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Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

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Natasha Simonovska[1,†], Beti Zafirova-Ivanovska[2], Aleksandra Babulovska[1]

Physical birth outcomes in neonates prenatally exposed to buprenorphine – our first experiences

Физичке карактеристике новорођенчади пренатално изложене бупренорфину – наша прва искуства

[1]University Clinic of Toxicology, Mother Teresa Clinical Center, Medical Faculty, Skopje, Republic of North Macedonia
[2]Institute of Epidemiology and Biostatistics, Medical Faculty, Skopje, Republic of North Macedonia

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†**Correspondence to:**
Natasha SIMONOVSKA
University Clinic of Toxicology, Mother Teresa Clinical Center, Vodnjanska 17, 1000 Skopje, Republic of North Macedonia
E-mail: **n.simonovska@yahoo.com**

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SUMMARY

Introduction/Objective Buprenorphine appears generally similar to, and in some cases superior to, methadone in terms of maternal, fetal, and neonatal outcomes.

Objective The objective of the study was to assess some physical birth outcomes in neonates prenatally exposed to buprenorphine.

Methods During a 7-year-period, 9 patients have been treated with buprenorphine during their pregnancy. All women underwent: interview, clinical investigations, biochemical analysis, toxicological screening, viral markers for hepatitis B, C, HIV, and were regularly controlled by an obstetrician and a psychiatrist. Newborn outcomes included: birth weight in grams, birth length in centimeters, physical anomalies, head/chest circumference in centimeters, Apgar score 1 min. / 5 min., gestational age (weeks), newborn length of hospital stay in days, breast-feeding, need of a newborn for pharmacologic treatment after delivery.

Results The mean birth weight was 2991.11 ± 37 gm; birth length 49.44 ± 2.29 cm; head circumference 33.11 ± 0.78 cm; chest circumference 32.33 ± 1 cm; Apgar score 8.22 first minute, fifth minute 9.22; age at delivery 38.77 ± 1.09 weeks; hospitalization after delivery 4.44 ± 1.13 days. None of the newborns had physical anomalies. Six of the newborns were breastfed.

Conclusion Buprenorphine is a safe and important part of a complete comprehensive treatment approach in pregnant women with opioid use disorder. Buprenorphine treatment of maternal opioid use disorder indicated a low risk of preterm birth, normal birth weight and length, head and chest circumference, Apgar score, short hospitalization after delivery.

Keywords: Buprenorphine; pregnancy; neonates; physical birth outcomes

САЖЕТАК

Увод/Циљ Бупренорфин је уопштено сличан а у неким случајевима бољи од метадона у смислу исхода код мајке, фетуса, и новорођенчади. Циљ рада је процена неке физичке карактеристике новорођенчади пренатално изложене бупренорфину.

Методе У периоду од 7 година, 9 жена са болест овисности од опиоида лечено је бупренорфином током трудноће. Све су труднице подвргнуте на интервју, клиничка испитивања, биохемијске анализе, токсиколошки скрининг, одређивање вирусних маркера за хепатитис Б, Ц, ХИВ, редовно контролисани од стране акушера и психијатра. Прослеђени параметри код новорођенчади су порођајна тежина у грамима, порођајна дужина у центиметрима, физичке аномалије, обим главе / груди у центиметрима, Апгар скор 1 мин. / 5мин., гестацијска старост (недеља), дужина болничког боравка у данима, дојење, фармаколошки третман након порођаја.

Резултати Просечна порођајна тежина је 2991,13 ± 37 гм; просечна порођајна дужина је 49,44 ± 2,29 цм; обим главе 33,11 ± 0,78 цм; обим груди 32,33 ± 1 цм; Апгар скор 8,22/9,22; гестацијска старост 38,77 ± 1,09 седмица; дужина болничког боравка4,44 ± 1,13 дана. Сва новорођенчад била је здрава, без конгениталних аномалија.

Закључак Бупренорфин је сигуран и важан део свеобухватног третмана код трудница са болешћу зависности од опиоида. Бупренорфин показао је низак ризик од превременог порођаја, нормална порођајна тежина и дужина, обим главе и груди, Апгар скоп, кратке хоспитализације након порођаја.

Кључне речи: Бупренорфин; трудноћа; новорођенчад; физичке карактеристике након порођаја

INTRODUCTION

Substance use disorder among pregnant women continues to be a major public health concern, posing risk to the child's development, and imposing socioeconomic burdens on society by increasing needs for medical and social services [1].Given the increasing prevalence of use of opioids by pregnant women, and the potentially serious maternal, fetal,

and neonatal risks attendant to such use, the provision of effective treatment for this population should be a public health priority [2].

From 2002 to 2013, the largest increase in heroin use was among women. The rate of opioid use during pregnancy is approximately 5.6 per 1000 live births, with one study reporting greater than 85% of pregnancies in women with opioid use disorder (OUD) were unintended. Opioid agonist therapy (OAT) is the first-line recommendation for pregnant women with opioid use disorders. The goals of treatment are to manage withdrawal, reduce cravings, and provide opioid blockade (preventing euphoria from illicit use). The goals of OAT in pregnancy are to prevent illicit opioid use which can increase the risk of fetal growth restriction, abruptio placentae, fetal death, preterm labor, and intrauterine passage of meconium. OAT has been shown to increase adherence to prenatal care, reduce illicit drug use, reduce infection exposure secondary to intravenous drug use (IVDU), such as HIV, HCV, improve maternal nutrition, and improve infant birth weight [3].

The accepted treatment for OUD during pregnancy is long-acting opioid agonist medication-assisted treatment (OMAT), such as methadone (MET) or buprenorphine (BUP), within the context of a comprehensive program of obstetric care and psychosocial interventions [4].

Buprenorphine appears generally similar to, and in some cases superior to, methadone in terms of maternal, fetal, and neonatal outcomes. Like methadone, prenatal buprenorphine exposure appears to be associated with a clinically significant neonatal abstinence syndrome (NAS) requiring pharmacological intervention in approximately half of the cases. However, results from the MOTHER study suggest that buprenorphine is associated with a less severe NAS than methadone. The generally positive outcomes for both mother and child following buprenorphine exposure in the randomized controlled trials were achieved in the context of receipt of flexible and adequate buprenorphine dosing during pregnancy and postpartum, and comprehensive treatment from a multi-disciplinary team. While the nature of science is to compare and contrast treatments in order to discover which treatment is better, the reality is that no one treatment will be maximally effective for all patients. Our collective commitment should be towards researching which treatment works best for which patients [2].

Objective To assess physical birth outcomes in neonates prenatally exposed to buprenorphine (way of delivery, gender, birth weight, birth length, physical anomalies,

head/chest circumference, Apgar score, gestational age, newborn length of hospital stay in days, breast feeding, newborn required pharmacologic treatment after delivery)

METHODS

The University Clinic of Toxicology, Mother Teresa Clinical Center started the treatment of opioid use disorder with buprenorphinein our country for the first time on August 1, 2009. Patients with Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) diagnosis of opioid use disorder were treated according to Clinical Guidelines for the Use of buprenorphine in the Treatment of Opioid use disorder –Treatment Improvement Protocol (TIP 40). Patients were treated with buprenorphine sublingual tablets. By January 31, 2017 a total of 235 patients are receiving treatment of opioid use disorder with buprenorphine and 23 of them are women. This number varies from month to month. During this period, 9 patients were treated with buprenorphine throughout their entire pregnancy. All women had previously started treatment of OUD with buprenorphine. Besides previously made examinations, all of the women who became pregnant underwent additional investigations: interview, clinical investigations, biochemical analysis, toxicological screening, viral markers for hepatitis B, C, HIV, were regularly controlled by an obstetrician and a psychiatrist. All patients have had regular controls, they were positive on buprenorphine in urine sample. On several occasions during pregnancy one patient was positive on THC, and one patient was twice positive on benzodiazepines during pregnancy. All patients during pregnancy were negative on opiates, methadone, cocaine, amphetamines, tramadol. They were also Hbs Ag, antiHCV and HIV negative. All mothers were receiving buprenorphine and there was no medication change. Women remained on their opioid maintenance therapy. Breastfeeding was encouraged.

Newborn outcomes included: way of delivery, gender (male/female), birth weight in grams, birth length in centimeters, physical anomalies, head/chest circumference in centimeters, Apgar score 1min/5min, gestational age (weeks), newborn length of hospital stay in days, breast feeding, need of a newborn for pharmacologic treatment after delivery.

The following instruments were used for testing: toxicological analyses in urine samples (FPIA); qualitative tests for buprenorphine and tramadol. All tests were performed at the Institute of Forensic Medicine, University Clinic of Toxicology. The head circumference

was measured above the ears equally on both sides and across the occipital font. The chest circumference was measured across the nipple line around the back of the newborn during exhalation. The circumference measurements and body length were taken with a measuring tape. The body weight was measured according to the Procedure for Weighing Infants/Children using a Digital Infant Scale. Gestational age assessment was according to Dubovitz–Ballard score.

Maternal characteristics included: age (years), education, which psychoactive substances were used before treatment, route of psychoactive substances administration before treatment, which pregnancy in a row, way of parturition, miscarriage, buprenorphine dose (mg) during pregnancy, time of treatment before pregnancy (months).

Inclusion criteria All pregnant women had a Diagnostic and Statistical Manual of Mental Disorders IV, diagnosis of current OUD and maintenance treatment with buprenorphine, positive buprenorphine test, negative opiates, methadone, cocaine, amphetamines and tramadol test.

Exclusion criteria: Patients who dropped out the maintenance treatment with buprenorphine by their own choice; patients who did not come on regular controls, patients with negative buprenorphine test.

This treatment was carried out with approval from Ministry of Health (national program for treatment of patients with OUD) and from the Institutional Board of University Clinic of Toxicology. All patients underwent this treatment with written consent.

Descriptive statistics was done with the statistical program SPSS for Windows, version 13.0.

RESULTS

This study included 9 pregnant women on treatment with Buprenorphine for OUD. The mean age of these patients was 27.22 ± 2.58 years. Before treatment, five of these patients had heroin use disorder alone, three of them had polydrug use disorder and one of them took methadone from the “black market.” Two of them took opioid intravenously, but all were HbsAg, antiHCV and HIV negative. It was first pregnancy for all of them. Only one patient

had spontaneous miscarriage after her first pregnancy, due to unknown reason. Two patients had cesarean section. The mean dose of buprenorphine during pregnancy was 11.11 ± 4.37 mg. The lowest dose was 6 mg and the maximum dose was 16 mg. The average treatment duration with buprenorphine before pregnancy was 21.44 ± 9.72 months. In the end, in two of all included patients two after delivery the dose was slowly reduced and they finished the treatment with buprenorphine.

Maternal characteristics are outlined in Table 1.

In Table 2 newborn outcomes are presented, with serial number corresponding to the serial number of the mother in Table 1. Most of the patients (n=7) had spontaneous parturition, only two patients had cesarean section. Five of the newborns were boys. The mean birth weight was 2991.11±37gm and the mean length was 49.44±2,29cm. None of the newborns had physical anomalies. The mean head circumference was 33.11±0,78cm and the mean chest circumference was 32.33±1,00cm. The mean Apgar score was 8.22 in the first minute, and 9.22 in the fifth minute after delivery. The mean age at delivery was 38.77±1,09 weeks. The mean length of hospital stay was 4.44±1,13 days. Six of the newborns underwent breastfeeding. One of the patients stopped with breastfeeding on suggestion of her mother, and the other two newborns were formula-fed. Phenobarbitone was prescribed in only one newborn as prevention from seizures, while the remaining eighth newborns received no treatment.

Physical birth outcomes in neonates prenatally exposed to buprenorphine are outlined in Table 2.

DISCUSSION

In 2009 for the first time in our country, University Clinic of Toxicology offered patients with OUD an alternative way of treatment with buprenorphine. By 2017, 9 patients were treated with buprenorphine throughout their entire pregnancy. The American College of Obstetricians and Gynecologists has urged that buprenorphine be considered first-line treatment, but methadone is likely still the gold standard due to slightly higher adherence, more tightly controlled dosing, and insufficient evidence that buprenorphine is superior than methadone treatment [1].

As far as dose of buprenorphine during pregnancy in this study the mean dose of buprenorphine was 11.11 ± 4.37 mg. The lowest dose was 6 mg and the maximum dose was 16 mg. Similar results were shown in one study from Farid where buprenorphine doses used to maintain the pregnant woman were variable, with a mean dose range of 5.3–18.7 mg/day [5].In our study the mean gestational age was 38.77 ± 1.09 weeks. Fourteen other non-randomized studies got similar results [2, 6].

This study reported no physical birth anomalies. Similar results were reported in MOTHER and PROMISE study [2].

In our work the mean birth weight of neonates was 2991.11 ± 37 gm and the mean length was 49.44 ± 2.29cm. The mean head circumference was 33.11 ± 0.78 cm and the mean chest circumference was 32.33 ± 1 cm. The mean Apgar score was 8.22 in the first minute, and 9.22 in the fifth minute after delivery. Similar studies that reported summary data, suggest most neonates were full-term and within normal limits: birth weight (20 studies: 3,087.2 gm), birth length (10 studies: 49.4 cm), and head circumference (9 studies: 34 cm) [2, 7]. Coulson in one retrospective cohort study which was conducted in a comprehensive, perinatal program in western North Carolina reported that differences in neonatal outcomes reached statistical significance for larger head circumference for buprenorphine doses and for longer length with low to moderate dose buprenorphine versus high dose methadone [8]. Similar results were reported in national registry studies from the Czech Republic and Norway, with total number of 333 and 235 women used opioid maintenance treatment (OMT) during pregnancy [9].

Findings in one study by Nguyen [6] showed neonatal outcomes (prenatally exposed to Buprenorphine) within normal ranges for delivery and growth parameters. Moreover, mean birth weights have been mostly above 2.9 kg, with the lowest reported at 2.796 kg. Farid in his study reported that in most pregnancies birth weight, APGAR scores, head circumference and body length were within normal ranges [5].

Methadone and buprenorphine are widely used to treat OUD, however, compared with methadone, buprenorphine is associated with shorter treatment duration, less medication needed to treat NAS, and shorter hospitalizations for neonates [7, 10]. In our study the mean length of hospital stay was 4.44 ± 1.13 days. Six of the newborns underwent breastfeeding.

Phenobarbitone was prescribed in only one newborn as prevention from seizures, while the remaining eighth newborns received no treatment.

Limitation of the study The presented patients are the only ones who are on maintenance treatment with buprenorphine at the University Clinic of Toxicology; this study included only 9 cases; a larger series of patients is necessary in order to reach conclusions on the association between pregnancy and OUD treatment with buprenorphine ; more neonatal growth factors have to be observed.

CONCLUSION

Buprenorphine is a safe and important part of a complete comprehensive treatment approach for pregnant women with opioid use disorder. Buprenorphine treatment of maternal OUD indicated a low risk of preterm birth, normal birth weight and length, head and chest circumference.

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Conflict of interest: None declared.

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Table 1. Maternal characteristics

Patient	Age (year)	Education	Use of PAS before treatment	Route of PAS administration before treatment	Pregnancy	Miscarriage	Buprenorphine dose(mg) during pregnancy (mg)	Time of treatment before pregnancy (months)
1	27	secondary	heroin	inhalation	First	none	16	18
2	25	secondary	heroin	inhalation	First	none	6	9
3	29	university degree	Methadone, benzodiazepines	Per os	First	none	10	24
4	31	university degree	Methadone, benzodiazepines, Tramadol, heroin	Inhalation, per os	First	none	12	19
5	30	secondary	heroin	inhalation	First	none	16	11
6	29	secondary	methadone	intravenously	First	none	16	14
7	24	university degree	heroin	intravenously	First	one	6	28
8	25	university degree	Methadone, heroin, benzodiazepines	Inhalation, per os	First	none	12	36
9	25	secondary	heroin	inhalation	First	none	6	34

Table 2. Physical birth outcomes in neonates prenatally exposed to buprenorphine with serial number corresponding to the serial number of the mother in Table 1

Neonates	Way of delivery	sex	Mean birth weight (gm)	Mean length (cm)	Physical anomalies	Head/chest circumference (cm)	Mean Apgar score 1min/5min	Age at delivery (weeks)	Days of hospitalization	Breast feeding	Treatment after delivery
1	spontaneous	f	2750	50	no	33/32	9/10	39	4	No	/
2	spontaneous	m	2950	51	no	33/32	8/9	38	5	Yes	/
3	spontaneous	f	3100	49	no	32/31	8/9	39	6	Yes	/
4	caesarean section	m	3350	51	no	34/33	9/10	40	5	No	/
5	spontaneous	f	2200	44	no	32/31	8/9	38	4	Yes	/
6	spontaneous	f	2830	48	no	34/32	8/9	38	3	Yes	/
7	cesarean section	m	3150	50	no	33/33	8/9	40	6	Yes	/
8	spontaneous	m	3150	51	no	33/33	8/9	38	3	No	Phenobarbitone 2 × 5 mg
9	spontaneous	m	3440	51	no	34/34	8/9	40	4	yes	/

