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Original Article

# Comparison of the Severity of Neonatal Abstinence Syndrome Manifestations in Newborns Exposed the Natural and Synthetic Opioids

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## ABSTRACT

***Background:*** The study aimed to investigate the severity of Neonatal Abstinence Syndrome (NAS) complications in newborns (NBs) in the eastern region of Iran.

***Methods:*** The retrospective study was conducted among mothers and singleton live births between March 2022 and March 2023.

***Results:*** Twenty-nine mothers (53.7%) used natural opioids (NO) and 25 (46.3%) synthetic opioids (SO). The highest number with the 20-30 age range. Of the NBs from the NO, 31.03% were before 37 weeks. In contrast, in the SO, 88% were before 37 weeks ($p < 0.05$). In the NO, 89.65% weighed < 2.5 kg. In contrast, 100% of those in the SO weighed > 2.5 kg. In SO exhibited crying for >10 minutes at a high. Additionally, SO had a high frequency of sleep ($P<0.05$). The SO showed a high frequency of metabolic disorders ($P<0.05$). The frequency of sneezing was high in the SO ($P<0.05$). Nasal flaring was high in the SO ($P<0.05$). Respiratory rate index, defined as more than 60 breaths per minute and retractions> 60 breaths per minute, were high in the NO and SOs, respectively ($P<0.05$). Excessive sucking and poor nutrition were high in the NO, and SO, respectively ($P<0.05$). The regurgitation index (grade 3), and loose stools and watery stools were high in the SO ($P < 0.05$).

***Conclusion:*** The study highlighted the impact of the NB's gender and age at birth on the severity of the NAS symptoms, esprcially in SO group.

***Keywords:*** Gastrointestinal disorders, Neonatal abstinence syndrome, Nervous system diseases, Opioids, Pregnancy, Respiration disorders

## Introduction

Opioid dependence is recognized can lead to various health and social complications for individuals especially pregnant women and their fetuses (1). Most opioid receptors are located in the central nervous system (CNS) and the gastrointestinal tract. Damage to these areas by opioid overuse may manifest as increased autonomic activity, heightened irritability, and gastrointestinal dysfunction (2). These symptoms are known as Neonatal Abstinence Syndrome

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(NAS), which can appear in the newborn (NB) from the first day after birth (3). The clinical manifestations of the disease depend on the type of opioid and its dose, the frequency, and duration of use, as well as maternal and placental metabolism and drug transfer across the placenta (4). The low molecular weight and lipophilicity of opioids enable them to easily cross the placenta. Furthermore, they can penetrate the blood-brain barrier and accumulate in the developing fetus's brain. Semi-synthetic and natural opioids are less likely to do so (5). The mechanism of the disease involves activating opioid receptors, especially the mu-opioid receptor (OPRM1). This leads to sensitization of alpha-2 adrenergic receptors and decreases the adenylate cyclase function.

When opioids are withdrawn, this inhibitory effect is lost, leading to an increase in noradrenaline, and the incidence of NAS symptoms (6).

The prevalence of NAS in developed countries, such as the United States, ranges from 6 to 20 cases per 1,000 live births(7). Its incidence in Spain (9.3%), Denmark (6.3%), Italy (4%), and Iran between 2% to 5.4% has been reported. Major contributing factors to the disease include illiteracy, unemployment, low income, homelessness, and poor sanitation (8).

The severity of physical, psychological, social, and familial harm is greater in women than in men (1). Intrauterine growth restriction (IUGR), low birth weight, preterm delivery, increased incidence of respiratory distress, intrauterine death, and a higher risk of miscarriage are complications associated with opioid. The severity of these complications can be depended on whether the opioid is natural or synthetic (9). Since NAS can be life-threatening for NBs, the study explored the relationship between the severity of NAS symptoms and the type of opioid in eastern Iran.

## Methods

This retrospective cohort study was approved by the Research Council of Zabol University of Medical Sciences in 2024 and received the ethics code. After obtaining institutional ethics committee approval, written consent was obtained from the legal guardians of the children enrolled in the present study. This study analyzed all patients (totally 54 individuals) referred during a one-year period who had complete files, and there was thorough information from their mothers, assessed.

Pregnant women who used opioids were divided into two groups: natural opioids (NO) (such as opium) (10) and synthetic opioids (SO) users (like methamphetamine) (11). Demographic characteristics as well as the health of their NBs, focusing on several factors including gender, weight, neurological and digestive disorders were assessed. It was used the Modified Finnegan Neonatal Abstinence Score questionnaire, (12) which assesses the NBs' conditions related to CNS, metabolic/vasomotor/ respiratory, and gastrointestinal disturbances.

### *Inclusion and exclusion criteria*

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For mather: Informed consent; The mother used opioids (Opium or Methamphetamine) during pregnancy; No concomitant use of medications affecting NAS, such as Selective serotonin reuptake inhibitors (SSRIs).

For newborms: Fetal age: Infants born at a gestational age of≥ 35 weeks; No serious comorbidities, such as sepsis, severe prematurity, or major congenital anomalies;

### *Exclusion Criteria*

For Mothers: Informed consent; The mother must have used opioids (either opium or methamphetamine) during pregnancy; There should be no concurrent use of medications that could affect Neonatal Abstinence Syndrome (NAS), such as selective serotonin reuptake inhibitors (SSRIs).

For Newborns: Infants with severe comorbidities such as respiratory failure requiring mechanical ventilation, severe infections like sepsis or meningitis, and major congenital anomalies, including significant heart defects, have been excluded; Absence of complete data also lead to exclusion, particularly if there was incomplete information regarding maternal drug use or infant follow-up; Lack of parental consent for participation in the study.

### *Statistical analysis*

The data were analyzed using SPSS version 26. A chi-square statistical test and t-test or Mann–Whitney U test were performed, and results were considered significant with a P value of less than 0.05.

### *Ethical approval*

This study was approved by the Ethics Committee of Zabol University of Medical Sciences in 2023 (Ethical code: IR.ZBMU.REC.1403.002). Written informed consent was obtained from the parents or legal guardians of all participating neonates prior to enrollment. All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki.

## Results

In total, 29 mothers (53.70%) used NOs, while 25 mothers (46.30%) used SO. The highest frequency of mothers' ages dependent on NO and SO was in the 20-30 age range. There was no significant difference in the education levels. (Table 1) In both groups, primary education was more common. (Table 1)

The NO, and SO groups consisted of 4(13.79%), 10(40%) unemployed and 25(86.20%), 15(60%) housewives, respectively (P = 0.03). Moreover, there was a direct relationship between the occupation index and the type of opioid. Housewives demonstrated a higher likelihood of using both types of opioids (P = 0.028).

Twenty-six of NO users (89%) were permanent (every day) and 3 (10.34%) were occasional ( three times per week). In contrast, all SO users were permanent. Twenty-seven subjects (93.10%) of the NO group gave birth via cesarean section, while 2 (6.89%) had vaginal deliveries. In contrast, all individuals in the SO group underwent cesarean sections (Table 1). Additionally, there was a difference in the gestational age between groups (P < 0.001). Thirteen male NBs (44.82%) and sixteen female NBs (55.17%) were born to the NO group, while seventeen male NBs (68%) and eight female NBs (32%) were born to the SO group. The weights of the NBs differed between groups (P < 0.001). (Table 2)

CNS-Related Disorders: There was a significant difference between groups in the duration of crying among newborns (NBs), with some crying for less than 10 minutes while others cried for more than 10 minutes (P < 0.001). Additionally, the amount of time NBs slept after breastfeeding also showed a significant difference between the groups (P < 0.001). Other factors such as reflex levels, severity of tremors, muscle tone, and the occurrence of peeling skin in NBs varied significantly (P < 0.001 for reflex levels, P = 0.002 for muscle tone). However, the rate of peeling skin did not show a significant difference. The degree of myoclonic activity in NBs was associated with the type of opioid administered, with the NO group showing 13 individuals (44.82%) compared to the SO group at 24 individuals (96%) (P < 0.001). Furthermore, the index of generalized seizures was also related to the type of opioid used (P = 0.001). (Table 2)

Metabolic, Vasomotor, and Respiratory Related Disorders: The index of generalized seizures was associated with the type of opioid used, showing a significant difference between the NO group (5 individuals, 17.24%) and the SO group (15 individuals, 60%) (P < 0.001). Symptoms such as

**Table 1.** Demographic data of women dependent on natural and synthetic opioids including age, education level, occupation, duration of dependence, and method of delivery is shown. (* significant)

| Variables of Women | Type of Opioids | <20 | 20-30 | 31-40 | >40 | Total |
|---|---|---|---|---|---|---|
| Age | Natural | 1(3.4%) | 17 (58.62%) | 9 (31.04%) | 2 (6.89%) | 29 |
| | Synthetic | 2 (8%) | 12 (48%) | 11 (44%) | 0 (0%) | 25 |
| | Total | 3 (5.56%) | 29 (53.70) | 20 (37.03) | 2 (3.70%) | 54 |
| | P value | | P>0.05 | | | |
| | | Un Education | Primary School | Under Diploma | University | |
| Education | Natural | 4 (13.79) | 15 (51.72) | 8 (27.56%) | 2 (6.89%) | 29 |
| | Synthetic | 5 (20%) | 14 (56%) | 5 (20%) | 1 (4%) | 25 |
| | Total | 9 (16.67%) | 29 (53.70) | 13 (24.07) | 3 (5.57) | 54 |
| | P value | | P>0.05 | | | |
| | | Unemployment | | Housekeeper | | |
| Employment | Natural | 4 (13.79%) | | 25 (86.20%) | | 29 |
| | Synthetic | 10 (40%) | | 15 (60%) | | 25 |
| | Total | 14 (25.92%) | | 40 (74.07%) | | 54 |
| | P value | | | 0.03* | | |
| | | Permanent | | Occasional | | |
| Duration of opioid dependence | Natural | 26 (89.65%) | | 3 (10.34%) | | 29 |
| | Synthetic | 25 (100%) | | 0 | | 25 |
| | Total | 51 | | 3 | | 54 |
| | P value | | P>0.05 | | | |
| | | Cesarean | | Natural | | |
| The method of delivery | Natural | 27 (93.10%) | | 2 (6.89%) | | 29 |
| | Synthetic | 25 (100%) | | 0 (0.00%) | | 25 |
| | Total | 52 (96.29%) | | 2 (3.70%) | | 54 |
| | P value | | P>0.05 | | | |

**Table 2.** Alongside demographic indicators, specific health indicators such as neurological, digestive, respiratory, and vasomotor disorders are reported separately for infants born to mothers with opioid dependence. There was a significant difference in age and weight between the two groups. Additionally, neurological, digestive, and respiratory disorders showed significant differences between the groups as well. Further details can be found in the table. (* Significant)

| Variables of Newborn | Type of Opioids | <37weeks | ≥37weeks | | | Total |
|---|---|---|---|---|---|---|
| Age | Natural | 9 (31.03%) | 20 (68.96%) | | | 29 |
| | Synthetic | 22 (88%) | 3 (12%) | | | 25 |
| | Total | 31(57.40%) | 23 (42.59%) | | | 54 |
| | P value | | P < 0.001* | | | |
| | | Male | Female | | | |
| Gender | Natural | 13 (44.82%) | 16 (55.17%) | | | 29 |
| | Synthetic | 17 (68%) | 8 (32%) | | | 25 |
| | Total | 30 (55.56%) | 24 (44.44%) | | | 54 |
| | P value | | P>0.05 | | | |
| | | <2.5kg | ≥2.5kg | | | |
| Weight | Natural | 26 (89.65%) | 3 (10.34%) | | | 29 |
| | Synthetic | 25 (100%) | 0 | | | 25 |
| | Total | 51 (94.44%) | 3 (55.56%) | | | 54 |
| | P value | | P < 0.001* | | | |
| | | Crying<10 min | Crying≥10 min | | | |
| Neurological complications | Natural | 20 (68.96%) | 9 (31.03%) | | | 29 |
| | Synthetic | 3 (12%) | 22 (88%) | | | 25 |
| | Total | 23 (42.59%) | 31 (57.40%) | | | 54 |
| | P value | | P < 0.001* | | | |
| | | Sleep<3h after feeding | Sleep<2h after feeding | Sleep<1h after feeding | | |
| Sleep after feeding | Natural | 7 (24.13%) | 13 (44.82%) | 9 (31.04$) | | 29 |
| | Synthetic | 0 (0.00%) | 6 (24%) | 19 (76%) | | 25 |
| | Total | 7 (12.96%) | 19 (35.18%) | 28 (51.85%) | | 54 |
| | P value | | P < 0.001* | | | |
| | | Hyperactive Moro reflex | Hyperactive Moro reflex Significantly | | | |
| Sleep after feeding | Natural | 18 (62.06%) | 11 (37.93%) | | | 29 |
| | Synthetic | 3 (12%) | 22 (88%) | | | 25 |
| | Total | 21 (38.89%) | 33 (61.11%) | | | 54 |
| | P value | | P < 0.001* | | | |
| | | Mild with disturbed | Moderate to severe | Mild without disturbed | Moderate.to.severe, without disturbed | |
| Tremor | Natural | 13 (44.82%) | 1 (3.44%) | 12 (41.37%) | 3 (10.34%) | 29 |
| | Synthetic | 1 (4%) | 3 (12%) | 6 (24%) | 15 (60%) | 25 |
| | Total | 14 (25.92%) | 4 (7.40%) | 18 (33.34%) | 18 (33.34%) | 54 |
| | P value | | P < 0.001* | | | |
| | | No | High | | | |
| Muscle tone | Natural | 15 (51.72%) | 14 (48.27%) | | | 29 |
| | Synthetic | 3 (12%) | 22 (88%) | | | 25 |
| | Total | 18 (33.34%) | 36 (66.66%) | | | 54 |
| | P value | | P=0.002* | | | |
| | | No | Yes | | | |
| Peeling skin | Natural | 27 (93.10%) | 2 (6.89%) | | | 29 |
| | Synthetic | 19 (76%) | 6 (24%) | | | 25 |
| | Total | 46 (85.18%) | 8 (14.81%) | | | 54 |
| | P value | | P>0.05 | | | |
| | | No | Yes | | | |
| Myoclonic Tonic | Natural | 16 (55.17%) | 13 (44.82%) | | | 29 |
| | Synthetic | 1 (4%) | 24 (96%) | | | 25 |
| | Total | 17 (31.48%) | 37 (68.51%) | | | 54 |
| | P value | | P < 0.001* | | | |

**Table 2.** Continued

| | | | | |
|---|---|---|---|---|
| | | No | Yes | |
| Generalized seizures or epilepsy | Natural | 24 (82.75%) | 5 (17.24%) | 29 |
| | Synthetic | 10 (40%) | 15 (60%) | 25 |
| | Total | 34 (62.96%) | 20 (37.03%) | 54 |
| | P value | | P=0.001* | |
| | | No | Yes | |
| Metabolic Disorders | Natural | 21 (72.41%) | 8 (27.58%) | 29 |
| | Synthetic | 3 (12%) | 22 (88%) | 25 |
| | Total | 24 (44.44%) | 30 (55.56%) | 54 |
| | P value | | P < 0.001* | |
| | | No | Yes | |
| Hyperthermia | Natural | 27 (93.10%) | 2 (6.89%) | 29 |
| | Synthetic | 20 (80%) | 5 (20%) | 25 |
| | Total | 47 (87.04%) | 7 (12.96%) | 54 |
| | P value | | P>0.05 | |
| | | No | >3-4 times | |
| Frequency of Yawning | Natural | 21 (72.41%) | 8 (27.58%) | 29 |
| | Synthetic | 17 (68%) | 8 (32%) | 25 |
| | Total | 38 (70.37%) | 16 (29.63%) | 54 |
| | P value | | P>0.05 | |
| | | No | >3-4 times | |
| The mottled skin | Natural | 28 (96.55%) | 1 (3.45%) | 29 |
| | Synthetic | 21 (84%) | 4 (16%) | 25 |
| | Total | 49 (90.74%) | 5 (9.26%) | 54 |
| | P value | | P>0.05 | |
| | | No | >3-4 times | |
| Nasal Congestion | Natural | 24 (82.75%) | 5 (17.26%) | 29 |
| | Synthetic | 17 (68%) | 8 (32%) | 25 |
| | Total | 41 (75.92%) | 13 (24.07) | 54 |
| | P value | | P>0.05 | |
| | | No | >3-4 times | |
| Frequency of Sneezing | Natural | 20 (68.96%) | 9 (31.04%) | 29 |
| | Synthetic | 10 (40%) | 15 (60%) | 25 |
| | Total | 30 (55.56%) | 24 (44.46%) | 54 |
| | P value | | P=0.033* | |
| | | No | Yes | |
| Nasal Flaring | Natural | 23 (79.31%) | 6 (20.69%) | 29 |
| | Synthetic | 10 (40%) | 15 (60%) | 25 |
| | Total | 33 (61.12%) | 21 (38.88%) | 54 |
| | P value | | P=0.003* | |
| | | > 60 breaths per minute | Contraction>60 breaths per minute | |
| Respiratory rate | Natural | 23 (79.31%) | 6 (20.69%) | 29 |
| | Synthetic | 5 (20%) | 20 (80%) | 25 |
| | Total | 28 (51.85%) | 26 (48.16%) | 54 |
| | P value | | P < 0.001* | |
| | | No | Yes | |
| Digestive Disorders (Excessive Sucking) | Natural | 11 (37.93%) | 18 (62.07%) | 29 |
| | Synthetic | 24 (96%) | 1 (4%) | 25 |
| | Total | 35 (64.81%) | 19 (35.19%) | 54 |
| | P value | | P < 0.001* | |
| | | No | Yes | |
| Poor nutrition | Natural | 21 (72.41%) | 8 (27.59%) | 29 |
| | Synthetic | 2 (8%) | 23 (92%) | 25 |
| | Total | 23 (42.59%) | 31(57.41%) | 54 |
| | P value | | P < 0.001* | |

**Table 2.** Continued

| | | | | |
|---|---|---|---|---|
| | | Grade2 | Grade3 | |
| Regurgitation | Natural | 19 (65.51%) | 10 (34.49%) | 29 |
| | Synthetic | 5 (20%) | 20 (80%) | 25 |
| | Total | 24 (44.45%) | 30 (55.57%) | 54 |
| | P value | | P=0.001* | |
| | | No | Yes (Grade2) | |
| Loose stools | Natural | 18 (62.06%) | 11 (37.94%) | 29 |
| | Synthetic | 8 (32%) | 17 (68%) | 25 |
| | Total | 26 (48.14%) | 28 (51.86%) | 54 |
| | P value | | P=0.027* | |
| | | No | Yes (Grade3) | |
| Watery stools | Natural | 29 (100%) | 0 (0.00%) | 29 |
| | Synthetic | 16 (64%) | 9 (36%) | 25 |
| | Total | 45 (83.33%) | 9 (16.17%) | 54 |
| | P value | | P < 0.001* | |

hypothermia, yawning, nasal congestion, and mottled skin were more in the SO group. Additionally, there was a higher frequency of sneezing, nasal flaring, and breathing rates exceeding 60 breaths per minute (retractions>60 breaths per minute) in the SO group (P < 0.05). Conversely, the NO group exhibited a significantly lower incidence of breathing rates over 60 breaths per minute (P < 0.001). (Table 2)

Gastro-intestinal disorders: The Excessive Sucking Index increased in the NO group (P < 0.001). However, the poor nutrition index increased in the SO group (P < 0.001). The regurgitation index (grade 2) was increased in the NO group (P = 0.001). However, the grade 3 scale was increased in the SO group (P = 0.001). Loose, and Watery Stools indices showed a decrease in the NO group. (P = 0.027, P < 0.001). (Table 2).

The means of all indices related to Gastrointestinal Disturbances, Metabolic/ Vasomotor/Respiratory Disturbances, Central Nervous System Disturbances, and the Total Score showed significant differences between the NO and SO groups. Infants in the SO group exhibited higher mean values across all these indices compared to those in the NO group (Table 3 and Figure 1).

**Table 3.** The mean indices of gastrointestinal disturbances, metabolic/vasomotor/respiratory disturbances, central nervous system disturbances, and the total score for infants in the NO and SO groups are shown.

| Indices | Opium | Metamphetamine | P value |
|---|---|---|---|
| Gastrointestinal Disturbances | 4.3±0.3 | 7.1±0.2 | 0.01 |
| Metabolic/ Vasomotor | 3.7±0.4 | 6.4±0.5 | <0.001 |
| Central Nervous System Disturbance | 13.7±1.1 | 20.8±0.9 | <0.001 |
| Overall | 21.2±1.7 | 34.4±1.2 | 0.04 |

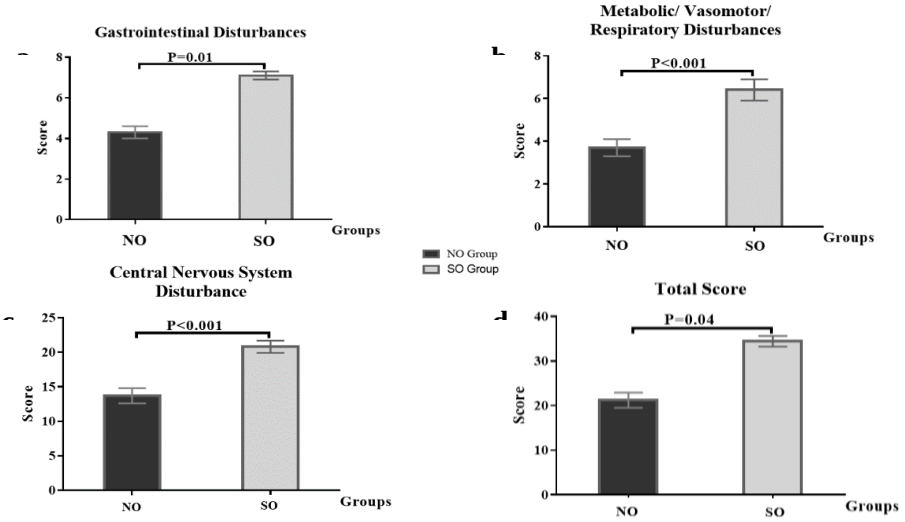


**Figure 1.** The details of significant differenc of indices including (a) Gastrointestinal Disturbances ، (b) Metabolic/ Vasomotor/Respiratory Disturbances, (c) Central Nervous System Disturbances, and (d) Total score between NO and SO groups was presented

## Discussion

This study aimed to compare the severity of NAS symptoms based on the type of opioid, specifically NO and SO, in the eastern region of Iran from March 2022 to March 2023. Given that mothers and NBs are among the most vulnerable groups in society when it comes to social issues like opioid abuse, (13) they were the focus of this research.

Of the total subjects, 53.70% of mothers were dependent on NO, while 46.30% were dependent on SO. All of these had NBs who experienced NAS. In this regard, we can refer to the 2014 study by Ebrahim et al., which found that 60% who used SO (crack) had infants with NAS (2).

The analysis of demographic indicators revealed mostly insignificant findings, such as an increase in the use of both NO and SO among mothers aged 20-30 years.

In a 2021 study, the average age of mothers whose NBs had NAS was calculated to be 28.8 years, with a gestational age of 38.4 weeks, indicating an increasing trend from 2010 to 2017 (14). There was no significant difference noted between education levels and dependence on NO versus SO. In a study by Ebrahim et al., the highest incidence and severity of NAS symptoms were observed in infants born to mothers who were dependent on SO. The most frequently reported NAS symptoms included muscle tonicity (7.60%), irritability (6.59%), and the Moro reflex (51.8%) (2).

Our study revealed a noteworthy difference regarding their employment status. Specifically, 86.20% of mothers dependent on NO, and 60% dependent on SO were housewives ($p<0.05$). In both groups, housewives comprised the largest proportion of opioid users ($p<0.05$). Some evidence shows unemployment, along with economic and social issues, has been identified as the contributing factors to the increased occurrence of NAS (15).

Among mothers dependent on NO, 93.1% delivered via cesarean section, while 6.89% had vaginal deliveries. In contrast, all mothers in the SO group delivered by cesarean section ($P > 0.05$). Additionally, Ebrahim et al. reported a higher rate of vaginal deliveries among NO group (2).

Of the gestational age of the NBs in the NO group, 68.96% were over 37 weeks, while 31.03% were before 37 weeks. In contrast, in the SO group, 88% were before 37 weeks, and only 12% were after 37 weeks ($p < 0.05$).

The severity of NAS symptoms is thought to be inversely related to the age of the NB at the time of birth, often requiring medical intervention. Our study, which examined two types of opioids with the most involved, diagnosed that NBs born to the NO group tend to be at a more appropriate gestational age at birth compared to those born to the SO group.

In line with this, Dysart et al. found a higher incidence of NAS in premature infants (opioid group) who were less than 37 weeks gestation (16).

A study by Gibson et al. did not find any significant correlation between the age of infants—whether preterm, late preterm, or full-term—and the necessity for drug therapy to alleviate the severity of NAS symptoms (17). In addition, Stover et al. reported that the incidence of NAS in preterm was lower compared to that in full-term. They suggested that this could be attributed to several factors, including the immaturity of the fetal CNS, reduced cumulative drug exposure, lower placental transfer, delayed hepatic and placental metabolism, and decreased drug deposition due to lower lipid content (18).

Some studies have recognized the influence of birth weight on the occurrence and severity of NAS symptoms (18). In our research, we found that 89.65% of NBs born to the NO group weighed less than 2.5 kg, while 10.34% weighed more than 2.5 kg. In contrast, all NBs born to the SO group weighed less than 2.5 kg. Overall, gastrointestinal issues like diarrhea and vomiting in NAS can result in dehydration, electrolyte imbalances, weight loss, pneumonia, aspiration, respiratory alkalosis, and seizures (16).

The gender analysis revealed that among NBs born to mothers who depended on NO, 44.82% were male and 55.17% were female. In contrast, in the SO group, 68% were male and 32% were female ($p > 0.05$). These findings align with some studies suggesting that male infants may be more susceptible to brain development issues, particularly those born to mothers with SO dependence (19). Conversely, Unger et al. did not find any significant impact of NB gender on NAS regarding the duration of illness, medication requirements, or the severity of the condition (20). An analysis of the crying index over a period of more than 10 minutes revealed that NBs born to SO group had a higher crying index compared to those born to NO group ($P < 0.05$). Crying and insomnia are behavioral patterns that can disrupt NB feeding. Generally, the crying index in NBs is considered an indication of their demand for feeding. However, in NBs with NAS, irritability leads to an increase in crying duration and

subsequently results in inadequate feeding. Consequently, these infants experience more fussing episodes than those without NAS (21). The highest frequency of sleep occurred one hour after feeding for NBs born to mothers who were dependent on SO ($P<0.05$). Both breastfeeding and adequate sleep are important non-pharmacological treatments for NAS (22). In this context, Maguire et al. highlighted that infants who did not complete their feedings exhibited disrupted sleep patterns (21).

It appears NBs born to the SO group exhibited a significant increase in symptoms such as a hyperactive Moro reflex, tremors, changes in muscle tone, myoclonic tonic, and generalized epilepsy, compared to NO group ($P < 0.05$). However, the peeling skin rate in NBs from the SO group was insignificantly higher than that in the NO group.

In this regard, Gaalema et al. reported undisturbed tremors and hyperactive Moro reflexes of NAS as more common in the group that was methadone-dependent (23).

In general, the frequency of metabolic disorders was significantly higher in the SO group compared to the NO group ($P < 0.05$). While hypothermia, yawning, mottled skin, and nasal congestion were observed at slightly higher rates in the SO group, were not statistically significant. However, NBs born to the SO group did exhibit a significantly higher frequency of sneezing compared to the NO group. In this regard, we can refer to a clinical trial conducted by Davis et al. that investigated the dose-dependent administration of methadone and morphine to prevent metabolic symptoms, such as hypothermia, in NBs with NAS. While methadone was more effective than morphine, it also led to neonatal hypothermia in some instances (24).

The frequency of nasal flaring in the SO group was higher than the NO group ($P < 0.05$). Additionally, the respiratory rate index, defined as a rate of more than 60 breaths per minute, showed that NBs born to the NO group had the highest frequency of respiratory rates over 60 breaths per minute. In contrast, the highest frequency of respiratory retractions exceeding 60 breaths per minute was observed in the SO group ($P < 0.05$).

In this regard, Allocco et al. investigated the manifestations of NAS in relation to SO, specifically methadone. They found that the frequency of scoring in premature NBs differed significantly in 14 out of 19 indicators, such as sleep disturbances, tremors, and restlessnes.

Additionally, prematures exhibited higher instances of an overactive moro reflex, tachypnea, and poor feeding. The scores for sweating, yawning, nasal flaring, and regurgitation/vomiting were less than 5% (25).

The frequency of excessive sucking in NBs in the NO group was significantly higher SO group. Conversely, the occurrence of poor nutrition in NBs in the SO group was significantly higher NO group. The index of food regurgitation, classified as grades 2 and 3, revealed that grade 3 was the highest in the SO group. This finding was significantly different from the NO group. Additionally, the occurrence of loose and watery stool was significantly higher in the SO group.

Our findings are comparable to those of Allocco et al. concerning the incidence of regurgitation and loose stools in preterm and term NBs with NAS. However, they did not observe significant differences (25). Furthermore, the study measured overall scores for Gastrointestinal Disturbances, Metabolic/Vasomotor/ Respiratory Disturbances, Central Nervous System Disturbances, and Total scores between the NO and SO groups, revealing a significant increase in the SO group compared to the NO group. In this context, we can refer to the 2019 study by O'Connor et al. that indicated an increase in methamphetamine use among pregnant women. They demonstrated a significant rise in Finnen scale scores in infants diagnosed with NAS syndrome (26). Jamali et al. conducted a study on NAS syndrome in 2024, utilizing the Finnegan scoring system. They evaluated infants born to mothers with substance abuse issues, such as morphine use. The researchers assessed the severity of NAS syndrome symptoms in infants following the administration of levetiracetam and phenobarbital. Their findings indicated no significant difference in the length of hospitalization for these children (27). Evidence suggests a connection between the severity of NAS and the gut microbiome (28). Considering to the increased severity of digestive disorders in the SO group supports the hypothesis that there may be impaired immune system development related to the intestinal microbiome.

Establishing a healthy gut microbiome is crucial for infants, as it is vital in immunity and protection against pathogens. Infants who experience dysbiosis, an imbalance in gut bacteria, may be at risk for negative health outcomes throughout their lives. Opioid exposure during pregnancy may adversely affect the development of the microbiome. The severe gastrointestinal and neurological symptoms observed in infants

with NAS could be linked to the disruption of normal growth of the microbiome, leading to dysbiosis (28).

## Conclusion

The study investigated the severity of NAS complications in NBs. Overall, the severity of NAS symptoms was found to be higher in the SO group. This analysis highlighted the impact of the NB's gender and age at birth on the severity of the symptoms. In the study of NAS, several tools for scoring system, can be used. Additionally, it's important to consider the influence of genetic and epigenetic factors on the metabolism of substances, as these may impact the severity of NAS.

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## Conflicts of interest

The authors have no conflict of interest.

## References

1. Vucinovic M, Roje D, Vucinovic Z, Capkun V, Bucat M, Banovic I. Maternal and neonatal effects of substance abuse during pregnancy: our ten-year experience. Yonsei Med J. 2008;49(5):705-713.
2. Ebrahim B, Firozi M, Nayeri F, Shariat M, Kalani M. Frequency of neonatal abstinence syndrome (NAS) and type of the narcotic substance in neonates born from drug addicted mothers. Iran J Neonatol. 2015;5(4):1–5.
3. Reynolds EW, Riel-Romero RM, Bada HS. Neonatal abstinence syndrome and cerebral infarction following maternal codeine use during pregnancy. Clin Pediatr (Phila). 2007;46(7):639-645.
4. Sweeney PJ, Schwartz RM, Mattis NG, Vohr B. The effect of integrating substance abuse treatment with prenatal care on birth outcome. J Perinatol. 2000;20(4):219-224.
5. Albano GD, La Spina C, Pitingaro W, Milazzo V, Triolo V, Argo A, et al. Intrauterine and neonatal exposure to opioids: toxicological, clinical, and medico-legal issues. Toxics. 2023;11(1):62.
6. Kale-Çekinmez E, Mutlu B, Yapıcıoğlu H, Ozlü F, Asker H, Mert K, et al. Two newborns of heroin-addicted mothers suffering neonatal withdrawal syndrome. Turk J Pediatr. 2012;54(4):421-424.
7. Wachman EM, Schiff DM, Silverstein M. Neonatal abstinence syndrome: Advances in diagnosis and treatment. JAMA. 2018;319(13):1362-1374.
8. Gheshlaghi F, Khezri E, Malekzadeh N. The prevalence of substance abuse and its relationship with demographic factors among pregnant women. J Isfahan Med Schoo. 2021;39(617):167-173.
9. Oei J, Lui K. Management of the newborn infant affected by maternal opiates and other drugs of dependency. ournal Paediatr child Heal. 2007;43(1–2):9–18.
10. Duarte DF. Opium and opiates: a brief history. Rev Bras Anestesiol. 2005;55(1):135–146.
11. Jones CM, Bekheet F, Park JN, Alexander GC. The evolving overdose epidemic: Synthetic opioids and rising stimulant-related harms. Epidemiol Rev. 2020;42(1):154–166.
12. Finnegan LP, Connaughton Jr JF, Kron RE, Emich JP. Neonatal abstinence syndrome: Assessment and management. Addictive diseases. 1975;2(1-2):141-158.
13. Hussaini KS, Garcia Saavedra LF. Neonatal abstinence syndrome (NAS) in Southwestern Border States: Examining trends, population correlates, and implications for policy. Matern Child Health J. 2018;22(9):1352-1359.
14. Hirai AH, Ko JY, Owens PL, Stocks C, Patrick SW. Neonatal abstinence syndrome and maternal opioid-related diagnoses in the US, 2010-2017. JAMA. 2021;325(2):146-155. Erratum in: JAMA. 2021; 325(22):2316.
15. Patrick SW, Faherty LJ, Dick AW, Scott TA, Dudley J, Stein BD. Association among county-level economic factors, clinician supply, metropolitan or rural location, and neonatal abstinence syndrome. JAMA. 2019;321(4):385-393.
16. Dysart K, Hsieh HC, Kaltenbach K, Greenspan JS. Sequela of preterm versus term infants born to mothers on a methadone maintenance program: Differential course of neonatal abstinence syndrome. J Perinat Med. 2007;35(4):344-346.
17. Gibson KS, Stark S, Kumar D, Bailit JL. The relationship between gestational age and the severity of neonatal abstinence syndrome. Addiction. 2017;112(4):711-716.
18. Stover MW, Davis JM. Opioids in pregnancy and neonatal abstinence syndrome Prevalence of opiate use in pregnancy. Semin Perinatol. 2015;39(7):561–565.
19. Nagy E, Loveland KA, Orvos H, Molnár P. Gender-related physiologic differences in human neonates and the greater vulnerability of males to developmental brain disorders. J Gend Specif Med. 2001;4(1):41-49.
20. Unger A, Jagsch R, Bäwert A, Winklbaur B, Rohrmeister K, Martin PR, et al. Are male neonates more vulnerable to neonatal abstinence syndrome than female neonates? Gend Med. 2011;8(6): 355-364.
21. Maguire DJ, Rowe MA, Spring H, Elliott AF. Patterns of disruptive feeding behaviors in infants with neonatal abstinence syndrome. Adv Neonatal Care. 2015;15(6):429-439.
22. Sandoval MP, Gonzalez DF, Suarez KJ, Medina DF, Torres DA, Farfán JC. Neonatal abstinence syndrome and non-pharmacological nursing care. A scoping review. J Neonatal Nurs. 2024;30(1):5-10.

23. Gaalema DE, Scott TL, Heil SH, Coyle MG, Kaltenbach K, Badger GJ, et al. Differences in the profile of neonatal abstinence syndrome signs in methadone-versus buprenorphine-exposed neonates. Addiction. 2012;107(Suppl. 1):53–62.
24. Davis JM, Shenberger J, Terrin N, Breeze JL, Hudak M, Wachman EM, et al. Comparison of safety and efficacy ofmethadone vs morphine for treatment of neonatal abstinence syndrome a randomized clinical trial. JAMA Pediatr. 2018;172(8):741-748.
25. Allocco E, Melker M, Rojas-Miguez F, Bradley C, Hahn KA, Wachman EM. Comparison of neonatal abstinence syndrome manifestations in preterm versus term opioid-exposed infants. Adv Neonatal Care. 2016;16(5):329–336.
26. O'Connor A, Harris E, Hamilton D, Fisher C, Sachmann M. Neonatal abstinence syndrome (NAS) And methamphetamine use: A review of finnegan's as an assessment tool in the women and newborn drug and alcohol service. Int J Nurs Heal Care Res. 2019;5(6).
27. Jamali Z, Molaei-Farsangi MH, Ahmadipour H, Bahmanbijari B, Sabzevari F, Parizi ZD. Comparison of the effect of phenobarbital & levetiracetam in the treatment of neonatal abstinence syndrome (NAS) as adjuvant treatment in neonates admitted to the neonatal intensive care unit: A randomized clinical trial. BMC Pregnancy Childbirth. 2024;24(1):242.
28. Maguire D, Gröer M. Neonatal abstinence syndrome and the gastrointestinal tract. Med Hypotheses. 2016;97(12):11–15.