

# Prenatal Substance Abuse: a 1-Year Single-Center Experience at a Tertiary Neonatal Intensive Care Unit

## Prenatal Madde Maruziyeti: Tek Merkezli Bir Üçüncü Düzey Yenidoğan Yoğun Bakım Ünitesinde Bir Yıllık Deneyim

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### ABSTRACT

**Objective:** Eight newborns diagnosed with prenatal substance abuse were evaluated for the clinical course of neonatal abstinence syndrome depending on the type of substances used by their mothers during pregnancy.

**Material and Methods:** A retrospective study of neonates with prenatal substance abuse admitted to our tertiary care university hospital's Neonatal Intensive Care Unit (NICU) was conducted between February 2022 and March 2023. Demographic data, withdrawal symptoms, need for pharmacological treatment, and duration of hospitalization were collected. Newborns exposed to substances were divided into two groups: opioid and non-opioid (methamphetamine, Bonsai, marijuana).

**Results:** Eight infants were included in the study. Four cases (50%) were in the group exposed to opioids. Pregnant users of opioids were older ( $28\pm 6.73$ ) than non-opioid substance users ( $21\pm 4.83$ ). The mean birth weight of newborns exposed to opioids (2541 g) was lower than that of the non-opioid group (3020 g). The average length of hospital stay was longer in the opioid group (34 days) compared to the non-opioid group (10 days). All newborns exposed to substances were born preterm (<37 gestational weeks). Withdrawal symptoms were observed in all cases in the opioid group and three cases in the non-opioid group to varying degrees. Medical treatment was required in three out of the seven cases with withdrawal symptoms. All patients requiring treatment were in the opioid group. All infants were discharged in good health.

**Conclusion:** Substance exposure during the prenatal period is a significant cause of preterm birth in neonates. Many of these substances can cause varying degrees of withdrawal syndrome in newborns. Replacement therapies used during pregnancy containing heroin and naloxone can lead to a more severe, prolonged, and treatment-requiring neonatal withdrawal syndrome than other substances. In cases where morphine and methadone are unavailable, the symptoms of withdrawal syndrome can be managed with phenobarbital. It is crucial to monitor all newborns with prenatal exposure to substances early because it allows for appropriate intervention and treatment.

**Key Words:** Abstinence, Newborn, Phenobarbital, Pregnancy, Substance use

### ÖZ

**Amaç:** Doğum öncesi yasadışı uyuşturucu maruziyeti olan sekiz yenidoğan, gebelik sırasında kullanılan maddelerin türüne bağlı olarak gelişen neonatal yoksunluk sendromunun klinik seyri açısından değerlendirilmiştir.

**Gereç ve Yöntemler:** Hastanemizin üçüncü basamak Yenidoğan Yoğun Bakım Ünitesine (YYBÜ) Şubat 2022 ile Mart 2023 tarihleri arasında, doğum öncesi yasadışı madde maruziyeti nedeniyle yatırılan yenidoğanlarda retrospektif



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**Ethics Committee Approval / Etik Kurul Onayı:** This study was conducted in accordance with the Helsinki Declaration Principles. Health Sciences University, Bakırköy Dr. Sadi Konuk Training, and Research Hospital Ethics Committee approved the study (Approval number 2022-20-05, 17/10/2022).

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bir çalışma yürütüldü. Demografik veriler, yoksunluk belirtileri, farmakolojik tedavi ihtiyacı ve hastenede kalış süreleri kaydedildi. Madde maruziyeti olan yenidoğanlar opioid ve opioid-dışı (metamfetamin, Bonsai, esrar) olarak 2 gruba ayrıldı.

**Bulgular:** Çalışmaya toplam sekiz yenidoğan dahil edildi. Vakaların 4'ü (50%) opioide maruz kalan gruptaydı. Opioid kullanan gebeler ( $28\pm 6.73$ ), non-opioid madde kullanan gebelerden daha yaşlıydı ( $21\pm 4.83$ ). Opioid maruz kalan yenidoğanlarda ortalama doğum tartısı (2541 gr), non-opioid gruptan (3020 gr) daha düşüktü. Ortalama hastane yatış günü opioid grupta (34 gün), non-opioid gruptan daha uzundu (10 gün). Madde maruziyeti olan tüm yenidoğanlar preterm (<37 gestasyon haftası) doğmuştu. Opioid grubundaki tüm vakalar ile non-opioid grubundaki üç vakada çeşitli derecelerde çekilme semptomları gözlemlendi. Çekilme semptomları gözlenen vakaların 3'ünde medikal tedavi gerekti. Tedavi gerektiren hastaların tamamı opioid grubundaydı. Tüm yenidoğanlar sağlıklı olarak taburcu edildi.

**Sonuç:** Prenatal dönemde yasadışı madde maruziyeti yenidoğanlarda preterm doğumun önemli nedenlerindedir. Bu maddelerin birçoğu yenidoğanlarda çeşitli derecelerde yoksunluk sendromuna neden olmaktadır. Gebelikte kullanılan eroin ve nalokson içeren ikame tedavileri, diğer maddelere göre daha şiddetli, uzun seyirli ve tedavi gerektiren neonatal yoksunluk sendromuna neden olabilir. Morfin ve metadonun temin edilemediği durumlarda, yoksunluk sendromu bulguları fenobarbital ile kontrol altına alınabilir, Prenatal dönemde madde maruziyeti olan tüm yenidoğanların doğum sonrası erken izleme alınması, uygun müdahale ve tedaviye olanak sağladığından çok önemlidir.

**Anahtar Sözcükler:** Yoksunluk, Yenidoğan, Fenobarbital, Gebelik, Madde kullanımı

## INTRODUCTION

Substance use remains an ever-growing global public health concern in all societies. Even though no studies have been conducted in our country, in the United States of America, the prevalence of using one or more substances during pregnancy was reported as 5.9% (1). The use of substances during pregnancy carries significant medical and social consequences for both the mother and the newborn (2). Many frequently used illegal substances, such as heroin, marijuana/hashish, synthetic cannabinoids (Bonsai), and stimulants like cocaine and methamphetamines, can cross the placenta and have various effects on the developing fetus (3). These effects include neonatal abstinence syndrome (NAS), cognitive deficit, sudden infant death syndrome, congenital defects, and behavioral problems (4). NAS has been reported to occur in 50 and 90% of neonates with intrauterine substance exposure. However, a considerable variation exists in NAS, the need for pharmacological treatment, hospitalization duration, and other associated morbidities (5, 6). In this article, we aim to evaluate withdrawal symptoms and clinical courses of neonates born to women with a history of substance use during pregnancy.

## MATERIALS and METHODS

We evaluated neonates born at the University of Medical Science, Bakirkoy Dr. Sadi Konuk Training & Research Hospital between February 2022 and March 2023 and exposed to illicit substances in the prenatal period in this retrospective study. Health Sciences University, Bakirkoy Dr. Sadi Konuk Training, and Research Hospital Ethics Committee approved the study (Approval number 2022-20-05, 17/10/2022). The cases included in this study were selected based on the maternal history of substance use during pregnancy. We gathered demographic data of both the mothers and infants and other factors such as the necessity and duration of pharmacological treatment and the length of hospitalization. The demographic information collected encompassed gender, birth weight, gestational age at birth, mode of delivery, maternal age, and

APGAR scores at 1 and 5 minutes. Eventually, eight infants were born to mothers meeting this criterion. In addition, we conducted interviews with the women to inquire about the specific types of substances they had used. Based on their responses, we categorized the substances into two groups: opioid and non-opioid. Similarly, the infants included in the study were also evaluated and classified into two groups: heroin and non-heroin (metamphetamine, Bonsai, hashish, marijuana). All newborns with a history of prenatal substance abuse were admitted to our neonatal intensive care unit for a post-delivery follow-up. The primary objective of their admission was to recognize any withdrawal symptoms and provide appropriate interventions promptly. Upon admission to the unit, routine hematological examinations (complete blood count, blood glucose, serum calcium, CRP, blood gas, serum vitamin D levels, blood group, and blood culture) were conducted and sent to the laboratory. In cases of respiratory distress, chest imaging was performed. Comprehensive cardiological evaluations and cranial-abdominal ultrasound examinations were conducted for all neonates. However, it was impossible to detect the substances in urine samples for all newborns due to collection difficulties and the unavailability of these tests in our laboratory during the study period. Withdrawal symptoms were assessed using a modified Finnegan scoring system every three hours for all newborns. Newborns with a birth weight below the 10% percentile (SGA) score according to the gestational week were recorded. Pharmacologic treatment was initiated for those with a score of  $\geq 8$ . Furthermore, a consultation with a pediatric neurologist was sought for all cases.

## RESULT

Eight newborns were born to pregnant women with a history of illicit substance abuse between February 2022 and March 2023. Therefore, our study included these newborns with substance exposure in utero. Five (62.5%) newborns were boys, while three (37.5%) were girls. All the neonates were inborn and were admitted to the NICU of our hospital on the first day of life. SGA was observed in one patient, accounting

**Table I: Demographic Characteristics of Mothers With a History of Illicit Substance Use During Pregnancy**

Variable	Mother 1	Mother 2	Mother 3	Mother 4	Mother 5	Mother 6	Mother 7	Mother 8
Age	32	30	17	28	18	19	20	32
Gestational Age (week)	38	34	37	35	35	35	36	36
Gravidae	multiparae	multiparae	multiparae	multiparae	primiparae	multiparae	primiparae	multiparae
Education	Primary School	Primary School	-	Primary School	Primary School	-	High school	Primary school
Delivery Mode	c/s	Vaginal	Vaginal	c/s	c/s	c/s	Vaginal	c/s
Hepatitis B	-	-	-	-	-	-	-	-
Hepatitis C	+	+	-	-	-	-	-	-
HIV	-	-	-	-	-	-	-	-
Alcohol	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Cigarette (per/day)	15	10-15	15-20	10-15	40-60	20-25	10-15	20-25
Pre-pregnancy Illicit Use	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Marital Status	Yes	Single	Single	Single	Single	Single	Single	Single
Prenatal Visits	Irregular	No	No	No	No	No	Irregular	No
Illicit Drug Choice	Heroin Buprenorphin/ Naloxone	Heroin	Metamphetamine, Bonzai, Hashish	Metamphetamine, Cannabinoid	Heroin	Methamphetamine/ Bonzai	Metamphetamine	Heroin
Employment Status	-	-	-	-	-	-	-	-
Paternal/Partner Substance Use	Intermittant	Unknown	Unknown	Unknown	Unknown	Unknown	Yes	Unknown

**Table II: Demographic Features and Clinical Properties of the Newborn Cases**

Case No	1	2	3	4	5	6	7	8
Gender	male	female	female	male	male	male	male	female
Age on admission (days)	1	1	1	1	1	1	1	1
Gestational age (weeks)	38	34	37	35	35	35	36	36
Birth weight (g)	2320	2625	3275	2990	2620	2915	2900	2600
APGAR 1-minute	7	7	8	4	8	4	7	6
APGAR 5-minute	8	9	9	6	9	6	8	8
Minimum-Maximum Finnegan scores	12-16	11	1-6	0-2	2-6	1-5	0	4-11
NAS* (signs&symptoms)	+	+	+	+	+	+	-	+
fever	-	-	-	-	-	-	-	-
tremor/myoclonic jerks	+	+	-	-	-	-	-	+
tachypnea/retractions	+	-	-	-	+	+	-	+
increased moro/sucking reflex	+	-	-	-	-	-	-	+
high pitched cry	+	+	+	+	-	+	-	+
watery stools	-	-	+	-	-	-	-	-
feeding difficulty	+	+	-	-	+	-	-	-
NAS onset (day of life)	1	3	4	2	2	2	-	1
Treatment	Phenobarbital Clonazepam Midazolam	Phenobarbital	-	-	-	-	-	Phenobarbital
Hospital stay (days)	62	17	10	12	34	12	6	21
Need of social service	+	+	+	+	+	+	+	+

**NAS:** Neonatal Abstinence Syndrome

**Table III: Key features of Opioid and non-Opioid Groups**

Substance	Mother Age	Gest. Age (week)	Birth Weight (g)	APGAR-1	APGAR-5	Onset of NAS (days)	Hospital stay (days)	Vit-D Levels
Opioid Group								
Heroin Buprenorphine /Naloxone	32	39	2320	7	8	1	62	5
Heroin	30	34	2625	7	9	3	17	9
Heroin	18	35	2620	8	9	2	34	7.2
Heroin	32	36	2600	6	8	1	21	3
Non-Opioid Group								
Meth <sup>†</sup> /bonz <sup>‡</sup>	17	37	3275	8	9	4	10	19
Meth/hashish	28	35	2990	4	6	2	12	6.7
Meth/bonz	19	35	2915	4	6	2	12	8.9
Meth	20	36	2900	7	8	0	6	7.8

<sup>†</sup>: Methamphetamine, <sup>‡</sup>: Bonzai

for 12.5% of the cases, born to mothers with a history of heroin abuse. The demographic characteristics of mothers with a history of illicit substance use during pregnancy are presented in Table I, while Table II provides an overview of the characteristics of the newborns. The exact duration and amount of substance use could not be ascertained. Table III depicts the key features of opioid and non-opioid groups. Analysis of maternal serological status revealed two positive cases of Hepatitis C (25%), with neither being HIV positive. NAS occurred in seven newborns (87.5%), with three (37.5%) requiring medical treatment. Our treatment approach involved a combination of non-pharmacological and pharmacological management. Because morphine and methadone preparations were unavailable in our unit, our primary treatment option was phenobarbital. Newborns with a Finnegan score of 8 and higher received phenobarbital treatment. In one case where the signs of neonatal abstinence syndrome (NAS) were challenging to control, clonazepam and midazolam were added to the phenobarbital treatment, following a recommendation from pediatric neurology. After discharge, all infants were referred to a government social service because of parental incapacity and an unsuitable home environment.

## DISCUSSION

Many studies worldwide suggest that substance use among pregnant women varies widely and reflects differences in drug availability, age, socioeconomic status, and screening modes. Substance abuse, including alcohol, nicotine, cocaine, cannabis, methamphetamine, and opioids during pregnancy, has been associated with preterm birth (1). According to previous research, tobacco is the most frequently used substance during pregnancy, followed by alcohol, cannabis, and cocaine (7). In our study, approximately 75% of the cases were classified as preterm (gestational age below 37 weeks). Notably, all mothers who delivered before term had a smoking history and 75% had a positive history of alcohol consumption. Even though opioid abuse during pregnancy has rapidly increased in the United States, studies also report increased methamphetamine

abuse in women of childbearing age worldwide (8-10). Mothers who use methamphetamines during pregnancy exhibit characteristics such as being younger, having lower levels of education, having lower socioeconomic status, having a higher likelihood of drinking and smoking during pregnancy, and receiving less prenatal care before childbirth (11, 12). In the pregnant women who participated in our study, the prevalence of methamphetamine and heroin use was similar. Additionally, the mean age of mothers using methamphetamine was lower than that of mothers using heroin, aligning with existing literature on the subject.

Substance use during pregnancy has critical implications because it impacts the mother and negatively affects the developing fetus. One of these effects is Neonatal Abstinence Syndrome (NAS). NAS is a withdrawal syndrome that occurs when the placental transfer of substances, particularly opioids, is abruptly halted following chronic use by the mother. This phenomenon can disrupt postnatal adaptation to varying degrees. The opioid replacement therapy administered to the mother throughout pregnancy may also cause the development of NAS (13). The most characteristic symptoms of NAS include feeding problems, sleeping disorder, fever, jitteriness, myoclonic jerk, episodic activity, irritability, diarrhea, and high-pitched crying. The modified Finnegan scoring system is utilized to assess the severity of these symptoms and guide treatment, which assigns scores to each symptom based on their intensity. A score of eight or higher ( $\geq 8$  points) indicates the need for close monitoring and treatment (14). The treatment of NAS can sometimes extend over several weeks. Currently, no standardized treatment protocol for NAS exists. Treatment approaches involve both pharmacological and non-pharmacological methods. Non-pharmacological interventions primarily focus on providing the baby with a calm and less stimulated environment. These measures include gentle and minimal touching, maintaining a quiet and dimly lit environment, swaddling, skin-to-skin care, offering a pacifier, and promoting breastfeeding (15).

Even though non-pharmacological interventions are effective, pharmacological treatment is recommended for newborns

with substantial abstinence symptoms (Finnegan score  $\geq 8$ ). Commonly recommended medications include oral morphine, diluted tincture of opium, methadone, clonidine, phenobarbital, and buprenorphine (16). In our study, three cases exposed to opioids and opioid replacement therapy in utero had a Finnegan score of 8 or higher, warranting pharmacological treatment. Managing the symptoms in the neonate of the first pregnant woman (Mother 1), who used heroin and Suboxone®, proved challenging as the onset of withdrawal symptoms occurred earlier compared to other cases. The presence of naloxone in the Suboxone® used by the mother contributed to a longer stay in the neonatal intensive care unit (NICU).

The most common treatment for managing substance addiction during pregnancy is replacement therapy with methadone. It is associated with improved obstetric care and is considered the gold standard for pregnant women with opioid addiction (17). However, in many centers, replacement therapy using buprenorphine during pregnancy has been reported to result in a milder abstinence syndrome (18, 19). A study involving ten pregnant women receiving buprenorphine/naloxone replacement therapy for opioid addiction during pregnancy reported no significant adverse effects for both the mother and the newborn. Nevertheless, the daily buprenorphine/naloxone dose used in that study did not exceed 16/4 (20). The FDA does not recommend the use of combined buprenorphine/naloxone treatment during pregnancy. However, if the prospective mother has already received this treatment before becoming pregnant and has achieved clinical stability, no further concerns were reported about continuing the same replacement therapy during pregnancy (21). In our study, the first mother received a buprenorphine/naloxone dose ranging from 24/6 to 32/8, higher than the doses reported in the literature. Additionally, the replacement therapy with the combined preparation containing naloxone was initiated during the 14<sup>th</sup> week of gestation, while the mother actively used heroin until the second trimester of her pregnancy. This finding was the reason for the severe abstinence syndrome observed. In our country, it is usually not possible to provide methadone treatment in daily clinical practice. Therefore, the combination of buprenorphine/naloxone remains the only replacement therapy option for pregnant women with opioid addiction.

Withdrawal symptoms in newborns typically become apparent within the first 24–72 hours after birth, but it is also possible for the symptoms to manifest later ( $>5$  days) (22). In our study, withdrawal syndrome symptoms were observed in all newborns within the first five days of life. Because the onset of withdrawal symptoms may be delayed up to postnatal day five, it is safer to monitor newborns with in utero substance exposure in NICU for at least 5–7 days (22). Mild NAS was observed in newborns born to two pregnant women using synthetic cannabinoids, commonly known as Bonsai, in our country. Bonsai is a synthetic cannabinoid with similar effects and psychoactive properties to natural cannabis. Limited literature is available regarding synthetic cannabinoids during pregnancy, mainly in

case presentations (23). In our study, pharmacological treatment was not required as the NAS symptoms were transient and resolved independently in both cases born to these pregnant women.

It is well-established that mothers with addiction issues are often young, unemployed, have low socioeconomic status, and have limited education. They may have extramarital pregnancies and lead irregular lifestyles. Their utilization of prenatal care services is typically minimal (12, 24). In our study, all the mothers were unemployed, the majority had low levels of education, and only one woman was married.

Most mothers in our study did not have prenatal visits. In addition to the medical importance, the participation of expectant mothers in prenatal visits is crucial for micronutrient supplementation, maternal preparation, and emotional bonding with the baby. Unfortunately, the rate of prenatal visits was only 22.5% in our study, and they were irregular.

In our study, newborns' serum vitamin D levels in both the opioid and non-opioid groups participating were found to be deficient ( $< 20$  ng/ml) (25). This finding was attributed to inadequate nutrition and lack of vitamin D supplementation due to poor prenatal care, preterm birth, and low socioeconomic status associated with unemployment.

Women who engage in substance use during pregnancy are at a higher risk of acquiring HIV, hepatitis B, hepatitis C infections, and syphilis. Routine screening for HIV, HBV, and syphilis in pregnant women enables early detection and intervention (12, 26). Even though no routine screening test is conducted for HCV in pregnant women, the ever-increasing substance addiction rates during pregnancy also increase HCV infections (27). In our study, two cases tested positive for HCV, supporting this observation. Including HCV screening as part of the routine tests for pregnant women with substance use is critical for identifying vertical virus transmission and determining the infant's seroconversion after discharge.

It is encouraging to note that many women with substance abuse issues are motivated to quit or reduce their substance use when they become pregnant due to concerns about the potential harm to their babies (19). This motivation was also observed in our cases, with all women striving to quit the substances they were using. Pregnancy poses a unique opportunity for healthcare providers to support and assist pregnant women in discontinuing substance use. By providing appropriate medical care, counseling and support, physicians can help pregnant women achieve substance-free pregnancies.

## CONCLUSION

In our study, we observed that illicit substance, especially opioid use during pregnancy, seems to cause NAS, with a severe course in the neonatal period, usually requiring pharmacological treatment. The preference for combined preparations containing



naloxone in replacement therapy used for treating substance abuse in pregnant women has been associated with increased severity and duration of the abstinence syndrome in newborns. However, the likelihood of illegal substances other than opioids causing severe withdrawal syndrome requiring pharmacological treatment seems low. All clinicians responsible for neonatal care should be alert about this issue.

It is important to note that the onset of abstinence symptoms may be delayed, necessitating close observation of newborns with a history of prenatal substance exposure for at least one week.

Phenobarbital is an effective adjuvant treatment option for controlling withdrawal symptoms in cases where morphine and methadone drugs are unavailable. Regular prenatal care, like all pregnant women, can contribute to achieving more reasonable vitamin D levels for pregnant women with addiction issues. Even cases with the most severe prognosis of abstinence syndrome can be successfully managed with early monitoring, intervention, and treatment. By ensuring timely and appropriate care, healthcare professionals can positively impact the outcomes of newborns affected by prenatal substance exposure.

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