

Neonatal outcomes after fetal exposure to methadone and buprenorphine: national registry studies from the Czech Republic and Norway

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ABSTRACT

Background and Aims Opioid maintenance treatment (OMT) is recommended to opioid-dependent females during pregnancy. However, it is not clear which medication should be preferred. We aimed to compare neonatal outcomes after prenatal exposure to methadone (M) and buprenorphine (B) in two European countries. **Design** Nation-wide register-based cohort study using personalized IDs assigned to all citizens for data linkage. **Setting** The Czech Republic (2000–14) and Norway (2004–13). [Correction added after online publication on 26 April 2018: The Czech Republic (2000–04) corrected to (2000–14).] **Participants** Opioid-dependent pregnant Czech ($n = 333$) and Norwegian ($n = 235$) women in OMT who received either B or M during pregnancy and their newborns. **Measurements** We linked data from health registries to identify the neonatal outcomes: gestational age, preterm birth, birth weight, length and head circumference, small for gestational age, miscarriages and stillbirth, neonatal abstinence syndrome (NAS) and Apgar score. We performed multivariate linear regression and binary logistic regression to explore the associations between M and B exposure and outcomes. Regression coefficient (β) and odds ratio (OR) were computed. **Findings** Most neonatal outcomes were more favourable after exposure to B compared with M, but none of the differences was statistically significant. For instance, in the multivariate analysis, birth weight was $\beta = 111.6$ g [95% confidence interval (CI) = -10.5 to 233.6 and $\beta = 83.1$ g, 95% CI = -100.8 to 267.0] higher after B exposure in the Czech Republic and Norway, respectively. Adjusted OR of NAS for B compared with M was 0.94 (95% CI = 0.46–1.92) in the Norwegian cohort. **Conclusions** Two national cohorts of women receiving opioid maintenance treatment during pregnancy showed small but not statistically significant differences in neonatal outcomes in favour of buprenorphine compared with methadone.

Keywords Buprenorphine, health registries, methadone, neonatal outcomes, opioid maintenance treatment, prenatal exposure.

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Submitted 12 April 2017; initial review completed 7 June 2017; final version accepted 5 February 2018

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INTRODUCTION

Pregnant women with opioid dependence, according to the World Health Organization (WHO) guidelines for identification and management of substance use and substance use disorders in pregnancy, should be advised to continue or commence pharmacotherapy with either methadone or buprenorphine [1,2]. Such pharmacotherapy combined with psychosocial support is often called opioid maintenance treatment (OMT). However, while WHO

strongly recommends OMT during pregnancy, the same guidelines underscore that the quality of the evidence behind this recommendation is, to date, very low.

The most used medications for OMT are methadone (M), and buprenorphine (B), alone or in combination with naloxone (BN). M and B are both long-acting opioid agonists, but differ somewhat with respect to pharmacological properties [3]. While the WHO guidelines recommend M for pregnant opioid-dependent women, national recommendations for this patient group might

differ, and in some countries B is recommended as the OMT drug of choice [4,5]. In the United States, both M and B are considered as treatment options for pregnant women [6].

The first studies, in the 1970s, compared neonatal outcomes of children born to opioid-dependent women who received M treatment to that of children born to pregnant women using heroin [7–9]. Except for more severe neonatal abstinence syndrome (NAS), children exposed to M had better neonatal outcomes than children exposed to heroin but worse than children born to mothers in the general population [7]. B was approved as an OMT drug in 2000 in some European countries. In contrast to M, which is a full agonist, B is a partial agonist [10]. Thus, B may not be as good choice as M to treat the most severely addicted patients.

Two recently published systematic reviews and meta-analyses reported that prenatal exposure to B gave more favourable neonatal outcomes compared to M exposure [11,12]. However, in one study the authors also performed simulation analysis, suggesting that confounding by indication could explain some of the more favourable effects of B, and the authors stated that more evidence is needed to guide treatment choices [11].

Most previous studies of M versus B treatment during pregnancy were based on small samples [13–17]; some were not representative of the entire population of pregnant women who receive OMT [11,12], and many were based mainly on urban populations [18]. In contrast to most countries, both the Czech Republic and Norway have nation-wide health registries that use personalized identification number for all citizens; this makes linkage of registry data on individual and family levels possible [19]. Employing registry data allows us to study large unselected populations of pregnant OMT women from countries with different socio-economic and treatment settings.

Our aim was to compare neonatal outcomes from prenatal exposure to B versus M in the Czech Republic and Norway.

METHODS

Setting

Czech Republic

M became available for pregnant women at one treatment facility in 1997 [20], B in 2000 and BN in 2008 [21]. OMT treatment facilities have expanded gradually, from six facilities in 2000 [22] to 63 facilities in 2015. Of these, 13 were methadone centres providing M and B/BN; the rest provide B/BN only [23].

M is provided at OMT clinics only, but B and BN are available in pharmacies and may be prescribed by any physician [24]. M is provided free of charge at clinics, while B and BN is typically paid fully by the patients.

Norway

OMT became available nation-wide in 1998, first with M and later with B (2000) and BN (2007) [25]. M was recommended early as the first choice but, from 2005, B has been recommended as the first-line drug. OMT is organized through regional centres under the specialist health-care service, and to receive OMT patients must be included in the national OMT programme. OMT is free of charge. For most patients contact with specialist health care is ambulatory, and most pregnant women in OMT receive their OMT medication at pharmacies [26].

Health-care providers are obliged by law to report use of illicit drugs during pregnancy [27]. Repeated use may result in the woman being detained, with or without her consent, at clinics that specialize in treating pregnant women with substance use problems [28].

Data sources

We provide a short description of the registries used in this study; a more detailed description is provided elsewhere [19,26].

Czech Republic

National Register of Reproduction Health (NRRH). The NRRH have several subregistries, including the mothers at childbirth registry and the registry of newborns. The first includes information about the mothers during pregnancy, such as demographic and socio-economic information, information about alcohol, tobacco and illegal drug use during pregnancy and information about delivery. The latter includes information about the neonate, such as birth parameters, congenital malformations and death [29].

National Register of Addiction Treatment (NRAT). The NRAT includes information concerning patients who receive opioid maintenance treatment, e.g. date of initiation and termination of treatment and type of OMT drug [30,31].

Physicians are obliged by law to report data to NRRH and NRAT.

Norway

Medical Birth Registry of Norway (MBRN). MBRN is based on compulsory notification of every birth or late abortion from physicians or midwives attending the birth. The MBRN includes information concerning all births and late abortions from the 12th gestational week and onwards, and includes information concerning pregnancy and delivery; the neonate (gestational age, birth parameters, NAS, congenital malformations); demographic and socio-economic background of mothers; and also maternal tobacco smoking during pregnancy.

Norwegian Prescription Database (NorPD). The NorPD includes information about all prescription drugs, including OMT drugs, dispensed at pharmacies to patients in ambulatory care. The drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system [32]. Pharmacies are obliged by law to forward prescription data to NorPD.

Statistics Norway (SSB). From Statistics Norway we included information about maternal education. Educational institutions are obliged to report completed education on an individual level to SSB.

Linkage of registry data

Linkage of data between the registries was based on the personal identification numbers assigned to all individuals in the Czech Republic and Norway [19].

Study population and study period

The study population consisted of pregnant women in OMT and their children born during the study period: 2000–14 in the Czech Republic and 2004–13 in Norway.

Exposure to OMT drugs during pregnancy

Only M, B and BN are used as pharmacotherapy in OMT in the Czech Republic and Norway.

In the Czech Republic, data from the NRAT were used to identify which women were in OMT and, if so, which OMT drug they received.

In Norway, we used NorPD data to identify whether the women had used M (ATC code N07 BC02), B (N07 BC01) or BN (N07 BC51). Women who were dispensed OMT drugs from a pharmacy at least once during pregnancy were defined as using OMT drugs during pregnancy. More than 95% of all OMT women receive more than one prescription during pregnancy.

Some women switch from one substitution drug to another during pregnancy. There were no such cases in the Czech sample. In the Norwegian sample, women who switched between M and B ($n = 1$) during pregnancy were assigned into the M group; women who switched between BN and B ($n = 29$) were assigned into the BN group.

Outcomes

Neonatal outcomes were identified in the NRRH in the Czech data and in the MBRN in the Norwegian data.

Outcomes included: gestational age (based mainly on ultrasound examination or, if missing, the first day of the last menstrual period), preterm birth (< 37 weeks of gestation), anthropometric data (birth weight, length and head circumference), small for gestational age (SGA) [33], miscarriage (death of a fetus between gestational weeks 12 and 22), stillbirth (death of a fetus gestational

week 22 or later), NAS and Apgar scores < 7 at 1 and 5 minutes.

Other variables

We obtained information on socio-demographic variables, drug use and tobacco smoking from the NRRH in the Czech Republic and from the MBRN and Statistics Norway in Norway.

Analysis strategy and statistics

First, we analysed socio-demographic background and substance use during pregnancy for women who received pharmacotherapy with M, B or BN in the Czech Republic and Norway, respectively. Confidence intervals for proportions were calculated using the continuity-corrected score interval method [34].

Next, we presented neonatal outcomes, restricted to singleton births in both countries. Anthropometric data (except SGA) were restricted to term births (≥ 37 gestational weeks). Gestational age, SGA, NAS and Apgar scores were restricted to live births.

To control for relevant background characteristics, we performed linear regression for continuous dependent variables and binary logistic regression for categorical dependent variables. We adjusted for maternal age, marital status, education and tobacco smoking during pregnancy. We compared B to M, using M as the reference group. Unadjusted analyses in Norway were performed both in the total sample and in a sample restricted to the same study sample, as in the adjusted analysis.

Some of the neonatal outcomes were infrequent, and we only performed multivariate analysis of outcomes observed in more than four individuals. Statistical significance level was set to 0.05.

Statistical analyses were conducted using SPSS for Windows version 21.

Ethics

The study was approved by the Institutional Review Board of the General University Hospital in Prague (IRB00002705) and the Regional Committees for Medical and Health Research Ethics (REK, AE: 2012–222) and the Norwegian Data Inspectorate.

RESULTS

Background characteristics of women in OMT

A total number of 333 and 235 women used OMT drugs during pregnancy in the Czech Republic and Norway, respectively. Tables 1 and 2 illustrate background characteristics of pregnant women in OMT in the Czech Republic and Norway. In both countries, the main difference

Table 1 Socio-economic characteristics of women in opioid maintenance treatment during pregnancy in the Czech Republic.

	Methadone (M)			Buprenorphine (B)			Buprenorphine with naloxone (BN)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
Total number	158			154			21		
Age, years									
≤ 24	49	31.0	24.0–38.9	42	27.3	20.6–35.1	7	33.3	15.5–56.9
25–29	67	42.4	34.7–50.5	68	44.2	36.2–52.4	4	19.0	6.3–42.6
30–34	32	20.3	14.4–27.5	35	22.7	16.5–30.3	10	47.6	26.4–69.6
≥ 35	10	6.3	3.2–11.7	9	5.8	2.9–11.1	0	0.0	0.0–16.1
Marital status									
Not married	126	79.7	72.5–85.6	123	79.9	72.5–85.7	17	81.0	57.4–93.7
Married	28	17.7	12.3–24.8	18	11.7	7.3–18.1	3	14.3	3.8–37.4
Unknown	4	2.5	0.8–6.8	13	8.4	4.8–14.3	1	4.8	0.3–25.9
Education									
Primary	90	57.0	48.9–64.7	63	40.9	33.2–49.1	6	28.6	12.2–52.3
Secondary	59	37.3	29.9–45.4	84	54.5	46.3–62.5	11	52.4	30.3–73.6
University	0	0.0	0.0–2.3	1	0.6	0.3–4.1	3	14.3	3.8–37.4
Unknown	9	5.7	2.8–10.9	6	3.9	1.6–8.7	1	4.8	0.3–25.9
Occupation									
Unemployed	143	90.5	84.6–94.4	117	76.0	68.3–82.3	14	66.7	43.1–84.5
Employed	11	7.0	3.7–12.4	12	7.8	4.3–13.5	2	9.5	1.7–31.8
Unknown	4	2.5	0.8–6.8	25	16.2	11.1–23.2	5	23.8	9.1–47.6
Use of addictive substances during pregnancy									
Alcohol	8	5.1	2.4–10.1	9	5.8	2.9–11.1	0	0.0	0.0–16.1
Smoking	64	40.5	32.9–48.6	60	39.0	31.3–47.1	12	57.1	34.4–77.4
Illicit drugs	58	36.7	29.3–44.8	63	40.9	33.2–49.1	8	38.1	19.0–61.3
Deliveries by multiplicity									
Single	152	96.2	91.6–98.5	152	98.7	94.9–99.8	20	95.2	74.1–99.8
Twins and more	6	3.8	1.6–8.5	2	1.3	0.2–5.1	1	4.8	0.3–25.9

CI = confidence interval.

between the M and B groups were that women who received M had lower education than women who received B during pregnancy; the proportion with primary education in the Czech Republic was 57.0 versus 40.9% and in Norway was 83.2 versus 57.6% (Tables 1). However, in Norway a larger proportion of B women were younger, single and smoked tobacco than M women, but the differences were not significant.

Neonatal outcomes

Tables 3 and 4 show the neonatal outcomes after exposure to M, B or BN in the Czech Republic and Norway, respectively. In both countries, there were approximately the same numbers of children exposed to M and B. Only 20 and 33 of the neonates were exposed to BN in the Czech Republic and Norway, respectively. The mean gestational age was in the range of 38.3–39.5 weeks in all exposure groups in both countries. The mean gestational ages tended to be higher in Norway compared to in the Czech Republic and higher in B-exposed than in M-exposed in both countries. When we studied neonates born

at term (≥ 37 weeks of gestation), neonates exposed to M tended to have slightly lower mean values on all anthropometric parameters (weight, length and head circumference) in both countries compared to B exposure. In addition, in Norway, the proportion of SGA tended to be higher among M-exposed newborns. Very few pregnancies resulted in a miscarriage or stillbirth; no stillbirths were observed after B and BN exposure in both countries. The proportion with NAS was available only in Norway, where 54.7% of the M-exposed and 53.7% of the B-exposed newborns had NAS (Table 4). Twenty BN-exposed newborns in the Czech Republic did not have different neonatal outcomes than newborns exposed to M or B (Table 3).

Table 5 shows the results of linear and logistic regression analyses of neonatal outcomes comparing B with M in each country. In all analyses, except the SGA in the Czech Republic, the β and ORs were in the direction of more favourable outcomes in B-exposed newborns, but we observed no significant differences in neonatal outcomes in either the unadjusted or adjusted analyses between B- and M-exposed children in both countries.

Table 2 Socio-economic characteristics of women in opioid maintenance treatment during pregnancy in Norway.

	Methadone (M)			Buprenorphine (B)			Buprenorphine with naloxone (BN)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
Total number	101			99			35		
Age, years									
≤ 24	5	5.0	1.8–11.7	9	9.1	4.5–17.0	4	11.1	3.7–27.7
25–29	26	25.7	17.8–35.6	28	28.3	19.9–38.4	16	45.7	29.2–63.1
30–34	37	36.6	27.4–46.9	42	42.4	32.7–52.8	10	28.6	15.2–46.5
≥ 35	33	32.7	23.9–42.9	20	20.2	13.1–29.7	5	14.3	5.4–31.0
Marital status									
Not married	33	32.7	23.9–42.8	41	41.4	31.7–51.8	17	48.6	31.7–65.7
Married/living with partner	66	65.3	55.2–74.4	58	58.6	48.2–68.3	18	51.4	34.3–68.3
Unknown	<4			0	0.0	0.0–3.7	0	0.0	0.0–10.0
Education									
Primary	84	83.2	74.1–89.6	57	57.6	47.2–67.3	27	77.1	59.5–89.0
Secondary	13	12.9	7.3–21.4	39	39.4	29.9–49.8	7	20.0	9.1–37.5
University	<4			<4			<4		
Unknown	<4			<4			<4		
Smoking during pregnancy									
Yes	64	63.4	53.1–72.6	76	76.8	67.0–84.4	21	60.0	42.2–75.7
Unknown	29	28.7	20.4–38.7	12	12.1	6.7–20.6	6	17.1	7.2–34.3
Deliveries by multiplicity									
Single	99	98.0	92.3–99.7	97	98.0	92.2–99.7	33	94.3	79.5–99.0
Twins and more	<4			<4			<4		

CI = confidence interval; < 4 denotes fewer than four individuals in the group. Exact numbers are not shown because of regulation from the Registries.

Table 3 Birth outcomes of children of women in opioid maintenance treatment during pregnancy in the Czech Republic; singleton pregnancy.

	Methadone (M)		Buprenorphine (B)		Buprenorphine with naloxone (BN)	
Total number	152		152		20	
Gestational age ^a (weeks), mean (SD)	38.3	(2.6)	38.5	(2.7)	38.5	(1.89)
Birth weight ^b (g), mean (SD)	3017	(476)	3115	(453)	2897	(450)
Birth length ^b (cm), mean (SD)	48.1	(2.4)	48.6	(2.3)	47.8	(2.3)
Head circumference ^b (cm), mean (SD)	33.8	(1.8)	34.0	(1.6)	33.7	(1.7)
Caesarian section ^a						
Elective, n (%; CI)	5	(3.4; 1.3–8.1)	10	(6.6; 3.4–12.1)	3	(15.0; 4.0–38.9)
Acute, n (%; CI)	17	(11.2; 6.8–17.6)	22	(14.5; 9.5–21.3)	1	(5.0; 0.3–26.9)
Stillbirth, n (%; CI)	4	(2.6; 0.8–7.0)	0	(0.0; 0.0–2.4)	0	(0.0; 0.0–16.8)
Preterm birth ^a , n (%; CI)	25	(16.9; 11.4–24.1)	25	(16.4; 11.1–23.5)	4	(20.0; 6.6–44.3)
Small for gestational age ^a (SGA), n (%; CI)	19	(12.8; 8.1–19.6)	21	(13.8; 8.9–20.6)	3	(15.0; 4.0–38.9)
Apgar score ^a < 7 at 1 min						
Yes, n (%; CI)	13	(8.8; 5.0–14.9)	13	(8.6; 4.8–14.5)	2	(10.0; 1.8–33.1)
No, n (%; CI)	135	(91.2; 85.1–95.0)	139	(91.4; 85.5–95.2)	18	(90.0; 66.9–98.2)
Apgar score ^a < 7 at 5 min						
Yes, n (%; CI)	5	(3.4; 1.3–8.1)	2	(1.3; 0.2–5.2)	0	(0.0; 0.0–16.8)
No, n (%; CI)	143	(96.6; 91.9–98.7)	150	(98.7; 94.8–99.8)	20	(100; 83.2–100)

^aSingleton and live births; ^bsingleton births with gestational age ≥ 37 weeks. CI = confidence interval; SD = standard deviation.

DISCUSSION

In this observational study of two nation-wide cohorts, we investigated neonatal outcomes from prenatal exposure to

M and B during pregnancy. Overall, the findings were very similar in the two countries. The neonatal outcomes in the B groups were better, albeit not significantly, compared to the M groups.

Table 4 Birth outcomes of children of women in opioid maintenance treatment during pregnancy in Norway; singleton pregnancy.

	<i>Methadone (M)</i>	<i>Buprenorphine (B)</i>	<i>Buprenorphine with naloxone (BN)</i>
Total number	99	97	33
Gestational age ^b (weeks), mean (SD)	38.9 (1.9)	39.2 (2.4)	39.5 (1.7)
Birth weight ^a (g), mean (SD)	3268 (603)	3333 (437)	3325 (393)
Birth length ^a (cm), mean (SD)	48.7 (3.0)	49.3 (2.0)	49.0 (1.8)
Head circumference ^a (cm), mean (SD)	34.4 (1.5)	34.7 (1.6)	34.7 (1.2)
Abortion induced			
Yes, <i>n</i> (%; CI)	< 4	0 (0.0; 0.0–3.7)	< 4
No, <i>n</i> (%; CI)	97 (98.0; 92.2–99.6)	97 (100; 96.3–100)	32 (97.0; 82.5–99.8)
Miscarriage			
Yes, <i>n</i> (%; CI)	0 (0.0; 0.0–3.7)	< 4	0 (0.0; 0.0–10.6)
No, <i>n</i> (%; CI)	99 (100; 96.3–100)	95 (97.9; 92.0–99.6)	33 (100; 89.4–100)
Caesarian section ^b			
Elective, <i>n</i> (%; CI)	10 (10.3; 5.3–18.6)	12 (12.4; 6.8–21.0)	< 4
Acute, <i>n</i> (%; CI)	13 (13.4; 7.6–22.2)	9 (9.3; 4.6–17.3)	< 4
Stillbirth, <i>n</i> (%; CI)	< 4	0 (0.0; 0.0–3.7)	0 (0.0; 0.0–10.6)
Preterm birth ^b , <i>n</i> (%; CI)	9 (9.3; 4.6–17.3)	5 (5.2; 1.9–12.2)	< 4
Small for gestational age ^b (SGA), <i>n</i> (%; CI)	10 (10.3; 5.3–18.6)	5 (5.2; 1.9–12.2)	0 (0.0; 0.0–10.6)
Apgar score ^b < 7 at 1 min			
Yes, <i>n</i> (%; CI)	7 (7.4; 3.3–15.2)	5 (5.3; 2.0–12.5)	< 4
No, <i>n</i> (%; CI)	87 (92.6; 84.8–96.7)	89 (94.7; 87.5–98.0)	31 (96.9; 82.0–99.8)
Apgar score ^b < 7 at 5 min			
Yes, <i>n</i> (%; CI)	< 4	< 4	< 4
No, <i>n</i> (%; CI)	93 (98.9; 93.4–99.9)	93 (97.9; 91.9–99.6)	31 (96.9; 82.0–99.8)
Neonatal abstinence syndrome ^b			
Yes, <i>n</i> (%; CI)	52 (54.7; 44.2–64.9)	51 (53.7; 43.2–63.9)	17 (53.1; 35.0–70.5)
No, <i>n</i> (%; CI)	43 (45.3; 35.1–55.8)	44 (46.3; 36.1–56.8)	15 (46.9; 29.5–65.0)

CI = confidence interval; SD = standard deviation; < 4 denotes fewer than four individuals in the group. Exact numbers are not shown because of regulation from the Registries. ^aSingleton births with gestational age ≥ 37 weeks; ^bsingleton and live births.

A systematic review and meta-analysis concluded that B treatment, compared to M, during pregnancy seemed to have a lower risk of unfavourable birth outcomes, such as lower anthropometric data in the unadjusted analyses [12]. In our study, the B-exposed neonates born at term had higher birth weight (about 50–100 g) than the M-exposed group, but these differences were not significant. Apart from the statistical significance, the clinical perspective is also important. To put these observed differences into context, tobacco smoking reduces birth weight by approximately 200 g—a difference considered clinically relevant [35].

Some earlier studies showed a lower NAS prevalence after exposure to B compared to M [36,37]. We found no difference in prevalence of NAS in the M and B groups in the Norwegian sample. This is in line with findings in an RCT performed by Jones *et al.* [38], who reported no significant difference in prevalence of NAS in B and M groups in the adjusted analysis, although B-exposed newborns required less intensive NAS treatment than M-exposed newborns. A systematic review and a meta-analysis, where the unadjusted results from Jones *et al.* were also included, showed differences between M and B in unadjusted NAS treatment risk. However, the

authors point out that some of these differences may be due to confounding by indication, and when Jones *et al.* performed an adjusted analysis the differences disappeared [11]. Indeed, only few studies comparing the safety of B versus M on the neonate adjust for confounding [39].

A small group of women in the Czech sample received BN throughout pregnancy. The findings suggest that the neonatal outcomes in BN-exposed newborns were not different from those who were exposed to B or M. However, the confidence intervals in the BN group were wide because of the low number of exposed newborns. Our findings are in line with other studies that have looked at the safety of BN [16], suggesting that it may be a safe treatment alternative. Note that all existing studies on safety of BN use very small study samples.

Methodological considerations

As almost all women in OMT are registered in the national registries, our study had two national cohorts and selection bias is less of a problem in the current study compared to previous studies. Further, the size of the sample is a strength of our study [19], as the majority of previous

Table 5 Linear^a and binary logistic regression^b comparing buprenorphine to methadone during pregnancy in the Czech Republic and in Norway.

	Czech Republic <i>buprenorphine versus methadone (ref.)</i>		Norway <i>buprenorphine versus methadone (ref.)</i>	
	β	95% CI	β	95% CI
Gestational age ^c				
Unadjusted	0.16	−0.44 to 0.77	0.28	−0.33 to 0.90
Adjusted ^d	0.05	−0.68 to 0.59	0.48	−0.29 to 1.25
Birth weight ^e				
Unadjusted	98.4	−17.2 to 214.0	64.9	−91.0 to 220.8
Adjusted ^d	111.6	−10.5 to 233.6	83.1	−100.8 to 267.0
Birth length ^e				
Unadjusted	0.47	−0.12 to 1.06	0.56	−0.22 to 1.33
Adjusted ^d	0.45	−0.17 to 1.08	0.47	−0.35 to 1.29
Head circumference ^e				
Unadjusted	0.19	−0.31 to 0.69	0.36	−0.11 to 0.82
Adjusted ^d	0.12	−0.41 to 0.65	0.57	−0.04 to 1.18
	OR	95% CI	OR	95% CI
Preterm birth ^c				
Unadjusted	0.97	0.53 to 1.78	0.53	0.17 to 1.65
Adjusted ^d	0.92	0.48 to 1.74	0.73	0.16 to 3.36
SGA ^c				
Unadjusted	1.09	0.56 to 2.12	0.47	0.16 to 1.44
Adjusted ^d	1.07	0.52 to 2.21	0.83	0.22 to 3.20
Apgar score ^c < 7 at 5 min				
Unadjusted	0.38	0.07 to 2.00	NA	NA
Adjusted ^d	0.20	0.02 to 2.13	NA	NA
Neonatal abstinence syndrome ^c				
Unadjusted	NA	NA	0.96	0.54 to 1.70
Adjusted ^d	NA	NA	0.94	0.46 to 1.92

^a β (regression coefficients) from linear regression for gestational age, birth weight, length and head circumference; ^bodds ratios (ORs) from binary logistic regression of having child birth small for gestation age (SGA), premature birth and Apgar score < 7, neonatal abstinence syndrome (Norway); ^csingleton and live births; ^dadjusted for age, marital status, education, smoking; ^esingleton births with gestational age \geq 37 weeks. Data were not available (NA) for the Czech Republic sample; there were fewer than four individuals in the Norwegian sample.

studies on neonatal outcomes included small samples. The two cohorts represent different parts of Europe and are heterogeneous, which may increase the generalizability of the results.

Using information from the registries reduces the risk of recall bias, and studies based on data from health registries can identify and follow more women in OMT over time than can feasibly be included in clinical samples. There is an indication that some previous studies may have been affected by selection bias. For example, Welle-Strand and colleagues [27] based their study on a Norwegian clinical sample from 1996 to 2009, while our register study used data starting from 2004. Approximately two-thirds of the women from the clinical study were also included in our study. When comparing differences after M and B exposure in birth weights, not restricted to term pregnancies in any of the studies, these differed notably. In the study by Welle-Strand and

colleagues the difference was 310 g. In contrast, our study showed a difference of only 53 g (not shown in the table, where we show only the birth weight restricted to term pregnancies). Including an almost complete national sample of OMT-exposed newborns gave a more precise mean value of birth weight than did the clinical sample. The comparison between these studies shows how selection may give rise to imprecise estimates.

Another possible explanation for the observed difference in birth weight between the clinical study by Welle-Strand and our registry study is that confounding by indication is more of a problem in the clinical study. In Norway, the criteria for OMT used to be very strict; only the most severely addicted women qualified for OMT. Since then, the criteria have become less strict, and B is now the recommended treatment for pregnant women who are opioid-dependent. A great proportion of the women included in the first years of the Welle-Strand study were probably

more severely addicted than many women in our study, as they qualified for the strict OMT regimen, and probably received M because this was the recommended drug. This might have induced confounding by indication; newborns exposed to M probably had more severely addicted mothers than newborns exposed to B.

Because M is a full opioid agonist, pregnant women who receive M under today's recommendations are typically heavier drug users than women treated with the partial agonist B. In the Czech Republic, opioid-dependent women treated with B are probably also in a better socio-economic situation compared to women treated with M, as they must pay a substantial amount of money for B and M is free of charge. Adjusting for variables representing socio-economic status tended to decrease the estimates very slightly in the Czech Republic. M women in Norway are probably also heavier drug users than B women. However, in the Norwegian sample a higher proportion of B women smoked and were single compared to M women. These factors may contribute to the slight increase in the estimates after adjustment. A limitation with using registry data is that the registries include fewer confounding factors than do clinical studies. Some important information is under-reported, or reported in insufficient format in the registries, e.g. use of alcohol, tobacco and illicit drugs in the Czech sample [29] and smoking in the Norwegian sample, or missing, e.g. use of alcohol and illicit drugs in Norwegian sample. Further, information on nutrition, infections during pregnancy and the women's body mass index (BMI) is lacking. Missing values in any of the maternal background variables reduce the sample size in the multivariate regression analyses and may introduce selection bias. In this study, this was relevant for the smoking variable.

Only information concerning prescription drugs dispensed to out-patients in Norway is included in NorPD. Thus, pregnant women receiving OMT in residential treatment were not included in our OMT groups. We assume this is true for a limited number of cases [26].

Multiple pregnancies have an effect on several neonatal outcomes. In our study, therefore, only singleton pregnancies were included in the analysis of the neonatal outcomes.

Even though our samples of pregnant women in OMT are among the largest to date they are still relatively small, resulting in difficulty when studying rare outcomes such as stillbirths and miscarriages. There was a tendency in many of the outcomes in both countries for B to perform better than M, but the differences were not statistically significant. If these tendencies are real, larger sample sizes are needed.

CONCLUSION

Although B exposure resulted in more favourable neonatal outcomes compared to M, the differences were not

significant and the tendencies observed might possibly still be attributed to residual confounding.

Declaration of interests

None.

Acknowledgements

This study was supported by the Ministry of Health of the Czech Republic, grant no. 16-28157A, the Grant Agency of the Czech Republic grant no. 14-07822S and the Charles University institutional support no. Progres Q06/LF1. The Scandinavian cohort study has received grants from the Norwegian Research Council, grant no. 240197/H10.

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