Birth and Neonatal Outcomes Following Opioid Use in Pregnancy: A Danish Population-Based Study

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Supplementary Issue: Harm to Others from Substance Use and Abuse

ABSTRACT

BACKGROUND: Few population-based data exist on birth outcomes in women who received opioid maintenance treatment during pregnancy. We therefore examined adverse birth outcomes in women exposed to methadone or buprenorphine during pregnancy and the risk of neonatal abstinence syndrome (NAS) among neonates exposed to buprenorphine, methadone, and/or heroin *in utero*.

PATIENTS AND METHODS: This study included all female Danish residents with a live birth or a stillbirth from 1997 to 2011. We identified the study population, use of opioids and opioid substitution treatment, birth outcomes, and NAS through medical registers. Birth outcomes included preterm birth (born before 38th gestational week), low-birth weight (LBW) (<2,500 g, restricted to term births), small for gestational age (SGA) (weight <2 standard deviations from the sex- and gestational-week-specific mean), congenital malformations, and stillbirths. We used log-binomial regression to estimate the prevalence ratio (PR) for birth outcomes.

RESULTS: Among 950,172 pregnancies in a total of 571,823 women, we identified 557 pregnancies exposed to buprenorphine, methadone, and/or heroin (167 to buprenorphine, 197 to methadone, 28 to self-reported heroin, and 165 to combinations). Compared with nonexposed pregnancies, prenatal opioid use was associated with greater prevalence of preterm birth (PR of 2.8 (95% confidence interval (CI), 2.3–3.4)), LBW among infants born at term (PR of 4.3 (95% CI, 3.0–6.1)), and being SGA (PR of 2.7 (95% CI, 1.9–4.3)). Restricting the analyses to women who smoked slightly lowered these estimates. The prevalence of congenital malformations was 8.3% in opioid-exposed women compared with 4.2% in nonexposed women (PR of 2.0 (95% CI, 1.5–2.6)). The risk of NAS ranged from 7% in neonates exposed to buprenorphine only to 55% in neonates exposed to methadone only or to opioid combinations.

CONCLUSION: The maternal use of buprenorphine and methadone during pregnancy was associated with increased prevalence of adverse birth outcomes, and this increase could only be explained to a smaller extent by increased prevalence of smoking. The risk of NAS was eight-fold higher in methadone-exposed neonates than that in buprenorphine-exposed neonates, but this difference may at least partly be explained by differences in underlying indications (analgesic versus opioid maintenance treatment) between the two groups.

KEYWORDS: drug safety, pregnancy, opioid maintenance treatment, epidemiology

SUPPLEMENT: Harm to Others from Substance Use and Abuse

CITATION: Nørgaard et al. Birth and Neonatal Outcomes Following Opioid Use in Pregnancy: A Danish Population-Based Study. *Substance Abuse: Research and Treatment* 2015:9(S2) 5–11 doi: 10.4137/SART.S23547.

TYPE: Original Research

RECEIVED: July 02, 2015. **RESUBMITTED:** September 03, 2015. **ACCEPTED FOR PUBLICATION:** September 07, 2015.

ACADEMIC EDITOR: Gregory Stuart, Editor in Chief

PEER REVIEW: Five peer reviewers contributed to the peer review report. Reviewers' reports totaled 2,719 words, excluding any confidential comments to the academic editor.

FUNDING: None of the authors reported receiving fees, honoraria, grants, or consultancies. The Department of Clinical Epidemiology is, however, involved in studies with funding from various companies, including Schering Plough and Reckitt Benckiser Pharmaceuticals, given as research grants to (and administered by) Aarhus University. The authors confirm that the funder had no influence over the study design, content of the article, or selection of this journal.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

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Introduction

Around 33,000 illicit drug users aged 15–64 years are estimated to live in Denmark, of whom around 11,000 are using cannabis only and 13,000 (corresponding to 3.6/1,000 inhabitants) are using intravenous opioids.[1] The majority of women with opioid abuse are of childbearing age.[2] Opioids cross the placenta, and use of opioids during pregnancy increases the risk of adverse birth outcomes and perinatal complications.[3,4] All commonly used opioids can produce neonatal abstinence syndrome (NAS), which consists of serious withdrawal symptoms necessitating neonatal intensive care.[5–7] In addition, women with opioid abuse may have unhealthier lifestyle than women without opioid use. Among pregnant women in opioid agonist maintenance treatment, the prevalence of smoking is four times higher than that of the general population of pregnant women and smoking may additionally compromise birth outcomes.[8]

Treatment with methadone has been the standard of care for pregnant women with opioid dependence since the early 1970s.[9] Methadone maintenance treatment given during pregnancy enhances compliance with obstetrical care and is associated with improved neonatal outcome, including higher birth weight compared with continued use of heroin during pregnancy.[4] Methadone treatment during pregnancy is, however, also known to induce NAS.[5,10]

Buprenorphine is an alternative to methadone opioid-dependent treatment.[11] Buprenorphine-exposed neonates have

less severe NAS than methadone-exposed neonates, but findings regarding the rates of NAS are inconsistent.[6,12–16] To examine the birth and neonatal outcomes following the use of buprenorphine, methadone, and/or heroin during pregnancy, we conducted a nationwide study including all births in Denmark from 1997 to 2011.

Methods

Study population and design. We conducted a nationwide prevalence study in Denmark within a population of 5.4 million inhabitants. We included all pregnant women who during the period 1997–2011 gave a live birth or a stillbirth after the 20th week of gestation. The women were identified through the Danish Medical Birth Registry,[17] which contains computerized records of all births in Denmark since January 1, 1973. Data were recorded by the midwives or the physicians attending the deliveries. The registry includes information on maternal age, parity, multiplicity of gestation, birth weight, gestational age, self-reported maternal smoking status, and delivery. We obtained information on exposure by combining data from the Danish Register of Medicinal Product Statistics[18] and from the Registry of Drug Abusers Undergoing Treatment.[19] We linked all data using the 10-digit civil registration number (the CPR number) which is a unique identifier assigned, since 1968, to all Danish residents by the Central Office of Civil Registration and used in all Danish healthcare registries.[20,21]

Data on opioid use. From the Danish Register of Medicinal Product Statistics, we retrieved all records of prescriptions for buprenorphine and methadone used by pregnant women in the period from 30 days preconception to delivery. This registry contains information on the total sales of medicinal products in Denmark since 1994, including data on all prescriptions for drugs dispensed from all Danish pharmacies. Data include the CPR number, information on the dispensed drug (Anatomical Therapeutic Chemical (ATC) classification, name, package size, formulation, and quantity), and date of dispensing. We used the ATC codes N02 AE01, N07BC01, and N07BC51 to identify buprenorphine use and N07BC02 to identify methadone use.

Information on the abusers enrolled in drug treatment has been reported to the National Board of Health since January 1, 1996. Treatments offered at different Danish treatment centers include gradual reduction of the addictive drug and substitute treatment, and the treatment can be based on either inpatients or outpatients. Approximately 10–20% of treatment institutions are privately funded, while the majority are public institutions. All public institutions are required to report information to the Danish Registry of Drug Abusers Undergoing Treatment. The reporting for private institutions is voluntary. All reporting takes place electronically. The registry provides national data for both national surveillance and surveillance in connection with the pan-European cooperation in the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Data include the CPR number of the person under treatment, municipality of residence, nationality, socioeconomic characteristics (education, income, housing, marital status, children, etc.), and the main substance of abuse; drugs taken in the past month as indicator variables for prescribed methadone, illegal methadone, buprenorphine, heroin, morphine, and other opioids; age at first intake; mode of intake (injection, smoking, etc.); date of treatment; type of stay (outpatient or inpatient); and type of treatment, if any (dedicated codes for methadone, buprenorphine, substance-free treatment, and others).

In order to identify pregnancies exposed to the opiates of interest, we identified records with main substance of abuse being recorded as use of methadone (illegal or prescribed), buprenorphine (illegal or prescribed), heroin, morphine, or other opiates. Furthermore, we identified women under treatment for whom the substitute treatment was recorded as either methadone or buprenorphine. Because the exact date of use of illegal drugs is not recorded in the registry, the date of treatment was considered the day of use.

We classified drug use based on the date of filling a relevant prescription or having a relevant visit recorded in the Registry of Drug Abusers Undergoing Treatment as anytime during pregnancy (from 30 days before conception to delivery), use in first trimester (from 30 days preconception to 12th completed week of gestation), and use in third trimester (from >28 completed weeks of gestation to delivery).

Outcome data. Through the Danish Medical Birth Registry, we retrieved information on birth weight, gestational age, and stillbirth. We defined low-birth weight (LBW) as a birth weight <2,500 g restricted to infants born at term. Preterm birth was defined as birth before 37 full gestational weeks, and very preterm birth as birth before 30 full gestational weeks. Small for gestational age (SGA) was defined as birth weight <2 standard deviations from the sex- and gestational-week-specific mean values. We defined low Apgar scores as those <7 at 5 minutes. Stillbirth was defined as a record of a child born dead after 20th gestational week.

We retrieved data on congenital malformations from the Danish National Registry of Patients. This registry was established in 1977, and visits at outpatient clinics at hospitals have been included since 1995. Data include dates of admission and discharge, surgical procedures, and up to 20 discharge diagnoses coded by medical doctors at discharge according to the *International Classification of Diseases*, 10th revision (ICD-10) since 1994. The codes for malformations are Q00–Q99. We only included malformations registered during the first year of life. We excluded diagnoses of congenital dislocation of the hip (ICD-10 code: Q65) due to the expected poor validity of these diagnoses.

We recorded NAS if the infant had a hospital record carrying ICD-10 codes P96.1 or P96.2 within the first 30 days of life.

We additionally recorded maternal age at delivery, parity (defined as the total number of births, live or still, including

present birth), multiplicity of gestation, and self-reported smoking status (yes/no).

For descriptive purposes, we also recorded contacts (admissions or emergency room or outpatient clinic visits at hospitals) due to opioid intoxication from the Danish National Patient Registry (DNPR) (ICD-10 codes: T40.0, T40.4, or F11.x) for the period from 30 days before conception to delivery.

Statistical analysis. We compared, according to the substance use, the prevalence of preterm birth, very preterm birth, LBW, very LBW, SGA, Apgar score <7 at five minutes, and stillbirth. In addition, we examined the prevalence of congenital malformations with respect to substance use during the first trimester (from 30 days preconception to 12th completed week of gestation). For the outcome of NAS, we examined the substance use during the third trimester (from >28 completed weeks of gestation to delivery). We used log-binomial regression to estimate the prevalence ratios (PRs) of preterm birth, very preterm birth, LBW, Apgar score <7 at five minutes, and stillbirth, following opioid exposure (any opioid, buprenorphine, methadone, heroin, and combinations) anytime during pregnancy. To account for potential correlation when women contributed with more than one birth, we used generalized estimating equation (GEE). Pregnancies with no record of opioid use were the reference group for all comparisons. Similarly, we used log-binomial regression and GEE to compute PR of congenital malformations, following opioid exposure in the first trimester. To address confounding by smoking, we reanalyzed data restricting the population to pregnant women who reported smoking during pregnancy. In additional analyses, we restricted the exposure to only women with a record in the Registry of Drug Abusers Undergoing Treatment and we also restricted the study population to singleton pregnancies. All analyses were done using the SAS 9.3 software. This study was approved by the Danish Data Protection Agency (Jr number: 2013-41-1789).

Results

Descriptive data. Of the 950,172 pregnancies, 557 pregnancies (564 infants of which 550 were singletons) could be identified as exposed to any of the opioids under study, based on the information combined from the prescription records and from the Registry of Drug Abusers Undergoing Treatment.

Characteristics of the pregnancies according to exposure are shown in Table 1. The maternal age did not differ between overall exposed and unexposed pregnancies. The median age was 30.0 years (quartiles, 26.4–33.9) in exposed pregnant women and 30.2 years (quartiles, 27.0–33.6) in unexposed pregnant women. Yet, pregnant women who used heroin but did not receive any maintenance treatment were slightly younger with a median age of 25.9 years (quartiles, 22.3–31.4). Smoking during pregnancy was more often reported in exposed pregnancies than in unexposed pregnancies, 72,5% of any of the exposed pregnancies versus 17.6% of unexposed pregnancies. Among the 557 opioid-exposed pregnant women, 266 (47.8%) had a previous hospital contact (admission, emergency room visit, or visit at a hospital outpatient clinic) due to opioid intoxication compared with 335 (<0.1%) of opioid-unexposed pregnant women. The prevalence of a hospital contact due to opioid intoxication during pregnancy varied by exposure status from 10.8% in buprenorphine-exposed women to 59.9% in methadone-exposed women.

Of the 557 exposed pregnancies, 167 (30.0%) had buprenorphine as the only recorded opioid (163 were identified by at least one filled prescription and 4 were identified in the Registry of Drug Abusers Undergoing Treatment). Methadone as the only recorded opioid was found in 197 pregnancies (35.4%) (167 identified by a filled prescription and 79 were identified in the Registry of Drug Abusers Undergoing Treatment). In total, 28 (5.0%) women recorded in the Registry of Drug Abusers Undergoing Treatment reported that they used heroin as the only opioid but did not receive any treatment with either buprenorphine or methadone, while the remaining 165 (29.6%) reported that they used the combinations of opioids.

Risk estimates. Of the 950,172 pregnancies, 4,052 (0.4%) ended in a stillbirth. Of these stillbirths, six had been exposed to opioids (1.1% of all opioid exposed).Among the 946,126 pregnancies in the study population resulting in a live birth, median gestational age at birth in pregnancies with no record of substance use was 40 weeks (quartiles, 39–41) compared with a median gestational week of 39 weeks (quartiles, 38–40) in buprenorphine-exposed pregnancies, 38 weeks (quartiles, 37–40) in methadone-exposed pregnancies, 40 weeks (quartiles, 39–40) in heroin-exposed pregnancies, and 39 weeks (quartiles, 38–40) in pregnancies exposed to other combinations. The corresponding median (quartiles) values for birth weight in grams were 3,530 (3,180–3,880) in unexposed infants, 3,295 (2,750–3,708) in buprenorphine-exposed infants, 2,985 (2,500–3,340) in methadone-exposed infants, 3,250 (2,873–3,639) in heroin-exposed infants, and 3,050 (2,687–3,400) in infants exposed to opioid combinations.

Among opioid-exposed infants, 46 had at least one congenital malformation (Table 2). These infants had 68 different types of malformations recorded in total. The most common diagnoses were atrial and ventricular septal defects that combinedly accounted for almost one-third of the congenital malformations accounted for (data not shown).

All opioid use was associated with the greater prevalence of preterm delivery (PR of 2.8 (95% confidence interval (CI), 2.3–3.4)), LBW restricted to full-term births (PR of 4.3 (95% CI, 3.0–6.1)), and being SGA (PR of 2.7 (95% CI, 1.8–4.1)) compared with the prevalence in the general population (Tables 2 and 3). A similar pattern was seen for all exposure groups (Table 3). Still, the risk of having an Apgar score <7 at five minutes did not seem to be increased when comparing any exposure to an unexposed group (PR of 0.7 (95% CI, 0.2–2.3)).

Table 1. Characteristics of pregnancies according to the use of opioids during pregnancy, which was further classified as any recorded opioid exposure or recorded exposure to only buprenorphine, only methadone, treatment for self-reported heroin use only (without receiving buprenorphine or methadone), or combinations of opioid use. Information on illicit drug use in pregnant women without any contact to a treatment facility was not available and thus not included.

	UNEXPOSED		ANY EXPOSURE		BUPRENORPHINE ALONE		METHADONE ALONE		SELF-REPORTED HEROIN USE ONLY		OTHER COMBINATIONS	
	N	%	N	%	N	%	N	%	N	%	N	%
Overall	949,615	100.0	557	100.0	167	100.0	197	100.0	28	100.0	165	100.0
Parity												
1	404,330	42.6	236	42.4	63	37.7	80	40.6	22	78.6	71	43.0
2	345,205	36.4	186	33.4	57	34.1	69	35.0	6	21.4	54	32.7
3+	179,862	18.9	117	21.0	43	25.7	42	21.3	–	–	32	19.4
Missing	20,218	2.1	18	3.2	4	2.4	6	3.0	–	–	8	4.8
Maternal age, years												
≤25	171,242	18.0	120	21.5	31	18.6	32	16.2	14	50.0	43	26.1
26–30	354,249	37.3	188	33.8	52	31.1	61	31.0	6	21.4	69	41.8
31–34	260,084	27.4	135	24.2	47	28.1	51	25.9	5	17.9	32	19.4
>34	164,040	17.3	114	20.5	37	22.2	53	26.9	3	10.7	21	12.7
Smoking in pregnancy												
No	752,731	79.3	118	21.2	74	44.3	35	17.8	3	10.7	6	3.6
Yes	167,316	17.6	404	72.5	85	50.9	148	75.1	22	78.6	149	90.3
Missing	29,568	3.1	35	6.3	8	4.8	14	7.1	3	10.7	10	6.1
Multifetal gestation												
No	929,404	97.9	550	98.7	164	98.2	193	98.0	28	100.0	165	100.0
Yes	20,211	2.1	7	1.3	3	1.8	4	2.0	–	–	–	–
Previous hospital contact due to opioid intoxication												
No	949,280	100.0	291	52.2	149	89.2	79	40.1	15	53.6	48	29.1
Yes	335	<0.1	266	47.8	18	10.8	118	59.9	13	46.4	117	70.9

However, among infants exposed prenatally to methadone, the risk of low Apgar score was increased two-fold (Table 3). Except for women who reported exposure to heroin only but received no maintenance treatment, all other recorded data on substance use were associated with a 1.6–2.4-fold increase in the prevalence of congenital malformations compared with the background level (Table 3).

The 30-day risk of NAS was elevated among all neonates with recorded prenatal opioid exposure varying from 6.6% in those exposed to buprenorphine to 54.9% in those exposed to methadone (Table 2). Among unexposed infants, 530 (0.1%) had a diagnosis of NAS.

Restricting the analyses to pregnant women who reported smoking during pregnancy generally lowered the PRs of the various outcomes (Table 4), most notably for being SGA. Still, the prevalence of preterm birth, LBW, and congenital malformations was more than two-fold higher in smoking women with the concomitant use of opioids than that in smoking women without the use of opioids.

The restriction of opioid exposure to the 264 pregnancies in women who were registered as drug abusers undergoing treatment slightly accentuated the relative estimates. The PR for preterm delivery was 3.1 (95% CI, 2.4–4.0), PR for LBW among full-term births was 5.7 (95% CI, 3.6–8.8), PR for being SGA was 4.1 (95% CI, 2.6–6.4), and PR for congenital malformations was 1.8 (95% CI, 1.2–2.7). A total of 142 (53.8%) infants' mothers registered as drug abusers undergoing treatment had a NAS diagnosis.

Restriction to singletons did not substantially change the estimates (data not shown).

Discussion

This study, based on >500 opioid-exposed pregnancies, found that the maternal use of buprenorphine and methadone during pregnancy was associated with the increased prevalence of adverse birth outcomes. This increase could only slightly be explained by the increased prevalence of smoking in women who use opioids.

It is important to acknowledge the study weaknesses when interpreting these results. To measure the exposure to opioids, we combined prescription data and data from the Registry of Drug Abusers Undergoing Treatment. Our study

Table 2. Prevalence of the various outcomes among pregnancies ending in a live birth according to the use of any opioids during pregnancy. The use of opioids was additionally classified as recorded exposure to only buprenorphine, only methadone, treatment for self-reported heroin use only (without receiving any buprenorphine or methadone treatment), or combinations of reported opioid use. Information on illicit drug use in pregnant women without any contact to a treatment facility was not available.

	UNEXPOSED		ANY OPIOID EXPOSURE		BUPRENORPHINE		METHADONE		SELF-REPORTED HEROIN USE		OTHER COMBINATIONS	
	N	%	N	%	N	%	N	%	N	%	N	%
Overall	945,569	100.0	551	100.0	167	100.0	193	100.0	28	100.0	163	100.0
Preterm birth (<37 weeks)												
No	890,807	94.2	457	82.9	142	85.0	152	78.8	26	92.9	137	84.0
Yes	54,348	5.7	94	17.1	25	15.0	41	21.2	2	7.1	26	16.0
Missing	414	0.0	–	–	–	–	–	–	–	–	–	–
Very preterm birth (<30 weeks)												
No	940,524	99.5	546	99.1	165	98.8	190	98.4	28	100.0	163	100.0
Yes	4,631	0.5	5	0.9	2	1.2	3	1.6	–	–	–	–
Missing	414	0.0	–	–	–	–	–	–	–	–	–	–
Low birth weight* (<2500 g)												
No	875,118	98.5	426	93,4	139	97,9	137	90.7	25	96,2%	125	90.6
Yes	13,074	1,5	30	6.6	3	2,1	14	9.3	–	–	13	9.4
Missing	2,615	0.3	1	0.2	0	0	1	0.6	–	–	0	0.0
Small for gestational age												
No	923,553	97.7	520	94.4	162	97.0	184	95.3	25	89.3	149	91.4
Yes	16,499	1.7	27	4.9	4	2.4	7	3.6	3	10.7	13	8.0
Missing	5,517	0.6	4	0.7	1	0.6	2	1.0	–	–	1	0.6
Apgar score <7 at 5 minutes												
No	929,837	98.3	530	96.2	164	98.2	182	94.3	27	96.4	157	96.3
Yes	7,173	0.8	3	0.5	–	–	3	1.6	–	–	–	–
Missing	8,559	0.9	18	3.3	3	1.8	8	4.1	1	3.6	6	3.7
Neonatal abstinence syndrome												
No	945,039	99.9	340	61.7	156	93.4	87	45.1	23	82.1	74	45.4
Yes	530	0.1	211	38.3	11	6.6	106	54.9	5	17.9	89	54.6
Congenital malformation												
No	905,635	95.8	505	91.7	153	91.6	173	89.6	27	96.4	152	93.3
Yes	39,934	4.2	46	8.3	14	8.4	20	10.4	1	3.6	11	6.7

Note: *Restricted to infants born at term.

thus included women who filled a prescription for any of the drugs of interest or had contact to a treatment facility. We had no method of identifying women with an illicit use of opioids who were not undergoing treatment. According to the 2012 Danish report (2011 data) to the EMCDDA, an estimated 13,000 active intravenous drug users were living in Denmark in 2004–2008. Between half and two-third were unknown to the treatment system.[1] It is thus likely that we have misclassified some of the exposed women as unexposed, which would bias our relative estimates toward the null. Still, <0.1% of unexposed women had a previous hospital contact due to opioid intoxication compared with nearly half of the exposed women. Also, <0.1% of the unexposed neonates had a diagnosis of NAS. Thus, the bias on the relative estimates should be minor. Moreover, pregnant women using opioid who were incorrectly classified as unexposed in our study are not likely to have a lower rate of adverse pregnancy outcomes than the general pregnant population. Therefore, the lack of completeness of exposure status cannot explain our findings of an increased risk of adverse birth outcomes among opioid-exposed women. Data on malformations were obtained from a patient registry, where data were entered by trained medical staff. Validation studies have shown high quality of these diagnoses, with the misclassification rates of 11.8% for overall congenital malformations and 12.0% for congenital cardiac malformations.[22,23] Still, infants exposed to opioids could receive more medical attention at birth to monitor signs for NAS, and such potential surveillance bias could explain at

Table 3. PRs of the various outcomes and 95% CIs for users of opioids. Reference is women without the use of opioids during pregnancy.

TYPE OF OPIOID	PRETERM BIRTH	VERY PRETERM BIRTH	LOW BIRTH WEIGHT*	SMALL FOR GESTATIONAL AGE	LOW APGAR SCORE	CONGENITAL MALFORMATIONS
Any opioid use	2.8 (2.3–3.4)	1.8 (0.7–4.4)	4.3 (3.0–6.1)	2.7 (1.8–4.1)	0.7 (0.2–2.3)	2.0 (1.5–2.6)
Buprenorphine	2.4 (1.6–3.5)	2.4 (0.6–9.7)	0.9 (0.2–3.6)	1.4 (0.4–4.2)	–	2.0 (1.2–3.2)
Methadone	3.5 (2.6–4.7)	2.9 (0.8–10.1)	6.3 (3.8–10.5)	2.0 (0.9–4.3)	2.1 (0.7–6.6)	2.4 (1.6–3.7)
Self-reported heroin use	1.3 (0.4–4.5)	–	2.7 (0.4–17.7)	6.1 (2.1–17.8)	–	0.9 (0.1–5.7)
Combinations	2.7 (1.8–3.8)	–	5.9 (3.4–10.2)	4.5 (2.6–7.8)	–	1.6 (0.9–2.8)

Note: *Restricted to infants born at term.

Table 4. PRs of the various outcomes and 95% CIs for users of opioids who also smoked during pregnancy. Reference is women without the use of opioids during pregnancy who smoked during pregnancy.

TYPE OF OPIOID	PRETERM BIRTH	VERY PRETERM BIRTH	LOW BIRTH WEIGHT*	SMALL FOR GESTATIONAL AGE	LOW APGAR SCORE	CONGENITAL MALFORMATIONS
Any opioid use	2.4 (1.9–3.0)	1.3 (0.4–4.0)	2.7 (1.9–3.9)	1.5 (1.0–2.3)	1.0 (0.3–3.0)	1.9 (1.4–2.7)
Buprenorphine	1.7 (0.9–3.1)	–	–	1.3 (0.4–3.8)	–	1.9 (0.9–3.8)
Methadone	3.4 (2.5–4.6)	3.6 (1.2–10.9)	4.4 (2.7–7.2)	1.3 (0.6–2.8)	2.7 (0.9–8.2)	2.5 (1.6–4.1)
Self reported heroin	1.3 (0.4–4.8)	–	1.7 (0.3–11.4)	1.3 (0.2–8.4)	–	1.0 (0.2–7.0)
Combinations	2.1 (1.4–3.1)	–	3.3 (1.9–5.7)	1.8 (1.0–3.5)	–	1.6 (0.9–2.8)

Note: *Restricted to infants born at term.

least a part of the increased prevalence of malformations associated with opioid exposure.

Our findings of a two-to-three-fold increased prevalence of preterm birth, being SGA, and congenital malformations are very similar to findings from Ireland based on 61,030 singleton births, of which 618 were exposed to maternal methadone use during pregnancy.[10] In this study, methadone exposure was associated with an increased risk of very preterm birth (adjusted odds ratio (aOR), 2.47; 95% CI, 1.40–4.34), being SGA (aOR, 3.27; 95% CI, 2.49–4.28), and diagnosis of a major congenital anomaly (aOR, 1.94; 95% CI, 1.10–3.43). Our study thus demonstrated that this increased prevalence was not confined to methadone exposure, as we found buprenorphine exposure to be associated with similar high prevalence.

The finding of a higher risk of NAS in methadone-exposed women than that in buprenorphine-exposed women corresponds with previous findings. Similar to our findings, a smaller study including 62 mother–neonate dyads from North Carolina, USA, found that the use of methadone was followed by a >50% risk of NAS.[6] In the US study, the use of buprenorphine was followed by a 25% risk of NAS in the neonate, which is higher than the <7% risk we found. Yet, a cohort study from Norway including 90 pregnant women in maintenance treatment with methadone and 49 in treatment with buprenorphine found similar risks of NAS (58% versus 60%) in the two groups.[16] A major weakness of our study is that the use of prescription data to identify the users of buprenorphine did not allow us to distinguish between prescriptions for analgesic purposes only and prescriptions to opioid-dependent women. It is likely that buprenorphine to a larger extent than methadone was prescribed as an analgesic and that the buprenorphine-exposed group thus included a lower proportion of opioid-dependent women than the methadone-exposed group. In a study based on Medicaid-enrolled pregnant women, the absolute risk of NAS following exposure to prescription opioid analgesics was 5.9/1,000 deliveries, while the risk increased to 220.8/1,000 deliveries in the presence of known opioid misuse.[5] The fact that nearly 60% of methadone-exposed women in our study had a hospital diagnosis of opioid intoxication compared with only 11% of the buprenorphine-exposed women additionally suggests that the proportion of opioid dependency differed between the groups.

Other factors than the opioid use in itself could explain our findings as socioeconomic position, and lifestyle may also differ between the different exposure groups. We had data on self-reported smoking status, and smoking is a well-known risk factor for LBW.[24] Yet, restricting the analysis to women who reported smoking during pregnancy only slightly lowered the PRs, speaking against substantial confounding by smoking in our relative estimates. We did not have any information on the use of other substances, such as cocaine, socioeconomic positions, other lifestyles factors, and use of medication and vitamins, such as folic acid, which could further prove our findings.

In conclusion, the maternal use of buprenorphine and methadone during pregnancy was associated with the increased prevalence of adverse birth outcomes, and smoking did only explain a minor part of this increase. Still, we cannot rule out that confounding by socioeconomic position and other lifestyle factors may have influenced our estimates.

The risk of NAS was eight-fold higher in methadone-exposed neonates than that in buprenorphine-exposed neonates. It is, however, possible that differences in the underlying indications for opioid treatment, such as purely analgesic purpose versus opioid-dependent treatment, may explain at least some of these differences.

Author Contributions

Conceived and designed the experiments: MN. Analyzed the data: UHJ. Wrote the first draft of the manuscript: MN, MSN. Contributed to the writing of the manuscript: UHJ. Agree with manuscript results and conclusions: MN, MSN, UHJ. Jointly developed the structure and arguments for the paper: MN, MSN, UHJ. Made critical revisions and approved final version: MN, MSN, UHJ. All authors reviewed and approved of the final manuscript.

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