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Case Report

Neonatal abstinence syndrome in three days old female infant from a HIV infected mother with twelve years of using methadone

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ABSTRACT

Neonatal Abstinence Syndrome (NAS) is a group of symptoms that occur in a newborn as a result of the sudden discontinuation of fetal exposure to substances that were abused by the mother during pregnancy period. NAS is a rare case in Indonesia; however the incidence of NAS among foreign countries, namely England, Canada, and Western Australia, is increasing. The symptoms of NAS are very similar to other neonatal diseases, such as sepsis and hypoglycemia neonatal; therefore, the diagnosis approach of NAS should be done properly. This report described management of a rare case of NAS in three days old female infant from a HIV infected mother with 12 years of using methadone. A three days old female infant was hospitalized with symptoms of high pitch cry, fever, tremor, poor feeding and vomiting. She was very irritable, sweating, and had highly fluctuating body temperature. She also found with high respiration rate, and hypoglycemia. Her mother has been using methadone for 12 years. At the baseline, we found Neonatal Abstinence Syndromes (NAS) score was 18 based on Finnegan Neonatal Abstinence Severity Score (FNAS) score. According to the guideline, oral morphine was given as a definitive medication together with other supportive therapy. After four days of therapy, morphine dose was tapered and continued until ninth days of treatment. Patient was discharged at 14 days of hospitalization. In conclusion, this report presents a case of three days old female infant with severe NAS, based on FNAS score is 18. This patient was treated with morphine and revealed with good outcome. However, in the future, proper evaluation of growth and development should be done.

Keywords: Neonatal Abstinence Syndrome, methadone user mother, morphine therapy.

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INTRODUCTION

Neonatal Abstinence Syndrome (NAS) is a group of symptoms that occur in a newborn as a result of the sudden discontinuation of fetal exposure to substances that were used or abused by the mother during pregnancy (Prabhakar, 2014). The incidence of NAS has increased substantially in the past decade. In 2012, the syndrome was diagnosed in 21,732 infants in United States, which represents an increase 5 times during the previous 12 years (Prabhakar, 2014). This is consistent with the increasing prevalence of NAS in other locations, including England, Canada and Western Australia which reflects an increasing global problem (McQueen and Murphy-Oikonen, 2016). The increasing of NAS cases corresponds with the increasing in opioid use during pregnancy (Wolff and Perez-Montejano, 2014). NAS is very cautious with the increasing incidence of drug abuse among pregnant woman. The prevalence of drug abuse in Indonesia in 2017 is 2.9% or 3.5 million people with 28% population is woman (Badan Narkotika Nasional Republik Indonesia, 2017).

Many variant symptoms of NAS according to the severity of illness were described have been

characterized under three different biological systems: neurological, gastrointestinal and autonomic symptoms. Onset of the withdrawal symptoms are within 24 and 72 hours after birth and lasting up to five days, however, some symptoms can be present much earlier (Ordean and Chisamore, 2014). Severity of withdrawal is estimated using various scoring systems; the most common score is the Finnegan Neonatal Abstinence Severity (FNAS) score. The difficulty in diagnoses occurred with the variety of clinical features and clinical syndrome which potential for differential diagnosis with other physical conditions that may affect the NAS scores (Zimmermann-Baer et al, 2010).

The NAS score correlates with many factors such as prenatal maternal methadone dose and the duration of drug exposure *in utero*, it is due to the high permeability of the placental barrier during the third trimester that results in increased levels of fetal methadone exposure nearing delivery. There are also genetic conditions and smoking exposure increased the need for postnatal pharmacological treatment in the case of NAS (O'Donnell et al., 2009; Seligman et al., 2010; Krans et al., 2015).

Management of the neonate includes both pharmacological and non-pharmacological care. Worsening symptoms of the baby often requires pharmacological intervention with methadone or morphine. Decisions regarding treatment onset and rate are made based on a cumulative threshold score, typically two or more consecutive FNAS scores of eight or nine (Kaltenbach et al., 2012; Davis et al., 2018). Pharmacological intervention is required for 50 to 70% of infants.

This report described management of a rare case of NAS in three days old female infant from a HIV infected mother with 12 years of using methadone.

CASE REPORT

History of present illness

We reported a case of three days old baby girl with NAS from methadone user mother. The symptoms appeared since three days of hospitalization, it were fussy crying, fever, tremor, poor feeding, vomiting more than six times every day. The baby was crying and irritable overtime, sweating a lot, and fever up to 38°C. The body temperature was unstable, the upper and lower extremity founded tremor all the times. She was given small amount of formula milk every 2 hour, however, she has had vomiting frequently.

Prenatal history

Patient was the fourth child in the family, and there was no history of congenital anomalies or NAS in parents, brothers and sisters. She was born vigorously by caesarian section with birth weight was 2700 grams and in term gestational age. There were no risk factors in the baby. During pregnancy, the mother routinely took methadone replacement therapy at the dose of 110 mg every 24 hours along with the Anti-Retroviral (ARV) therapy. The mother has used ARV since she was diagnosed with HIV 10 years ago. The mother was also an active smoker during pregnancy. She had regular checked up for the pregnancy, and no abnormality was found on the fetus according to ultrasound examination.

Preliminary assessment of the baby

On examination, the vital sign were found with pulse 140 to 198 beat/min, respiration rate was 60 to 80 times/min, temperature was 38 to 40.3°C, oxygen saturation was 90 to 98% with room air. The head was normal in shape, hair was black in color, and fontanel was flat. There were no sunken eyes, no jaundice on sclera, nor conjunctiva injection and anemia. The pupils light reflection was normal. The ears, nose, and throat examination were within normal limit. There were no lymph nodes enlargements were found on the neck nor on both axilla. The chest was symmetrical both on rest and movement. Breath sound was vesicular without rales or wheezing, the first and second heart sounds were normal, regular and no murmur in auscultation. Abdomen was within normal. Bowel sound was normal. No liver or spleen nor mass were palpable. Anal and genital examination was normal. Rectal touch examination was normal, no palpable mass.

The laboratory test of septic marker, electrolyte and blood sugar revealed normal result. We used the FNAS score to evaluate the severity of the NAS symptoms on this baby. The total FNAS score were evaluated every 4 hours. Initial evaluation showed that the total FNAS score for this baby was 18. Since then, patient was diagnosed with NAS.

Patient was given treatment as the management algorithm of NAS (Figure 1) with morphine initial dose 0.12 mg orally and adjusted according to the FNAS score after evaluated every 4 hours. The other therapy are Zidovudin 4 mg/kg/dose equivalent with 15 mg dose (1.5 ml) every 12 hour for six weeks, Paracetamol 10 mg/kg/dose ~ 27 mg if body temperature was more than 38.5°C and can be repeated every 4 hour.

During the treatment there was no improvement regarding to the FNAS score with initial dose of morphine. The dose was adjusted dose up to four time initial dose during three days of duration. After one week of treatment, there was improvement of the FNAS score, it was down slowly until the total score was 4, since then the morphine dose was tap down up to 10% from the initial dose. After 11 days of hospitalization, she was getting better with FNAS score 0 and morphine was

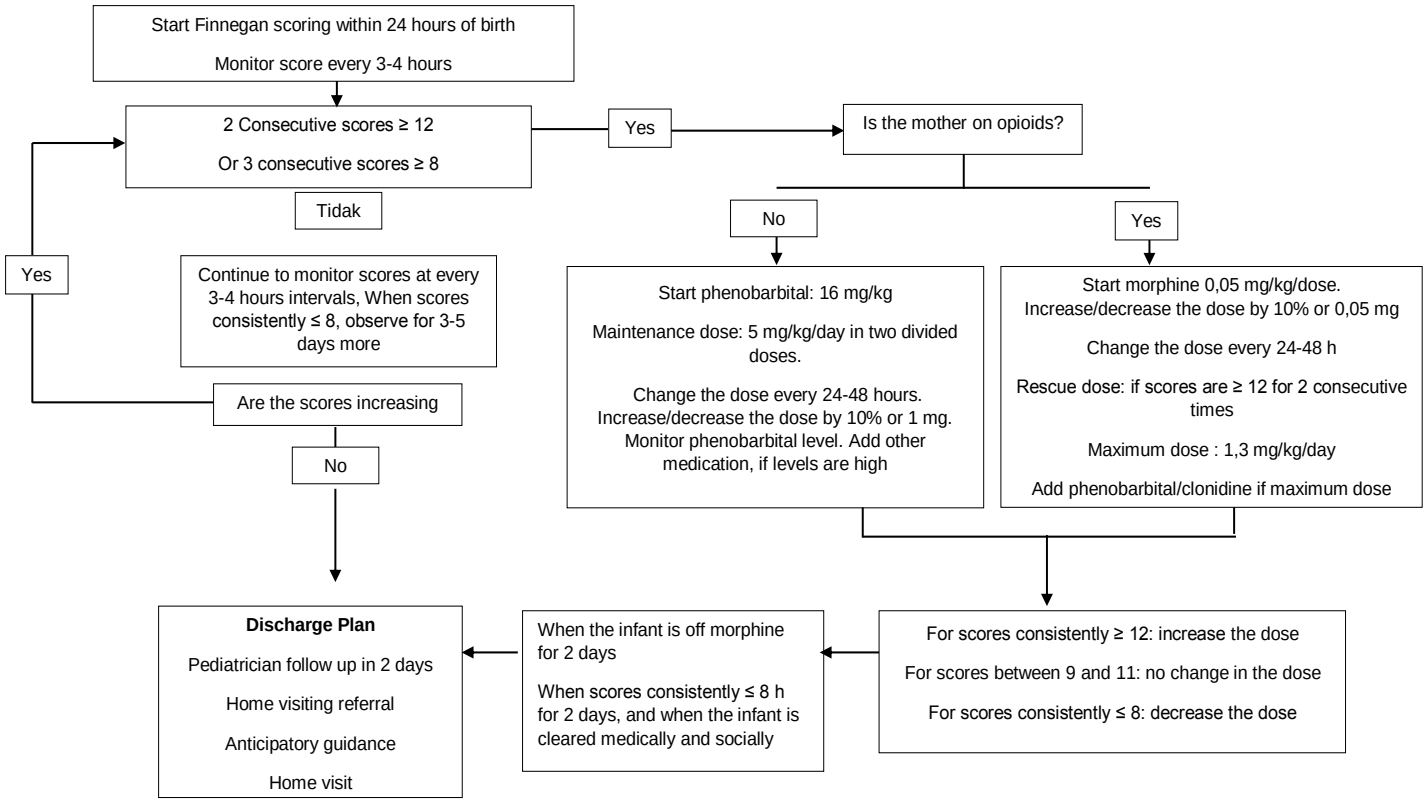

Figure 1. Management algorithm of NAS (Wiles et al., 2013).

stopped totally. Two days after stop the morphine, the patient was discharged in good condition. At 6 weeks old, patient was tested for PCR DNA HIV and the result was negative.

DISCUSSION

Neonatal Abstinence Syndrome (NAS) is a result of the sudden discontinuation of fetal exposure to substances that were used or abused by the mother during pregnancy. These and other substances pass from the mother through the umbilical cord and placenta to the developing baby in the womb (Prabhakar, 2014). Then baby develops a dependency on narcotics while inside the womb. Because the baby is no longer getting the drug after birth, the sudden stop of these substances can result in withdrawal symptoms on the baby. Common medications, drugs or substances that are linked to NAS are: amphetamines and codeine containing medications including Tylenol, Heroine, Hydrocodone, Methadone, Percocet, Subutex/Suboxone, Tussionex and Vicodin (McQueen and Murphy-Oikonen, 2016).

Neonatal Abstinence Syndrome are modulated by a combination of maternal and neonatal factor, including the opioid dose, frequency and timing before delivery, maternal pharmacokinetic, placental metabolism, concurrent medication, and neonatal pharmacokinetic and pharmacogenomics. The pathophysiological mechanism of opioid withdrawal in neonates is not known. Several factors can affect the accumulation of opioids in the fetus. Opiate drugs have low molecular weights, are water soluble, and are lipophilic substances; hence, they are easily transferable across the placenta to the fetus. The transmission of opioids across the placenta increases as gestation increases. During the third trimester, dose increases are typical, and a higher concentration of methadone is transferred across the placental barrier as it becomes more permeable, resulting in reduced maternal plasma methadone concentrations despite an unchanged dose (Ordean and Chisamore, 2014).

The duration of drug exposure in utero is an additional factor that dictates severity of withdrawal. Liu and colleagues found that a combination of higher dose before delivery and longer gestational age was associated with NAS treatment, and infants with longer gestation have increased LOS compared to those born with shorter gestation (less than 36 weeks). Longer gestation contributes to NAS severity due to the high permeability of the placental barrier during the third trimester results in increased levels of fetal methadone exposure nearing delivery. Polydrugs and tobacco use also affected the incidence of NAS, polysubstance of

drug and tobacco can elicit NAS case in neonates (Wolff et al., 2014). Breast-feeding should therefore be encouraged for mothers who are stable and receiving opioid-substitute treatment, unless there are contraindications, such as human immunodeficiency virus infection or concurrent use of illicit substances (Wolff and Perez-Montejano, 2014). We performed journal search to find out the factor of development NAS in infant. Dryden et al. (2009) concluded that development of NAS is related to prescribed maternal methadone dose and may be ameliorated by breastfeeding. Pregnant drug-misusing women should be maintained on the lowest dose of methadone compatible with stability and encouraged and supported to breastfeed their infants. Another study by Balcioglu and Umut (2019) described the benefit of substitute the methadone used by buprenorphine-naloxone maintenance during pregnancy to decrease the change of NAS of the infant. In our case, infant delivery at term gestational age, mother of the infant use high dose of methadone up to 110 mg/day during pregnancy and was an active tobacco user. Patient was not breastfed because the mother was HIV positive.

HIV can be transmitted from an HIV-positive woman to her child during pregnancy, childbirth and breastfeeding. Mother-to-child transmission (MTCT), which is also known as 'vertical transmission', accounts for the vast majority of infections in children (0 to 14 years). Without treatment, if a pregnant woman is living with HIV the likelihood of the virus passing from mother-to-child is 15 to 45%. However, antiretroviral treatment (ART) and other interventions can reduce this risk to below 5%. Another strategy included giving the prophylaxis, zidovudine, within 12 hour of baby born until 6 weeks of age then conducting an HIV test with PCR DNA HIV to diagnose the possibility of the virus transmission (Kasie et al., 2020). In this case, mother is HIV positive and is being treated with ART for 10 years. During pregnancy she followed the PMTCT programme. She also did not breastfeed this baby since she was born. The baby was given zidovudine as the prophylaxis from birth until 6 weeks old, and then proceeded for the HIV test (PCR DNA HIV), which result came out negative.

NAS leads to a constellation of signs and symptoms involving multiple system. Many spectrum of NAS symptoms, are well described and have usually been characterized under three different biological systems: neurological, gastrointestinal and autonomic (Ordean and Chisamore, 2014). In terms of neurological symptoms, increasing of wakefulness, irritability, hyperreflexia, hypertonicity and sleep disturbances are commonly described. Generalized and myoclonic seizures tend to be the predominant convulsive manifestations, with the occurrence ranging from 2% until 10% for infants withdrawing from opioids (Wolff and Perez-Montejano, 2014). Gastrointestinal dysfunction such as uncoordinated and constant sucking, poor feeding, poorweight gain, vomiting, diarrhea and dehydration have often been recorded (Wolff and Perez-Montejano, 2014). Autonomic reactivity, symptoms of autonomic over-reactivity have been consistently reported as increased sweating, yawning and sneezing, hyperactivity, hyperexcitability, hyperacusis and sleep disturbances have also been described in a biphasic withdrawal for neonates exposed to methadone *in utero.* Thirty one symptoms have been observed by those assessing neonatal opioid withdrawal. In terms of neurological symptoms, increased of wakefulness, irritability, hyperreflexia, hypertonicity and sleep disturbances are commonly described as shown in Table 1.

Late opioid withdrawal symptoms represented a direct opioid effect on the developing brain induced some neurobehavioral abnormalities, decreasing the ability to the auditory or visual stimuli. The occurrence of seizures, there are generalized and myoclonic seizures, which tend to be the predominant convulsion manifestations reported ranging from 2 to 10% for infants withdrawing from opioids (Wolff and Perez-Montejano, 2014). In our case, patient was observed to have some symptoms such as fussy crying and tremor at three days old. Fussy crying was sign of irritability caused by withdrawal syndrome and tremor of all extremities was sign of neurological symptoms on this patient. Symptoms of poor feeding and vomiting more than six time every day. Even she only took small amount of formula milk two hourly, she almost always vomited after drinking milk. The vomiting contained about 10-20 ml of milk each time. Patient also had high fever of up to 40°C; it was decreased with antipyretic. The respiratory rate was about 40-60 breaths/minute, with oxygen saturation at 90 to 98%. Regarding to many spectrums of NAS symptoms, we referred to another study to find out the clinical symptoms of NAS especially as the effect of methadone substances. Gaalema et al. (2012) (level of evidence 2B grade of recommendation B) showed that NAS symptoms due to methadone use during pregnancy were dominantly with tremor and hyperactive Moro reflex, excessive irritability were significant difference symptoms with buprenorphine substances used during pregnancy.

The Finnegan scoring system is commonly used to assess the severity of NAS; scoring can be helpful for initiating, monitoring and terminating treatment in neonates. A difficulty with many different features and clinical syndrome having so many different features is potential for differential diagnosis with other physical conditions that may exaggerate FNAS scores such as sepsis, hypoglycemia, hypocalcemia and hyperthyroidism, such that other investigations may be necessary. Further work is needed to explore which symptoms are core components of NAS and definitive of opioid withdrawal (Wolff and Perez-Montejano, 2014). In clinical practice, score above 8 are considered high and suggestive of neonatal withdrawal. Pharmacological treatment of withdrawal is started if the FNAS score is above 9 on at least two occasions. Originally, the scoring

Table 1. Variant clinical symptoms of NAS (Ordean and Chisamore, 2014).

Neurological excitability	Gastrointestinal dysfunction	CNS: Autonomic over-reactivity
• High-pitched crying	• Poor feeding	• Increased sweating
• Irritability	• Uncoordinated and constant sucking	• Yawning
• Increased wakefulness/sleep disturbance	• Vomiting	• Nasal congestion
• Hyperactive deep tendon reflexes	• Diarrhea	• Sneezing
• Hypertonia	• Dehydration	• Tachypnea
• Exaggerated moro reflex	• Regurgitation	• Mottled skin
• Tremor	• Poor weight gain/ weight loss	• Fever
• Seizures	• Hyperphagic	• Temperature instability
• Myoclonic jerks/Opisthotonic posturing	• Excessive salivation	• Other
• Hiperacuis	•	• Increased Rapid eye movement
• Intraventricular haemorrhage	•	• Skin excoriation/ stretching
• EEG abnormalities	•	• Tachycardia/hypertension

was applied every 4 hours. In general, positive symptoms are given a weighted score and summed every four hours (Table 2). In this case, withdrawal syndrome was appeared in patient after three days old with NAS score 18 resulted from neurological, gastrointestinal and autonomic symptoms which were mean needed earlier treatment to controlling the symptoms.

Management of the neonate includes both pharmacological and non-pharmacological care. Non-pharmacological therapy is the first option in all cases, and may suffice in cases of mild withdrawal. Non-pharmacological therapy is easily acceptable, less expensive, and less controversial. Non-pharmacological therapy can be attempted in all infants before initiating pharmacological therapy. Successful management comprises gentle handling, demand feeding, and careful avoidance of waking the sleeping infant. Non-pharmacological options, including breastfeeding, may also be effective at improving outcomes in NAS populations. Little methadone or buprenorphine is present in breast milk (Kaltenbach et al., 2012; Davis et al., 2018). The American College of Obstetrics and Gynecologists and the American Academy of Pediatrics support breastfeeding among opioid-dependent women if the women are enrolled in substance abuse treatment and there are no contraindications to breastfeeding. Benefits to breastfeeding for substance using mothers include protecting against relapse and stress (Balain and Johnson, 2014; Wu and Carre, 2018). While breastfeeding is well-established as beneficial for all infants, evidence is growing that breastfeeding and breast milk have specific benefits for the NAS population by preventing or limiting treatment or reducing the length of hospital stay (Abdel-Latif et al., 2006). To find out the association between breastfeeding and length of hospital stay in neonates with NAS, we refer to a study by Short et al. (2016) (level of evidence 2B and grade recommendation B), which concludes that breastfeeding may be beneficial for infants diagnosed with NAS by shortening the length of hospital stay. Future prospective studies are warranted to further examine the benefits of breastfeeding and other non-pharmaceutical interventions in NAS populations. In this case, the patient was not breastfed due to the mother's HIV infection, thus patient length of hospital stay was 14 days.

Pharmacologic treatment is an important component of management when non-pharmacologic care is insufficient to mitigate signs and symptoms of the NAS. Approximately 60 to 80% of infants with the syndrome do not respond to non-pharmacologic treatment and require medication. The main objective of pharmacologic treatment is to relieve moderate to severe signs such as seizures, fever and weight loss or dehydration (Wiles et al., 2013; Wolff and Perez-Montejano, 2014). There is current consensus in practice that first-line pharmacotherapy consists of opioid replacement with either oral morphine solution or methadone. Oral morphine is the most common treatment in the United States. Morphine is a full mu-opioid receptor agonist with well-established pharmacokinetic features and a short half-life, which may facilitate dose adjustment. Morphine is the most commonly preferred medication. Morphine decreases the incidence of seizures, improves feeding, eliminates diarrhea, decreases agitation and can control severe symptoms. However, morphine treatment also prolongs the length of hospital stay. Incremental increase or decrease of the dose of morphine depending on the severity of withdrawal is often a common practice.

Table 2. Modified Finnegan score (Zimmermann-Baer et al., 2010). Roe

CNS symptoms	
High-pithed cry	2
High-pithed cry > 2 hours	3
Sleeps less than 3 hours after feeding	1
Sleeps less than 2 hours after feeding	2
Sleeps less than 1 hours after feeding	3
Mild tremors when disturbed	1
Marked tremors when disturbed	2
Mild tremors when undisturbed	3
Marked tremors when undisturbed	4
Increased muscle tone	2
Excoriation of skin	1
Myoclonic jerks in sleep	3
Generalized convulsion	5
Vegetative symptoms	
Sweating	1
Temperature 37.5-38°C	1
Temperature > 38°C	2
Frequent yawning	1
Mottling	1
Nasal congestion	2
Sneezing	1
Gastrointestinal symptoms	
Frantic sucking	1
Poor feeding	2
Regurgitation	2
Projectile vomiting	3
Loose stools	2
Watery stools	3
Respiratory symptoms	
Thachypnea > 60/minute	1
Thachypnea > 60/minute with retraction	2
Total score (minimum 0, maximum 37)	

Because morphine has short half-life, it must be provided every 3 to 4 hours. Morphine solution is stable and easy to administer. Additionally, morphine treatment is relatively safer and more suitable for NAS management. Morphine dose can be escalated rapidly for higher scores however, weaning has to be gradual. When an optimal response is not attained with the maximal dose, additional medications may be considered. Methadone is a synthetic full mu-opioid–receptor agonist with a longer half-life (25 to 32 hours), which may provide a more consistent blood concentration over time and result in less frequent dosing. The disadvantages of each medication must also be considered. Morphine is associated with increased risks of sedation and respiratory depression and a prolonged hospital stay, and methadone contains ethanol.

Adjunctive second-line agents may be considered if the infant does not have a response to monotherapy regimens. Specific guidelines are lacking on when to add second-line agent and diverse situations in practice are often observed. Phenobarbital, a long-acting barbiturate, and clonidine, an α2-adrenergic agonist, have been identified as second-line agents that may be useful in reducing the severity of the neonatal abstinence syndrome. Phenobarbital has several disadvantages. It is not effective for gastrointestinal manifestations of the syndrome, it results in central nervous system depression and impairment of the sucking reflex; also, it has a prolonged half-life (45 to 100 hours). Limited data from a systematic review suggest that clonidine may be as effective as an opioid in the treatment of the neonatal abstinence syndrome. This finding provides some optimism regarding the potential for a non-narcotic treatment option; however, further evaluation must be completed before clonidine can be recommended as monotherapy (Wiles et al., 2013; Wolff and Perez-Montejano, 2014). In this case, patient has been treated with morphine as the first drug of choice according to the guideline therapy. Treatment start as soon as possible regarding to the NAS score 18 (>8) using Finnegan assessment score. Weaning morphine programs were started after stable NAS score lower than 8 at ten days of hospitalization, since then the morphine therapy was reduced 10% every four hour until completely stop.

Long-term developmental outcomes and potential long-term effects of prenatal methadone exposure on infant and toddler development are not known, primarily because of the scientific issue of isolating independent effects of methadone, comorbid substance exposure (e.g., alcohol, tobacco, other illicit drugs) and environmental and medical factors risk factors (e.g., low socioeconomic status, poor prenatal care, severity and treatment for NAS). The increase in opiate-exposed children is becoming a major problem at the interface of healthcare and public policy, yet few studies have used both biological and clinical measures to evaluate developmental outcomes. In this case, an early developmental intervention was planning after patient discharge from hospital

SUMMARY

This report presents a case of three days old female infant with severe NAS, with maternal risk factor of prolonged intake and excess dosage of methadone; there was no history of breastfeeding because maternal HIV status was positive. We assessed this patient with severe NAS, due to FNAS score of 18. This patient was treated with morphine and revealed good outcome. However, in the future, proper evaluation of growth and development should be done.

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