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Introduction

Drug abuse and addiction have significantly increased over the last few decades; specifically, opioid abuse and dependence have increased to epidemic proportions. This increased use of drugs includes women of childbearing age and those who are pregnant. Drug abuse during pregnancy is a serious health risk for both mother and newborn infant. Infants exposed to maternal drugs in fetal life develop signs of drug withdrawal during early neonatal life. This group of withdrawal signs is known as neonatal abstinence syndrome (NAS). Although NAS is not a fatal condition, it results in significant illness and prolonged hospitalization.

Etiology

Opioids are the most commonly abused drugs and are associated with significant neonatal complications. Poly-drug abuse is extremely common. Various other drugs identified used illicitly are nicotine, cocaine, heroin, benzodiazepines, amphetamines, and selective serotonin reuptake inhibitors (SSRIs).

Epidemiology

Based on 2013 data, 5.4% of pregnant women aged 15 to 44 years were using illicit drugs. However, the rate was higher in women aged 18 to 25. Though maternal substance use disorders are equally common in different socioeconomic classes and races, they more common in younger, unmarried women and women with lower educational status.[1][2]

In last two decades, the incidence of opioid use has increased almost five times. Simultaneously, the incidence of neonatal abstinence syndrome has increased from 1.2 to 3.4 per 1000 live births per year. There has been a significant increase in

hospital costs associated with the care of opioid-addicted women and their newborns who remain hospitalized for several weeks for management of their withdrawal signs. [3]

Pathophysiology

Clinical presentation of an infant with withdrawal symptoms depends on the type of drugs used, timing, and amount of last maternal use, along with genetic factors that have not been completely evaluated. Pathophysiology of drug withdrawal is a complex biological phenomenon and seems to involve cerebral alterations in levels of norepinephrine, serotonin, and dopamine. The exact molecular mechanisms remain poorly understood.[4]

Some studies have linked genetic variations of mu opioid receptor and catechol-o-methyl transferase enzyme to the need and length of pharmacotherapy in neonates with prenatal opioid exposure.[5]

The incidence and severity of withdrawal remain low in premature infants. This can be explained by decreased exposure, decreased morphine clearance due to functional immaturity and decreased receptors.[4]

History and Physical

Majority of newborns exhibiting signs of withdrawal will have a maternal history of drug use before and during pregnancy. The timing of withdrawal depends on the most recent history of drug dose and half-life of that drug. For example, in infants exposed to short-acting substances like heroin, withdrawal signs can be seen within first 24 hours. However, for long-acting agents like methadone and buprenorphine, the withdrawal signs may be seen 1 to 3 days after birth. Occasionally, withdrawal signs may be delayed until five days of age or later. As a result, opioid-exposed infants should be observed in the hospital for at least 5 to 7 days with a close follow up care in place.

The classic signs of withdrawal include[6][4][7]:

- High pitched excessive cry
- Tremors and irritability
- Poor sleep
- Increased tone
- Exaggerated Moro reflex
- Poorly coordinated feeding, vomiting, and failure to thrive
- Loose stools and perianal excoriation
- Sweating, sneezing, fever, mottling, temperature instability

- Tachypnea and tachycardia
- Seizures

The timing of onset of withdrawal signs along with the type and severity of signs has a wide variability. The pathophysiology of this variability is not well understood but may be related to a variety of factors such as:

- Type and dosages of the maternal drugs
- Concomitant use of other opioid and non-opioid drugs
- Maternal factors such as nutritional status, infections, and psychiatric conditions
- Genetic factors
- Prematurity and other comorbid infant morbidities
- Breastfeeding preferences
- Environmental factors like availability of infant handlers, excessive stimulation including noise and light levels

Evaluation

Prenatal maternal history and urine drug screening form the basis of evaluation. Identification of drug or its metabolite can be performed on maternal and/or neonatal urine specimens. Neonatal meconium can also be used for this purpose. Tests have been developed to identify drugs from neonatal hair and umbilical cord tissue.[4][7]

However, all these tests have limitations. Urine drug screening has low sensitivity and is positive only in infants with recent exposures. Meconium testing has high sensitivity and specificity, but the test is time-consuming and likely be done at reference laboratories only. Also, the presence of the drug in meconium may not be indicative of recent exposure, since meconium testing has a longer window of detection. Occasionally, meconium may not be passed for several days. Testing the neonatal hair for drugs has difficulties due to a small amount of drug in the hair and a slow rate of growth.

Despite limited clinical utility, such assays may be helpful in cases where an infant exhibits signs of withdrawal and mother denies substance use.

Treatment / Management

Multidisciplinary approach provides optimal care for the infant and the mother. Various disciplines including occupational and physical therapy; social services and child life should be included in patient care in addition to physician and nursing staff. Appropriate post-discharge planning and follow-up care are as important as services during the hospital stay.[6][4][7]

Each unit taking care of drug-withdrawing infants should have a standardized policy for management of neonatal abstinence syndrome. Adherence to a standardized policy has shown to reduce the length of hospital stay for these infants.

Management during hospital stay includes supportive care with pharmacological and non-pharmacological interventions.

The goal of non-pharmacological interventions is to reduce the need for pharmacotherapy. These interventions should be individualized based on behavioral patterns of each infant. They include appropriate swaddling, positioning, rocking, reducing auditory and visual stimulation, small but frequent feedings, nutritional support, and management of associated morbidities such as loose stools and perianal excoriation.

Breastfeeding should be encouraged in women who are on stable maintenance regimens such as methadone, suboxone, and similar drugs. Breastfeeding increases mother-infant bonding and encourages maternal participation in infant care. Studies have shown that breastfeeding reduces the need for treatment in opioid-exposed infants[8]. These women should be abstinent from illicit drugs, should have received appropriate prenatal care, and should not have medical contraindications to breastfeeding like HIV. Breastfeeding should be discouraged for mothers who had used illicit drugs in the recent period before delivery, had a lack of adequate prenatal care, and have comorbid conditions like HIV.

The goal of pharmacotherapy is to provide short-term relief in symptoms of drug withdrawal. Opioid therapy is the preferred therapy based on available studies. Current literature does not establish an optimal opioid agent. However, morphine is the most commonly used medication. Methadone and buprenorphine are also commonly used. Older opioids such as tincture of opium and paregoric are no longer used.[4][7]

Some infants with severe withdrawal may need a second medication. Again, data is limited on the ideal choice of a second agent. Clonidine and phenobarbital are the most commonly used additional choices. Phenobarbital is the drug of choice for nonopiate withdrawal.

Different scoring systems such as Lipsitz tool, the Finnegan Neonatal Abstinence scoring system, and others have been used to guide initiation, titration, and weaning of opioid therapy. These scoring systems are based on presence and severity of clinical signs. All these scoring systems involve monitoring for withdrawal signs starting at birth and assessment every three to four hours during the entire hospitalization. Although Finnegan scoring system is the most widely used, there is no data to support the use of one system over the other.

Once an infant has been completely weaned off from pharmacotherapy and stable for at least 24 hours, the infant can be discharged from the hospital. Some units discharge the infants needing multiple medications, after they are weaned off opioid

medications. They are then discharged with a prescription of the second line agent they have been on, to be later weaned off by the pediatrician on close follow up.

Differential Diagnosis

Due to the similarity in presentation, clinical signs of drug withdrawal should be differentiated from conditions like[7]:

- Sepsis presenting with temperature instability, irritability
- Hypoxic ischemic encephalopathy presenting with tone abnormalities, irritability, and seizures
- Metabolic abnormalities like hypocalcemia and hypoglycemia
- Endocrine disorders like hyperthyroidism presenting with temperature instability, irritability, and loose stools

Pearls and Other Issues

Opioids are the most common drugs that cause withdrawal symptoms.

The neonatal abstinence syndrome has a myriad of presenting symptoms that need to be differentiated from other clinical disorders such as sepsis, endocrine, and metabolic disturbances as well as hypoxic-ischemic encephalopathy.

A combination of pharmacologic and nonpharmacologic measures are needed for optimal care of the infants. Multidisciplinary teams should be involved in the care of the mother-infant dyad.

Utilization of a scoring system and adherence to unit based treatment protocol has been shown to reduce the length of stay.

Long-term outcomes have been difficult to assess due to several prenatal and postnatal confounding variables including socioeconomic exposure, educational level of parents, exposure to other drugs, prematurity, low birth weight, among others. Several observational studies have shown developmental delay and behavioral problems in opioid-exposed infants.

Enhancing Healthcare Team Outcomes

Perinatal drug addiction is best managed by an interprofessional approach which provides optimal care for the infant and the mother. Various disciplines including occupational, nursing and physical therapy; social services and child life should be included in patient care in addition to physician and nursing staff. Appropriate post-discharge planning and follow-up care are as important as services during the hospital stay.

The outcomes for patients with addiction to drugs are guarded. Failure to comply with therapy is a problem and relapses are common.

Questions

To access free multiple choice questions on this topic, [click here](#).

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