clinical care guidelines (Metz et al., 2011). Infant characteristics such as gestational age (Dabek, Poeschl, Englert, & Ruef, 2013; Dysart, Hsieh, Kaltenbach, & Greenspan, 2007; Liu, Jones, Murray, Cook, & Nanan, 2010), birthweight (Kaltenbach et al., 2012; Liu et al., 2010), and sex (Holbrook & Kaltenbach, 2010; Jansson, Dipietro, Elko, & Velez, 2010; Unger et al., 2011) have also been recognized as factors associated with severity of NAS. A more thorough examination of such non-pharmacologic factors could direct future research and facilitate development of more innovative and effective interventions related to care delivery for NAS patients. The full conceptual model based on the review of literature of potential factors associated with incidence and severity of NAS and an abbreviated model used for this study are included in **Appendix B**.

Maternal and infant screening and clinical care guidelines that have potential to decrease infant illness, medication needs, lengths of inpatient hospital stay, and hospital costs are priorities for this population. A single-center retrospective medical record review was undertaken to examine maternal, infant, and environmental factors which may be associated with severity of NAS, as measured by need for medication treatment,

in infants exposed to opioids prenatally. Specific research questions addressed in this study were: 1) what proportion of infants exposed to opioids prenatally require medication treatment for NAS? And 2) what maternal, infant, and environmental factors are associated with the need for neonatal medication treatment for NAS?

Methods

Design

A retrospective review of electronic and paper medical records was conducted with a convenience sample of 204 infants born to mothers who used opioids during pregnancy from April 2011 to September 2017 at the clinical site of a large suburban Midwestern hospital. Initial descriptive statistics on incidence of infant drug exposure per number of live births was obtained by electronic medical record query of diagnoses codes of intrauterine drug exposure ICD-9 760.72 and ICD-10 P04.9 and maternal drug use complicating pregnancy ICD-9 648.43 and ICD-10 099.320. Eligibility criteria for inclusion in the next phase, the examination of related factors, was a diagnosis of NAS verified by a recorded ICD-9 code of 779.5 or, after 2015 ICD-10 code of P96.1, neonatal drug withdrawal or neonatal abstinence syndrome or treatment with morphine solution. Infants were excluded if further examination of the medical record did not indicate prenatal opioid exposure by maternal report or maternal or infant toxicology screen.

Sample

Approval was obtained from the Indiana University-Purdue University Indianapolis institutional review board as well as a statement of clinical cooperation from the health care facility's administration. A retrospective review of electronic and paper medical records was conducted with a final sample of 204 confirmed cases of infants

born to mothers who used opioids during pregnancy and 121 who were subsequently diagnosed with NAS from April 2011 to September 2017 at the clinical site.

Criteria for Inclusion/Exclusion

- Diagnosis of maternal drug use verified by diagnosis code of intrauterine drug exposure: ICD-9 of 760.72 or after 2015, ICD-10 P04.9 or maternal drug use complicating pregnancy: ICD-9 of 648.31 or ICD-10 of P99.320.
- Diagnosis of NAS verified by a recorded ICD-9 code of 779.5 or, after 2015 ICD-10 code of P96.1, neonatal drug withdrawal or neonatal abstinence syndrome.
- Infants were excluded if further review of the medical record did not indicate prenatal opioid exposure by maternal report or maternal or infant toxicology screen.

The hospital in which the data for study of maternal, infant, and environmental factors affecting medication use and length of hospital stay was conducted has a 26-bed NICU and a 15-bed pediatric inpatient unit. The average daily census for the NICU is 15 patients. There are 2-4 patients in the daily census with a diagnosis of NAS. During the time period for the study, the annual number of patients with the diagnosis varied from 17 to 35. A survey of case management records for the facility over the past six years, using cases identified for this study indicated an average cost for infants with a diagnosis of NAS of $4238 per day when cared for in the NICU. Daily costs for infants transferred to the inpatient pediatric unit for weaning of medication after initial treatment in NICU was lower at $2852. The charge for newborn nursery/ post-partum days was much lower at about $750 per day. The excessive cost of inpatient care makes reducing length of stay a

priority, even 2-6 days results in a significant cost savings. There are other potential deleterious factors related to transfer of the newborn to the NICU such as separation from mother, difficulty maintaining breastfeeding, and interruption of maternal infant bonding (Brenneman & Price, 2014).

In the clinical facility used for this study, standardized clinical screening and treatment guidelines were adopted in 2010 and then revised in 2014. The guidelines include a specific screening tool (modified Finnegan), primary treatment with morphine solution, and standard recommendations for adjunct therapy and weaning. These are all key factors to examine related to outcomes for NAS, but due to the use of these standard guidelines, there is not sufficient variability in the current sample to examine these factors.

Data Collection/Construction of the Dataset

After Institutional Review Board approval was obtained, medical records were queried from the Epic electronic charting system in a large Midwestern Hospital from April 2011 to September 2017. This timeframe was chosen as it corresponds with the introduction of an electronic medical record system in the health care facility which facilitates the extraction of data. Data were extracted both electronically and manually from the EPIC charting system. A data extraction algorithm was developed by an informatics specialist employed by the clinical facility. Two separate queries were conducted. The first query identified eligible infants from electronic medical records and the second query extracted data needed for the study. Both queries were piloted on a small group of patients prior to the full query to assess completeness and adequacy of data obtained and to establish a secure database. Medication use, Finnegan scores, and

length of stay, as well as possible covariates from maternal, infant and environmental factors (maternal opioid used, other drug use, tobacco use, infant gestational age, sex, and other medical complications, feeding method, location of care, and primary caregiver involvement) were obtained. Information was also collected concerning potential confounding variables, attending physician, infant health complications, and infant adjunct medication (phenobarbital and clonidine). Hospital costs were obtained by a query of the case management and utilization review database. The data were transferred by the informatics consultant from the electronic medical record (EMR) to an Excel spreadsheet, which served as the study database.

A minimal amount of clinical records continued to be kept on paper charts after transition to the EMR system. These paper records included information about maternal prenatal history, neonatal drug withdrawal scores (modified Finnegan scores), and morphine dosing. This additional data were then added to the study database. After data collection was complete, data extracted from the EMR were de-identified and subject numbers were used to match electronic and paper records. The database was stored in a secure server (IU Box Health) which is password protected and HIPPA compliant. A copy of the data collection sheet is included in **Appendix D**.

Data Cleaning

The data were prepared for transfer to the statistical program in three phases. The original worksheet with data as extracted directly from the medical record was maintained as originally captured. A copy was created as an interim data sheet to complete and clean the original data. First, missing fields were identified and completed by accessing the individual's paper records. Then, data were cleaned by removing any

elements which should not be transferred to the final dataset because they may impede the ability to run the analyses effectively or affect the quality of the statistical analysis, such as duplicate entries, out-of-range data, and extraneous characters. Each infant was assigned a unique identifier number based on name and medical record number to assist with identifying and eliminating any duplicate records. Fields were then recoded according to standardized values and coding suitable for analysis in SPSS (see **Appendix E** for additional information on coding). Parameters or reference ranges were set for fields with continuous or interval data to help in identifying out of range values which needed to be corrected. A third and final dataset was prepared and used for analyses.

Data Analysis

Two hundred and sixty-one eligible subjects were originally identified by EMR query during the six-year period from April 2011 to September 2017. Subjects were initially identified by ICD-9 or 10 codes of intrauterine opioid exposure/ intrauterine drug exposure or neonatal abstinence syndrome/ neonatal drug withdrawal. On closer examination of the medical record, 57 or 28% did not meet inclusion criteria due to improper diagnostic coding in which examination of the medical record did not confirm neonatal intrauterine opioid exposure. Independent variables (maternal age, parity, insurer, reason for maternal opioid use, maternal opioid type, other maternal drug use, maternal tobacco use, infant's sex, infant's birthweight, infant's gestational age, primary caregiver involvement, feeding method, and inpatient hospital unit for stay) were compared with outcome variable of initiation of infant treatment with morphine solution. All analyses were conducted using IBM SPSS statistical software package. Exploratory analysis to visualize main characteristics was done using histograms and scatter plots and

descriptive statistics were performed to summarize characteristics. Associations between the independent variables and the outcomes of interest were then analyzed using chi-square test of association, independent samples t-test, analysis of variance, and logistic regression.

Results

Demographics of Sample

The average maternal age ranged from 17 to 45 years with a mean of 27.5 years. The sample consisted of 17% primiparous and 83% multiparous mothers. The reasons for maternal opioid use were categorized as illicit use (48%), prescription use (12%), and opioid use disorder (OUD) treatment (40%). The types of opioid used by mothers were methadone (24%), buprenorphine (21%), heroin (9%), other opioid analgesics (26%), and unspecified opiate (20%). Sixty-eight per cent of mothers reported current tobacco use and 32% were not using tobacco. Some of the women included in the non-tobacco use group had stopped smoking during this pregnancy. In 83% of mothers there were no other health complications described in the prenatal record, 7% had other behavioral health diagnosis such as schizophrenia, depression, post-traumatic stress disorder, and bipolar disorder. Three percent had a diagnosis of chronic pain, 0.5% had other neurological diagnosis, such as a seizure disorder, 1% had another diagnosis related to metabolic disease, and 5% had a variety of other diagnoses. The infants had gestational ages ranging from 28 to 41 weeks with mean of 37.2 and median of 38 weeks. Male infants compromised 60% of sample and females 40%. Infant weights ranged from 1.23 to 4.29 kilograms with a mean of 2.82 kg.

Research Question 1. What proportion of infants exposed to opioids prenatally require medication treatment for NAS?

Of the 204 neonates who were exposed to opioids prenatally, 121 (59%) developed symptoms of NAS requiring neonatal medication treatment with morphine solution. The use of non-pharmacologic comfort measures during care was recorded in 96% of all infants.

Research Question 2: What maternal, infant, and environmental factors are associated with the need for neonatal medication treatment for NAS?

Maternal Factors

Associations between neonatal medication treatment and maternal factors of race, parity, type of payment (insurer), source of mother's opioid use (illicit use, prescription use, or opioid use disorder treatment), primary type of opioid used (methadone, buprenorphine, heroin, other opioid analgesics-which included codeine, hydrocodone, oxycodone, or opiate unspecified from toxicology screen), tobacco use (yes/ no), and use of benzodiazepines (yes/no) were examined. The need for neonatal medication treatment for NAS was significantly associated with mother's race χ^2 (2) = 12.008, p = .002, source of mother's opioid use, χ^2 (2) = 8.523, p = .014, primary type of opioid used, χ^2 (4) = 27.520, p = .001), tobacco use, χ^2 (1) = 5.148, p = .023 and use of benzodiazepines, χ^2 (1) = 10.158, p = .001. Mother's age, parity, and type of payment were not associated with the need for neonatal medication treatment. However, there were a large amount of missing data for the factors of parity and type of payment (insurer), 59% and 85% of cases respectively were missing this information.

Data were collected on additional medications mothers were taking during pregnancy. Sixty mothers (45%) were taking medication in addition to opioids based on prenatal history or toxicology screening results (information available on 181 mothers or 89% of sample). There were a total of 24 different medications from seven categories (benzodiazepines, barbiturates, selective serotonin re-uptake inhibitors, stimulants, and others). The most common additional medication was a benzodiazepine (n=27). Maternal use of benzodiazepines was associated with an increased need for neonatal treatment with morphine solution, $\chi^2(1) = 8.702$, $p = .003$. There were not a sufficient number of occurrences to determine the association of the other additional medication categories with need for neonatal medication treatment. **Table 6** summarizes maternal factors, which were associated with the need for neonatal morphine treatment.

Table 6

Maternal Factors Associated with Need for Neonatal Medication Treatment

Maternal Factors	**Neonates who required medication**	**Neonates who did not require medication**	**Statistic**	**Value**	***p*-value**
Source of Opioid Use:	N =110	N = 83	x^2 (2)	8.523	.014
Illicit	49 (.56)*	39 (.44)			
Prescription	9 (.41)	13 (.59			
Opioid Dependence Treatment	52 (.72)	20 (.28)			
Primary Type of Opioid Used:	N = 112	N = 73	x^2 (4)	27.52	.001
Methadone	40 (.89)	5 (.06)			
Buprenorphine	21 (.55)	17 (.45)			
Heroin	13 (.76)	4 (.24)			
Other Opioid Analgesic**	19 (.40)	29 (.60)			
Unspecified Opiate	19 (.53)	17 (.47)			
Use of Tobacco:	N = 107	N = 61	x^2 (1)	5.148	.023
Yes	78 (.70)	34 (.30)			
No	29 (.52)	27 (.48)			
Use of benzodiazepine	N = 111	N = 70	x^2 (1)	10.158	.001
Yes	22 (.88)	3 (.12)			
No	89 (.57)	67 (.43)			
Race:	N = 120	N = 81	x^2 (1)	12.008	.002
White	113 (.64)	64 (.36)			
Black	7 (.29)	17 (.71)			

*Proportion of infants needing treatment versus those who did not
** includes codeine, hydrocodone, and oxycodone

Infant Factors

Infants requiring medication treatment for NAS had significantly higher gestational ages (37.7 weeks vs 36.4 weeks; $p = < .001$). There was no association found between infant's sex, infant's weight, or presence of other health complications.

Environmental Factors

The need for medication treatment for NAS was significantly associated with feeding method ($\chi^2(1) = 11.693$, $p = .003$) and with primary caregiver involvement. More infants who were exclusively formula fed required neonatal medication treatment than infants receiving breastmilk, either exclusively or in combination with formula. However, information about feeding method was missing in 59% of cases.

Primary caregiver involvement, measured by percentage of the total hospital days when mother or other designated primary caregiver spent at the infant's bedside, was associated with the need for medication treatment. Infants who required medication treatment for NAS had a lower percentage of their hospital stay where their primary caregiver (usually mother) was present at the bedside (mean = 57% vs 74% of hospital days/length of stay; $p < .001$). A summary of infant and environmental factors associated the need for neonatal morphine medication is included in **Table 7**.

Table 7

Infant and Environmental Factors Associated with Need for Neonatal Medication Treatment

Infant & Environmental Factors	**Neonates who required medication**	**Neonates who did not require medication**	**Statistic**	**Value**	***p*-value**
Infant Gestational Age Mean SD	N = 121 37.7 1.550	N = 83 36.4 2.929	t-test	3.406	.001
Mother's time at bedside (%)	57% .3059	74% .2647	t-test	-3.834	< .001
Breastmilk Feeding Yes No	 34.9% 65.6%	 57.9% 42.1%	x^2	11.693	.003

Regression Analysis

A binomial logistic regression was performed to ascertain the effects of mother's race, mother's reason for opioid use, mother's opioid type, maternal tobacco use, maternal use of benzodiazepine, infant gestational age, and percentage of visitation time by primary caregiver during infant's hospital stay on the likelihood that the infant needed medication treatment. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell (1962) procedure. A Bonferroni correction was applied using all nine terms in the model resulting in statistical significance being accepted when $p < .00556$ (Tabachnick & Fidell, 2014). Based on this assessment, the two continuous independent variables, infant's gestational age and mother's percentage of days at the bedside, were found to be linearly related to the logit of the dependent variable. The logistic regression model was statistically significant, χ^2 (11) = 42.922, $p < .001$. The model explained 41.2 % (Nagelkerke R^2) of the variance in

and correctly classified 76.5% of cases. Sensitivity was 83.8%, specificity was 64.4%, positive predictive value was 79.5% and negative predictive value was 70.7%. Of the seven predictor variables, only three were statistically significant predictors of need for medication treatment for NAS (see Table 4-4). Higher gestational age was associated with an increased likelihood of needing neonatal medication treatment. The type of maternal opioid used was a predictor, with buprenorphine use decreasing the likelihood of need for neonatal medication treatment. A higher percentage of days during the hospital stay the primary caregiver/mother was present at the infant's bedside decreased the likelihood of medication treatment.

Strengths and Limitations

Strengths of this study include that it is one of the few studies to accurately estimate the proportion of infants who were exposed to opioids prenatally who went on to require neonatal medication treatment. In addition, clinical guidelines used to guide care in the hospital setting controlled for several important variables, such as selection of medication, criteria for weaning, and preparation of caregivers. This provided consistency on these factors between subjects and throughout the timeline of data collection strengthening the comparisons between groups. Third, this study was guided by a strong evidence-based conceptual framework. Few studies in this area are guided by theory or frameworks, making it difficult to understand the full complement of factors that influence the need for medication treatment for NAS. A conceptual framework provides a solid foundation for many aspects of the study including identifying the variables, guiding the literature review, formulating the research questions, and directing the methods and analysis. It provides a consistent context and rationale to clearly identify

relationships (Meleis, 2011). To minimize potential bias, the specific inclusion and exclusion criteria were identified before any EMR query was developed. The researcher met with the informatics specialist to provide information about the query and supplied the conceptual model and operational definitions of the variables prior to the development of the electronic query. Once the EMR query was completed detailed records were kept throughout the evaluation of inclusion/exclusion review for potential subjects, as well as during the data cleaning process. Specific definitions, precise research questions, and a detailed plan prior to the beginning of abstraction helped to increase the potential quality of the information. The study was conducted in a single health care setting, which increases consistency in identification of subjects and in clinical care, however this limits generalizability.

Several limitations to this study should be noted. Retrospective medical record review studies have several inherent limitations including the potential for incomplete documentation due to information that was unrecoverable or unrecorded, difficulty interpreting information found in the documents due to inconsistent abbreviations or acronyms, problems with verification of information, variance in the quality of information recorded by individual providers, and difficulty establishing cause and effect (Gearing, Mian, Barber, & Ickowicz, 2006). In this study, the prenatal care information was particularly incomplete. On the mother's admission, information from the outpatient EMR system is transcribed by the nursing staff into the Epic EMR system used by the hospital. The completeness and consistency of what was transcribed was not assessed. This may have been the cause of the low number of mothers with other complicating health care diagnoses listed in the EMR. Specifically, the low behavioral health

complication rate of 7% is much lower than anticipated. The literature indicates that this prevalence may be as high as 56% among all patients with prescription use/misuse or opioid use disorder (Han et al., 2017). Data were not originally collected for research purposes and consequently, are limited by incomplete or inaccurate data due to inconsistency in the quality and thoroughness of information across records.

The retrospective, cross-sectional, single-group design limits the ability to determine cause and effect. A cross-sectional design is helpful in determining prevalence and associations, but because the independent variables and outcomes were measured simultaneously it was not possible to determine the specific relationship between exposure variables and outcomes (Carlson & Morrison, 2009). Using ICD-9 and ICD-10 codes for initial screening was a potential limitation due to inconsistent use of the codes among various individual healthcare providers. Specific information could not be obtained about differences in coding between providers. It also creates a potential bias toward including more severely affected patients with NAS. Patients with milder symptoms and those, whose symptoms develop after the initial 2-3 day hospitalization and are identified on readmission, may not have been captured. There were two infants included in the study that were discharged within 2-3 days from birth and re-admitted in the first week of life for symptoms of NAS. These two infants received morphine treatment. There may be affected infants who were re-admitted to other facilities. Thus, the estimated proportion of infants who require treatment for NAS in our cohort may be lower than the actual frequency in the population at the facility. The retrospective nature of the chart review over a 6-year period leads to inconsistencies in the clinical documentation which may have occurred due to changes in clinical practice over time.

There may have been better identification and greater utilization of coding for intrauterine drug exposure and NAS in more recent years due to increasing attention on topic, increased provider training, and heightened awareness. Therefore, increasing use of the ICD-10 code may not reflect a true increase in the number of affected patients. Much of the mother's prenatal history was derived from the initial prenatal visit and admission patient interviews. Determining whether documentation of patient-reported information into the EMR was accurate and what information may have been lost or distorted in this process was not possible.

Discussion

The results of this study provide some interesting insights into factors which may affect the incidence and severity of neonatal abstinence syndrome. There were several factors which were shown to be associated with the initiation of medication treatment. Mother's reason for opioid use, type of opioid used, use of tobacco, use of benzodiazepines, infant's gestational age, feeding with breastmilk, and amount of time the primary caregiver spent at the infant's bedside all were significantly associated with the initiation of medication. Although previous studies have not specifically examined need for neonatal medication treatment, these results are consistent with previous studies which identified factors of type of maternal medication (methadone versus buprenorphine), use of tobacco, and use of benzodiazepine with outcome variables of an increased peak neonatal medication dose, increased length of treatment, and increased hospital LOS (Chisolm et al., 2011; Pritham, 2009; Schindler et al., 2003; Seligman et al., 2008). The findings of factors of infant's gestational age (< 36 weeks) and the use of breastmilk or breastfeeding as factors which decrease need for neonatal medication is

also consistent with previous studies which used peak medication dose and length of hospital stay as outcome variables (Abdel-Latif et al., 2006; Dysart, Hsieh, Kaltenbach, & Greenspan, 2007; McQueen, Murphy-Oikonen, Gerlach, & Montelpare, 2011; Seligman et al., 2008; Welle-Strand et al., 2013). The variable of percentage of days the primary caregiver was present at the bedside was used as a proxy for maternal or primary caregiver involvement and was significant in reducing the number of infant's who needed medication treatment. Although there is no direct comparison of this variable in previous studies, others have examined this factor in several diverse ways, such as rooming-in or parent care arrangements which have been shown to decrease need for neonatal medication and hospital length of stay (Abrahams et al., 2007; Grossman et al., 2017; Hodgson & Abrahams, 2012).

There was a significant association between race and need for neonatal medication which has not been identified in previous studies. Infants of black mothers were less likely to need medication treatment. There was limited variability in the sample of infants exposed to opioids prenatally, 87% were white, 12% of mothers were black, and only 1% Hispanic. The distribution of opioid exposure itself is an interesting point but may be related more to the single facility design and the distribution in the facility's patient population than reflective of the distribution of opioid use during pregnancy among races.

Two factors which were associated with a decreased need for neonatal medication treatment were primary caregiver involvement and use of breastmilk feeding, even using very general measures for these variables in the current study. Studies with more precise measurement techniques for these variables are an important next step. A future study,

which collects information on both quality and quantity of time spent by primary caregiver would provide valuable information to guide both preparation of the family prenatally and design of the neonatal care environment. The ability to assess the impact of breastmilk feeding was very limited in this study due to the large amount of missing information, a better query, or a study which collects this information accurately prospectively with measures of quantity, could provide more useful information to help prepare mothers prenatally and direct clinical care of the infant.

Several factors examined could be useful for identifying infants at risk and used to determine need for surveillance and anticipate potential need for medication such as mother's reason for opioid use, infant's gestational age, and sex, although they are not modifiable, and therefore not amenable to intervention. Several factors may be modifiable prenatally, such as type of opioid used, use of benzodiazepines, and use of tobacco. Future prospective studies which manipulate these factors are needed. Variables related to the environment of care, such as encouraging participation by primary caregiver, and facilitating breastmilk feeding are additional modifiable factors that have potential to improve outcomes for these infants. Additional studies using a prospective design with thorough exploration of maternal history and documentation is needed to accurately assess the impact of the maternal factors.

These results should be interpreted with caution because of the problems and limitations inherent in retrospective chart-review research, however, the results provide a starting point for researchers for further research based on the significant associations. These results can be used to inform future prospective research studies both descriptive and interventional which can direct care for both the mother and infant. Plans of care are

needed that decrease hospital length of stay which will then decrease costs, as well as optimize developmental outcomes, maternal role adaptation, and decrease family disruption.

Growing numbers of infants are experiencing NAS and the resources needed for both short and long-term complications are extensive. Current research with the aim of decreasing incidence and severity of NAS has many limitations including lack of a theoretical framework or conceptual model to guide design and intervention, lack of standardized measures for diagnosing and treating NAS, and largely retrospective designs. Future goals for research should include studies which address these shortcomings. Appropriate future aims are gaining knowledge about predicting NAS incidence and severity, developing evidence-based recommendations for optimal prenatal and neonatal care, and recognizing the importance of compassionate and holistic care for both the mother and infant.

CHAPTER FIVE: Discussion and Conclusions

Introduction

This chapter presents a summary of the three studies conducted to examine maternal opioid use and neonatal abstinence syndrome, followed by discussion and synthesis of the major findings. In addition, limitations of the studies, implications for future research, and conclusions will be presented.

Significance of the Problem

There are over 24,000 pregnancies estimated to be affected by opioid use each year (Whiteman et al., 2014). In 2012, almost 22,000 neonates per year were diagnosed with neonatal abstinence syndrome in the United States, translating to one neonate born every 30 minutes (Patrick, Davis, Lehmann, & Cooper, 2015). Health care costs related to maternal opioid use and NAS are estimated to be greater than $1.5 billion nationwide (Patrick et al., 2015).

Summary of the Included Studies

Risk factors that contribute to the incidence and severity of NAS have not been well established in the literature and research in this area has been problematic for several reasons. Some of the weaknesses of research to date include study design differences, lack of theoretical framework or conceptual model to guide design, inconsistency in definitions and measurement, constantly evolving clinical care practices, and variation in measurement of outcomes. In first undertaking a broad research mission in the area of NAS my original aims were focused on the clinical care of the infant after diagnosis. On closer examination of the issue this approach was too narrow to appreciably impact the problem. Research which included assessment and care of the mother, as well as health

systems and policies related to opioid use were essential for the ultimate aim of identifying, treating, and preventing NAS.

Exploring the Experiences and Needs of Women and Mothers

A qualitative approach offered insights into the personal experience of pregnant women and new mothers who use or misuse opioids and experienced fetal and infant loss. Eleven women with histories of prescription or illicit opioid use who experienced fetal or infant loss participated in the semi-structured telephone or in-person interview portion of the mortality case review. Thematic analysis was used to analyze interview data and identify themes. Five themes were identified related to the care experiences of participants throughout pregnancy and fetal/infant loss: Frustration and anger related to not being heard, feeling minimalized; Being overwhelmed with attempts to process and understand medical complications and outcomes; Profound sense of grief and coping with loss; Need to understand why and make difficult decisions; Placing blame and guilt over death.

Especially striking was the mothers' experience of not being heard or feeling undervalued which appeared in every interview. These findings suggest that women who use opioids and experience fetal/infant loss have complex care, educational, and emotional needs. When developing interventions for these women, it is important to address their unique and complex circumstances.

Facilitating Prevention and Optimal Treatment of Maternal OUD and NAS through Health Policy

The problem of maternal opioid use disorder and NAS cannot be fully addressed while focusing only on clinical care. Advocacy and policy development are essential

components to effective and comprehensive solutions. A non-experimental descriptive study using an electronic survey with telephone follow-up for non-respondents was used to assess current US States' trends in policy development and public health practices related to maternal opioid use in pregnancy and treatment of NAS. A 19-question survey instrument formatted in REDcap was distributed to a convenience sample of 145 representatives from individual U.S. state departments of child welfare/ child and family services and representatives of state health departments in the divisions of substance abuse and mental health.

Examining Factors Associated with Incidence and Severity of NAS in Infants Exposed to Opioids Prenatally

A retrospective chart review was conducted for the purpose of examining factors associated with the incidence and severity of NAS as measured by the outcomes of need for initiation of neonatal medication among newborns born to opioid-dependent mothers. There were 204 infants born to mothers who used opioids during pregnancy. Data from April 2011 to September 2017 were collected from medical records of a large Midwestern hospital. Exploratory analysis and descriptive statistics were performed. Associations between independent variables and outcomes were examined using correlations, chi-square, t-tests, analyses of variance, and logistic regression. Of the 204 neonates who were exposed to opioids prenatally, 121 (59%) developed symptoms of NAS requiring medication treatment with morphine. Factors were divided into three categories maternal (age, parity, race, reason for opioid use, type of opioid used, use of other drugs, and tobacco use), infant (gestational age, sex, and other health complications), and environment (hospital unit used for inpatient care, feeding method,

and primary caregiver involvement). The outcome measure was the need for neonatal medication treatment with morphine solution.

Discussion and Synthesis of Major Findings

The results of the descriptive qualitative study in the population of women who used opioids and experienced fetal or infant loss indicate the women who used opioids and experienced infant/fetal loss had complex needs which were often unmet. Of note, participants in our study repeatedly voiced concerns about not being heard, being ignored, and being undervalued. The participants' perception was that caregivers who did not listen to them, minimized their feelings, and were unsupportive, contributed to their pain, guilt, and bereavement experience. For health care provider, projecting acceptance, accessibility, and readiness to listen is essential, as well as providing understandable medical information about the care provided and procedures performed is essential (Fleischer, Berg, Zimmermann, Wüste, & Behrens, 2009).

Many participants in the study had difficulty understanding why devastating medical complications occurred for them and their infants and often felt the communication from health care providers was inadequate, incomplete, or difficult to understand. This problem of incomplete understanding may be caused partially by the stress and uncertainty of the situation itself, but also may reflect a lack of communication skills among health care providers (Pozzo, Brusati, & Cetin, 2010). Dealing with grief, guilt, and blame was an ongoing process for participants from the first time infant complications were identified through the infant's death and months later.

The findings in the survey of US state policies identifies common trends and differences in individual states' responses to the opioid crisis. The majority of states have

recently initiated new programs to address opioid use and misuse and the majority are planning for additional programs to meet their states' needs in the treatment and prevention of opioid use disorder. Some states are experiencing problems between the development of policies and the funding and delivery of program services. Although the recognition of the scope and severity of the problem was slow, the current progression from policy statements to program implementation has been accomplished in a timely manner in many states. There is evidence in the survey results of continuing conflicts in attitudes on substance use disorder as a criminal act as opposed to a public health issue and chronic disease, with 20% of states indicating prosecution of maternal substance abuse is sometimes pursued. The trend toward interdisciplinary problem solving by planning committees and task forces indicates states are recognizing the importance of a diverse and comprehensive plan to address maternal opioid use and NAS.

In the retrospective chart review which focused on clinical care of maternal opioid use and NAS, there were several significant associations between the factors examined and the outcome variable in the retrospective chart review. Neonates requiring morphine had significantly higher gestational ages than those who did not, infants also exposed to tobacco and benzodiazepines prenatally were at increased risk of needing medication treatment. The mother's reason for opioid use and the type of opioid she used were also associated with differences in the proportion of infants who required medication treatment. Breastmilk feeding and increased primary caregiver involvement were also associated with a decrease in need for neonatal medication treatment.

These three studies represent an inclusive approach to the research question of what factors are associated with increased severity of NAS. The mother's experience and

her needs for complete care, clinical care issues for the mothers and infants, and policy decisions which ultimately affect the availability and funding of research are all components of comprehensive solutions. A variety of methods can balance the strengths and weaknesses of each approach to obtain reliable and robust results (Creswell & Creswell, 2017). Considering public health practices and policy is also a key component for this issue that determines availability and affordability of care for mothers and infants. Public health policy facilitates availability and accessibility of services and determines reimbursement for patients and providers. Clinical research informs providers and policymakers decisions on best practice guidelines and funding. The problem of opioid use in pregnancy is changing rapidly and becoming more complex, no single type of study can address all the components that contribute to the severity of the problem. Sharing information and resources between disciplines and investigating and interpreting the current needs of the population, the delivery of care, and the policy response is key to informed decisions in both individual clinical care and population health related to opioid use. Ongoing research in this area will continue to address the gaps in information for patients, health care providers, and policymakers.

Limitations of the Studies

There are important limitations to note in the included studies. The sample sizes were limited in all three of the studies. Studies in a larger sample size could have generated more accurate results. This is particularly important in the two quantitative studies as saturation was achieved on the major themes in the qualitative study, however a richer, more complete description of the mothers' experience might have been achieved with a larger sample. The retrospective nature of the studies is problematic in an area

which is changing so quickly. There may be major differences in assessment and clinical care during the time period studied from the subjects in the earliest year to the latest.

In both the studies using secondary data, Fetal Infant Mortality Review (FIMR) records and the retrospective EMR review, available data was collected for other purposes. In paper one, there are specific objectives of the FIMR review, to explore ways to decrease infant mortality, and the interview questions were constructed for this purpose. An independent study with interviews conducted specific to the research objective of documenting the mother's lived experiences would enhance the quality of the insights generated. The study on associated factors utilized data initially collected for clinical purposes and this limited ability to explore certain variables because of inconsistent, incomplete, or ambiguous entry in the EMR.

In the survey on US state policies, even though research objectives were formulated early and the survey was designed to meet these purposes, the inexperience of the researcher caused gaps in information and limited the sample. The formulated research aims, and objectives were too broad to capture the objectives accurately in the brief survey. In a future survey, with research aims and objectives narrowed perhaps to pregnant women only, the level of focus could be increased and results more specific.

Literature review in the topic area of maternal opioid use and NAS is challenging because of the focus and urgency assigned to this particular problem and the amount of new material published each month. It is a contemporary and evolving research problem with frequent changes in assessment, clinical care, and policy. Parts of the literature review findings used as the foundation to formulate the research objectives in these

studies were outdated before the study was completed due to the abundant research conducted and published during the study time period.

The scope and depth of discussions in these papers is compromised on many levels compared to the works of experienced scholars. The researcher's expertise is extensive in clinical care of mothers and infants exposed to opioids prenatally, but very limited in conducting research and evaluating and communicating findings, particularly the areas of conclusions and limitations

Implications for Future Research

There are many aspects of the problem of opioid use in pregnancy and NAS which need continued systematic evaluation. Rather than focusing on any single factor, a collaborative and diverse research approach is most likely to produce viable solutions. Collaboration should start with those most affected by the issue, the mothers who use and misuse opioids and their families. Further qualitative research with this population is needed to gain a richer understanding of their needs, frustrations, facilitators and barriers to care, and underlying and motivations. Additional qualitative research in this population with interview and recruitment strategies guided by research questions specific to the life experience of pregnant women and mothers who use and misuse opioids will provide a more in-depth exploration than what can be achieved with a survey question approach, or open interview data originally collected to answer other research questions. Insight gained about beliefs, values, feelings, and motivations that underlie behaviors will provide a starting point to further research in prevention and clinical care strategies.

The substantial increase in patients with the diagnosis of NAS has helped clinicians gain experience with the population. However, the rapidly increasing number

of patients caused frequent alterations and accommodations in the delivery of clinical care which may have interfered with the quality of research. The immediate clinical needs and lack of available resources necessitated protocols based on either clinical expert advice or poorly designed studies. Studies based on historical controls are difficult to interpret with guidelines constantly changing for both mother and infant. Instead of targeting specific factors, multiple parts of the care model often changed between the control patients and the intervention group making it difficult to compare and discern which factors contributed, and to what degree, to the differences in outcomes.

Further research is needed to understand optimal treatment for both pregnant woman who use and misuse opioids and their infants. Factors which are associated with the incidence and severity of NAS that can be modified during prenatal care have been identified in this study. These include medication chosen for opioid use disorder treatment, smoking cessation, and limited use of adjunct medications. Interventions that are designed to alter these factors can be developed and implemented to improve management of the mother's illness and neonatal outcomes. As the next step, these factors should be examined prospectively with attention to consistency and control of confounding variables. Once associations with maternal and neonatal outcomes are established, promising interventions can be designed and tested.

More research is required to develop consistent and reliable screening tools which are appropriate for infants throughout the course of treatment. Consistent screening is essential for determining incidence of NAS, as well as comparing the success of various treatment strategies. Developmentally appropriate screening tools which are reliable and

valid will improve the consistency of decisions to initiation medication and assist with weaning strategies.

Many concepts that are included in the full conceptual model developed for this dissertation could not be examined in the included studies. Several factors in the model could not be explored due to limitations of retrospective chart review and no appropriate proxy for measurement. Particularly feeding method, primary caregiver involvement, and a rooming-in model of care are areas identified in the review of literature which show promise for improving short-term outcomes and should be prioritized for further study. There is a lack of studies designed to examine these factors thoroughly, and to limit the influence of other potentially confounding variables, such as variations in assessment tool and treatment guidelines. A prospective design which begins during pregnancy, rather than after the infant is born, including optimizing mother's treatment, as well as preparation for parenthood and for care of her infant during observation and treatment of NAS, would be suited to answer questions on these factors and their relationship to short and intermediate outcomes.

Other aspects of the model which were not assessed include an examination of maternal-infant attachment related to stress neurobiology in opioid dependence and the factors of infant temperament, maternal temperament, reactivity, and reciprocity (Schore, 2001). A thorough examination of reliable and valid instruments to measure these variables in the population of affected mothers and infants would facilitate testing of the conceptual model. More research is also needed to understand the long-term outcomes included in the model, such as re-hospitalization, foster placement, developmental outcomes, neglect, abuse, and future addiction, due to the very limited timeframe

available for the current studies. Long-term follow up of families affected by opioid use and misuse is the only way to develop a complete understanding of the population at greatest risk and develop strategies to provide them with optimal care. The optimum goal of research on maternal opioid use in pregnancy and NAS is to reduce the burden of this problem on the individual, the healthcare system, and society. Future research conducted prospectively in a larger and more diverse sample is needed to examine the relationships between factors associated with incidence and severity of NAS and to assess their impact on the outcome variables.

Conclusions

Maternal use and misuse of opioids during pregnancy is a poorly understood cause of significant infant and maternal morbidity, currently there is a lack of sufficient evidence to determine optimal evaluation or treatment. Women who used opioids in pregnancy and experienced fetal and infant loss have complex emotional and clinical care needs. Health care providers have a responsibility to partner with women who use opioids in designing care and making treatment decisions that acknowledge their physical and emotional needs. Care providers should be sensitive to the needs of these women to help reduce their perception of stigmatization and increase their perception of being valued.

Public health policy and management in the area of use and misuse of opioids is evolving to meet the demands of increased incidence and severity of this issue. U.S. states have initiated new programs and the majority of states continue to plan for additional services for opioid dependency prevention and treatment. There is evidence in the survey results of continuing conflict in the United States on the view of substance use disorder as a criminal act rather than a chronic illness and public health. Allocation of

funding and adequate availability of OUD treatment providers and facilities continue to be problematic in most states. The survey respondents indicate a trend toward expanding services, acknowledging evidence-based care, improving treatment for pregnant women, and for the general population with opioid use disorder. There continues to be gaps identified in gender-related issues, including responsibility for children, increased need for social support and services, and greater incidence of comorbidities such as behavioral health issues, most have expanded services for pregnant women and heightened standards of care.

Clinical care of mothers who use opioids during pregnancy, and their neonates requires ongoing systematic research to determine optimal risk assessment, surveillance, and treatment. In the current study, several factors were shown to be associated with the initiation of medication treatment. Mother's source of opioid use, primary type of opioid used, use of tobacco, use of benzodiazepines, infant's gestational age, feeding with breastmilk, and amount of time the primary caregiver spent at the infant's bedside all were significantly associated with the initiation of medication. These results should be interpreted with caution because of the problems and limitations inherent in retrospective chart-review research, however, the results provide a starting point for researchers for further descriptive and interventional studies based on the significant associations.

Assessment of the individual experiences of women with opioid use disorder, development of health policies for prevention and treatment of opioid use disorder, and clinical research to support clinical decision-making for mother and infant are all required to adequately address the current problem of maternal opioid use during pregnancy and neonatal abstinence syndrome. An effective response to the epidemics of opioid use

during pregnancy and the incidence of NAS requires ongoing coordinated research and intervention in clinical care of mothers and infants, public health, and health policy.

APPENDICES

Appendix A: Copyright Release

Appendix B: Conceptual Models

Appendix C: Conceptual and Operational Definitions

Appendix D: Data Collection Sheet

Appendix E: Codebook NAS Factors Analysis

Appendix A

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Title: Care Experiences of Women Who Used Opioids and Experienced Fetal or Infant Loss

Author: Lisa F. Scott,Carol Shieh,Rachel A. Umoren,Teri Conard

Publication: Journal of Obstetric, Gynecologic & Neonatal Nursing

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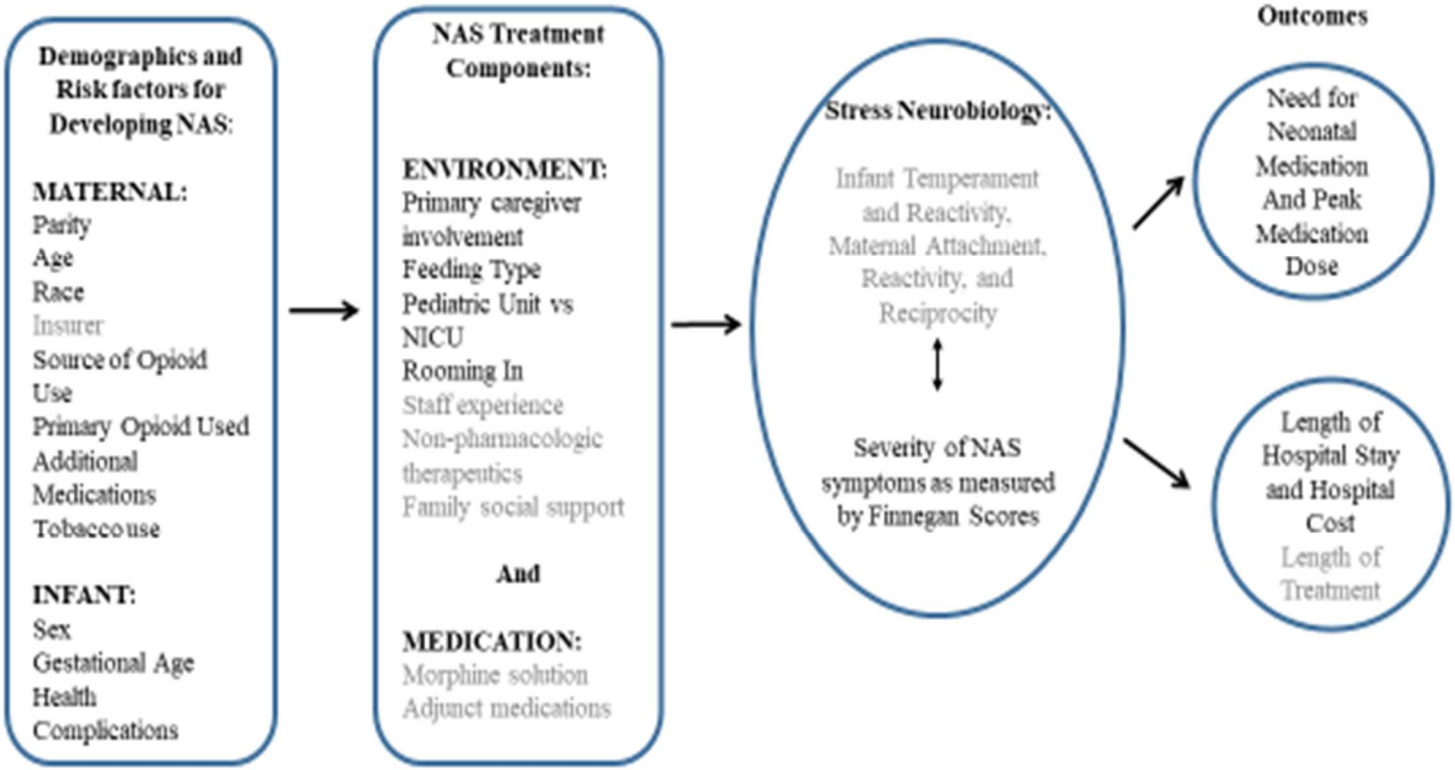
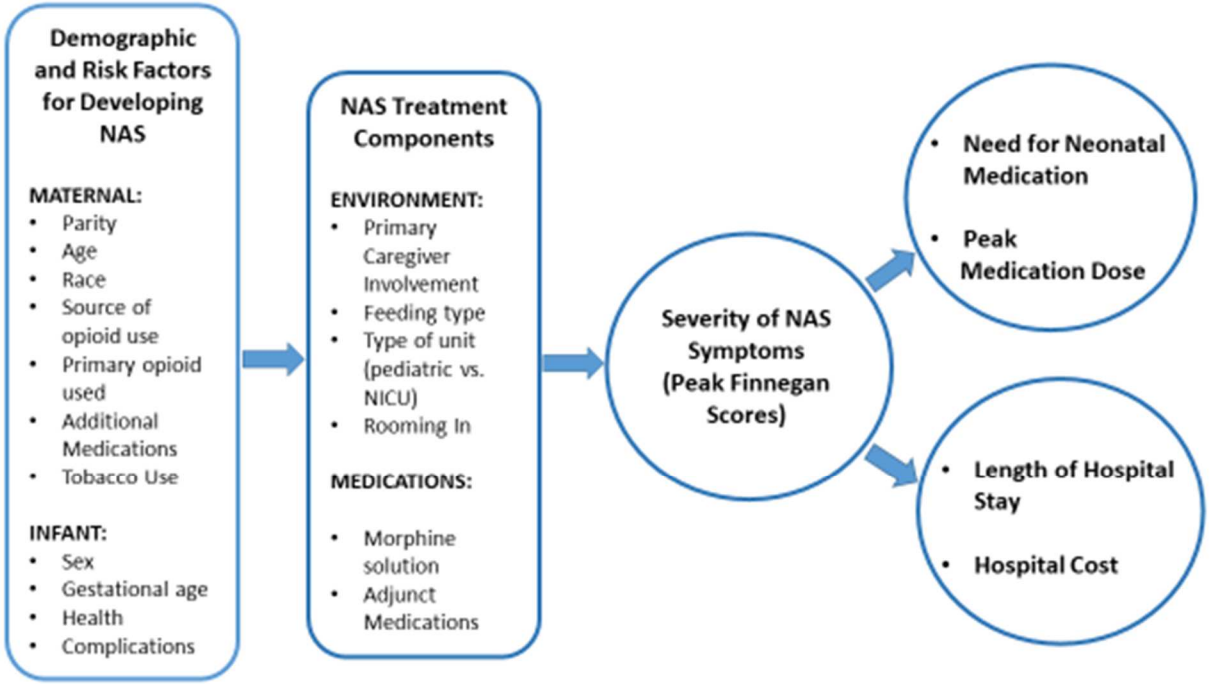
Appendix B: Conceptual Models

Conceptual Model Neonatal Abstinence Syndrome (NAS): Treatment, Associated Factors, and Outcomes

Adapted from Attachment Theory (Blowby) and Schore's Regulation Theory



Abbreviated Model of NAS: Treatment, Associated Factors, and Outcomes Adapted from Attachment Theory (Blowby) and Schore's Regulation Theory



Appendix C: Conceptual and Operational Definitions

Construct/ Variable	Conceptual Definition	Operational Definition	Source of Data Field
Intrauterine opioid exposure	Exposure of fetus via placental circulation to opioids ingested by the mother during pregnancy (R. J. Desai et al., 2015).	ICD-9/10 code 760.7/ 099.32 or P04.4 and confirmed by review of maternal self-report during prenatal history or positive urine toxicology screen during prenatal care or at admission for labor (Rishi J Desai, Hernandez-Diaz, Bateman, & Huybrechts, 2014; S. Patrick et al., 2015).	Electronic medical record (EMR) review (Prenatal History and Neonate admission)
NAS	A constellation of symptoms associated with drug withdrawal in neonates exposed to drugs in-utero, most commonly opioids. NAS is characterized by symptoms in three categories central nervous system, autonomic, and gastrointestinal functioning (Lauren M Jansson & Velez, 2012).	ICD-9/10 code 779.5/P96.1 and confirmed by review of record indicating prenatal opioid exposure and either initiation of neonatal MAT or Finnegan score > 8 (R. J. Desai et al., 2015; S. Patrick et al., 2015)}.	Electronic medical record (EMR) review (medication administration and Finnegan score)
Type of maternal opioid use (prescribed for MAT or other medical use or illicit opioid use)	Opioid medications ingested by the mother either prescribed or illicit	Medication self-reported in prenatal history or results recovered by urine toxicology screen during prenatal care or at hospital admission.	Electronic medical record (EMR) review (Prenatal Hx and laboratory results)

Other maternal drug use	Other medications ingested by mother which may affect neonatal symptoms of withdrawal (benzodiazepines, barbiturates, selective serotonin reuptake inhibitors, caffeine)	Medications self-reported in prenatal history or results recovered by urine toxicology screen during prenatal care or at hospital admission.	Electronic medical record (EMR) review (Prenatal Hx)
Maternal tobacco use	Mother's continued cigarette smoking or use of nicotine patches throughout pregnancy	Self-reported in prenatal history	Electronic medical record (EMR) review (Prenatal Hx)
Infant sex	Infant sex as determined by physical examination at birth	Recorded sex by healthcare provider on birth record	Electronic medical record (EMR) review (Birth history)
Infant birthweight	Infant weight immediately following birth	Birthweight in grams as recorded on the delivery summary/ birth record	Electronic medical record (EMR) review (Birth history)
Infant gestational age	Number of completed weeks of gestation at birth (Battaglia & Lubchenco, 1967).	Based on estimated date of delivery recorded in prenatal chart assigned by best obstetric estimate (first trimester ultrasound, last menstrual period, late prenatal ultrasound)	Electronic medical record (EMR) review (Birth history)
Infant complications	Other health complications experienced by neonate during initial hospitalization	Diagnoses, other than those related to NAS, recorded in neonate's chart during initial hospitalization. These may include, but are not limited to prematurity, congenital anomalies, and birth injuries/asphyxia (S. W. Patrick et al., 2012).	Electronic medical record (EMR) review (Neonate admission note and progress notes)
Need for	Use of an opioid	Recorded dose of oral	Electronic medical

neonatal morphine treatment	medication to treat and control symptoms of opioid dependence and withdrawal (Lauren M Jansson & Velez, 2012)	morphine solution to infant.	record (EMR) review (medication administration hx)
Peak Dose of Neonatal opioid medication	Maximum morphine dose administered (David A Osborn et al., 2010)	Highest morphine dose in mg/kg/day with administration recorded in EMR (Colombini et al., 2008)	EMR review nursing medication administration record
Use of Neonatal Adjunct Medication	Other medication used to assist in control of NAS symptoms, such as phenobarbital or clonidine (Colombini et al., 2008)	Medication administration recorded of phenobarbital, clonidine, or other medication which is indicated in physician progress note as being used for the purpose of adjunct therapy to neonatal opioid medication	Electronic medical record (EMR) review (medication administration hx and physician progress note)
Primary Caregiver involvement	Amount of neonate's care which was provided by a primary caregiver (mother, family member, foster parent) during the neonate's inpatient stay	Percentage of time infant was hospitalized that primary caregiver (mother, father, foster parent) was recorded at bedside (number of days of mother visits / total hospital stay)	Electronic medical record (EMR) review (nursing flowsheet)
Feeding Method	Type of feeding method and substance	Feeding methods and type recorded during hospital stay feeding with exclusive breastmilk, exclusive formula or combination of breastmilk and formula(Okan, Ozdil, Bulbul, Yapici, & Nuhoglu, 2010; Welle-Strand,	Electronic medical record (EMR) review (nursing flowsheet)

		Skurtveit, Jansson, Bakstad, Bjarkø, et al., 2013)	
Unit of Care	Location of neonate's room during inpatient stay	Total number of days of neonate's inpatient stay in each unit: post-partum/ NBN, neonatal intensive care unit, and pediatric unit (Grossman et al., 2017; Loudin et al., 2017)	Electronic medical record (EMR) review (hospital room number)
Finnegan Score	An observation scale dividing symptoms in three broad categories of neurological, metabolic, and gastrointestinal used to quantify the severity of NAS symptoms (K. C. D'Apolito, 2014; L. P. Finnegan, R. E. Kron, et al., 1975).	Highest modified Finnegan score recorded during hospitalization and day of life of highest Finnegan score (K. C. D'Apolito, 2014)	Electronic medical record (EMR) review (Finnegan score NAS flowsheet)
Hospital LOS	Total number of days neonate remained an inpatient after birth	Number of days from admission at birth to discharge to home or foster care (S. W. Patrick et al., 2012)	Electronic medical record (EMR) review
Hospital Cost	Total cost of neonate's initial hospital stay	Total cost in dollars billed to neonate by hospital for inpatient stay (S. W. Patrick et al., 2012)	Case Management Record Review
Calculated Hospital Cost	Total cost of infant's hospital stay calculated based on average daily cost for infants with diagnosis of NAS for newborn nursery, pediatrics and neonatal intensive care unit.	Total in dollars calculated form averages supplied by the hospital's case management department and compared to infants with actual cost to determine correlation and accuracy	Case management and hospital administration records; calculations by SPSS

Appendix D: Data Collection Sheet

Factors related to Severity of NAS: Data Collection Tool

Subject No._____ Date _____

Maternal

- Mother's Name _____
- Mother's MRN_____

- Maternal age: _____ years
- Maternal race: Caus / Black / Hispanic / Burmese / Other
- Marital status: Married/ Single / Divorced / Separated
- Employed: Full time / Part time / Student / Unemployed / Disabled
- Gravida (#pregnancies): ____
- Parity (#live births):_____
- Insurer: Medicaid / Private Insurance/ self-pay
- Opioid use diagnoses: illicit / prescription / opioid dependence disorder treatment
- Type of opioid used: methadone / buprenorphine / heroin / other opioid analgesic / opiate unspecified
- Other maternal drug use: benzodiazepine / barbiturate / SSRI / other_____
- Tobacco use: yes/ no

Infant

- Infant's Name_____
- Infant's MRN_____
- Infant's DOB_____
- Gestational age: ___ weeks____ days

- Gender: male/ female
- Weight : _____ grams
- Feeding Method: exclusive breastfeeding/ exclusive bottle feeding/ breast and bottle/ exclusive breastmilk from bottle/ bottle feeding with formula
- Infant health complications: prematurity/ respiratory distress / hypoglycemia/

  /congenital anomalies/ sepsis/ other _____

Enviroment/ Treatment

- Peak Finnegan score:_____ DOL#: _____
- Peak morphine dose: _____ DOL#:_____
- Adjunct Medication: phenobarbital / clonidine / other_____
- Number of days in NICU : _____
- Number of days in Pediatric Unit: _____
- Number of days attending physician #1: _____
- Number of days attending physician #2: _____
- Number of days other attending physician : _____
- Number of days of parent visitation: _____
- Length of hospital stay: _____ days
- Proportion of hospital stay primary caregiver at bedside (days of visitation/ total hospital stay: _____
- Total Hospital charges #: $_____

Appendix E: Codebook NAS Factors Analysis

Scott_Codebook_NASFactors

Variable Label	Variable	Values	Coding
Subject #	Assigned Subject #	1-204	1-204
BABY NAME	Infant name	Identifying information	
BABY MRN	Infant medical record number	Identifying information	
Baby DOB	Infant date of birth	Identifying information	
ADMIT_DT	Infant admit date	Identifying information	
YEAR	Year of Admission	2011-2017	2011, 2012, 2013, 2014, 2015, 2016, 2017
BABY DX 1	Infant diagnosis related to maternal drug use	Intrauterine opioid exposure; maternal drug abuse; intrauterine drug exposure	ICD 9; 10 codes search criteria
BABY DX 2	Infant diagnosis related to withdrawal symptoms	Neonatal abstinence syndrome; neonatal drug withdrawal; newborn affected by maternal drug use	ICD 9; 10 codes search criteria
BABY OTHER DX (r)	Other infant health complications	Other health complications including prematurity; respiratory (RDS, TTNB, Mec Aspiration, PPHN); congenital anomalies (cleft lip and palate,	1- Prematurity 2- Respiratory 3- Congenital Anomalies 4- Other 0- None

		undescended testes, hearing loss); Other (SVT, SGA, jaundice, perinatal asphyxia, suspected sepsis)	
BABYOtherHealthY_N	Other health diagnosis for infant	Yes or no	1- Yes 2- No
MOM_AGE	Maternal Age	number in years	# yrs
Insurer (r)	Insurer	Medicaid/ Private/self-pay	1-Medicaid 2-Private 3-self-pay
MOM Race (r)	Maternal Race	Caucasian; Black; Hispanic; other	1=Caus 2=Black 3=Hispanic 4=other
Marital	Marital Status	Single; married; divorced	1=single; 2=married; 3=divorced
Gravida	Gravida	number of pregnancies	# pregnancies
Para	Para	Number of live births	# births
MOM Parity (r)	Maternal Parity	Primiparous or multiparous mother	1- Primip 2- multip
MOM DRUG USE DX (r)	Source of maternal opioid use	Illicit Use; Prescription Use (Rx); Treatment for Opioid Dependence (Tx)	1-illicit 2-prescription 3- treatment
MOM DX Type (r)	Other health care diagnosis for mother	None or Behavioral Health: Bipolar, depression, schizophrenia, anxiety, PTSD;	1-Behavioral Health 2-Chronic Pain

		Chronic Pain: Trauma, motor vehicle accident, fibromyalgia; Neurological: brain tumor; seizure disorder; Metabolic: hypothyroidism, diabetes; Other: HTN, asthma, Hep C positive	3-Neurological 4-Metabolic 5- other 0- None
MOMTOBACCO	Maternal use of tobacco during pregnancy per prenatal records	Never; Yes; No; Quit during pregnancy	1-never, 2-quit, -3-yes, 4-no
3TOBACCOYN (r)	Maternal Use during pregnancy	Yes or No	1-Yes 2-No
MOM Primary Opioid (r)	Maternal Opioid most used	Methadone; buprenorphine; heroin; other opioid analgesics (hydrocodone, oxycodone, codeine, tramadol, morphine); opiate not specified (toxicology screen)	**Coding by Group** 1-methadone 2-buprenorphine 3-heroin 4- Other opioid anlagesic 5- Opiate unspecified (toxicology screen)
MOM other opioid	Any other occasional maternal opioids used	Including Methadone; buprenorphine; codeine, other opioid analgesics (hydrocodone, oxycodone, tramadol); Morphine; heroin; opiate not specified (toxicology	Text string list of opioids

		screen)	
MOM other opioidYNr	Additional opioids used either by maternal history or toxicology screen	Including Methadone; buprenorphine; codeine, other opioid analgesics (hydrocodone, oxycodone, tramadol); Morphine; heroin; opiate not specified (toxicology screen)	1-yes 2-no
MOM other drugs (#1 and #2)	Other maternal drugs taken during pregnancy	Barbiturate; benzodiazepine; SSRI; Stimulants (cocaine, methamphetamine, amphetamine), THC, other (labetalol, proton pump inhibitors, muscle relaxants, anti=convulsants)	List of drugs/ medication
MOMDrugTyper2	Other drug by class	Barbiturate, benzodiazepine, SSRI, stimulants, THC, other	1-Barbiturate; 2-benzodiazepine; 3-SSRI; 4-Stimulants 5- THC 6-other 0-None
MOMBenzoY_N	Benzodiazepine use by maternal hx or by urine toxicology screen	Yes or no	1 Yes 2 No
BABY_GA	Infant's gestational age at delivery in completed weeks	Gestational age in weeks	# for GA

BABY SEX	Infant's sex	male, female	1- male 2-female
BABY WEIGHT KG	Infant's weight at birth	Weight in kilograms	# kg
PEAK FINNEGAN SCORE	Highest Finnegan score recorded	Score in whole numbers 1-22	# score
Morphine Y/N	Infant Treatment with oral morphine solution	Morphine solution started for the treatment of NAS symptoms	1- Yes 2- No
MS Peak/ KG	Highest dose of morphine solution in mg per Kg	# in mg/kg/dose	# in mg/kg/dose
MS Peak MG/dose	Highest dose of morphine solution in mg per dose	# mg/dose	# mg/dose
MS Peak MG/Day	Highest dose of morphine solution in mg per day	# total mg/day	# total mg/day
Addtl TX Meds #1- #2	Additional infants medications used for treatment of withdrawal	None, Phenobarbital, clonidine, Ativan	0-None 1-Phenobarb 2 Clonidine 3- Ativan
Addtl TX MedsY_N	Additional infants medications used for treatment of withdrawal	Given yes or no	0-No 1-Yes
Infant_Meds1	Additional infant medications for treatment of other diagnosis	List other medications not related to NAS treatment	
Infant_Meds 2	Additional infant medications for treatment of other diagnosis	List other medications not related to NAS treatment	

Infant_MedsR	Additional infant medications for treatment of other diagnosis	Other medications not related to NAS treatment yes or no	1- Yes 2-No
FDG (r)	Infant feeding methods	Exclusive breast feeding; formula feeding; combination of breast and formula feeding	1- Breast 2- formula 3-breast/formula
NON-MED COMFORT	Use of non-medication comfort measures	Use of non-medication comfort measures including swaddling, low light, low stimulation, rocking bed, pacifier	1- Yes 2- No
Transfer	Infant born at facility or transferred in	Yes (outborn transferred); No (inborn)	1- Yes 2- no
NBN LOS (HRS)	Length of stay in newborn nursery by hours	Number of hours in NBN	# in hours
PEDIATRICS LOS (HRS)	Length of stay on pediatric unit in hours	Number of hours on pediatric unit	# in hours
PEDS/NBN LOS (Days)	Length of stay in newborn nursery and Pediatric unit in days	Number of days on newborn nursery and pediatrics combined	# in days
NICU LOS (HRS)	Length of stay in neonatal intensive care unit in hours	Number of hours on NICU	# in hours
NICU LOS 1 (DAYS)	Length of stay in neonatal intensive care unit 1st admission in days	Number of days in NICU on 1st admission	# in days
NICU LOS 2 (DAYS)	Length of stay in neonatal intensive care	Number of days in NICU on 2nd admission	# in days

	unit 1st admission in days		
NICU Total (Days)	Total length of stay in neonatal intensive care unit in days	Number of days in NICU combined 1st and 2nd admission	# in days
HOSPITAL LOS (HRS)	Total hospital length of stay in hours	Number in hours of hospital stay	# in hours
HOSPITAL LOS (DAYS)	Total hospital length of stay in days	Number in days of hospital stay	# in days
@# OF DAYS MOM AT BEDSIDE	Number of days during stay mother was present at bedside	Number in days mother was recorded at bedside	# in days
MOMSTAY	Percentage of total stay mother was present at bedside	Amount of time mother was at beside as a percent of the total hospital stay	% of days
MOMSTAYr	Proportion of total Hospital Stay Mom was recorded at bedside	Fraction of hospital stay mother was at bedside	#Days Mom at bedside/ #Hospital LOS in days
Provider #1	Days with attending physician-Durbin	Number of days attending was physician 1	# of days
Provider #2	Days with attending physician-Guilfoy	Number of days attending was physician 2	# of days
Provider #3	Days with attending physician-Winchester	Number of days attending was physician 3	# of days
OTHER MD	Days with attending physician-Other	Number of days attending was physician 4	# of days
Hospital Cost $	Cost of hospital stay for this admission,	Cost of hospital stay in dollars	# in dollars

	hospital billing only (does not include fees for professional services)		
Calculated Hospital Cost	Calculated cost of hospital stay in dollars	Cost of hospital stay for this admission, calculated from identified patients (actual cost) and de-identified patients cost (average cost for diagnosis of NAS in newborn nursery, NICU, and pediatric ward)	# in dollars

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CURRICULUM VITAE

Lisa Anne Scott

EDUCATION

- Bachelor of Science in Nursing, Purdue University, West Lafayette, IN (1980-1982)
- Master of Science in Nursing, Perinatal-Neonatal Nursing, Indiana University, earned at IUPUI, Indianapolis, IN (1986-1988)
- Post-Master Fellowship, Neonatal Nurse Practitioner, Indiana University, earned at IUPUI, Indianapolis, IN (1997-1998)
- Doctor of Philosophy in Nursing Science (Minor-Health Policy and Management), Indiana University, earned at IUPUI, Indianapolis, IN (2015-2018)

PROFESSIONAL EXPERIENCE

- Staff nurse, Mother Infant Unit, Home Hospital, Lafayette, IN (1982-1984)
- Staff nurse, Post Anesthesia Recovery Unit, Wesley Medical Center, Wichita, KS (1984-1985)
- Staff nurse, Labor and Delivery Unit, Indiana University Hospital, Indianapolis, IN (1985-1989)
- Clinical Nurse Specialist, Perinatology, IUSOM, Dept. of Obstetrics and Gynecology, Indianapolis, IN (1989 to 1995)
- Research Nurse, IUSOM, Dept. of Pediatrics, Neonatal-Perinatal, Indianapolis, IN (1995 to 1998)
- Neonatal Nurse Practitioner, IUSOM, Dept. of Pediatrics, Neonatal-Perinatal, Indianapolis, IN (1998-2000)
- Neonatal Nurse Practitioner, Dept. of Nursing Services, Seattle Children's Hospital, Seattle, WA (2000-2003)
- Neonatal Nurse Practitioner, IUSOM, Dept. of Pediatrics and Indiana University Health Physicians, Neonatal-Perinatal, Indianapolis, IN (2003-2017)
- Neonatal Nurse Practitioner, Commonwealth Neonatology, Pediatrix, Richmond, VA (2017-present)

TEACHING EXPERIENCE

- Adjunct faculty, Neonatal nurse clinical nurse specialist/ neonatal nurse practitioner program, Indiana University School of Nursing, Indianapolis, IN (1990-1992)
- Adjunct faculty, Neonatal nurse clinical nurse specialist/ neonatal nurse practitioner program, University of Washington School of Nursing, Seattle WA (2000-2003)
- Adjunct faculty, Neonatal nurse clinical nurse specialist/ neonatal nurse practitioner program, University of Indianapolis, Indianapolis, IN (2007-1017)

HONORS AND AWARDS

- Future of Nursing Scholars Fellowship Recipient, Robert Wood Johnson Foundations, Princeton, NJ (2015-2018)

PROFESSIONAL MEMBERSHIPS AND SERVICE

- Member, Association of Women's Health, Obstetric, and Neonatal Nurses (AWHONN) (1984-present)
- Member, National Association of Neonatal Nurses (NANN) (1994-present)
- Member, National Association of Nurse Practitioners (NANP) (2010-present)
- Member, Indiana Perinatal Network (2015-present)
- Task Force Committee, Neonatal Abstinence, Indiana Perinatal Quality Initiative (2015-2017)
- Indiana State Representative, NANN Public Policy Special Interest Group (2015-2017)
- Co-chairperson and Member, Allied Health Credentialing Committee; Franciscan Health, Indianapolis, IN (member 2014-2017, co-chairperson 2016-2017)

RESEARCH

- Care experiences of women who used opioids and experienced fetal or infant loss (2016)
- Survey of US states policies and practices regarding maternal opioid use and neonatal abstinence syndrome (2017)
- Factors associated with use of neonatal medications, length of hospital stay and hospital cost in infants exposed to opioids prenatally (2017-2018)

PUBLICATIONS

Scott, L. F., Shieh, C., Umoren, R. A., & Conard, T. (2017). Care experiences of women who used opioids and experienced fetal or infant loss. *Journal of Obstetric, Gynecologic & Neonatal Nursing, 46*(6), 846-856. doi:https://doi.org/10.1016/j.jogn.2017.08.006

Scott, Lisa and Farney, Jane. "A Parent's Guide to Neonatal Abstinence Syndrome." St Francis Hospital Indianapolis and Mooresville, IN. 7 November 2014. Brochure.

Scott, Lisa and Farney, Jane. "A Parent's Guide for Care of the Late Preterm Infant." St Francis Hospital Indianapolis and Mooresville, IN. 6 June 2013. Brochure.

PRESENTATIONS

Posters Presentations:

Care Experiences of Women Who Used Opioids and Experienced Fetal or Infant Loss. Labor of Love: Indiana Infant Mortality Summit. Indianapolis, IN, November, 2016.

Care Experiences of Women Who Used Opioids and Experienced Fetal or Infant Loss. Spring Research Day. Indiana University-Purdue University at Indianapolis. Indianapolis, IN, April, 2016.

Podium Presentations:

Scott, Lisa. Factors associated with the use of neonatal medication, length of hospital stay, and hospital cost among infants born to opioid dependent mothers. National Association of Neonatal Nurses (NANN) annual conference. Anaheim, CA. October 2018.

Scott, Lisa. Factors associated with severity of neonatal abstinence syndrome. Central Indiana Association of Neonatal Nurses. Franciscan Health, Indianapolis, IN. September 2017.
Scott, Lisa. Identifying and treating neonatal abstinence syndrome. Marion County Health Department Visiting Nurse Service. Indianapolis, IN. January 2017.

Scott, Lisa and Conard, Teri. Care Experiences of Women Who Used Opioids and Experienced Fetal or Infant Loss. Fetal Infant Mortality Review Case Review Committee. Indianapolis, IN. October 2016.

Scott, Lisa. "Total Parenteral Nutrition for the High Risk Newborn." University of Indianapolis School of Nursing; Neonatal-Perinatal Nursing. Fall 2014. Lecture.
Scott, Lisa. "Care of the Very Low Birthweight Infant (VLBW). St Francis Hospital Indianapolis and Mooresville, IN. 19 July 2013. Lecture.

Scott, Lisa and Phafler, Cheri. "Thoracostomy Tube Insertion and Maintenance". Neonatal Solutions LLC. St Francis Hospital Indianapolis and Mooresville, IN. 21 January 2012 and ongoing. Multimedia presentation and self-study module.

Scott, Lisa and Phafler, Cheri. "The Golden Hour: Post Resuscitation". Neonatal Solutions LLC. St Francis Hospital Indianapolis and Mooresville, IN. January 2011 and ongoing. Multimedia presentation and self-study module.

Scott, Lisa. "Use of High Frequency Ventilation in the Neonate". Respiratory Care Clinical Conference. Indianapolis, IN. 30 October 2008. Lecture.
Scott, Lisa. "Total Parenteral Nutrition for the High Risk Newborn." Indiana University School of Nursing; Neonatal-Perinatal Nursing. Fall 2004 and Fall 2005. Lecture.

Scott, Lisa. “Oxygen and Retinopathy of Prematurity.” University of Washington Continuing Education for Advanced Practice Conference. 20 April 2002. Lecture.

Scott, Lisa. “Identification and Treatment of Early and Late Onset Sepsis in the Neonate.” Pacific Northwest Perinatal Consortium. Presented bi-annually October 2000 to March 2003. Lecture.