The Effect of Breastfeeding on the Neonatal Abstinence Scores of Infants Born to Mothers on a Methadone Maintenance Program: An Epidemiological Study

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Abstract

The objective of this research study is to determine the effects that breastfeeding has on methadone exposed infants with Neonatal Abstinence Syndrome (NAS), born at Thunder Bay Regional Health Sciences Centre. Methadone has been identified as the optimal treatment for pregnant women who are addicted to opiates. However, intrauterine exposure to drugs, including methadone, may lead to neonatal intoxication or withdrawal, also known as Neonatal Abstinence Syndrome (NAS). Treatment of NAS is dependent on the severity of symptoms. Breastfeeding may have an effect on the NAS symptoms by way of methadone excretion in breast milk. Subjects were a convenience sample of 28 mother and infant pairs ($n_{mothers}$= 28, $n_{infants}$= 28) who were exposed to methadone. This group was further divided according to the chosen feeding method (n_{breast}= 8, $n_{formula}$= 9, $n_{combination}$= 11). An area score was computed for each infant via their NAS scores to show that infant's area under the curve. A one-way analysis of variance was used to test the differences in the area under the curve scores for each group ($p<0.05$). The area scores differed significantly where, $F(2, 26) = 3.69$, $p = 0.0401$. Methadone exposed infants who were breastfed exhibited less overall neonatal abstinence symptoms when looking at the magnitude, duration and area of scores. This means their NAS symptoms were relatively low compared to infants who were formula fed, or both breast and formula fed combined.

Chapter 1: Introduction

This chapter will provide a brief discussion on the importance of researching the effect that breastfeeding has on the neonatal abstinence scores of infants born to mothers on a methadone maintenance program.

1.1 Statement of the Problem

Maternal drug use during pregnancy is recognized as an important risk factor for adverse pregnancy and neonatal outcomes (Marcellus, 2002). Some examples of these adverse outcomes are: late prenatal care, engagement in high risk social behaviours, increased risk of miscarriage, pre-term labour, and poor fetal growth. Intrauterine exposure to drugs, including methadone, may lead to neonatal intoxication or withdrawal, also known as Neonatal Abstinence Syndrome (NAS) (Crocetti, Amin, & Jansson, 2007; D'Apolito, & Hepworth, 2000; Marcellus, 2002; Schempf, 2007).

Methadone has been identified as the optimal treatment for pregnant women who are addicted to opiates. Methadone is a controlled substance and therefore reduces illicit opiate use, improves health, reduces infectious disease transmission, and reduces risky social behaviours such as theft and prostitution. Some benefits of methadone for the population of pregnant women are: improvement in prenatal care, fewer complications of pregnancy, improved birth outcomes such as increased birth weight, and it may even reduce withdrawal

symptoms in infants through breastfeeding (Jansson, Velez, & Harrow, 2004). Although there are also significant negative effects of methadone, such as NAS, the benefits of methadone maintenance treatment out weigh the risks and this is why it remains the treatment of choice (Crocetti, Amin, & Jansson, 2007; Jansson et al, 2004; Winklbaur, Jung, & Fischer, 2008; Health and Welfare Canada, 1992).

Neonatal Abstinence Syndrome (NAS), a clinical condition that has been recognized for over 30 years, is defined by Beauman (2005) as a constellation of symptoms seen in infants experiencing withdrawal from intrauterine exposure to drugs of addiction such as opiates, cocaine, barbiturates and methadone. The impact of NAS on the newborn has been noted extensively in the literature. It is manifested by a variety of symptoms of disturbances of the central nervous system, and gastrointestinal and respiratory dysfunction (American Academy of Pediatrics (AAP), 1998; Binder & Vavrinkova, 2008; Johnson, Gerada, & Greenough, 2002).

Long-term effects of methadone are difficult to study in infants exposed to methadone in utero and through breast milk because there are many confounding variables. Many studies of drug exposed infants and toddlers show a correlation between exposure and speech or language delays, altered sleep states, impaired motor and play behaviour, and poorer state control with irritability and difficulty to console (Greene & Goodman, 2003).

Treatment of NAS is dependent on the severity of symptoms and may

include both pharmacologic and supportive therapy. Breastfeeding may have an effect on the NAS symptoms by way of methadone excretion in breast milk.

1.2 Incidence and Prevalence

There is limited research on the prevalence of NAS both in the U.S. and Canada. However, generic information of the prevalence of drug use in Canada, the U.S., and North America is presenting itself in the literature.

In Canada, a survey by the Addiction Research Foundation has disclosed a rate of cocaine use in the range of 5.5% for all people 18 to 29 years of age. There are about 80 000 births a year in the greater Toronto area; hence as many as 4000 babies may be exposed in utero to cocaine (Forman, Klein, Meta, Barks, Greenwald, & Koren, 1993). In 2001, 3.8% of pregnant women aged 15 to 44 in the U.S. used drugs including opiates, marijuana, cocaine, alcohol, hallucinogens, inhalants, tranquilizers, stimulants, and sedatives, according to findings from the National Household Survey on Drug Abuse (NHSDA). The same survey determined that 15.1% of pregnant women between 15 and 17 years were exposed to drugs. Approximately 134 110 infants were exposed to illicit drugs in utero in the U.S. in 2001, or 1 in 10 infants were exposed to drugs in utero (Beauman, 2005). Polydrug use (concurrent use of 3 or more drug) is now the norm, not the exception (Green & Goodman, 2003) to the pattern of substance use.

The incidence of drug-exposed newborns has been reported to be from 3%

to 50%, depending on the patient population and societal trends (AAP, 1998). Neonatal withdrawal occurs in 55% to 94% of infants born to women on opiates and heroin, up to 85% of infants born to women on methadone, and neonatal morbidity and mortality have increased (AAP, 1998; Lifshitz, Gavrilov, Galil, & Landau, 2001;Jansson Veles, & Harrow, 2004). The incidence of perinatal drug abuse in Canada is not known, as few studies have been done in Canada (Marcellus, 2002). However, in the Metropolitan Toronto area there has been a steady increase in the number of newborns affected by maternal drug use (Bar-Oz, Klein, Karaskov, & Koren, 2003). Currently, estimates for the prevalence of substance use during pregnancy in Canada come from self-reporting by women. Even self-reports of smoking cigarettes during pregnancy, arguably the least stigmatized substance of abuse, are inaccurate and tend to underestimate exposure (Hutson, 2006).

1.3 Hypothesis

It is hypothesized that methadone will have a weaning treatment effect on newborns and therefore, infants exposed to methadone through breast milk will have less overall symptoms of NAS than infants who are bottle fed or who are fed with a combination of breast and bottle feeding.

1.4 Study Objective

The objective of this research study is to determine the effects that breastfeeding has on methadone exposed infants with NAS, born at Thunder Bay Regional Health Sciences Centre. It is the hope of the researcher that this study will draw conclusions that will have an influence on how caregivers recommend breastfeeding to methadone maintained women. Similarly, it is the hope of the researcher that any misgivings or reluctance by caregivers to recommend breastfeeding to women who are seeking substance abuse treatment, will be better understood by the medical community and society as a result of this study. Subsequently, based on the findings it is suspected that breastfeeding will be highly recommended for women on a methadone maintenance program, provided there are no other contraindications to breastfeeding present, as the benefits for breastfeeding outweigh the risks for this population (Jansson et al., 2004).

1.5 Rationale

Over the past three years, staff at Thunder Bay Regional Health Sciences Centre (TBRHSC), have noticed a dramatic increase in pregnant women and newborns affected by substances of addiction. Two methadone clinics were opened in the community and several others in the region. These clinics gave priority to pregnant women to receive methadone treatment for their addiction to opiates. The NICU staff and resources at TBRHSC were taxed to accommodate

the increasing number of infants with NAS. A multidisciplinary team was formed to develop an evidence-based Clinical Practice Guideline (CPG). Subsequently, a research study that evaluated the efficiency of the NAS clinical practice guidelines was initiated. Data was collected six months prior to and six months after the guidelines were introduced. Prior to the CPG there was not a standardized procedure for NAS scoring, infant urine screening was not widely practiced, costly meconium tests were done retrospectively, and admissions to NICU were indiscriminant. After the CPG was introduced, treatment for infants with NAS was standardized; there were lower overall scores, shorter length of stay, and less child welfare involvement.

Some limitations to the NAS study was the small sample size of methadone users in both the pre and post groups. Similarly, while chart reviewed breastfeeding was a variable in the study; the final analysis did not include observations of breastfeeding.

Building on the previously described research of infants with NAS at the TBRHSC, the purpose of the proposed study is to evaluate the effect of breastfeeding on infants exposed to methadone in utero. Women on a methadone treatment program who breastfeed their infants may protect the infant against NAS symptoms, as abrupt cessation of breastfeeding during high maternal dosing has been associated with NAS, and maternal dosage at delivery appears to relate strongly to the severity of neonatal withdrawal (Begg, Evan, Malpas, Hackett, & Ilett, 2001). This research is of importance because it could

change current opinions and attitudes of health care providers, as well as public opinion, regarding breastfeeding for methadone exposed infants. As well, it has important implications for the health of newborns, the benefits associated with breastfeeding and to whom it is currently recommended perhaps by health care providers caring for methadone exposed newborns.

1.6 Glossary of Important Terms

EMR (Enterprise Medical Record)

MEDITECH's Enterprise Medical Record (EMR) represents a single source for viewing all relevant patient information — from all aspects of clinical care — throughout the health care delivery system. Complete visit histories are electronically stored for each patient over the course of an entire lifetime. The EMR contains information from visits conducted anywhere along the continuum of care — ambulatory centers, hospitals, physicians' offices, home health agencies, long term care facilities, and satellite laboratories. The information contained in the EMR is updated on a real-time basis. Whenever an order is placed or a test is conducted, the patient's record of care is automatically updated (www.meditech.com). The EMR is the health record system utilized at TBRHSC.

Meditech (Medical Information Technology, Inc.)

A Massachusetts-based software and service company serving the medical community with information systems, which are installed in health care

organizations throughout the world. Founded in 1969 by Chairman and CEO A. Neil Pappalardo, MEDITECH currently has a market share of 28% in the United States and 40% in Canada (www.meditech.com).

Methadone Maintenance

"Methadone maintenance treatment (MMT) involves the daily administration of the oral opioid agonist methadone as a treatment for opioid dependence.... MMT improves health and reduces illicit heroin use, infectious-disease transmission, and overdose death." (Ward, Hall, Mattick, 1999, p. 221).

Neonatal Abstinence Syndrome (NAS)

Defined by Beauman (2005) as a constellation of symptoms seen in infants experiencing withdrawal from intrauterine exposure to drugs of addiction such as opiates, cocaine, barbiturates and methadone.

Score (NAS Score)

Refers to the Finnegan Scoring System (Finnegan et al., 1975a), that is used at TBRHSC to assess the severity of withdrawal symptoms.

Chapter 2: Review of Literature

2.1 Introduction

This chapter will provide an in depth review of literature of Neonatal Abstinence Syndrome (NAS) and its relationship to Methadone Maintenance Therapy (MMT), and Breastfeeding. This review of literature will also provide evidence that methadone maintenance and breastfeeding may be effective treatments for NAS.

2.2 Methadone Maintenance Treatment

A comprehensive approach to methadone maintenance treatment generally includes a number of components - which can be delivered in a variety of ways and at varying levels of intensity - including:

- methadone dose;
- medical care;
- treatment for other substance use;
- counseling and support;
- mental health services;
- health promotion, disease prevention and education;
- linkages with other community-based supports and services; and
- outreach and advocacy (Health Canada, 2002).

Although other forms of treatment for opioid dependence continue to be explored, in Canada and internationally, methadone maintenance treatment remains the most widely used form of treatment for people who are dependent on opioids. Methadone itself is a long-acting synthetic opioid agonist, which is prescribed as a treatment for opioid dependence. People who are dependent on opioids may be dependent on either oral or injectable forms of opioids such as heroin (diacetylmorphine), morphine or hydromorphone. Methadone maintenance treatment is an appropriate form of treatment for opioid dependence, regardless of the route of administration (oral or injection) (Health Canada, 2002).

2.2.1 History of Methadone Maintenance Treatment (MMT)

Methadone was originally developed in Germany as a substitute analgesic for morphine. World War II brought the formula to the attention of North American researchers, who subsequently discovered that methadone could be used to treat heroin withdrawal symptoms (Health Canada, 2002).

To date, methadone remains the only opioid authorized for long-term (more than 180 days) outpatient pharmacological treatment of people who are dependent on opioids in Canada (Health and Welfare Canada, 1992). In the almost forty years since methadone was first used in Canada, the number of people receiving treatment has fluctuated, as the regulations surrounding methadone have changed.

2.2.2 How MMT Works

Methadone works by alleviating the symptoms of opioid withdrawal. A stable and sufficient blood level of methadone decreases the chronic craving for opioids. Since methadone is a much longer acting drug than some other opioids, such as heroin, one oral dose daily prevents the onset of opioid withdrawal symptoms - including anxiety, restlessness, runny nose, tearing, nausea and vomiting - for 24 hours or longer (Health Canada, 2002).

Methadone diminishes the euphoric effects of other opioids (cross tolerance), without necessarily causing euphoria, sedation or analgesia (Lowinson, Marion, Joseph, & Dole, 1997). This means self-administered illicit opioids will not lead to euphoria, making it less likely that clients/patients will either use illicit opioids or overdose.

Individuals in a methadone maintenance treatment program take their medication orally once daily - often it is mixed into an orange drink. Since methadone is long-acting, the need to inject other opioids is decreased and this reduces the health risks associated with injection drug use (Health Canada, 2002). Methadone lessens high risk social behaviour associated with drug seeking (i.e. theft, and prostitution) therefore, minimizing risk on a comprehensive scale. Regular methadone given by a provider maintains a positive connection with a professional that can be used for support and assessment (Lowinson et al., 1997).

Tolerance to the effects of methadone develops very slowly, allowing many individuals who are dependent on opioids to be maintained on the same dose of methadone safely for many years. When appropriately prescribed and dispensed, methadone is considered a medically safe medication.

2.2.3 Methadone and Pregnancy

Generally, there are two social viewpoints regarding the use of methadone to treat the drug dependent pregnant woman: 1) Some feel that methadone is an effective treatment because it is prescribed and monitored by physicians, pharmacists, nurses, and other care givers and decreases many high risk drug seeking behaviours such as prostitution, theft, and polysubstance use. 2) Others feel that methadone is a drug used by addicts to simply replace one drug with another and it does not resolve some of the underlying issues which impact addictions such as poor self-concept, poverty, inability to cope, depression, and lack of support, among others. Such arguments are discussed in the articles by Saris (2008); Bratter & Kooyman (1981); and Valentine (2007).

Methadone is currently the opioid replacement therapy of choice for the population of pregnant, opioid-dependent women (Crocetti, Amin, & Jansson, 2007; Jansson et al., 2004; Winklbaur, Jung, & Fischer, 2008; Health Canada, 2002). There are significant benefits for this group, not the least of which includes improvement in prenatal care, fewer complications of pregnancy, engagement in substance abuse treatment, and improved birth outcomes

(Jansson et al., 2004). There are significant negative consequences for methadone exposed newborns such as intoxication, withdrawal, low birth weight, premature birth, intrauterine growth restriction, microcephaly and congenital abnormalities, and death (Jansson et al., 2004; Sharpe & Kuschel 2004; Miles, Sugumar, Macrory, Sims, & D'Souza; 2006). However, studies show that methadone maintenance for opiate addiction is the optimal course of treatment in pregnancy because it is a controlled substance. Methadone is administered to the patient daily where the patient must go to a clinic to receive it. This can show responsibility and a willingness to get clean and can minimize other illicit behaviours for example, prostitution, leaving baby/children in car while seeking drugs, leaving baby/children unattended while on a high or unable to be lucid enough to handle children or feed a baby (Bratter & Kooyman, 1981).

While methadone has been identified as the optimal treatment method for opiate addicted pregnant women, it is not without risks. In 2008, Binder and Vavrinkonva concluded that the highest weight loss of newborns was recorded in the group of MMT women. They also found that babies from the MMT group exhibited symptoms of NAS in 100% of cases while, in the heroin group NAS developed in 89%. Subsequently, the methadone exposed newborns' symptoms were delayed and the most severe manifestations were revealed in babies born to the women from the MMT group. These newborns also required the longest treatment which may be explained by the gradual release of methadone from the newborn's tissues. Stimulant exposed infants (amphetamines, cocaine, or both)

have been shown to be less symptomatic than opiate-exposed infants, and infants exposed to stimulants and narcotics had abstinence scores similar to those for infants exposed only to opioids (AAP, 1998). The higher the methadone dose administered to the mother in late pregnancy, the more marked the newborn's abstinence symptoms (AAP, 1998; Binder & Vavrinkova, 2008; Crocetti et al., 2007).

In 2008, Binder and Vavrinkova said that inclusion in methadone program is more successful in women from higher social strata. Due to better financial conditions they can afford a higher quality and purer heroin, so they develop tolerance more quickly and have to increase the daily dose. Consequently, methadone substitution is in the end their only choice. Further, Binder reports that resocialization in this type of substitution is the most successful as compared to other forms (such as buprenorphine). Prenatal care usually improves and after the birth, children are in most cases entrusted to their mothers' care (Binder & Vavrinkova, 2008; Johnson et al., 2002). The negative aspect is the high degree of NAS. They further conclude that MMT eliminates drug level fluctuations in the womb and development of abstinence syndrome in pregnant women. They consider this stable level of drug a lesser evil for the developing fetus even at the cost of development of addiction. Although methadone has the most severe withdrawal, there are no reports of long term outcomes, and families are in better condition to care for their newborns.

2.3 Neonatal Abstinence Syndrome (NAS)

During the past two decades, illicit drug use has reached epidemic proportions in North America (Bar-Oz et al., 2003). Neonatal Abstinence Syndrome (NAS) is a constellation of symptoms seen in infants experiencing withdrawal from drugs of addiction such as opiates, barbiturates and methadone. Intrauterine exposure to such drugs can lead to physical dependence in the infant, manifested by distressing symptoms after birth (Beauman, 2005 and Croetti et al., 2007). NAS develops 24-48 hours after birth (Binder & Vavrinkova, 2008) but may be delayed as late as four weeks (AAP, 1998). The incidence of drug-exposed newborns has been reported to be from 3% to 50%, depending on the patient population and societal trends (AAP, 1998). Neonatal withdrawal occurs in 55% to 94% of infants born to women on opiates and heroin, up to 85% of infants born to women on methadone (AAP, 1998; Lifshitz, Gavrilov, Galil, & Landau, 2001; Jansson et al., 2004). The incidence of perinatal drug abuse in Canada is not known, as few studies have been done in Canada (Marcellus, 2002). However, in the Metropolitan Toronto area there has been a steady increase in the number of newborns affected by maternal drug use (Bar-Oz et al., 2003).

The effect of polydrug use on the occurrence and severity of neonatal abstinence is controversial. Abstinence scores of 61 infants whose mothers abused both cocaine and methadone were similar to the scores of 42 infants whose mothers received high dose maintenance methadone (AAP, 1998).

Similarly, the use of multiple opiates did not alter the severity of withdrawal (AAP, 1998).

2.3.1 Symptoms

Neonatal Abstinence Syndrome is manifested by a variety of symptoms of disturbances of the central nervous system, gastrointestinal and respiratory dysfunction (AAP, 1998; Binder & Vavrinkova, 2008; Johnson et al., 2002). NAS is a complex problem manifested by symptoms such as tremors, high pitched cry, irritability, hypertonicity, tachypnea, a disturbed Moro reflex, stuffy nose, yawning, sneezing, vomiting, diarrhea, fever, and poor sucking/feeding, convulsions on rare occasions, and death (Winklbaur, Jung, & Fischer, 2008; Johnson et al., 2002; Lifshitz et al., 2001).

In a study by Binder and Vavrinkova, results showed that up to 70% of newborns with NAS have symptoms of CNS disturbances manifested by increased irritability that may culminate in attacks of generalized convulsions; 50% of children have symptoms of tachypnea, apneic pauses and feeding difficulties. Infants exposed to methadone usually exhibit symptoms of withdrawal between two to seven days after birth but can be delayed up to four weeks (Crocetti et al., 2007; Marcellus, 2007; Ostrea, 2001). Maternal methadone dosages are believed to be correlated with severity of NAS symptoms (AAP, 1998). Consequently, knowledge of methadone exposure is critical for pediatricians caring for newborns given the risk that the newborn may be

discharged from hospital in a few short days due do the absence of NAS symptoms shortly after birth.

The clinical presentation of neonatal drug withdrawal is variable, depending on the drug(s), timing and amount of the last maternal use, maternal and infant metabolism and excretion and other unidentifiable factors (AAP, 1998 and Crocetti et al., 2007). Presentation can be similar to, and must be distinguished from: neonatal sepsis, hyperthyroidism, colic, anoxia, hypoglycemia, hypocalcaemia, CNS hemorrhage, and intracranial hemorrhage (AAP, 1998). If left untreated, or unrecognized, NAS can lead to neonatal seizures and death (Finnegan, Connaughton, Kron, & Emich, 1975).

2.3.2 Testing for Drug Abuse in Pregnancy

Although a detailed maternal drug history should be taken, including prescription and non-prescription drugs received, social habits, and whether the mother is breastfeeding, maternal self-reporting frequently underestimates drug exposure (AAP, 1998; Strano-Rossi, 1998). It has been shown that maternal reporting of drug use is far from accurate. Fearing legal consequences and embarrassment from admitting illicit substance use, most users tend to deny or to under-report drug consumption (Bar-Oz et al., 2003). The self-report method is usually coupled with an analytical evaluation in order to avoid a high percentage of false negative results; questionnaires and self-report are administered simultaneously with one or more toxicological analysis which are

performed on mothers or newborns (Strano-Rossi, 1998). By combining both types of data it is possible to obtain a more realistic assessment of substance exposure.

When screening is performed on the newborns at TBRHSC, samples employed are meconium, hair, and urine; other samples such as amniotic fluid, umbilical cord blood, nails, and gastric fluid are seldom used (Strano-Rossi, 1998). Urine screening of the newborn will have a high false-negative rate resulting from an average of 24-48 hour detection window for recent exposure. The validity of blood and urine tests depends on the elimination half life of the compound in question. Cocaine for instance, has a short elimination half life of less than one hour; the drug and its metabolites are not likely to be detected for more than a few days in either blood or urine (Bar-Oz et al., 2003). Meconium drug testing, although not conclusive if negative, is a very effective tool for verifying gestational drug exposure and therefore, more likely to identify infants of drug abusing mothers than is infant urine testing (AAP, 1998; Bar-Oz et al., 2003). A positive meconium test can reflect maternal use of illicit drugs from the second trimester of pregnancy onwards (AAP, 1998). Only meconium collected during the first one or two days of life or for the first three stools can be used to document in utero drug exposure due to the greater concentration of substances (Bar-Oz et al., 2003).

Analysis of the newborn's hair is a widely used test at present. In a study by Bar-Oz et al. (2003), it was concluded that since neonatal hair grows during

the third trimester, it may reflect exposure of drugs in utero during the third trimester and can stay positive for up to three months after birth; a possible combination of negative hair test and positive meconium test may reflect second trimester exposure to drugs, with no third trimester exposure (Bar-Oz et al., 2003). Furthermore, it is reported that meconuim may be more sensitive but it is only available up to two days after birth, whereas testable hair may be available for up to three months. Because meconium production begins in weeks 14-16, meconium testing may detect second trimester exposure to drugs, whereas hair present at birth only develops in the third trimester (Ostrea et al., 2001; Strano-Rossi, 1999). Although this may increase the sensitivity of the meconium test, third trimester exposure, evidenced by hair testing, reflects drug abuse long after pregnancy was detected and hence is diagnostic of continued maternal substance use, which has important implications for neonatal outcomes (Bar-Oz et al., 2003).

The presence of maternal or infant characteristics known to be associated with drug use in pregnancy can be considered indications to screen for intrauterine drug exposure, by using meconium or urine samples. Maternal characteristics that suggest a need for screening include family violence and instability; homelessness; no prenatal care; previous unexplained fetal demise; precipitous labour; abruptio placentae; hypertensive episodes; severe mood swings; cerebrovascular accidents; myocardial infarction; and repeated spontaneous abortions (Marcellus, 2002). Ostrea et al. (2001) suggest, initiating

clinical investigations with urine testing when risk factors are identified. If the urine test is negative, meconium or hair testing should be used depending on postnatal age. In cases with a high index of suspicion, both matrices should be used, rendering higher sensitivity.

2.3.3 Length of Hospital Stay

Infants born to mothers on a methadone treatment program have been shown to require pharmacological treatment for symptoms of NAS for a median of 47 days (Kashiwagi, Arlettaz, Lauper, Zimmermann, & Hebisch, 2005). Mean hospitalization was 6-61 days in the study by Lifshitz et al. (2001). Also, in the above mentioned study of the effects of breast milk on the serverity and outcome of NAS, Abdel-Latif et al. (2006), found that the mean duration of hospitalization was approximately 5 days longer in the formula group than the breast milk group. The maximum amount of morphine for NAS treatment was considerably lower in the breast milk group and overall treatment duration was approximately 20 days less in the breast milk group (Abdel-Latif, Pinner, Clews, Cooke, Lui & Oei, 2006).

2.3.4 NAS Scores (Measuring Tools)

The four most used scoring tools for NAS are the Lipsitz, the Ostrea, the Neonatal Abstinence Scoring System (NASS), and the Finnegan scoring tool (Zahorodny et al., 1998). The most widely used is the Finnegan or a modified

Finnegan scoring tool. The features for each are described in the table below (Table 2.1).

Table 2.1

Name of Tool	# of Items	Scoring Method	Therapy Guidelines
Lipsitz	11	-each symptom scores from 0-3 based on severity	-pharmacologic therapy recommended for score of 4 or greater
Ostrea	6	-each symptom scores from 1-3 based of severity	-no guidelines
NASS	32	-each symptom assigned a weight from 1-5 points -point summation	-no guidelines
Finnegan	20 (can be modified)	-point summation - scored 1-5	-score ≤7, supportive -score ≥8, pharmacologic

In 1975, Finnegan et al. developed an assessment tool for NAS. They noticed that the rate of narcotic addictions had reached epidemic proportions and that the ratio of addicted women of childbearing age had been steadily increasing; resulting in a large number of infants born who must undergo neonatal abstinence early in the neonatal period. They stated that the detection and treatment of infants undergoing NAS significantly reduced the infant mortality rate.

In order to provide an improved method for assessment of neonatal abstinence syndrome and to more carefully evaluate various therapeutic approaches, the comprehensive neonatal narcotic abstinence scoring system was devised (Finnegan et al., 1975a). The researchers constructed the scoring

system based on the literature available at the time and their own clinical experiences. They chose 20 of the many symptoms of CNS excitation that are most commonly found during neonatal narcotic withdrawal. They then ranked these symptoms into groups; those having the least pathological significance were given a score of 1 while those with the greatest potential for clinically adverse effects were scored as 5. Others were given intermediate point values.

All nurses at PGH (Philadelphia General Hospital) were trained in the application of this scoring system. The scoring system was then applied throughout the first 5 days of life to all infants born to drug dependent mothers, and thereafter only to those evidencing withdrawal. Scoring was accomplished at birth and once every hour during the first 24 hours of life. In the second 24 hours, the same signs were evaluated but the score was entered every 2 hours of the scoring sheet. After 48 hours, the infants were scored every 4 hours at time corresponding to their nursery feedings (Finnegan et al., 1975a).

In the study by Finnegan et al (1975), an infant with a score of 7 or less was not treated pharmacologically for NAS because in experience, infants with this score would recover rapidly with swaddling and demand feedings. Infants whose score was 8 or greater were treated pharmacologically (Finnegan et al, 1975a). A Finnegan score of greater than eight is when pharmacologic therapy usually begins (Crocetti et al., 2007; Lifshitz et al., 2001). In the 1975 study, infants received either phenobarbital or paregoric according to a specified dosage schedule, which was regulated according to the abstinence score and the weight

of the infant. The initial dosage determined by the schedule was not changed unless the abstinence score indicated the baby was not being controlled by that dose. Conversely, if the infant's score decreased, the drug dosage was decreased to the next level and when the score was less than 8 for two days, the dosage as reduced to 2 mg/lb/day in 3 divided doses for two days before the therapy was discontinued (Finnegan et al., 1975a).

Finnegan et al (1975a) found that the assessment of nursing personnel to administer the scoring system revealed an inter-rater reliability coefficient in the four pairs which ranged between 0.75-0.96, with a mean of 0.82. All the reliability coefficients were significant ($p<.005$). Also, in the group of infants who were not assessed by the scoring system (Group 1), less were managed without drug treatment, whereas significantly more of the group utilizing the abstinence score (Group 2) were managed without drug treatment (30% versus 46%). The average number of treatment days in Group1 was greater in contrast to Group 2 (8 versus 6 days). Fewer infants who were evaluated with the abstinence scoring system received treatment, therefore the average number of hospital days was reduced by nearly 25% (Finnegan et al., 1975a).

At PGH, the Finnegan scoring method was useful for: rating the severity of neonatal abstinence, regulating drug dosage level during therapy, and comparing the relative efficacy of various pharmacologic agents in the management of the abstinence syndrome (Finnegan et al., 1975b). This scoring system was implemented as both a clinical and investigative tool. The score

monitors the passively addicted infant in a more comprehensive and objective fashion, and facilitates a more precise evaluation of the clinical status of the infant undergoing withdrawal. In addition, the scoring system has been applied in research designed to test the comparative usefulness of various pharmacologic agents currently recommended for NAS, and has been found useful in following the progression and diminution of withdrawal symptomatology before, during , and after therapy. Furthermore, the scoring system provides a basis for developing uniform criteria for the assessment and treatment of the neonate born to the addicted mother (Finnegan et al., 1975b).

2.3.5 Treatment of NAS

There are two treatment procedures for NAS: supportive treatment and pharmacologic therapy. A potential third treatment for NAS is breastfeeding. Although amounts of methadone in breast milk may be small, there is potential that methadone could have a weaning treatment effect (Begg, Malpas, Hackett, & Ilett, 2001).

Supportive treatment includes swaddling to decrease sensory stimulation; frequent small feedings of hypercoloric formula to supply the additional caloric requirements; and observation of sleeping habits, temperature stability, weight gain or loss, or change in clinical status that might suggest another disease process (AAP, 1998; Lifshitz et al., 2001).

Pharmacologic treatment must be individualized, based on the severity of withdrawal symptoms and an assessment of the risks and benefits of therapy Abdel-Latif et al., 2006). The known benefit of pharmacologic treatment is short-term amelioration of clinical signs; whether long term morbidity related to neonatal drug withdrawal is decreased by pharmacologic management of symptomatic infants remain unproven (AAP, 1998).

Infants with confirmed drug exposure who do not have signs of withdrawal do not require therapy. If pharmacologic management is chosen, relatively specific therapy, that is, a drug from the same class as that causing withdrawal is preferable (AAP, 1998). However, opiate exposed newborns that are discharged from the hospital before the onset of NAS are at risk for developing significant NAS at home without medical support or access to treatment, thereby risking morbidity (Crocetti et al., 2007). Methadone, tincture of opium, paregoric, morphine, clonidine, phenobarbital, chlorpromazine, and diazepam are among the withdrawal treatments used. However, neither paregoric nor phenobarbital should be a first choice drug for narcotic withdrawal in neonates. This is because paregoric, in addition to morphine, contains antispasmodics (noscapine and papverine) and ingredients with known and potential toxic effects, including camphor (a CNS depressant), ethanol (45%), anise oil (which may cause habituation), and benzyl peroxide and phenobarbital may produce CNS depression and ideally requires blood levels for appropriate dosing (Crocetti et al., 2007; Lifshitz et al., 2001). At Thunder Bay Regional

Health Sciences Centre (TBRHSC), the practice indicates supportive treatment is given for as long as NAS scores remain less than 8 and pharmacologic treatment is given for 3 consecutive scores of 8 or greater.

Johnson et al. (2002), describe morphine and methadone as a treatment for NAS in more detail saying that, methadone and morphine activate receptors in the locus ceruleus, one of the major clusters of noradrenergic cells in the brain. Their action decreases the activity of adenylate cyclase, resulting in a reduction in cAMP (cyclic adenosine monophosphate) production. As a consequence, potassium afflux in increased and calcium influx into the cell is decreased, resulting in a decrease in noradrenergic (norepinephrine) release. During chronic opiate use, noradrenaline release gradually increases towards its normal level as tolerance develops. Once the opiates are withdrawn, there is loss of the inhibitory effect, and a significant increase in noradrenaline release to well above normal levels. The increase in noradrenergic activity coincides with the appearance of withdrawal symptoms in experimental methods. Administration of opioids results in a reduction in neuronal activity and hence a decrease in withdrawal symptoms. Methadone and morphine have cross dependence and similar receptor effects.

Improvement of abstinence scores (withdrawal symptoms) should assist in assessing the appropriate timing for decreasing the dose of the drug chosen. Guides to adequate therapy include a normal temperature curve, the ability of the infant to sleep between feeding and medications, a decrease in activity and

crying, a decrease in motor instability, and weight gain (AAP, 1998; Finnegan et al., 1975b).

At TBRHSC, neonates with a Finnegan score of 8 or higher were treated pharmacologically until the score was reduced to less than 8. They were then maintained on supportive therapy. Neonates with scores less than 8 were treated supportively which included holding, swaddling, minimal stimulation, feeding using a hypercaloric formula, intravenous fluids, and replacement electrolytes when needed. Lifshitz et al. (2001), found that tincture of opium was ineffective and phenobarbital was more effective at reducing the severity of withdrawal signs. With phenobarbital the average weekly weight gain was 210-242g for infants. Mean hospitalization was 6-61 days; 18 of the infants were discharged home to their mothers and 6 were placed in foster care. All infants were referred for developmental follow-up but only 10 were brought to the appointment; 3 children were examined at 6 months of age, 4 at 12 months of age and 3 at 22 months of age. At the time of examination they all showed normal development.

The authors conclude that this study demonstrated that about 75% of children exhibiting NAS symptoms require pharmacological treatment and that prior information on maternal drug abuse is a crucial factor for successful diagnosis and treatment (Lifshitz et al., 2001).

The clinical practice guidelines at TBRHSC maintain that pharmacotherapy is administered when 3 consecutive scores exceed 8. In cases of opiate

withdrawal, oral morphine is recommended; in cases of withdrawal from substances other than opioids (such as benzodiazepines, barbiturates, ethanol, sedatives, SSRIs and hypnotics), phenobarbital is recommended. Decisions regarding altering the morphine dosage are based on daily average scores or a trend in scores over 24 to 48 hours. The infant continues on the dose of morphine required to keep the scores <8 for 24 - 48 hours before weaning commences. Morphine weaning doses are listed in the following table (Table 2.2).

Table 2.2

NAS (Finnegan) Score	Morphine Daily Dosages
<2	**Observe infant closely for respiratory depression. If two consecutive scores <2, hold Morphine dose and notify Pediatrician. No treatment required**
<8	**No treatment required**
8 – 10	**Morphine 0.32mg/kg/day po Divided q4h**
11 – 13	**Morphine 0.48mg/kg/day po Divided q4h**
14 – 16	**Morphine 0.64mg/kg/day po Divided q4h**
17+	**Morphine 0.80mg/kg/day po Divided q4h**

2.4 Breastfeeding

2.4.1 Benefits of Breastfeeding

When it comes to feeding the newborn, human milk is, from an evolutionary perspective, the biological norm, the time-tested standard of care (Mead, 2008). The health benefits to the infant of breastfeeding have been amply documented; numerous studies strongly indicate significantly decreased risks of infection, allergy, asthma, arthritis, diabetes, obesity, cardiovascular disease, and various cancers in both childhood and adulthood (AAP, 1997). Among the more fundamental disadvantages of not being breastfed is a loss of immunologic protection afforded by maternal colostrum, a "pre-milk" fluid secreted only during the first days after delivery, as well as numerous other bioactive factors that help protect the infant through the first two years of life, when the immune and nervous systems are incompletely developed (Mead, 2008).

Breastfeeding has been shown to be beneficial in soothing agitated infants and successful encouragement of breastfeeding by health workers, whether during the prenatal or postnatal period, has also been shown to enhance parental bonding, promote attachment, and significantly reduce the rate of child removal from the home (Abdel-Latif et al., 2006).

As such, breastfeeding has been identified as the optimal source of nutrition for the first six months and beyond with the addition of solid, nutrient

rich foods at six months along with breastfeeding for up to two years and beyond (Health Canada, 2004).

2.4.2 Breastfeeding and Substance Abuse

There have been no large-scale studies examining the effects of breast milk on the severity of NAS. However, in a study performed in 2006, Abdel-Latif et al. conducted a retrospective chart review of 190 drug dependent mother and infants pairs. Patients were categorized according to the predominant type of milk consumed by the infant on the fifth day of life (breast milk: n=85 or formula: n=105). Those having greater than 2 feeds per day of formula during the fifth day (because of inadequate breast milk supply or subsequent decision to formula feed) were classified as part of the "formula" group whereas others were classified as part of the "breast milk" group. The fifth day of life was chosen because, by that time, the majority of mothers would have chosen the type of milk feeds that they were most comfortable with. They found that mean Finnegan scores were significantly lower in the breast milk group during the first 9 days of life even after stratifying for prematurity and exposure to polydrug and methadone. Similarly, significantly fewer infants required withdrawal treatment in the breast milk group. The median time to withdrawal occurred considerably later in the breast milk group.

Also, in a multivariate analysis of the same study, controlled for exposure to drugs of high risk of NAS (defined as those exposed to heroin, methadone,

and/or benzodiazepine), polydrug and prematurity, breast milk group was associated with lower need for NAS treatment (Abdel-latif et al., 2006). To discount the possibility that the effects noted were because of breastfeeding and not because of breast milk, Abdel-Latif et al. (2006), compared infants fed breast milk by bottle or by gavage tubes to those who exclusively breastfed and found no difference between the two. Finally, the maximum amount of morphine for NAS treatment was considerably lower in the breast milk group and overall treatment duration was ~20 days less in the breast milk group. In addition, the mean duration of hospitalization was approximately 5 days longer in the formula group than the breast milk group.

The researchers in this study concluded that breast milk intake is associated with reduced NAS severity, delayed onset of NAS, and decreased need for pharmacologic treatment, regardless of the gestation and the type of drug exposure. They also suggest that unless there are definitive medical contraindications to breastfeeding, mothers of all infants at risk of NAS be encouraged to breastfeed.

In contrast, a 2004 review of literature by Jansson et al. reported that if drug dependent women have inadequate prenatal care and/or no access to substance abuse treatment, it is likely that they are not good candidates for breast feeding. Thus, literature suggests that there are conflicting reports on whether substance abusing women should breastfeed.

2.4.3 Breastfeeding and Methadone

There are numerous benefits of breastfeeding by women on methadone that are cited in the literature. Some of the well documented benefits include: promotion of interaction between mother and infant; it provides passive immunity to infection; it has shown to confer some advantages to early brain development; it protects against sudden infant death syndrome; improved cognitive and intellectual development in early and middle childhood and it provides some benefits for protection against otitis media, obesity, allergy, and asthma (AAP, 1997; Health Canada, 2004; Mead, 2008). In addition, lactation is associated with the suppression of the secretion stress-responsive neurohormones resulting in an overall reduction in stress response (Jansson et al., 2004). Breastfeeding has been suggested as an appropriate treatment strategy for managing the symptoms of withdrawal in methadone exposed infants (Jansson et al., 2004).

Breastfeeding is not generally contraindicated in a methadone maintained patient if she is free of other drug use as well as being HIV seronegative (Winklbaur et al., 2008). There are multiple barriers to breastfeeding for women on methadone maintenance. Some are social in nature such that nurses are often uncomfortable feeding compromised infants with breast milk from women receiving methadone, which creates an adverse relationship between nurses and mothers (Winklbaur et al., 2008). Other social barriers include women experiencing postpartum depression often do not want to breastfeed; today's

society frequently promotes formula feeding; many drug dependent women come from drug-abusing families and are without positive role models for breastfeeding after birth and often lack support from their significant others (Winklbaur et al., 2008). There are barriers to breastfeeding that are directly related to NAS symptoms that preclude breastfeeding without intensive support from a lactation consultant skilled in treating this population. Infants with NAS may thrash or clamp down on the nipple, causing discomfort; infants who have difficulty with state regulation may spend a good deal of time crying or sleeping and may not be able to achieve the alert state required for nursing; hypertonic infants may be difficult to position properly; and infants with nasal stuffiness frequently pull away from the breast (Jansson et al., 2004). Finally, there is a physiological barrier, in that many women are polysubstance users and cocaine, heroin, PCP, and amphetamines all have adverse effects on infants when transmitted through breast milk (Jansson et al., 2004; Greene & Goodman, 2003; Winklbaur et al., 2008).

Abrupt cessation of breastfeeding during high maternal dosing has been associated with NAS (Begg et al., 2001; Greene & Goodman, 2003; Jansson et al., 2004) because small amounts of methadone are secreted through breast milk. Most addictive drugs, including methadone, are excreted in variable amounts into breast milk, but the quantity of transferred drug is so low that breastfeeding is considered unlikely to cause NAS (Abdel-Latif et al., 2006). Most studies have been performed on methadone because it is the easiest drug

to quantify, and it seems that the minute quantities of passively transferred drug are not sufficient to completely decrease the intensity and severity of NAS (Abdel-Latif et al., 2006; Jansson et al., 2004). Therefore, even though a mother is receiving methadone, her infant may require additional opiate treatment for NAS (Jansson et al., 2004). Abdel-Latif et al. (2006) also found that infants of women on higher methadone doses (greater than 80mg per day) had slightly higher scores than those on lower doses, but the observation held that infants fed on breast milk had lower scores than formula fed infants regardless of maternal methadone dose.

Until recently, the American Academy of Pediatrics recommended allowing breastfeeding for mothers on less than 20mg of methadone a day. This dose restriction for methadone was revised in 2001, and methadone is now deemed compatible with breastfeeding. However, anecdotal evidence suggests that mothers on a methadone maintenance treatment might not be encouraged to breastfeed. Today, many methadone-maintained mothers are prohibited from breastfeeding for a variety of reasons that stem from attitudes of health care providers, the effects on drug-exposed infants, or women requiring methadone maintenance themselves (Jansson et al., 2004).

Artificially lowering a pregnant woman's methadone dose in an attempt to prevent NAS may increase the woman's craving, because it is well established that a woman's volume of distribution increases during pregnancy and that the maintenance dose of methadone during the last trimester of pregnancy may

become considerably higher than her pregnancy requirements (Abdel-Latif et al., 2006). Since methadone maintenance is controlled, unlike other substances of abuse, safer outcomes for mother and baby result.

In another study, one by Begg at al. (2001), they aimed to examine the M/P_{AUC} for the R- and S- enantiomers of methadone during methadone maintenance at moderate to high doses in the early post partum period (immature milk), and again at greater than 15 days post partum (mature milk), and to assess likely infant exposure. R- methadone is of interest because of its potency as a competitive antagonist at the μ opioid receptor (some 10 times that of S- methadone) (Begg et al., 2001). Eight women were recruited that were established methadone users who were or were about to be breastfeeding their infants. Each of the women received their standard dose of methadone (10mg tablets) on the day of the study. It was assumed that these mothers were not taking extra methadone. Blood samples were taken just prior to the dose. Milk was expressed over the periods 0-4, 4-8, 8-12, 12-16, 16-20, and 20-24 hours after drug dosing.

Individual milk samples often have a variable matrix composition that can sometimes alter recovery of a drug. To avoid this, Begg et al. used the "method of addition" for the assay of methadone in milk. They concluded that the estimated dose of R-methadone that would be received by the infant via immature milk was 3.5% of the maternal R-methadone dose and 2.1% for S-methadone. For mature milk, the weight-adjusted doses of R- and S-methadone

were 1.9% and 2.5% and 1.6% and 2.2% respectively. They also state that infant dose ultimately depends primarily on the concentration of drug in milk and that breastfeeding in these infants may be thought of as a potential dosing source of methadone, which may protect against NAS. However, the amount received is likely to be insufficient to prevent NAS. Decisions about the safety of breastfeeding during high dose therapy need to be made on an individual basis (AAP, 1998; Begg et al., 2001).

Jansson et al. (2004) suggest that some drug-dependent women who elect to breastfeed should be discouraged. These include those who are unstable in their recoveries, prone to relapse, and women who are infected with HIV. Women who engage in frequent sexual risk-taking behaviours (e.g. prostitution) are at higher risk for HIV infection and according to Jansson, they should not breastfeed. Also, there are many drugs, including some antidepressants, that have unknown safety profiles for lactating women and therefore, breastfeeding among this group is not recommended.

Since breastfed infants tend to feed more frequently than formula fed infants, and in smaller amounts, these infants can be given their medication for NAS treatment at every other feeding; breastfed infants may require more careful monitoring in the neonatal period for the appropriate treatment of NAS as they are more likely to have increased irritable activity or to demand feeding more frequently (i.e. sleep for shorter intervals) than formula-fed infants (Jansson et al., 2004).

Chapter 3: Methodology

This chapter will provide information on how the researcher selected the sample, acquired and entered data, as well as a summary of the scoring tool used to score NAS at TBRHSC and the statistical analysis.

3.1 Research Design and Sample Selection

This study is a natural experiment design consisting of a retrospective chart review of a cohort of newborns exposed to methadone in utero. All infants born at Thunder Bay Regional Health Sciences Centre (TBRHSC), who were diagnosed with NAS or drug withdrawal, between March 12, 2007 and March 13, 2008 were included in the study. All infants not exposed to methadone were excluded from the study.

3.2 Data Acquisition

The research proposal was granted ethics approval from both TBRHSC and Lakehead University which allowed access the medical records of the infants and mothers in the chosen study period.

A request for all infants born between March 12, 2007 and March 13, 2008 who were scored for NAS and their mothers was made to the health records department at TBRHSC. A list of 141 mother/infant pairs was provided along with the date and time of each NAS score that was given for each infant. From

that list, smaller lists of approximately 30-35 infant/mother pairs' charts were requested at a time to be pulled. This was done on five occasions where the next few charts would be pulled when the researchers were finished extracting data from the previous group of charts.

3.3 Data Retrieval and Entry

The infants' charts were required for retrieving such data as daily feedings and any treatment for NAS, while the mother's charts were required for retrieving data that was located on the record of labour and delivery. The following data was collected from the record of labour and delivery from each mother: birth weight, birth date and time, 5 minute Apgar, gestational age at birth, and maternal analgesics in labour.

Certain information was collected via MediTech for both mother and baby. Data for such variables as: maternal smoking, maternal alcohol use, maternal age, regular prenatal care, prenatal classes, and reported type of drug mother used (as reported on the obstetrical history) was gathered for each mother, which was located in EMR.

Infant variable data was gathered from EMR as well; such as: gender of baby, feeding method, birth weight, time, gestational age at birth, whether or not a urine drug screen was done, whether or not a meconium drug screen was done, age on admission to NICU or not admitted to NICU, urine drug screen results if positive, meconium screen results if positive, discharge information

(child welfare involvement, no child welfare involvement, discharged to child welfare), whether or not baby was sent home with treatment, and underlying medical problems. These variables were comprehensive and not all variables were analyzed within this study.

Feeding method was determined by looking at all feeds given to baby at TBRHSC which were documented in the infant's EMR. If the infant was breastfed for >75% of the time, they were put in the breastfed group. If the infant was breastfed for <25% of the time, they were put in the formula fed group. Any infants breastfed >25% of the time but <75% were put in the combination fed group. Breastfeeding was defined as any breast milk; either by breast or by expressed breast milk via bottle. All feeds for each infant were added up and divided by the number of breast only feeds for each infant.

Mother's reported drug type was used in determining if there was methadone exposure, rather than infant's urine screen results or meconium screen results, because of the high rate of false positives. This makes the sample size susceptible to honesty in reporting, however given that data was collected retrospectively, unfortunately there was no way of controlling for honesty in reporting.

All data was collected and documented on paper and later entered electronically via web-based data entry template. This data was stored in a secure server at Lakehead University while the hard copies were then stored in a secure location at the Maternity Centre.

3.4 Summary of Instrument

The Finnegan Scoring tool was developed in 1975 by Finnegan, et al. Since then, the scoring tool has been tested and validated (AAP, 1998) and is the widely used tool of choice in Canada and the United States for the scoring of NAS symptoms (Zahorodny et al., 1998). The tool used at TBRHSC (Appendix 1) contains 30 of the most commonly observed NAS symptoms and it provides guidance for treatment. Each symptom is given a score between 0 and 5 then added to equal a score for NAS. Infants are assessed either before or during a feed. The infants are observed for approximately one minute and important signs and symptoms are noted. When drug exposure is suspected, scoring begins at birth. NICU nurses score the infants every 2 hours for the first 48 hours; then every 4 hours for 72 hours; and then as required. If the score is greater than 8, nurses score every 2 hours. If there are three consecutive scores greater than 8 for a particular infant, pharmacologic treatment is required to minimize distress and prevent harm.

3.5 Statistical Analysis

From the web-based data entry template, the data was stored in a file which was located in a secure server at Lakehead University. Statistical Analysis System (SAS) was used to create programs that would read the data in this file. Frequency distributions were completed for nominal variables such as: feeding type, reported type of drug mother used, maternal smoking, maternal alcohol

use, regular prenatal care and prenatal classes. Variables were cross tabulated to discover how many mothers were on methadone and what feeding type they chose, and this became the study group.

NAS scores (Finnegan scores) are a measure of the severity of the withdrawal symptoms and are used as a gauge to prescribe treatment. However, the scores are highly vulnerable to variability because of the range of scores that are possible with each infant; and are in this case extremely variable. Some infants start off with a high score and then gradually decrease to score below 8, while other infants respond differently and have scores that are variable, meaning they go up and down and back up again before they become stable enough to be discharged from hospital.

While the number of NAS scores (count) can provide information about the duration of scoring, count cannot be an indicator of magnitude of symptoms. Therefore, an area score was computed for each infant via their NAS scores to show that infant's area under the curve. This composite score is a measure of duration and magnitude since it includes the number of NAS scores (used as a proxy for duration) as well as the magnitude of all the scores. The formula for the area score is:

Area= 0.5 [(2x measure 1) + (2x measure 2)..... + last measure]

where the measures are the infant's individual NAS scores. The area scores were then tested via a one way ANOVA by feeding type.

Chapter 4: Results

This study intended to answer the question, do neonatal abstinence scores differ among feeding types of infants exposed to methadone? Based on data collected for the study, this chapter will describe the sample of mothers on a methadone maintenance program in Thunder Bay, the group profiles, and the results of the univariate analysis and one-way ANOVA.

4.1 Description of Study Sample

Subjects were a convenience sample of 28 mother and infant pairs ($n_{mothers}$= 28, $n_{infants}$= 28) who were exposed to methadone in the prenatal period. This group was further divided according to the chosen feeding method (n_{breast}= 8, $n_{formula}$= 9, $n_{combination}$= 11). The average maternal age in this sample was 25 ± 5. The maximum age was 38 and the minimum age was 16. The median age was 25 and the sample was bimodal with the ages 19 and 22 both having a count of 4.

Of the mothers who elected to breastfeed, all 8 smoked during their pregnancy and none of them used alcohol; while 6 mothers had regular prenatal care and 2 did not. Only 1 mother from this group attended prenatal classes while 7 did not. This is not to say that the mothers who did not have regular prenatal care had no prenatal care at all, but that it was not on a regular basis. The same is true for all three groups when looking at prenatal care. Of the mothers who elected to formula feed their infants, all 9 smoked during their

pregnancy while 2 used alcohol and 7 did not use alcohol. Only 3 of the mothers in this group received regular prenatal care while 8 did not. There was 1 mother who did not have data for prenatal care in her EMR. Only 2 mothers attended prenatal classes while 7 did not. Of the mothers who elected to combination feed their infants, 10 smoked during pregnancy while 1 did not. None of the mothers in this group used alcohol during pregnancy and 5 received regular prenatal care while 5 did not. There was 1 mother from this group that did not have data for prenatal care in her EMR. Only 3 mothers attended prenatal classes while 7 did not and one mother had missing data for prenatal classes in her EMR. The 3 groups are considered homogeneous in nature; the only difference being the feed types.

Table 4.1 Frequency Profile of Mothers

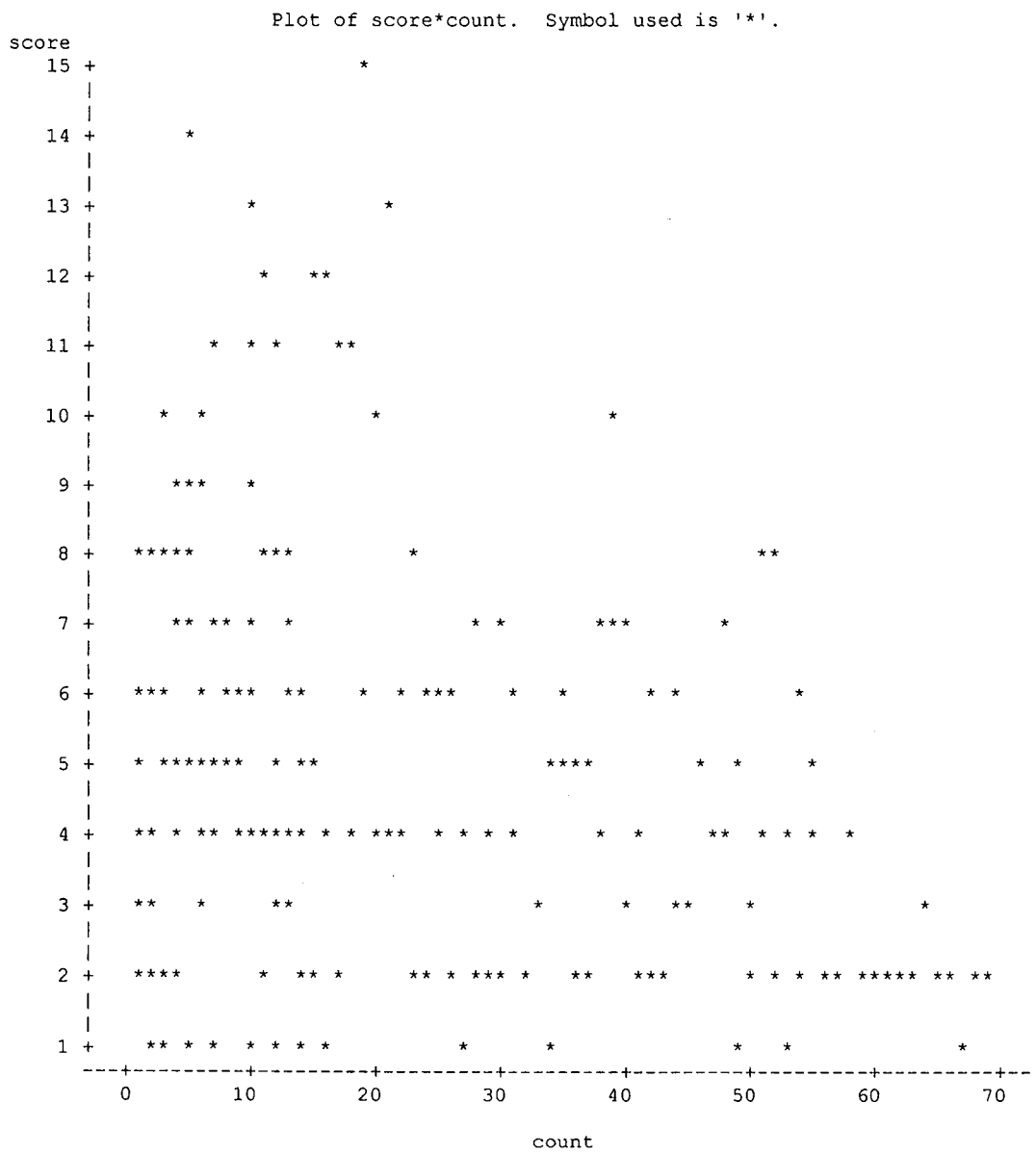
Group	Smoking	Alcohol Use	Regular Prenatal Care	Prenatal Classes
Breast (n= 8)	8	0	6	1
Formula (n= 9)	9	2	3	2
Combination (n= 11)	10	0	5	3

4.2 Group Profiles

The individual NAS scores the infants in each of the 3 feeding groups are extremely variable. Individual NAS scores are point estimates (they do not give an indication of duration of symptoms) and are highly vulnerable to variability. However, when amount of scores is taken into account, an estimate of duration

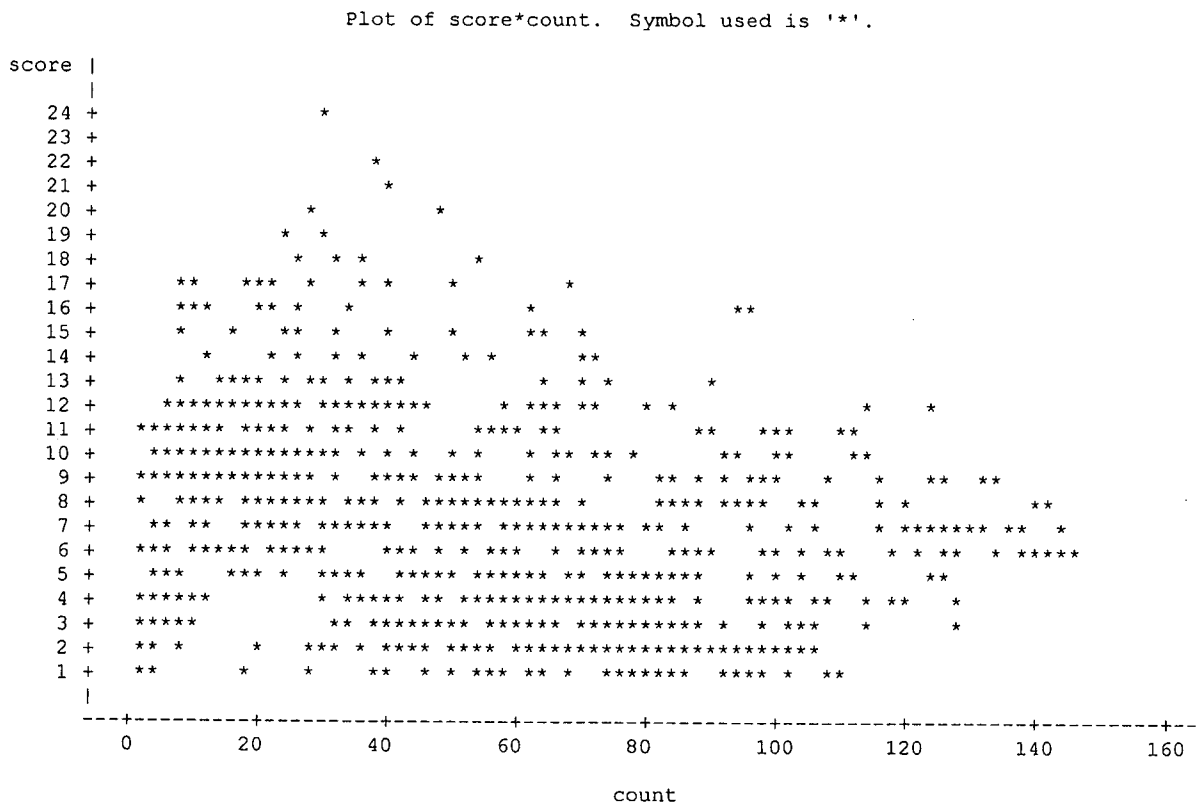
of NAS symptoms is provided. Score count is used as a proxy for duration of symptoms. Since there are multiple scores taken everyday for each infant there can be upwards of 200 scores for a particular case. An infant with 200 scores would indicate a longer score duration than an infant who had 50 or 100 NAS scores. The profiles of each group by feeding type are displayed in the following charts.

Chart 4.1 Breastfed Infants (Group 1)



From the above chart of breastfed infants, it is noticeable that the highest score was 15 and that the maximum number of scores was 69 and that most of the scores are relatively spread out. The area that contains the most amount of scores is the area below a score of 8 and no infants had more than 69 scores.

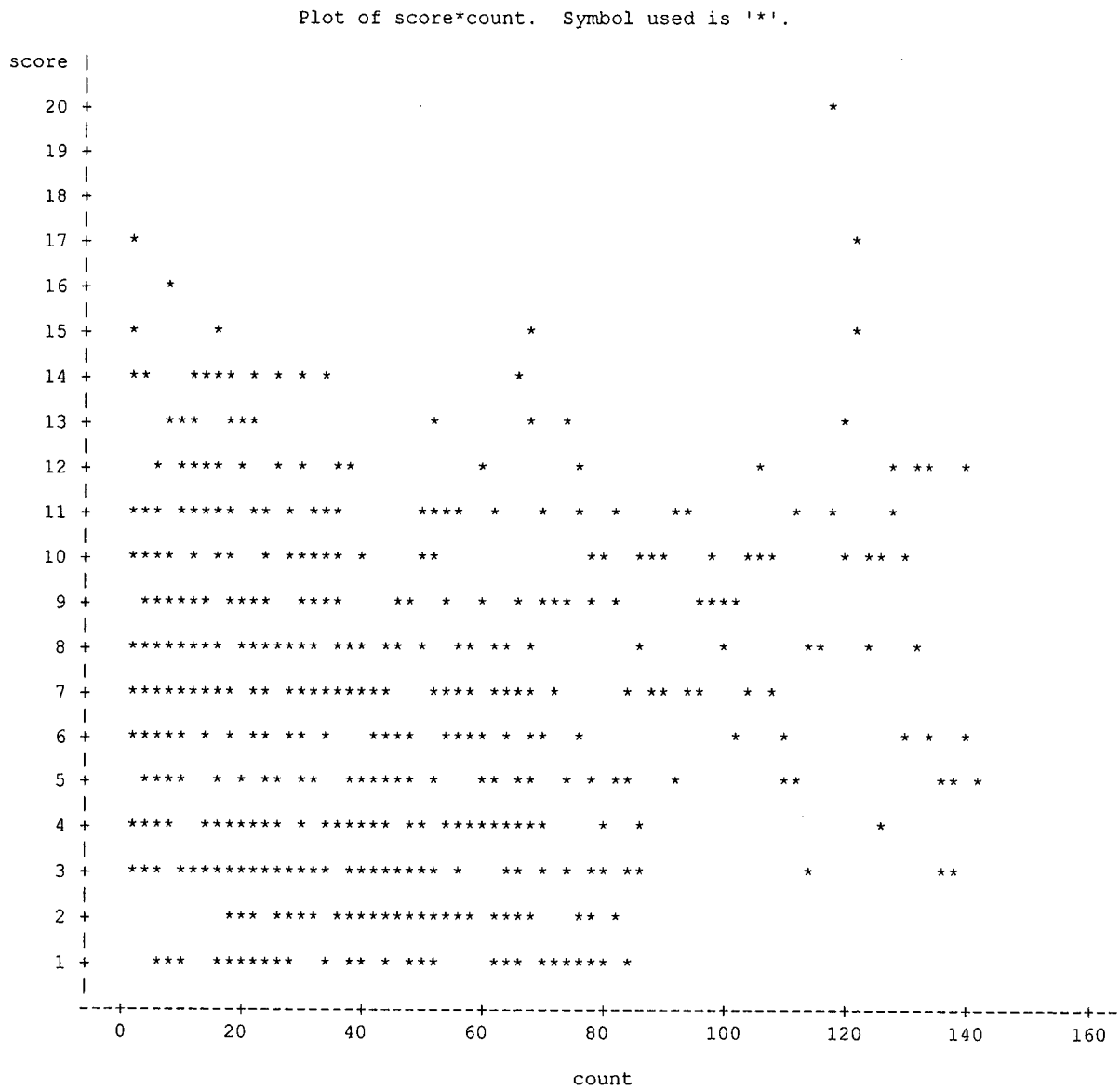
Chart 4.2 Formula Fed Infants (Group 2)



From this chart of formula fed infants, it can be seen that the highest score was 24 and the maximum number of scores was 145. It is also noticeable that most scores take up the area between scores of 13 and counts of 115

meaning that compared to the breastfed only group, the formula fed infants had a larger area under the curve and/or higher scores for a longer period of time.

Chart 4.3 Combination Fed Infants (Group 3)



In this last chart of combination fed infants, the highest observed score is 20, while the highest amount of scores observed is 141. This means that the combination fed infants have a slightly smaller area under the curve than the formula fed infants but is still larger than that of the breastfed only infants. In comparison to the breastfed and formula fed infants; while the combination fed infants' scores are still relatively high their amount of scores above 8 are slightly less than that of the formula fed group whose scores above and below 8 are similar. Simply by observing, it is easy to see that the amount of scores in total and the amount of those above 8 in the breastfed only group are less than those of both the formula fed and combination fed infants.

4.3 Magnitude

The NAS score measures the severity of NAS symptoms and therefore represents magnitude. A univariate analysis was done on the individual NAS scores for each group which provided an indication of overall NAS severity across groups.

Table 4.2 Mean NAS Scores (Magnitude)

Group	Mean NAS Score	Standard Deviation
Breast (n=7)	5	2.9
Formula (n=9)	7	4.2
Combination (n=11)	7	3.6

As observed in Table 4.2, the breast fed group shows lower overall severity of symptoms while the formula fed and combination fed groups both had the highest overall NAS severity.

One-way ANOVA results indicate significant differences between groups where, $F(2) = 23.88$, $p = <0.0001$. Duncan's post-hoc comparison shows that the breastfed group is statistically different than both the formula and combination fed groups.

4.4 Duration

The number of NAS scores provides an indication of the duration of symptoms. A univariate analysis of the number (count) of NAS scores was done for each group which provided information on the overall duration of symptoms across the three groups.

Table 4.3 Mean Count for NAS Scores

Group	Mean Count	Standard Deviation
Breast (n=7)	25 scores	23.5
Formula (n=9)	96 scores	34.6
Combination (n=11)	56 scores	39.0

As observed in Table 4.3, overall the breastfed group had the least amount of scores which can be indicative that the duration of their symptoms was shorter than that of the other groups. The formula fed infants had the highest amount of scores while the combination fed infants fall behind but were still greater than those of the breastfed infants.

One-way ANOVA results indicate significant differences between groups where, $F(2) = 9.38$, $p = 0.0009$. Scheffe's post-hoc comparison shows that the breastfed group is statistically different than the formula fed group, but is not

statistically different than the combination fed group. It also shows a significant difference between the formula and combination fed groups.

4.5 Area Scores

As described in the previous chapter, area scores were computed for each infant so as to provide one number that would include both magnitude and duration of all scores as a profile for each individual infant. A univariate analysis was done on these scores for each group.

Table 4.4 Mean Area Scores

Group	Mean Area Score	Standard Deviation
Breast (n=7)	7.7	3.3
Formula (n=9)	11.4	2.9
Combination (n=11)	12.4	4.2

As observed in the previous charts (charts 4.1, 4.2, and 4.3), when looking at the computed area scores for each group, on average the breastfed only infants have a smaller area under the curve, while both formula and combination fed infants have larger areas. One individual was eliminated from the breastfed group for these analyses, as that infant only showed 3 NAS scores, and therefore was deemed to have been screened for symptoms of NAS without having developed severe enough symptoms to be diagnosed as NAS, even though the mother in this case was on methadone.

A one-way analysis of variance was used to test the differences in the area under the curve scores for each group ($p<0.05$). The area scores differed

significantly where, $F(2, 26) = 3.69$, $p = 0.0401$. Duncan's Multiple Range post-hoc comparison of the three groups indicate that the average area score for breastfed infants (n=7) differed significantly from that of the formula (n=9) and combination (n=11) fed infants. Comparisons between the formula and combination fed infants were not statistically different at $p< 0.05$.

Taking sample size into consideration, a non-parametric one-way ANOVA: Kruskal-Wallis Test was also used to compare the area scores of the three groups ($p<0.05$). The area scores differed significantly in this method as well, where $H(2) =6.3$, $p= 0.0425$.

Chapter 5: Discussion

This chapter will discuss the findings of the study and also summarize the limitations, strengths and recommendations.

5.1 Conclusions

Methadone exposed infants who were breastfed exhibited less overall neonatal abstinence symptoms when looking at the magnitude, duration and area of scores. This means their NAS symptoms were relatively low compared to infants who were formula fed, or both breast and formula fed combined. These findings are congruent with those of Begg et al. (2001) and Abdel-Latif et al. (2006). The breastfed only group also had fewer scores taken (lower duration) which indicates that their scores where <8 for the majority of the time (scores are taken every 2 hours if the score remains above 8) and/or that they recovered from their symptoms relatively quickly compared to the other groups. This means that breastfed babies required pharmacologic treatment less often. This could be due to the small amounts of methadone excreted through breast milk, the physical bonding between mother and baby, the soothing effects of breastfeeding and other physiological effects, or a combination of all.

The formula and combination fed infants could have exhibited higher scores because of the abrupt cessation of methadone that they were receiving in utero. As previously mentioned by Begg et al. (2001), Greene & Goodman (2003), and Jansson et al. (2004), abrupt cessation of exposure to substances

(i.e. breastfeeding and therefore any methadone the infant would be receiving through breast milk) has been linked to NAS. However, breastfeeding less often would have less of a weaning effect as the dosage of methadone in the breast milk would be lower. The formula fed infants would have stopped receiving methadone through breast milk right away, and therefore exhibited the most severe symptoms as a result of the abrupt cessation of exposure to methadone. Some of the combination fed infants might have been put on formula for a few feeds before they received any breast milk, also receiving less breast milk and therefore less methadone and experienced an increase in NAS symptoms as a result of the brief cessation of methadone exposure in utero. This would explain why the combination fed infants had higher NAS scores than the breastfed infants but lower scores than the formula fed infants. The formula fed and combination fed groups may have also had less physical bonding and many other positive effects associated with breastfeeding.

5.2 Study Strengths and Limitations

Infants were considered breast fed even if they were fed with expressed breast milk in a bottle. This may give rise to the conclusion that the amounts of methadone infants may have been exposed to through breast milk were significant enough to have a weaning treatment effect on the NAS symptoms, which resulted in the lower overall scores, though future studies which examine

the amounts of methadone received by the infants from breast milk may be able to solidify this finding.

It was requested of the health records department at TBRHSC that all infants with NAS scores born in the study time period be listed. Therefore, some NAS scores from the list of all 141 infants and mother pairs could have been taken because it was mistaken for another condition with similar symptoms as NAS. Any infants deemed to have these erroneous scores were eliminated from the study sample simply by the inclusion criteria (infants with mothers reported being on methadone), and by the close inspection of scores where one individual was eliminated from the breastfed group because there were only 3 scores taken, which were all <8 and therefore this case was deemed not to be NAS.

Due to issues with self-report, it cannot be ruled out that the mothers were not taking other drugs while also on methadone and therefore the researcher could not control for the effects of poly substance use and how many poly substance users were in each group. However, all three groups were considered homogenous because all mothers reported being on methadone and they all gave birth to babies that exhibited symptoms of withdrawal. The only differences between the individuals in the sample were the chosen feeding methods.

5.3 Recommendations

As previously mentioned, further studies are necessary in the area of methadone and the effects that breastfeeding has on the NAS symptoms of infants. It would be beneficial to have studies with a much larger time period. While significant results were obtained with the current study, future studies with larger sample sizes are needed. This study's time period was one year, which only yielded 27 mothers on methadone who gave birth to infants who were experiencing NAS. In order to obtain a larger sample size, it is recommended that the study time period from which the data is obtained be 2 or more years. Perhaps, being able to control for honesty in reporting would also affect sample size, however this may prove to be a difficult feat. Studies that measure amounts of methadone in breast milk would also greatly contribute to the advancement of our knowledge of this particular area of research.

This study intended to investigate the notion that methadone, through breast milk, may be beneficial to the newborn experiencing neonatal withdrawal. It also intended to introduce an influence on the reluctance of caregivers to recommend breastfeeding to women on methadone maintenance program. Perhaps it will encourage caregivers to recommend breastfeeding to this population provided there are not other contraindications to breastfeeding; incidentally, this should be done on a case by case basis.

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Appendix

A.1 The Finnegan Scoring Tool for Neonatal Abstinence Syndrome

System	Signs & Symptoms	Score	TIME						Comments
CNS	excessive high pitched cry	2							
	continuous high pitched cry	3							
	sleeps < 1 hr after feeding	3							
	sleeps < 2 hrs after feeding	2							
	sleeps < 3 hrs after feeding	1							
	hyperactive Moro reflex	2							
	markedly hyperactive Moro reflex	3							
	tremors disturbed	2							
	mild tremors undisturbed	3							
	moderate-severe tremors undisturbed	4							
	increased muscle tone	2							
	excoriation (specify area)	1							
	myoclonic jerks	3							
	generalized convulsions	5							
Metabolic	sweating	1							
	fever 37.2 to 38.3° C	1							
	fever > 38.4° C	2							
	frequent yawning > 4 X /interval	1							
Vasomotor	mottling	1							
	nasal stuffiness	1							
	frequent sneezing > 4 X /interval	1							
Respiratory	nasal flaring	2							
	respiratory rate > 60/minute	1							
	respiratory rate > 60/minute + retractions	2							
	excessive sucking	1							
	poor feeding	1							
GI	regurgitation	2							
	projectile vomiting	3							

	loose stools	2							
	watery stools	3							
Total Score									
Scorer's Initials									