Clinical of Intrauterine Exposure to Opioids

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Opioids have a rapid transplacental passage (i.e., less than 60 min); furthermore, symptoms characterize the maternal and fetal withdrawal syndrome. Opioid withdrawal significantly impacts the fetus, inducing worse outcomes and a risk of mortality. Moreover, neonatal abstinence syndrome (NAS) follows the delivery, lasts up to 10 weeks, and requires intensive management. Therefore, the prevention and adequate management of NAS are relevant public health issues.

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1. Introduction

Heroin and methadone are the opioids most frequently used by pregnant women. It is estimated that approximately 7000 opiate-exposed births occur annually [1]. The degree of intrauterine exposure to drugs largely depends on the substance's molecular structures and the pregnancy physiology. Drugs cross the placenta more via passive diffusion and less via active transport and pinocytosis. The placenta can metabolize drugs; furthermore, it expresses enzymes, such as cytochrome P450. The fetus also metabolizes certain drugs, especially in the final stages of pregnancy. Opioids have a rapid transplacental passage (less than 60 min), and several symptoms characterize maternal and fetal withdrawal syndrome. Opioid withdrawal significantly impacts the fetus, inducing worse outcomes and a higher risk of mortality [1][2].

Moreover, neonatal abstinence syndrome (NAS) follows delivery, lasts up to 10 weeks, and requires intensive management [3]. NAS leads to irritability, tremulousness, and temperature dysregulation, as well as to a disorganized and subsequent failure to thrive. Therefore, the prevention of NAS and its adequate management are relevant public health issues [3]. Indeed, neonatal opioid intoxication requires cooperation between the public health system, social services, and the judicial system to guarantee the health of both the mother and the baby, as well as to better implement the neonatal welfare system [3][4].

2. Clinical Issues

Over the past 10 years, opiate use during pregnancy has drastically increased and is now considered to be a serious public health issue. Prescription opioids, illicit opioids, and opioid replacement therapy are all being used by more women. According to Walsh SL et al., they issued an increase in opioid use in pregnant women because of the widespread use of acute/chronic pain treatment during pregnancy [5].

In fact, patients may receive opioid prescriptions during pregnancy for untreated opioid-use disorder, opioid abuse, or persistent pain or addiction. In addition, as Casper et al. state, mixing benzodiazepines, alcohol, or nicotine is a practice that is fairly widespread [6]. Opioids have been utilized in maintenance therapy for heroin addicts since the 1960s, but heroin substitutes are now being administered [7].

Opioid maintenance therapy is practical for at least three reasons, according to the American College of Obstetricians and Gynecologists: it decreases the mother's risk of relapsing, reduces continued high-risk activity, and improves perinatal outcomes by preventing frequent withdrawal during pregnancy [8]. Opioid maintenance therapy regimens have traditionally relied heavily on methadone, while buprenorphine use has recently increased. Pregnant women have different methadone pharmacokinetics from the general population and these pharmacokinetics can alter dramatically over the course of the pregnancy [9]. For instance, as stated by Megan W. Stover et al., among pregnant women, the half-life of methadone, from an average of 22–24 h, is reduced to 8 h. Even though methadone is typically administered daily, split-dosing (every 12 h) can be used to account for increased clearance during pregnancy [3]. Buprenorphine is a more recent alternative to opiate maintenance therapy in pregnancy. It is a partial opioid agonist approved in 2002 for the medication-assisted treatment of opiate dependence [10].

According to Jones HE et al., Buprenorphine has been shown to be superior to methadone in several ways for the management of NAS, including a lower risk of overdose (caused by reduced intrinsic receptor efficacies), less-abrupt withdrawal, fewer drug interactions, and easier access to prescriptions [11].

The abrupt cessation of fetal exposure to substances that the mother consumed or abused while she was pregnant resulted in the formation of the NAS. The term NAS is used to describe withdrawal from substance exposure; the term neonatal opioid withdrawal syndrome (NOWS) refers to the symptoms and signs that are specifically due to opioid withdrawal. Newborns exposed to opioids in utero may develop neonatal opioid withdrawal syndrome (NOWS), lower birth weight, smaller head circumference, and a higher risk of sudden infant death syndrome [12].

NAS is a multidistrict systemic disorder. The signs of neonatal abstinence have classically been divided into four major categories: involving central nervous system, gastrointestinal system, respiratory system, and autonomic nervous system. Even though NOWS seldom results in death, it can lead to significant illness and frequently necessitates prolonged hospital stays. Depending on the kind and quantity of substance consumed, the severity of this pathology's symptoms may vary [11][12][13].

When compared to methadone, buprenorphine sometimes decreases in the frequency and gravity of NOWS, according to newly available research. Buprenorphine has a number of drawbacks, including high dropout rates, challenging treatment start-up, a higher risk of drug diversion, possible hepatic side effects, and lack of long-term data regarding safety during pregnancy and in young children [13].

According to the Maternal Opiate Treatment Human Experimental Research's findings, pregnant women who received buprenorphine treatment had less-severe cases of NOWS and required shorter stays in hospitals than

those mothers who received methadone treatment; despite this, limited evidence is available to determine the best pharmacological agents to help with maternal opioid abstinence [14].

It is widely known that the human placenta controls how chemicals and nutrients are transferred to the fetus. Drugs, pharmaceuticals, and their metabolites can pass through the placenta and into the bloodstream of the fetus with ease. A few factors that affect this placental transfer include the specific drug, the amounts of the drug in the mother's and fetus's circulations, the way and when it is administered, the mother's and fetus's genetic makeup, and the co-administration of other medications [15]. As opioids are used more often to treat chronic benign conditions, more infants are being treated for side effects from intrauterine opioid exposure. The naturally occurring opioid morphine has been the subject of almost all prenatal exposure investigations, but since 2014, there has been a 300% increase in interactions with synthetic opioids, especially fentanyl, which is 50–100 times more powerful than morphine [16][17]. Alipio et al. found that perinatal fentanyl exposure results in neurobiological deficits that last until adolescence. The effects of this exposure include the suppression of adaptation to sensory stimuli, impairment of synaptic transmission in the S1 and ACC, suppression of cortical oscillations, abnormal dendritic morphology of cortical pyramidal neurons, and altered mRNA expression of genes that regulate synaptic transmission and dendritic morphology [17]. Due to the widespread use of synthetic opioids, especially in Western countries [18], further research should focus on determining the short- and long-term effects on newborn caused by intrauterine exposure to these substances.

Healthy infants may find the shift to extrauterine life stressful; however, the adjustment is often significantly more difficult for newborns exposed to drugs while still in the womb. Several literature studies state that opioid exposure during pregnancy also greatly raises the risk of preeclampsia, stillbirth, preterm, and sudden infant death syndrome (SIDS) [14][15][19]. As suggested by Nicole A. Bailey et al., there may be a link between prenatal opioid usage and congenital defects, such spina bifida, gastroschisis, and congenital heart disease. This assertion, however, was not supported by a recent comprehensive analysis of case-control and cohort studies on the topic [19].

The first case of a neonate who manifested opioid withdrawal signs was documented in 1875, but only in 1903 was the first case successfully treated, and it was referred to as congenital morphinism in the early 1900s and is the most frequent consequence of utero opioid exposure [20]. Congenital morphinism was termed NAS by Dr. Loretta Finnegan in the 1970s [21]. Even while other drugs—including benzodiazepines, amphetamines, cocaine, and barbiturates—can cause NAS(as revealed within the study of Krans EE et al.), babies who have been exposed to opioids are more likely to develop it [21]. While opiate maintenance therapy lessens a number of unfavorable pregnancy outcomes, it does not stop the emergence of NAS [22]. All newborns exposed to opiates in utero should be closely monitored for the development of NAS/NOWS because there is a 60–80% chance that they will develop this severe illness [14], which is a finding that is in agreement with Johnson et al.

The NAS/NOWS condition, which is intricate and extremely variable, affects the newborn when the placenta is separated from the fetus at birth. It is distinguished by gastrointestinal difficulties, autonomic nervous system dysfunction, and hyperirritability of the central nervous system [23]. Excessive impatience, bad sleep, stronger muscles, tremors, and skin excoriations caused by excessive movement, overheating, diarrhea, excessive

sleepiness and sweating, stuffy nose, and sneezing are all among the most frequent symptoms. Additionally, 2–11% of newborns with NAS may experience seizures. According to the findings of Seib CA et al., newborns exposed to opiates show significant variance in the timing and presentation of symptoms [24]. The causes of this variability are unclear and probably multifaceted in nature. Examples of possible causes include differences in maternal treatment, abnormalities in placental opioid metabolism, pharmacogenomics, and neonatal comorbidities, to name a few. The signs of NOWS frequently occur between 24–48 h after delivery, 36–60 h for buprenorphine and 48–72 h for methadone, depending on the prior maternal dose (but up to 5 days because of the long half-life) [25].

As claimed by Chasnoff IJ et al., drug exposures in the past, such as from using benzodiazepines, anti-depressive medications, or smoking cigarettes, may change the development of symptoms and worsen NAS [26]. The most prevalent form of evaluation (often conducted with modifications) is the Finnegan scoring system, which can identify which newborns need pharmacologic therapy. Every 3 to 4 h, a 31-item scale from the classic Finnegan scoring system is used to evaluate the prevalence and severity of different NAS-related symptoms. Every assessment should consider the conduct that was seen throughout the preceding three to four hours. It should be noted that the Finnegan scoring system has a high intra-observer variability and is specifically intended for term newborns.

Non-pharmacologic therapy is the first line of defense in the treatment of NOWS. Usually, frequent hypercaloric meals are provided to encourage growth and reduce hunger. The care of the newborn by the mother is a crucial aspect of non-pharmacologic therapy. It is believed that non-pharmacologic care of infants with NOWS deserves more attention in the care of newborns. To develop their capacity for self-regulation, newborns and caregivers must continually alter their physiological and behavioral responses. This process is known as "co-regulation", which depends on continuing experiences of both. First, giving the dyad a secure living space and supportive environment is crucial. Rooming in and the environment for a newborn with NOWS during and after the hospitalization can provide neuroprotection for a brain that is sensitive, dysregulated, and growing quickly [27].

Furthermore, the majority of newborns with NOWS require pharmacologic treatment [28]. Opioid substances (such as morphine and methadone) are generally considered more effective than other medications in treating NOWS. However, a Cochrane review released in 2010 concluded that there was not enough proof to recommend one opioid over other sedatives (phenobarbitone or diazepam) or other supportive treatments (swaddling, relaxation baths, settling, or massage). However, the use of opiates raised the treatment efficacy compared to diazepam [29]. The most suggested first-line treatment is morphine or a diluted tincture of opium taken orally [29].

Since methadone has a longer (and more variable) half-life and needs less-frequent administration and titration, it can be used instead of morphine. It is also currently being investigated as a possible drug that could be used to treat NOWS with sublingual buprenorphine [30].

Every 3–4 h, a 31-item scale from the classic Finnegan scoring system is suggested for the evaluation of the presence and severity of various NAS-related symptoms [3]. The entire 3 to 4 h preceding the exam should be

considered in each evaluation. It should be noted that the Finnegan scoring system has high intra-observer variability and is mainly designed for term newborns. The maximum Finnegan score in regard to the infant's weight, or a combination of the two, is used to determine the dosage of these drugs. Second-line medications, such as phenobarbital and clonidine, are used when symptoms are still not under proper control on the highest dose of treatment. Once symptoms have been stable for 24–48 h, the tapering of pharmacologic treatment often starts [31]. Infants and children who were exposed to opioids in utero have been reported to experience negative neurodevelopmental consequences. However, the information on long-term neurodevelopmental function is scarce [32].

As stated by Megan W. and Stover et al., NOWS occurs less frequently in preterm newborns than in term babies for a variety of reasons, including the fetal CNS's immaturity, lower cumulative drug exposure, less placental transfer, delayed hepatic and placental metabolism, and a reduced drug deposition that is due to the lower fat content. It should be noted that the absence of a corroborate scoring system created specifically for these people restricts the ability to assess NAS/NOWS in preterm infants [3]. In comparison to children born without NOWS, recent research suggests that infants with NOWS are often more prone to experience developmental delays or speech or language impairments [33]. The key points of NOWS identification are summarized in **Table 1**.

Table 1. A summary of the key points for the identification of NOWS.

Neonatal Opioid Withdrawal Syndrome (NOWS)	
Predictive factors	• Maternal opiate dose; • Maternal maintenance agent; • Exposure to additional substances; • Gestational age.
Timing of onset of symptoms	• For heroin: 24–48 h of life; • For buprenorphine: 36–60 h of life; • For methadone: 48–72 h of life.
Symptoms	• Hyperirritability; • Autonomic nervous system dysfunction; • Seizures;

Neonatal Opioid Withdrawal Syndrome (NOWS)	
	• Irritability; • Poor sleep; • Hyperthermia; • Sweating; • Sneezing.
Long-term outcomes	• Attention deficit disorders; • Disruptive behavior; • Smaller brain; • Thinner cortex; • Reduced cognitive ability.
Assessment	• 4–7 days of inpatient monitoring; • Finnegan score every 3–4 h.
Non-pharmacologic treatment	• Gentle, soothing environment; • Hypercaloric feeds; • Maternal care.
Pharmacologic treatment	• Oral morphine; • Methadone; • Phenobarbital;

ture, and [34] ewborns, particularly those who have been exposed to heroin or methadone, had smaller head sizes overall, smaller brain volumes, and lower cognitive abilities [35]. Children who have been exposed to opioids are generally more prone to exhibit disruptive behavior, attention deficit issues, and the need for thorough psychiatric treatment.

In agreement with Honein MA et al., a longitudinal study of children exposed to opioids during pregnancy may increase researcher's understanding of the potential teratogenic effects of opioid use, such as the confounding

effects of exposure to other substances during pregnancy (such as alcohol), as well as environmental and psychosocial factors [36].

In a recent assessment of the topic of opioid use during pregnancy, healthcare professionals should routinely assess all pregnant women for drug use through history and physical examinations, as well as with proven screening tools [37]. Therefore, it is crucial that individuals who provide maternal care try to identify women who use drugs and direct them toward treatment choices.

According to the American Society of Addiction, a urine screening test to identify drug abuse should be conducted according to state regulations, which vary by state of residence, with the patient's permission, and to confirm reported or suspected drug usage [38]. Neonatal toxicology testing should start as soon as a baby is born to a mother who has used drugs previously or is suspected of doing so. All delivery staff members must be aware of drug use to help the neonate adapt to extrauterine life and provide neonatal or pediatric support.

In correspondence with the findings of Wong S. et al., the midwife may be tasked with ordering neonatal toxicological tests in the role of the intrapartum healthcare practitioner. If the collection takes place along with the first two emissions of urine, newborn pee analysis can identify recent maternal drug use [39]. As meconium toxicology tests show drug usage as early as the second trimester, the data provided a more detailed description of drug use by the pregnant mother. Umbilical blood collection is less invasive and more valuable than urine or meconium collection and is a possible third technique used for newborn toxicity testing. Finally, another form of toxicity screening involves the utilization of maternal and neonatal hair.

When a newborn toxicology test yields a positive result, healthcare professionals must take into consideration the fact that the baby had drug exposure during the pregnancy and is thus at risk for NOWS. The Finnegan neonatal abstinence scoring tool (FNAST) may be used by neonatal caregivers to thoroughly and objectively evaluate the newborn's withdrawal signs and symptoms. The scoring of the FNAST should start two hours after birth and should continue every three to four hours while the infant is receiving care. The FNAST extends for at least 48 to 72 h after withdrawal agents are stopped and includes all NOWS signs and symptoms experienced during withdrawal and management [40].

The eat, sleep, and console (ESC) approach, which was recently introduced and was first published by Grossman et al. in 2017, has introduced a different paradigm that emphasizes nonpharmacologic management of infants' symptoms and offers a framework for starting treatment based on functional impairment [41]. The clinical management of newborn opioid withdrawal syndrome is based on the ESC model (NOWS). The Finnegan scoring system and ESC system were compared in the study conducted by Kelsey Ryan et al. They found that ESC scores correlated with components of the Finnegan score system that predict the severity of NOWS; on the other hand, the ESC system did not associate with elements of the Finnegan score that do not predict the severity of NOWS. They also suggest that transitioning from the Finnegan score to the ESC system could reduce hospitalization and dependency on pharmacologic treatment for newborns affected by NOWS [42].

A neonatologist must be informed of the circumstances to adequately evaluate the child and perhaps even transfer care to a neonatal unit that is equipped to help a newborn with NOWS if the neonatal team is not currently caring for the baby. Infants and children exposed to opioids in utero have been reported to experience negative neurodevelopmental consequences. However, as most studies are small and cannot distinguish between the effects of in utero exposures, postnatal treatments, and environmental variables, there is a shortage of information addressing long-term neurodevelopmental function. Children exposed to opioids are more likely to exhibit disruptive behavior, attention deficit issues, and the requirement for a thorough psychiatric referral. Long-term follow-up is, for this reason, a relevant public health issue.

3. Medico-Legal Issues

Pregnancy-related opiate misuse carries a number of dangers, most of which are connected to the consequences of withdrawal for the mother and her fetus, or the concurrent hazards of any associated behaviors. It may be challenging for a pregnant mother to abruptly stop using opioids. Others may rely on drugs such as methadone to stop drug relapse during pregnancy [43]. A drug should be stopped if it is considered unsafe for both the mother and the fetus. In agreement with what the American Pregnancy Association states, any substance taken while pregnant must be viewed as potentially dangerous to the fetus; in addition, the risks versus the benefits of its use should be carefully weighed [44]. Furthermore, abusing these drugs puts the health of the developing child, the neonate, and the fetus at risk. As such, this represents a serious public health problem [45].

As reported by Megan T. Frey et al., many female opioid abusers engage in polysubstance misuse, frequently in an effort to treat an underlying mental health condition or alleviate withdrawal symptoms with more accessible drugs [46]. Women who use substances are more likely to self-report conditions like high poverty rates, intimate partner violence, a history of physical or sexual abuse, post-traumatic stress disorder, and mental illness [47]. Although there has been a simultaneous rise in both child welfare cases and opioid use disorders, according to Korry et al., the two developments cannot be directly connected at this time because of data limitations [48].

Local child welfare institutions state that the opioid epidemic can be blamed for the recent uptick in incidents of neglect and abuse [49]. Due to concerns about losing their children to child protection service investigations, as a study by Falletta et al. observed, some mothers were not allowed to receive treatment or were delayed, while other pregnant women avoided receiving treatment in order not to undergo drug tests [49].

According to the National Institute on Drug Abuse, addiction is a chronic condition that can be successfully managed and treated like other chronic disease processes. Social support, the quality of the patient–provider relationship, and access to therapy are all necessary to successfully treat substance-use disorders. In accordance with the ethical rule of nonmaleficence, doctors must refrain from employing humiliation or unfavorable criticism to persuade women to seek or continue receiving care. Pregnant addicts experience humiliation and criticism on top of their already high personal and societal obligations because they appear to go against the conventional moral expectation that pregnant women act in the best interest of the fetus. Criminalizing women for possessing chronic health issues while pregnant is unethical from a medical and moral standpoint and feeds societal stigmas.

Regardless of existence, the right to be born healthy and protected, including throughout the intrauterine phase, must be recognized, whether interpreted as a subject or as a person, based on the many interpretations.

The implementation of integrated care systems that offer medical treatment, social services, and mental support has resulted in a great decrease in substance usage and relapse [46][47][48][49].

When faced with the suspicion that a child may suffer or risk suffering injuries, physical or mental, handicap, or pathological conditions that highlight a condition of abuse or negligence, health professionals must report the case in question. According to the Italian jurisdiction, the patient must consent before any medical procedure. If the mother does not want to agree to have blood or urine taken, these tests cannot be conducted. In the case of a minor, especially a newborn, who cannot yet act, the parents must provide consent to proceed with the medical procedures. However, suppose the doctor decides that specific investigations are required because he believes the child's life may be at risk because of negligence or drug misuse. In that case, he must contact the appropriate judicial authority. In all healthcare settings worldwide, mainly where a high rate of opioid abuse is observed during pregnancy, standard protocol and screening and clinical testing strategies should be implemented to anticipate diagnosis and point out further actions in cooperation with social services and judicial authorities to protect and guarantee adequate health and assistance for both the mother and the newborn [50].

To inform the family about the best ways to care for the infant, the mother's healthcare professional should collaborate with neonatal care specialists. The consultation of social services guarantees that the newborn's post-hospital care is adequate and suitable in accordance with the Child Abuse Prevention and Treatment Act. It is imperative to motivate women who are opioid dependent to seek out and keep up with medical care. As a result, it will be important to test not only those women who voluntarily admit to abusing opioids but also those who have medical disorders and where doctors note the risk of abuse or neonatal suffering.

A study conducted by Green et al. states that children of substance-using mothers who finish at a minimum one recovery period spend a shorter time in protective custody and are successfully reunited with their parents more frequently [51]. Although it can be challenging to obtain Child Protection Services (CPS) clients for participation in substance-misuse treatment, according to Taplin et al., half of the women who enroll in these programs are mothers of dependent children, and one-third of these have lost parental rights [52]. Knowing how other social institutions, such as the criminal justice system, can either facilitate or obstruct treatment may provide one with a more comprehensive viewpoint on the best way to include opioid abusing in the child welfare system. Supplementary studies are required to better understand how child protection services and drug misuse treatment programs interact and what effects they have on individual results.

To give clarity and direction to policymakers at the national and local levels, it is crucial to collaborate and coordinate guidelines, advocacy positions, and research projects involving prenatal substance use and NAS. This research highlights the necessity of a multidisciplinary approach in cases of neonatal opioid intoxication. Cooperation between different professional figures is, in fact, crucial to substantially impacting the critical public health issue confronting our vulnerable population [1][53][54][55]. The gynecologist has the role of following the regular

course of pregnancy, identifying the risk conditions, and promoting the well-being of the fetus and mother. The pediatrician and the neonatologist must clinically identify the clinical factors suggesting an intoxication or a neonatal abstinence syndrome, thereby ensuring the newborn's health and initiating the process of protection, welfare, and judicial investigations. The role of the forensic toxicologist is essential for the purposes of detecting exposure to opioids, thereby choosing the appropriate matrix to be used and providing laboratory elements on which to base clinical, social, and forensic options [2][56][57]. A critical public health measure could consist of establishing territorial referral centers for these conditions to guarantee the presence of specialized personnel to recognize and identify neonatal opioid intoxication and NAS/NOWS. Research and development are urgently needed to improve the identification, care, and protection of high-risk neonates as the number of births impacted by maternal opiate dependency keeps growing.

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