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

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

Methods During a seven-year period, nine 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, with regular check-ups 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 at 1 minute / 5 minutes, gestational age (weeks), newborn length of hospital stay in days, breast-feeding, the newborn's need for pharmacologic treatment after delivery.

Results The mean birth weight was 2,991.11 ± 37 g; birth length was 49.44 ± 2.29 cm; head circumference was 33.11 ± 0.78 cm; chest circumference was 32.33 ± 1 cm; first minute Apgar score was 8.22, fifth minute 9.22; age at delivery was 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

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 1,000 live births, with one study reporting greater than 85% of pregnancies in women with opioid use disorder (OUD) were unintended. Opioid agonist therapy is the first-line recommendation for pregnant women with OUDs. The goals of treatment are to manage withdrawal, reduce cravings, and provide opioid blockade (preventing euphoria from illicit use). The goals of opioid agonist therapy in pregnancy are to prevent illicit opioid use, which can increase the risk of fetal growth restriction, *abruptio placen-*

tae, fetal death, preterm labor, and intrauterine passage of meconium. Opioid agonist therapy has been shown to increase adherence to prenatal care, reduce illicit drug use, reduce infection exposure secondary to intravenous drug use, 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, such as methadone or buprenorphine, 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. Generally positive outcomes for both mother and child following buprenorphine exposure in randomized controlled trials were achieved in the context

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of receiving 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].

The objective of the paper was to assess physical birth outcomes in neonates prenatally exposed to buprenorphine (the way of delivery, sex, 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 OUD with buprenorphine in 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 OUD 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 have been receiving treatment of OUD with buprenorphine and 23 of them have been women. This number varies from one month to the next. During this period, nine patients were treated with buprenorphine throughout their pregnancy. All the women had previously started OUD treatment 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, underwent regular check-ups by an obstetrician and a psychiatrist. All the patients underwent regular check-ups and 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 the patients during pregnancy were negative on opiates, methadone, cocaine, amphetamines, tramadol. They were also Hbs Ag, antiHCV, and HIV negative. All the mothers were receiving buprenorphine and there was no medication change. The women remained on their opioid maintenance therapy. Breastfeeding was encouraged.

Newborn outcomes included the following information: the way of delivery, sex (male/female), birth weight in grams, birth length in centimeters, physical anomalies, head/chest circumference in centimeters, Apgar score 1 minute / 5 minutes, gestational age (weeks), newborn length of hospital stay in days, breast feeding, the newborn's need for pharmacologic treatment after delivery.

The following instruments were used for testing: toxicological analyses in urine samples (fluorescence polarization immunoassay – FPIA); qualitative tests for buprenorphine and tramadol. All the 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. 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 the following: 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 were as follows: all the 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 were the following: patients who dropped out from the maintenance treatment with buprenorphine by their own volition; patients who did undergo regular check-ups, patients with negative buprenorphine test.

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

Descriptive statistics was done with the statistical program SPSS for Windows, Version 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

This study included nine pregnant women on treatment with buprenorphine for OUD. The mean age of these patients was 27.22 ± 2.58 years. Before treatment, five of the patients had heroin use disorder alone, three had polydrug use disorder, and one took methadone from the "black market." Two of them took opioid intravenously, but all were HbsAg, antiHCV, and HIV negative. It was the first pregnancy for all of them. Only one patient had spontaneous miscarriage after her first pregnancy, due to an 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 the included patients, the dose was slowly reduced and they finished the treatment with buprenorphine.

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

PAS – psychoactive substances

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 1 min. / 5 min.	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	/

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 2,991.11 ± 37 gm and the mean length was 49.44 ± 2.29 cm. None of the newborns had physical anomalies. 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. 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 at her mother's suggestion, 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, nine patients were treated with buprenorphine throughout their 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 to methadone treatment [1].

As far as the 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 a study by Farid et al. [5], where buprenorphine doses used to maintain the pregnant woman were variable, with a mean dose range of 5.3–18.7 mg/day. 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 2,991.11 ± 37 g and the mean length was 49.44 ± 2.29 cm. 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 g), birth length (10 studies: 49.4 cm), and head circumference (nine studies: 34 cm) [2, 7]. Coulson et al. [8] in one retrospective cohort study 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 greater length with low to moderate dose buprenorphine versus high dose methadone. Similar results were reported in national registry studies from the Czech Republic and Norway, with 333 and 235 women, respectively, using opioid maintenance treatment during pregnancy [9].

Findings in one study by Nguyen et al. [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 weight reported at 2.796 kg. Farid et al. [5] in their study reported that in most pregnancies birth weight, Apgar scores, head circumference, and body length were within normal ranges.

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 hospitalization 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.

The present study has some limitations. The presented patients were the only ones on maintenance treatment with buprenorphine at the University Clinic of Toxicology; this study included only nine 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 OUD. 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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Физичке карактеристике новорођенчади пренатално изложене бупренорфину – наша прва искуства

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САЖЕТАК

Увод/Циљ Бупренорфин је уопштено сличан а у неким случајевима бољи од метадона за мајку, фетус и новорођенчад. Циљ рада је процена неких физичких карактеристика новорођенчади пренатално изложених бупренорфину.

Методе У периоду од седам година, девет жена са болешћу зависности од опиоида лечено је бупренорфином током трудноће. Све труднице су подвргнуте интервјуу, клиничким испитивањима, биохемијским анализама, токсиколошком скринингу, одређивању вирусних маркера за хепатитис Б, Ц, ХИВ и редовно су контролисане 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. / 5 мин., гестацијска старост (недеља), дужина болничког боравка у данима, дојење, фармаколошки третман после порођаја.

Резултати Просечна порођајна тежина је 2991,13 ± 37 *g*; просечна порођајна дужина је 49,44 ± 2,29 *cm*; обим главе 33,11 ± 0,78 *cm*; обим груди 32,33 ± 1 *cm*; Апгар скор 8,22/9,22; гестацијска старост 38,77 ± 1,09 седмица; дужина болничког боравка 4,44 ± 1,13 дана. Сва новорођенчад била су здрава, без конгениталних аномалија.

Закључак Бупренорфин је сигуран и важан део свеобухватног третмана код трудница са болешћу зависности од опиоида. Лечење бупренорфином резултирало је ниским ризиком од превременог порођаја, нормалном порођајном тежином и дужином, обимом главе и груди, нормалним вредностима Апгар скора, кратким хоспитализацијама после порођаја.

Кључне речи: бупренорфин; трудноћа; новорођенчад; физичке карактеристике после порођаја