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Neonatology

SUBSTANCE ABUSE AMONG PREGNANT WOMEN AND NEONATAL OUTCOME

Ms Stephy Stephen Pharm D student, Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Kochi, 682041, Kerala, India.

Perraju Bendapudi* Associate Professor, Department of Neonatology, Amrita Institute of Medical Science and Research Centre, Amrita Vishwa Vidyapeetham, Kochi, 682041, Kerala, India. *Corresponding Author

ABSTRACT In recent years, there has been a disturbing increase in illicit drug use among pregnant women, leading to detrimental effects on their offspring's growth and development. Neonates born to these mothers often display negative foetal outcomes, such as extremely low birth weight, prematurity, and neurological developmental issues. The most prominent adverse effect of in-utero drug exposure is neonatal abstinence syndrome, characterized by gastrointestinal, central, and autonomous nervous system dysfunction following abrupt discontinuation of the drug substance during the postnatal period. This has created a demand for adequate pharmacological and non-pharmacological interventions and prompted researchers to investigate further. A consistent and comprehensive treatment approach is needed to enhance maternal and foetal life quality. This review of the current literature on neonatal abstinence syndrome emphasises the need for an empathetic, holistic approach and summarises effective therapies. We also compare Indian and Western approaches to this social issue.

KEYWORDS : Neonatal Abstinence Syndrome, Opioids, Pregnancy, Morphine, Buprenorphine

Neonatal Abstinence Syndrome

Neonatal abstinence syndrome (NAS) is a collection of withdrawal symptoms exhibited by neonates who were antenatally exposed to illicit drugs such as heroin, cocaine or opioids like morphine, buprenorphine and oxycodone, which have been used for recreational purposes resulting in physical dependence. This occurs due to a disrupted foetal-placental environment following exposure to such stressors, which alters normal foetal programming and development(Lester & Padbury, 2009). Such neonates are at a higher risk of exhibiting symptoms and signs consistent with withdrawal soon after birth due to the sudden discontinuation of the illicit drugs, affecting their normal growth pattern in various ways (Patrick et al., 2015; Visconti et al., 2015; Jansson & Velez, 2011). Neonates born to such mothers often display negative foetal outcomes, such as extremely low birth weight, prematurity, and neurodevelopmental (Epstein et al., 2013; KRANS et al., 2015; Stover & Davis, 2015) issues. Unfortunately, in recent decades, there has been an increase in such cases, which can be attributed to excessive drug abuse, especially among pregnant women.

Historical Aspects:

The earliest references to the use of narcotic medication such as Opium go back to Sumerians who were probably the first to isolate it goes back to 2000 years BC(Brownstein, 1993) when it was described as "the plant of joy" (Offit, 2017). Although it may have initially been used as a part of religious practices in the beginning, soon medicinal use was found for it to help people die without pain and help in calming inconsolable crying children (Brownstein, 1993; Offit, 2017). Gradually, opium was found to be useful in treating various medical conditions such as bronchitis, asthma, headaches, menstrual cramps and melancholy. The widespread use of opium in India, Europe and China, for the above conditions made it socially acceptable and contributed towards dependence and addiction. With the discovery of Morphine, the active ingredient of Opium, in 1803 and its subsequent unrestricted medical use, the addictive properties of Opium gained prominence as a public health issue (Brownstein, 1993; Offit, 2017). Commercial medical use of morphine was first done by Merck & Co. Inc in 1827 primarily to treat pain and alcoholism(H. E. Jones & Fielder, 2015). It went on to become the first intravenous pain relief medication to be used for minor surgeries (Brownstein, 1993; Offit, 2017). The revelation that morphine was as addictive as opium led to efforts to produce a synthetic opioid derivative which was not addictive. This very effort led Heinrich Dresser to develop Heroin, which is more potent than morphine by five times, in 1898(Brownstein, 1993; Offit, 2017). For over a decade (1898-1910), Heroin, believed to be non-addictive was used in the treatment of Morphine addiction(Offit, 2017) and was also used as a non-prescriptive medication for colds, coughs, and chest infections in pregnant women and infants as well (Offit, 2017). Opium abuse in the US was initially limited as it was consumed only through smoking devices and the poor reputation of smokers during that period was only seen amongst white criminals and Chinese labourers (Courtwright, 1992). The advent of oral and intravenous preparations enabled the spread of opioid abuse to upper and middle-class citizens. The initial public perception of individuals struggling with opioid addiction was considerably more favourable compared to the perception of alcoholics, which contributed to the proliferation of heroin and morphine usage. This resulted in a conservative estimate of 300,000 opioid addicts in the early twentieth century. Approximately 2/3rd of them were women, who were using them initially as prescribed medication which then led to addiction(Courtwright, 1992). The general lack of governmental oversight and control over the sale and distribution of opioids was an equal contributor to the same.

This started changing once the public perception of opioid addicts and who they are started changing along with the physicians recognising the addictive properties of opium, morphine and heroin(Case, 1905; Courtwright, 1992, 2015; Happel, 1892). Any kind of attempts at government regulation of opioid use first came about in 1875 in the form Opium Den Ordinance by San Francisco City which banned the open smoking of opium. The concerns raised by the medical profession around the same time brought about an increased awareness of the deleterious effects of opioids across the states leading to Federal law in the form Harrison Narcotic Act (Courtwright, 1992, 2015) in 1914, which was subsequently replaced by the Controlled Substance Act of 1970(Courtwright, 2015). Nation-wide efforts to create opioid de-addiction programs in the 1950s led to the use of methadone(Campbell & Lovell, 2012) for opioid dependence and the subsequent discovery of Buprenorphine in 1966 which was later approved for the treatment of both opioid and methadone (Campbell & Lovell, 2012; Shulman et al., 2019) dependence by the FDA in 1985.

Prevalence:

It is concerning to see the increasing trend of drug abuse among pregnant women globally (Finnegan et al., 1975; Patrick, Davis, et al., 2015; Patrick et al., 2012; Tolia et al., 2015) including countries like the UK, US, Canada, Australia, and India(Davies et al., 2016). The rise in NAS cases can be attributed to exposure to illicit drugs like methadone and heroin during in utero period(Cicero et al., 2015; Gomes & Juurlink, 2016), as well as the irrational prescribing of opioids for pain management (Ailes et al., 2015; Cicero et al., 2015; Gomes & Juurlink, 2016; Warren et al., 2015; Yazdy et al., 2015). Opioid de-addiction programs, with methadone or buprenorphine, during pregnancy also pose a risk for NAS in neonates born(Jansson & Velez, 2012). In India, heroin consumption tops the list of illicit drug use at 1.14%, followed by medically prescribed opioids at 0.96% (Ambekar et al., 2019). The female population comprised only 0.2% of the total opioid users in India(Ambekar et al., 2019). However, data on illicit drug abuse during pregnancy in India is limited, which calls for further research and awareness.

Signs & Symptoms:

NAS presents itself when a newborn shows signs and symptoms of withdrawal soon after cross-placental supply is suddenly terminated with the delivery of the baby. Clinical features of NAS include sleep disturbance, tachypnoea, poor feeding, excessive irritability, tremors, poor weight gain, and myoclonic jerks as listed below. **(Table 1).**

Table 1: Clinical Manifestations Of NAS

Clinical manifestation of NAS	
Autonomic manifestations	Fever
	Nassl stuffiness
	Respiratory distress
	Tachycardiaa
	Sneezing
	Sweating
	Tachypnoea
CNS manifestations	Tremor
	seizure
	High pitch cry
	Hyperirritability
	Myoclonic jerks
	Hypertonia
	Poor sucking reflex
Gastrointestinal manifestations	Abdominal distention
	Emesis
	Diarrhoea
	Impaired weight gain
	Failure to thrive

Foetal exposure to opioids disturbs the normal functioning of the gastrointestinal, central, and autonomous nervous systems (Kocherlakota, 2014; Stover & Davis, 2015) in neonates. Intrauterine growth restriction, fetal arrhythmias, preterm labour, low birth weight, small head circumference, visual disturbances, and even death are some of the well-established complications of fetal exposure to opioids (Finnegan et al., 1975; Hudak et al., 2012) . In the postnatal period, babies with NAS are at a higher risk of experiencing sudden infant death syndrome (SIDS).

Neonatal abstinence syndrome (NAS) can exhibit a wide range of manifestations that depend on various factors, such as the type of drug exposure, drug purity, pharmacokinetics, dose, length of exposure, and trimester of exposure (Wiles et al., 2014). Co-exposure to other central nervous system (CNS) drugs, such as SSRIs, SNRIs, TCAs, benzodiazepines, alcohol, antipsychotics, and nicotine, can also contribute to the variability and result in a higher NAS score in neonates (Kaltenbach & Jones, 2016; Patrick, Dudley, et al., 2015; Siu & Robinson, 2014). Genetic makeup, environmental factors, maternal health, and neonatal health (Kraft et al., 2016; Stover & Davis, 2015; Wachman et al., 2013) can also affect the severity of clinical manifestations and outcomes. Due to the complexity of the multifactorial mechanisms underlying NAS, a clear definition is needed. Identifying neonates with NAS can be difficult due to overlapping symptoms with other neonatal conditions, which may delay timely treatment (Jansson et al., 2009). Therefore, early identification of neonates with NAS is crucial

Withdrawal symptoms in neonates, due to Illicit drug exposure during pregnancy, are often present within the first 24-72 hours of life depending on the drug and its pharmacokinetics (Kuschel, 2007). Breastfed babies, due to the secretion of some of the opioids into breast milk, and those exposed to buprenorphine, due to a longer half-life, may exhibit delayed symptoms (Jansson & Velez, 2012). These neonates typically require admission to neonatal intensive care units for extended periods (Lee et al., 2015; Wachman et al., 2011), but preterm neonates may exhibit less severe and delayed symptoms that require less extensive therapy (J. & K., 2007; Kuschel, 2007). This difference could be attributed to altered hepatic and renal metabolism, as well as CNS immaturity (J. & K., 2007; Seligman et al., 2008). Treatment involves prolonged opioid therapy with morphine or buprenorphine, which may last more than 20 days (Patrick, Davis, et al., 2015). The American Academy of Paediatrics recommends an additional 5-7 days of observation before discharge (Hudak et al., 2012; Smirk et al., 2014). This need for prolonged hospitalization increases the risk of nosocomial infections and places additional demands on healthcare resources (Patrick, Davis, et al., 2015).

Pathophysiology

During foetal development, opioid drugs can cross the placental barrier and accumulate in the foetal blood, depending on their physical and chemical characteristics. Once these drugs cross the blood-brain barrier, they activate receptors in the locus coeruleus region of the brain, which leads to the inhibition of adenyl cyclase and cAMP production. As a result, the concentration of noradrenaline and dopamine decreases in the foetal brain. The foetal brain responds to this interference by sending signals to up-regulate receptors and maintain homeostasis. However, the sudden discontinuation of opioid drugs after birth disrupts this delicate balance, causing a surge in noradrenaline concentration and resulting in withdrawal symptoms (Kocherlakota, 2014).

Identification And Assessment

Efficient clinical assessment tools can be used to identify neonates at risk of developing NAS early on. These tools can help evaluate the severity of NAS and provide appropriate pharmacological intervention for gradual weaning (Lendoiro et al., 2013; Narkowicz et al., 2013). Establishing trust with patients and non-judgemental, effective evaluation of all medication consumed during pregnancy can help ensure accurate information sharing about drugs abused, which may otherwise be concealed for fear of social stigma and legal complications (Clark & Rohan, 2015; Hudak et al., 2012). Biological testing on pregnant women or neonates can also be used to ensure compliance (Hudak et al., 2012; Wexelblatt et al., 2015). Toxicology screening on neonates could be carried out on urine, meconium, hair and cord blood but each method has limitations and has not been accepted as a gold standard for identifying babies prone to withdrawal (Cotten, 2012; Farst et al., 2011; Lozano et al., 2007).

The Finnegan neonatal abstinence scoring scale and the MOTHER NAS scale are amongst the several neonatal assessment tools that have been devised, with modifications made to adapt to practical scenarios and enhance simplicity. However, the reliability and validity vary among the different scales, and none have been universally accepted. The Finnegan(D'Apolito, 2014) score is used as the baseline score for further assessment, and a score greater than or equal to 8 on three consecutive evaluations necessitates pharmacological intervention. Lipsitz neonatal drug withdrawal scoring is simple but lacks reliability, while the Neonatal narcotic withdrawal index and Neonatal withdrawal inventory have shown high inter-observer reliability (J. & K., 2007; ZAHORODNY et al., 1998). Therefore, research and modifications are necessary to create a universally accepted scoring scale, and inter-observer variation in the identification and treatment of withdrawal symptoms, as well as the lack of trained staff, should also be taken into account (K. McQueen & Murphy-Oikonen, 2016).

Management Of NAS:

The management of NAS requires a holistic approach from a non-judgmental multidisciplinary team. The ideal approach should begin with identifying babies at risk during the antenatal period and providing support and monitoring to mothers during this time. The goals of management are to promote infant and maternal regulation and to minimize the effects of withdrawal by optimizing the environment and handling of the baby with timely and appropriate pharmacological intervention. A treatment approach that includes both pharmacological and non-pharmacological aspects can hasten clinical improvement in infants and facilitate early discharge.

Pre-treatment Maternal Evaluation:

History: This would involve an accurate and thorough exploration of history in three important aspects of the patient's life:

Social: There is a strong association between parental drug abuse in these patients, with as much as 83% of women entering de-addiction programs coming from households where parents themselves have been drug abusers. Additionally, up to 67% of women have been victims of sexual assault and up to 60% have been victimized by physical assault. Exposure to adverse childhood events such as neglect and sexual or physical abuse are strong predisposing factors for substance abuse (Finnegan et al., 1991; Jansson et al., 1996).

Psychological: Low self-esteem, depression, and other behavioural issues are common in this patient population and may be well-hidden unless explored carefully. In studies among women enrolled in treatment programs, as high as 30% had moderate to severe depression, and 40% reported postnatal depression(Madsen et al., 2018).

Polydrug abuse is not uncommon. This may also affect the management of the mother antenatally and the neonates after birth. As

high as 80-90% of these women are smokers, which can alter the course of neonatal withdrawal.

Antenatal Measures:
Maternal screening: Investigations in addition to routine antenatal investigations of importance in these mothers include:
A) Urine drug monitoring for failure to comply with a treatment program or monitoring for relapses B) Screening for STDs such as HIV, Hep B, Hep C, chlamydia, gonorrhoea, and syphilis C) Screening for tuberculosis Maternal treatment programs: Methadone and Buprenorphine remain the standard drugs used.

Foetal Monitoring: There is no evidence supporting one protocol over another concerning the best method for foetal assessment once mothers have enrolled in treatment programs. Although there is no absolute need for in-patient care of these mothers when starting or on stabilization programs, it may facilitate ease of coordination of care in the initial stages. In the absence of evidence, a pragmatic approach towards foetal monitoring may include foetal biophysical monitoring and non-stress tests, which unfortunately may be influenced by the medications used in the treatment programs.

Labour and Delivery: It cannot be overemphasized how important it is to revisit the patient's history, and antenatal investigations, and to get feedback from program centres and health care professionals involved in the mother's pre and antenatal care. Given the difficulty of obtaining peripheral or central venous access in patients who are likely to have sclerosed blood vessels, securing early intravenous access in these patients would be a prudent move. Often, the patient themselves are experts in identifying the best vessel to gain access. The mode of delivery should be dictated by conventional obstetric decision pathways and protocols.

Management of Obstetric Pain: A careful balance between the tendency to undertreat pain in this patient group and the risk of facilitating opioid abuse is often a crucial step. Treatment of pain and selection of analgesics is a difficult needle to thread in substance abuse women or for that matter women in treatment programs. The aim of analgesic management in this group is maintaining a fine balance between overtreatment and contributory to withdrawal in the patients. Seeking the help and expertise of pain and palliative teams may just go a long way in achieving that balance.

Postnatal Measures:
Non-Pharmacological Care:
The non-pharmacological treatment modality towards NAS, when used in conjunction with pharmacological therapy, often hastens clinical improvement in infants. It includes the essential establishment of mother-infant bonding via rooming-in, throughout hospitalization and should be the preferred inpatient model of care for such neonates. Based on behavioural and physiological observation, individualized care should be provided to promote stability and competence.

Maintaining an appropriate physical environment for opioid-exposed neonates plays a crucial role in the management of NAS. The current standards involve creating a soothing and optimal environment for infants with limited exposure to external stimuli like light and noise. Minimal handling of the infant, as well as tight swaddling, are equally effective (Kocherlakota, 2014; Stover & Davis, 2015). For instance, excessive irritability may be overcome with gentle vertical rocking. This, in turn, would prevent overstimulation in many sensitive opioid-exposed infants and promote faster recovery.

Since most in-utero exposure results in low birth weight, necessary nutrient supplements should be included along with regular feeds. An increment in the frequency of feeds or employment of gastric feeding should be adopted if the infant shows an unimpressive weight gain, as well as non-nutritional sucking with the help of a pacifier (Jansson & Velez, 2012). An inadequate calorie intake could aggravate symptoms of NAS; thus, it is essential to ensure a regular high-caloric feed and fluid intake (Hudak et al., 2012). However, this could lead to the development of hyperphagia in some neonates and might show excessive weight gain(Madsen et al., 2018), so frequent monitoring needs to be carried out.

Some recent studies have emerged favouring breastfeeding and rooming-in as adjuvant non-pharmacological therapy, which has shown decreased hospital stay (Holmes et al., 2016; McKnight et al., 2016). Evidence of reduced NAS severity and treatment requirements in neonates following breastfeeding has provided an enhanced neonatal outcome.

Breastfeeding is considered safe by mothers on methadone maintenance, although methadone can be detected in minimal quantity in breast milk with a maternal dose of less than 20mg/day and the American Academy of Pediatrics (AAP) strongly recommends it not be considered a factor for breastfeeding eligibility (Bogen et al., 2011; K. A. McQueen et al., 2011). Similarly, buprenorphine is also excreted in low concentration into breast milk, making it considerably safe as well. Thus breastfeeding in such affected neonates should be continued unless contraindicated, as in the case of mothers with HIV infection or ongoing illicit drug use (Kuschel, 2007).

Pharmacotherapeutic Management:
Pharmacotherapeutic management is an essential aspect in over 60% of cases of NAS though there is a lack of consensus over the most optimal treatment protocols (Bagley et al., 2014). Inadequate knowledge about the threshold for initiating dosing based on body weight, appropriate weaning protocols, and the addition of adjuvant medication has remained the primary source of treatment variation from place to place. Frequent assessment of neonatal abstinence syndrome (NAS) using various scales is employed, not more than every 4 hours, to determine the need for pharmacological intervention (H. C. Jones, 1999).

Although morphine and methadone are the first-line treatments in exposed babies, morphine is more widely prescribed due to its well-established pharmacokinetic features and shorter half-life, facilitating dose adjustment. Methadone, being a synthetic mu receptor agonist, has a longer half-life of 25-32 hours, resulting in less frequent dose administration.

However, morphine has been associated with a high incidence of sedation and respiratory depression in neonates, and its use has led to prolonged hospital stays. A newer addition to this group is buprenorphine, a partial agonist. Sublingual administration of buprenorphine in affected neonates has subsequently been able to reduce the longer treatment period and hospital stay compared to its counterparts (Hall et al., 2016; Kraft et al., 2017). Once the infant is stable, opioids are gradually tapered along with symptomatic management (Jansson & Velez, 2012).

In addition to the mainstay treatment with opioids, adjunctive therapy with phenobarbital and clonidine has been noted to ameliorate the severity of NAS symptoms. Phenobarbital, being a long-acting barbiturate, has a prolonged half-life of 45-100 hours. It is often found to be effective in neonates exposed to polysubstance drug abuse; however, it is known to cause CNS depression and impairment in the sucking reflex in neonates.

Therefore, it may be considered when the neonate is unresponsive to first-line monotherapy regimens. It is prescribed as 10mg/kg (with a maximum of up to 20mg/kg) as a loading dose, followed by 2.5mg/kg given twice daily as maintenance. Clonidine, on the other hand, requires further evaluation to be effectively considered as an alternative therapy (Hudak et al., 2012). **(Table 2)**

***Table 2: Pharmacological Treatment Of NAS**

Medication	Mechanism Of Action	Dose	Advantage	Disadvantage
Morphine	Natural μ receptor agonist	0.05-0.2 mg/kg/dose Q3-4h	No alcohol	Sedation
		Increase by 0.05mg/kg	Short half life (9hrs)	Apnea
				Constipation
		Max dose: 1.3mg/kg/day		Frequent dosing
Methadone	Synthetic complete μ receptor agonist	0.05-0.1mg/kg/dose Q12h, increase by 0.05mg/kg Q48h	Long half life(26hr)	Longer duration of treatment
				Alcohol 8%
	N-methyl-d aspartate antagonist	Max dose: 1mg/kg/day	12 hourly doses	Frequent follow up needed

Phenobarbitone	Gamma-aminobutyric acid agoinst	Loading dose: 16mg/kg	Long half life (45-100 hr)	Possible hyperactivity
		Maintainence dose: 1-4mg/kg/dose Q12h		High treatment failure
			Monitor level	Alcohol 15%
				Drug drug interactions
				sedation
Clonidine	Alpha adrenergic receptor agonist	Initial dose: 0.5-1 mcg/kg, followed by 0.5-1.25mcg/kg/dose Q4-6h	Known narcotic antagonist	hypotension
			No sedation	Abrupt discontinuation may cause rapid rise of BP and HR
			No alcohol	
			Half life (44-72 hr)	
			Monitor level	
Buprenorphine	Semisynthetic partial μ receptor agonist, K receptor antagonist	Dose: 4-5mcg/kg/dose Q8h	Sublingual route	Alcohol 30%
		Max dose: 60mcg/kg/day	Half life (12hr)	Adjuvant medications required

*Kocherlakota P. Neonatal abstinence syndrome. Pediatrics 2014 Aug 1;134(2):e547-61.

Long-Term Outcome:

Due to varying confounding factors, long-term outcomes are often difficult to predict in such affected neonates. A study by Ornoy et al. demonstrated a possible relationship between the development of ADHD in NAS-affected neonates, but it requires more supporting research to substantiate that (Ornoy et al., 2001) . Environmental and social factors as well as polysubstance use contribute significantly to its complex nature. Some of the concerning issues such as maltreatment, mental health, behavioural problems, and neuropsychological development seem to be most affected in NAS. Furthermore, some advanced genetic studies have demonstrated a positive association between certain gene variations and the requirement for pharmacological treatment. In a study done by Wachman EM et al. on neonates with NAS, a shorter length of hospital stay and a lesser need for therapeutic management was observed among the neonates possessing variant genes of OPRM1 (mu-opioid receptor) and COMT (catechol-o-methyltransferase) (Wachman et al., 2013). Thus, extensive research evidence is required to confirm such findings and thereby help us preclude such negative implications on the neonate.

Preventive Strategies: Providing adequate psychological counselling and support to the mother is crucial in overcoming feelings of guilt, fostering maternal bonding, and ensuring normal psychological development in affected neonates. Education should also be provided to both mothers and caregivers on handling techniques and creating a soothing environment for the neonate, which can facilitate treatment and promote steadfast recovery(Jansson & Velez, 2012). If the mother is unable to participate, other family members should be encouraged to provide necessary care for the infant. Due to the complexity of understanding withdrawal symptoms, effective prevention and awareness strategies are better alternatives to addressing the problem. Identifying and addressing irrational opioid prescribing patterns among prescribers (Stover & Davis, 2015) and implementing ongoing surveillance programs (Warren et al., 2015) can provide insight into the issue. Prenatal evaluation can help identify potential candidates for early treatment of drug abuse, especially in women of childbearing age. Providing substantial education about potential healthcare outcomes should also be carried out. Illicit drug use is often obscured by drug-seeking behaviour, hindering effective treatment. A comprehensive approach is required to acknowledge and successfully curb social conundrums related to drug abuse. The social and cultural diversity between Western and Indian societies plays a vital role in shaping approaches to drug abuse issues. Social stigma in India often prevents women from seeking medical aid, which can harm neonates' quality of life and lead to sudden infant death. Lack of emotional support from society can also contribute to a vicious circle of drug abuse.

CONCLUSION:

The increasing incidence of NAS poses a concerning threat to the mother-infant relationship, potentially impacting physical, emotional, social, and economic factors of life. A multidisciplinary and systematic approach is needed, with an emphasis on prevention strategies and prenatal identification of potential candidates. The primary focus should be on education and awareness, and effective assessment tools must be designed to provide better clinical guidance for physicians. Providing adequate training to healthcare members is also recommended. In addition to essential pharmacotherapy, the psychosocial aspect between mother and infant should also be addressed.

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