A Swedish Population-based Study of Adverse Birth Outcomes among Pregnant Women Treated with Buprenorphine or Methadone: Preliminary Findings

Keele E. Wurst,[1,2] Barbara K. Zedler,[1] Andrew R. Joyce,[1] Maciek Sasinowski[1] and E. Lenn Murrelle[1]

[1]Consultant, Venebio Group, LLC, Richmond, VA, USA. [2]Current address: GlaxoSmithKline Research and Development, Research Triangle Park, NC, USA.

ABSTRACT

BACKGROUND: Untreated opioid dependence in pregnant women is associated with adverse birth outcomes. Buprenorphine and methadone are options for opioid agonist medication-assisted treatment during pregnancy.

OBJECTIVE: The aim of this study was to describe adverse birth outcomes observed with buprenorphine or methadone treatment compared to the general population in Sweden.

METHODS: Pregnant women and their corresponding births during 2005–2011 were identified in the Swedish Medical Birth Register. Data on stillbirth, neonatal/infant death, mode of delivery, gestational age at birth, Apgar score, growth outcomes, neonatal abstinence syndrome, and congenital malformations were examined. Frequencies were compared using two-sided Fisher's exact tests. Unadjusted estimates of birth outcomes for women treated with buprenorphine or methadone were compared to the registered general population.

RESULTS: A total of 746,257 pregnancies among 538,178 unique women resulted in 746,485 live births. Among the 194 women treated with buprenorphine ($N = 176$) or methadone ($N = 52$), no stillbirths or neonatal/infant deaths occurred. Neonatal abstinence syndrome developed in 23.3% and 38.5% of infants born to mothers treated with buprenorphine and methadone, respectively. The frequency of the selected adverse birth outcomes assessed in women treated with buprenorphine as compared to the general population was not significantly different. However, a significantly higher frequency of preterm birth and congenital malformations was observed in women treated with methadone as compared to the general population. Compared with the general population, methadone-treated women were significantly older than buprenorphine-treated women, and both treatment groups began prenatal care later, were more likely to smoke cigarettes, and did not cohabitate with the baby's father.

CONCLUSIONS: An increased frequency of the selected adverse birth outcomes was not observed with buprenorphine treatment during pregnancy. Twofold increased frequency of preterm birth [2.21 (1.11, 4,41)] and congenital malformations [2.05 (1.08, 3.87)] was observed in the methadone group, which may be partly explained by older average maternal age and differences in other measured and unmeasured confounders.

KEYWORDS: buprenorphine, methadone, opioid agonist medication-assisted treatment, opioid use disorder, pregnancy, opioid dependence

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CORRESPONDENCE: Lenn.murrelle@venebio.com

Background

The average annual prevalence of illicit opioid use among adults aged 15–64 years in Europe is estimated to be 4 in 1000 or 1.3 million people.[1,2] Approximately one-third of opioid users are women, and the majority are of childbearing age according to the European Monitoring Centre for Drugs and Drug Addiction.[2,3] The actual prevalence of opioid use disorder (OUD) among pregnant women in Europe is difficult to ascertain, and differences across countries or in certain areas may exist.[4,5]

Untreated OUD in pregnancy has adverse effects on maternal and fetal outcomes.[4,6,7] Recurrent fluctuations of opioid plasma levels due to repeated cycles of intoxication and withdrawal are associated with adverse fetal consequences.[8–10] Maternal OUD has been associated with increased risk of stillbirth, neonatal mortality, placental abruption, hemorrhage, prematurity, small for gestational age (SGA), low birth weight, neonatal abstinence syndrome (NAS), congenital malformations, Apgar scores less than 7, and longer stays in the neonatal care unit.[4,6,7,10] Adverse

pregnancy outcomes among women with OUD have been reported to be between two and six times higher than those in the general population.[6,7,10,11]

The primary goal of treatment of OUD during pregnancy is stabilization of the mother.[12] The recommended approach to management of OUD in pregnant women includes psychosocial support and obstetric care plus long-acting opioid agonist medication-assisted treatment (OMAT).[12,13] For more than 40 years, OMAT with methadone has been the standard treatment for opioid-dependent pregnant women. In the late 1990s, buprenorphine was introduced as an OMAT and has been prescribed for OUD in Sweden since 1999.[14]

The available clinical literature suggests that methadone and buprenorphine have similar efficacies in reducing heroin use by pregnant women with OUD.[15,16] A number of studies have compared treatment with methadone to buprenorphine and found no significant differences in several pregnancy outcomes, such as fetal death,[16–21] preterm birth,[15–17,19,20,22–24] low birth weight,[19,24] infants SGA,[18,19,21] and intrauterine growth restriction.[20,22] Some investigators have reported higher birth weight in infants with in utero exposure to buprenorphine versus methadone.[23,24] Placental transfer of buprenorphine may be lower than methadone, possibly reducing fetal exposure and development of NAS.[25] The largest randomized controlled trial to date demonstrated less severe NAS in infants with in utero exposure to buprenorphine as compared to methadone, with buprenorphine-exposed infants requiring significantly less morphine and having shorter lengths of hospital stays.[18] A study using a linked population-based data source from Denmark demonstrated that while both buprenorphine- and methadone-treated women had higher frequencies of some adverse pregnancy outcomes compared to the general population, the prevalence of preterm birth and low birth weight was lower in infants with in utero exposure to buprenorphine as compared to methadone.[26]

As part of the corporate postmarketing surveillance plan for buprenorphine, data from the Swedish Medical Birth Register (SMBR) and linked health-care databases were used to describe selected birth outcomes observed in women treated with buprenorphine or methadone during pregnancy in comparison to the general population in Sweden.

Methods

Study population. Pregnant women and their corresponding births between 2005 and 2011 were identified from the SMBR, a repository of medical records-based information on approximately 99% of all births in Sweden.[27] The SMBR originated in 1973 in order to collect information on maternal, obstetric, and neonatal factors.[27,28] Data on the SMBR were collected prospectively and in a standardized manner during antenatal care visits at maternal health-care centers and during and after delivery. Data on antenatal care and deliveries in the SMBR are relatively complete as antenatal care in Sweden is publicly funded with almost all pregnant women participating and almost all deliveries occurring in hospitals.[27,28]

Only drugs prescribed during pregnancy at maternal health-care centers or departments of obstetrics were recorded in the SMBR. Information on maternal characteristics, including other prescription drug exposure during pregnancy, pregnancy outcomes, birth outcomes, and infant diagnoses, was obtained by linking the unique SMBR Personal Identification Number with the Prescribed Drug Register (PDR), the nationwide Cause of Death Register (CDR), and the Patient Register (PAR). The PDR contained data on dispensed prescription drugs as classified by the Anatomical Therapeutic Chemical system, including brand name, formulation, amount dispensed, dosage, and dates of prescription and dispensing. The CDR contained underlying and contributing causes of death and date of death. The PAR contained individual-level dates of hospital admission, discharge, and outpatient visits and discharge diagnoses, classified according to the International Classification of Disease, 10th revision (ICD-10).[27]

Treatment was defined as filling one or more prescriptions from three months before pregnancy until delivery. In this analysis, treatment information pertaining to the use of either buprenorphine, in the form of buprenorphine alone or in combination with naloxone, or methadone was obtained from the SMBR and PDR. Data for the abuse-deterrent combination of naloxone with buprenorphine were analyzed with buprenorphine alone because 36 of the 37 women who filled a prescription for the combination product also filled for buprenorphine alone. In addition, oral naloxone has very low bioavailability (~3%).[29] Maternal treatment with other prescribed drugs during pregnancy was abstracted herein only for infants with congenital malformations.

Information on maternal characteristics of age, parity, smoking, viral hepatitis, cohabitation status, and gestational timing of the first antenatal visit was obtained from the SMBR. In the SMBR, gestational age was based on ultrasound measurement, generally performed at gestational weeks 16–18. More than 95% of all deliveries in Sweden had an estimated day of delivery by ultrasound. For the few women not examined with ultrasound, the last menstrual period was used to estimate gestational age.

Maternal characteristics. Maternal age was categorized by year in the following age strata: 13–19, 20–24, 25–29, 30–34, and more than 35 years. Parity was categorized as first pregnancy (nulliparous) or more than one pregnancy (multiparous). Maternal self-reported current cigarette smoking status was categorized as nonsmoker, smoking 1–9 cigarettes daily, or smoking more than 10 cigarettes per day. Data concerning maternal infection with viral hepatitis (B, C, and D) were obtained from diagnoses recorded in the maternal health-care records during pregnancy and forwarded to the SMBR when the mother was discharged from the delivery hospital. Cohabitation was examined by querying whether the woman was living with a partner at the time of the first antenatal

health-care visit. Information on previous adverse pregnancy outcomes of stillbirth, malformations, preterm birth, SGA and cesarean section (C-section) was obtained from the SMBR. Data on previous neonatal care were obtained from the SMBR and PAR.

Outcome definitions. Pregnancy and birth characteristics included infant gender and mode of delivery (vaginal or C-section, with C-section classified as elective or acute). Preterm birth was defined as live birth before 37 completed weeks of gestation, and very preterm was live birth before 32 completed weeks of gestation. SGA was defined as birth weight values below two standard deviations of the expected birth weight for gestational age and sex according to intrauterine growth curves of ultrasonically estimated fetal weights.[30] Apgar scores recorded at five minutes of age were obtained from the SMBR. NAS was defined by an ICD-10 code P96.1 at discharge of the infant from the delivery hospital and includes abstinence syndromes related to opioids as well as other illicit substances or certain prescribed drugs. Stillbirths registered in the SMBR through 2007 were defined as occurring at or after gestational week 28, and in 2008 and beyond changed to gestational week 22 or later. Information on neonatal and infant death (one-year mortality) was obtained by linkage to the CDR. Information on congenital malformations was based on neonatal diagnoses at discharge from the SMBR and also from the PAR through the first year of life.

Statistical methods. Maternal characteristics and previous pregnancy outcomes were compared using two-sided Fisher's exact tests. Variables were dichotomized based on qualitative differences and well-established clinical categories that are predictive of prognosis. The frequency of adverse birth outcomes of interest was calculated using the number of pregnancies or infants with the event of interest as the numerator and the number of infants (deliveries) within each exposure cohort as the denominator. Unadjusted relative risks [prevalence ratios (PRs)] were used as measures of effect. Multifetal pregnancies were not considered in any of the analyses. Unadjusted estimates with 95% confidence intervals (CIs) were calculated for each exposure in comparison to the general population for each outcome of interest. Analyses were performed using R *base* and *epiR* packages.[31,32] This research complied with the principles of the Declaration of Helsinki.

Results

During the study period of 2005–2011, a total of 746,257 pregnancies among 538,178 unique women were registered in the SMBR and resulted in 746,485 live births. A total of 194 women were treated with buprenorphine or methadone during pregnancy and gave birth to a total of 228 infants during the study period, of which 176 infants were buprenorphine exposed and 52 infants were methadone exposed. Trimester of use was further examined in a selected sample of women exposed to the combination of buprenorphine product. Among those women, 89% ($n = 33$) of women had records for buprenorphine prior to pregnancy and in at least one of the three trimesters, and 30% of these ($n = 10$) had a record every trimester. Only two of the women had a record of buprenorphine only prior to pregnancy. Two women did not have a record prior to pregnancy but had records during pregnancy.

The distribution of maternal age was statistically significantly different among the general population and women treated with buprenorphine ($P = 0.041$) or methadone ($P = 0.008$) (Table 1). Women treated with methadone were older than women treated with buprenorphine ($P = 0.001$) or the general population ($P = 0.008$). There was a significantly greater frequency of smokers among those treated with buprenorphine ($P = 0.001$) or methadone ($P = 0.001$) as compared to the general population. However, the proportion of smokers was not significantly different between the buprenorphine and methadone groups. Women treated with buprenorphine or methadone during pregnancy were more likely to begin prenatal care after gestational week 15 and be positive for viral hepatitis B, C, or D and were less likely to cohabitate with the father of the infant as compared to the general population. The onset of prenatal care, cohabitation, and hepatitis status were similar between women treated with buprenorphine or methadone (Table 1).

Parity was not significantly different among the three groups. Among the 416,680 women who had a previous pregnancy, the frequencies of previous C-sections, stillbirths, and malformations did not differ significantly among the treated groups and general population (Table 1). Women treated with buprenorphine were more likely than the general population to have had an infant SGA ($P = 0.005$) but not more likely than women treated with methadone. Women treated with methadone were more likely than the general population to have had a previous preterm birth ($P = 0.027$) but not more likely than women treated with buprenorphine. Women treated with buprenorphine ($P = 0.001$) or methadone ($P = 0.027$) during pregnancy were more likely than the general population to have had an infant requiring neonatal care for longer than four weeks (Table 1).

No stillbirths, neonatal deaths, or deaths within the first year of life occurred among the infants born to mothers treated with buprenorphine or methadone. Although the frequencies of C-section, preterm birth, low birth weight, infants SGA, and lower Apgar scores were higher among women treated with buprenorphine compared to the general population, the differences were not statistically significant (Table 2). Women treated with methadone were approximately two times more likely than the general population to have a C-section (mostly elective) [PR = 1.94 (95% CI = 1.34–2.82)] or preterm birth [PR = 2.21 (95% CI = 1.11–4.41)] (Table 2). The frequencies of low birth weight, infant SGA, and lower Apgar scores were higher among women treated with methadone compared to the general population, but they were not statistically significantly different. NAS developed in 23.3% (95% CI = 17.4–30.4) of infants born to mothers treated with buprenorphine and 38.5%

Table 1. Characteristics of pregnancies resulting in live births identified from the Swedish Medical Birth Register, 2005–2011.

VARIABLE		GENERAL POPULATION[a]		BUPRENORPHINE-TREATED (BUP)		METHADONE-TREATED (MET)		*P*-VALUE		
		NUMBER OF DELIVERIES	%	NUMBER OF DELIVERIES	%	NUMBER OF DELIVERIES	%	BUP VS. POPULATION	MET VS. POPULATION	BUP VS. MET
Overall		746,257	100.0	176	100.0	52	100.0			
Maternal age (years)	13–19	12,146	1.6	0	0.0	0	0.0	0.041	0.008	0.001
	20–24	94,671	12.7	27	15.3	0	0.0			
	25–29	213,731	28.6	64	36.4	16	30.8			
	30–34	262,452	35.2	52	29.5	18	34.6			
	35+	163,252	21.9	33	18.8	18	34.6			
	Missing	5	0.0	0	0.0	0	0.0			
Maternal smoking	Non-smoker	658,502	93.0	53	32.5	23	46.9	<0.001	<0.001	0.341
	1–9 cigarettes per day	38,122	5.4	65	39.9	15	30.6			
	≥10 cigarettes per day	11,567	1.6	45	27.6	11	22.4			
	Missing	38,066	5.1	13	7.4	3	5.8			
First visit for antenatal care	≤ week 15	635,917	89.7	121	73.3	35	72.9	<0.001	<0.001	0.896
	> week 15	72,763	10.3	44	26.7	13	27.1			
	Missing	37577	5.0	11	6.2	4	7.7			
Cohabiting with partner	Yes	669,154	94.0	104	63.8	32	66.7	<0.001	<0.001	0.969
	No	42,474	6.0	59	36.2	16	33.3			
	Missing	34,629	4.6	13	7.4	4	7.7			
Viral hepatitis positive (B,C, or D)	Yes	380	0.1	9	5.1	2	3.8	<0.001	<0.001	1.000
	No	745,877	99.9	167	94.9	50	96.2			
Parity	Nulliparous	329,444	44.2	82	46.6	19	36.5	0.510	0.272	0.209
	Multiparous	416,680	55.8	94	53.4	33	63.5			
	Missing	133	0.0	0	0.0	0	0.0			
Birth outcomes only among multiparous deliveries	Total	416,680	100.0	94	100.0	33	100.0			
Previous stillbirth	Yes	3,513	0.8	0	0.0	0	0.0	1.000	1.000	1.000
	No	413,167	99.2	94	100.0	33	100.0			
Previous malformation	Yes	19,780	4.7	7	7.4	4	12.1	0.218	0.070	0.474
	No	396,900	95.3	87	92.6	29	87.9			
Previous preterm birth	Yes	29,718	7.1	10	10.6	6	18.2	0.223	0.027	0.359
	No	386,962	92.9	84	89.4	27	81.8			
Previous infant small for gestational age[b]	Yes	14,091	3.4	9	9.6	3	9.1	0.005	0.100	1.000
	No	402,589	96.6	85	90.4	30	90.9			
Previous infant requiring neonatal care >4 weeks	Yes	3,246	0.8	5	5.3	2	6.1	0.001	0.027	1.000
	No	413,434	99.2	89	94.7	31	93.9			
Previous C-section	Yes	65,545	15.7	16	17.0	7	21.2	0.673	0.345	0.605
	No	351,135	84.3	78	83.0	26	78.8			

Notes: [a]All registered births in Sweden, 2005–2011, not including those exposed to buprenorphine or methadone. [b]Birth weight values below two standard deviations of the expected birth weight for gestational age and sex according to intrauterine growth curves based on ultrasonically estimated fetal weights.[30]
Abbreviations: BUP, buprenorphine; MET, methadone.

(95% CI = 25.6–53.0) of infants born to mothers treated with methadone (Table 2).

The frequency of infants with any congenital malformation or a major malformation alone was not statistically significantly different in women treated with buprenorphine compared to the general population. Conversely, women treated with methadone were two times more likely than the general population to have an infant with any congenital malformation

Table 2. Selected birth outcomes of infants, Swedish Medical Birth Register, 2005–2011.

VARIABLE	CATEGORY	GENERAL POPULATION[a]		BUPRENORPHINE-TREATED (BUP)		METHADONE-TREATED (MET)		BUPRENORPHINE[b]	METHADONE[b]
		NUMBER OF INFANTS	%	NUMBER OF INFANTS	%	NUMBER OF INFANTS	%	PREVALENCE RATIO (95% CI)	PREVALENCE RATIO (95% CI)
Overall		746,257	100.0	176[c]	100.0	52	100.0		
Route of delivery	Vaginal	613,287	82.2	137	77.8	34	65.4	1	1
	C-section	132,970	17.8	39	22.2	18	34.6	1.24 (0.94, 1.64)	***1.94 (1.34, 2.82)***
	Elective C-section	68,590	9.2	22	12.5	12	23.1	–	–
	Acute C-section	62,843	8.4	17	9.7	6	11.5	–	–
	Unknown C-section	1,537	0.2	0	0.0	0	0.0	–	–
Preterm birth (Gestational age)	≥37 weeks	700,577	93.9	162	92.5	45	86.5	1	1
	<37 weeks	45,366	6.1	14	8.0	7	13.5	1.31 (0.79, 2.16)	***2.21 (1.11, 4.41)***
	Missing	314	0.0	0	0.0	0	0.0	–	–
Small for gestational age	Yes	707,032	94.7	161	91.5	51	98.1	1.30 (0.55, 3.08)	0.83 (0.12, 5.78)
	No	16,765	2.3	5	2.8	1	1.9	1	1
	Missing	22,460	3.0	10	5.7	0	0.0	–	–
Low birth weight	≤2500 g	32,851	4.4	11	6.3	4	7.7	1.42 (0.80, 2.51)	1.74 (0.68, 4.47)
	>2500 g	712,289	95.4	165	93.8	48	92.3	1	1
	Missing	1,117	0.0	0	0.0	0	0.0	–	–
Apgar score at 5 minutes	8–10	723,211	97.5	168	95.5	47	94.0	1	1
	<8	18,110	2.4	7	4.0	3	5.8	1.64 (0.79, 3.38)	2.46 (0.82, 7.36)
	Missing	4,936	0.6	1	0.6	2	3.8	–	–
Neonatal abstinence syndrome (ICD 10: P96.1)	Yes	128	0.0	41	23.3	20	38.5	***1358.16 (987.04, 1868.82)***	***2242.36 (1525.85, 3295.32)***
	No	746,129	99.9	135	76.7	32	61.5	1	1
Any congenital malformation	Yes	56,135	7.5	10	5.7	8	15.4	0.76 (0.41, 1.38)	***2.05 (1.08, 3.87)***
	No	690,122	92.5	166	94.3	44	84.6	1	1
Major malformation	Yes	34,333	4.6	8	4.5	6	11.5	0.99 (0.50, 1.94)	***2.51 (1.18, 5.32)***
	No	711,924	95.4	168	95.4	46	88.5	1	1

Notes: [a]All registered births in Sweden, 2005–2011, not including those exposed to buprenorphine or methadone. [b]Compared to general population. [c]From three months before and during pregnancy, 139 women were treated with buprenorphine only, 36 women were treated with buprenorphine and buprenorphine/naloxone, and 1 woman was treated with buprenorphine/naloxone only.

[PR = 2.05 (95% CI = 1.08–3.87)] or major malformation alone [PR = 2.51 (95% CI = 1.18–5.32)] (Table 2). At least one congenital malformation was reported in 10 of the 176 pregnancies treated with buprenorphine (5.7%) and 8 of the 52 with methadone exposure (15.4%) (Table 3). Of the 10 buprenorphine-treated mothers of affected infants, 1 was 35 years or older at delivery and 5 were 30–34 years old. Of the eight methadone-treated mothers of affected infants, six were 35 years or older at delivery, and two were 30–34 years old. Congenital malformations of the cardiovascular system comprised 50% of all malformations in infants of mothers treated with buprenorphine (2.8% of the total number of infants of mother treated with buprenorphine) and 38% of those treated with methadone (5.7% of the total number of infants treated with methadone) (Table 3). No infants had congenital malformations of the nervous or digestive systems. Overall, a consistent pattern of clustering of malformations by organ system was not observed within or between the buprenorphine and methadone groups. The majority (94%) of mothers of infants with congenital malformations were prescribed drugs other than buprenorphine or methadone during pregnancy, including sedatives, antidepressants, antipsychotics, antibiotics, antihistamines, and analgesics that included other opioids.

Discussion

This population-based, linked health-care database analysis did not identify any of the selected adverse birth outcomes as occurring with statistically significantly greater frequency in pregnant women treated with buprenorphine as compared to the general population of Sweden, except for NAS. However, the results of this preliminary, descriptive analysis suggested that maternal use of methadone may be associated with a significantly higher frequency of preterm birth and congenital malformations, as well as NAS. The results of this Swedish

Table 3. Infants with congenital malformations categorized by ICD-10 coding group.

ICD-10 CATEGORY	BUPRENORPHINE EXPOSURE IN UTERO (N = 10 INFANTS)	METHADONE EXPOSURE IN UTERO (N = 8 INFANTS)
Q10–Q18 Congenital malformations of eye, ear, face and neck		Infant 1: Q10.0 Congenital ptosis[a]
Q20–Q28 Congenital malformations of the circulatory system	Infant 1: Q26.8 Malformation of the vena cava and Q21.0 ventricular septum defect[a] Infant 2: Q25.7 Malformation of the pulmonary artery[a] Infant 3: Q21.0 ventricular septum defect (VSD), and Q24.9 an unspecified cardiac malformation[a] Infant 4: Q25.6 Pulmonary artery stenosis[a] Infant 5: Q21.1 atrial septum defect[a]	Infant 2: Q40.0 Congenital hypertrophic pyloric stenosis[a] Infant 3: Q21.1 atrial septum defect[a] Infant 4: Q25.7 Malformation of the pulmonary artery and Q21.0 ventricular septum defect[a]
Q30–Q34 Congenital malformations of the respiratory system	Infant 6: Q32.0 Trachea malacia[a]	
Q35–Q37 Cleft lip and cleft palate	Infant 7: Q35.8 Cleft palate	
Q50–Q56 Congenital malformations of genital organs	Infant 8: Q54.0 Hypospadias[a,b]	Infant 5: Q53.1 One-sided cryptorchidism[a]
Q60–Q64 Congenital malformations of the urinary system		Infant 6: Q62.7 Vesicouretral reflux and Q60.0 agenesis of one kidney[a]
Q65–Q79 Congenital malformations and deformations of the musculoskeletal system	Infant 9: Q66.8 Foot deformity[a] Infant 10: Q74.8 Congenital malformation of limb[a]	Infant 7: Q66.0 Equinovarus[a,b] Infant 8: Q66.0 Equinovarus[a,b]

Notes: [a]Mothers were treated with other prescription drugs during first trimester including: clemastine, fluoxetine, zaleplon, doxycycline, heracillin, zopiclone, propiomazine, varenicline, morphine, azathioprine, zolpidem, diazepam, oxycodone, orphenadrine, metoprolol, betametason, dimenhydrinate, methylphenidate, pregabalin, alprazolam, aripiprazole, venlafaxine, terbinafine, ciprofloxacin, sertraline, oxazepam, tramadol, propriomazine, celexcoxib, levomepromazine, amitriptyline, promethazine, clonidine, tranexamic acid, ketoconazole, and metronidazole. [b]Mothers treated with buprenorphine or methadone during the second and/or third trimesters only (along with other prescription drugs).

study are consistent with those from a population-based registry in Denmark (1997–2011) that also found a significantly higher frequency of NAS with buprenorphine or methadone exposure in utero, as well as a greater frequency of preterm birth and congenital malformations in methadone-treated pregnancies as compared to the opioid-unexposed general population.[26]

As in the current study, the Danish study cited above showed an increased frequency of SGA with buprenorphine treatment, but this was not statistically significantly different from the general population in the current study. The Danish study also found that women treated with buprenorphine and methadone were 2.6-fold and 3.7-fold as likely, respectively, to have a preterm birth, whereas the current analysis showed only a statistically significant relationship for methadone. Although the frequency of low birth weight was numerically elevated in the current study for infants exposed in utero to methadone, it was not a statistically significant difference as was observed in the Danish study. In that study, the prevalence of preterm birth and congenital malformations remained statistically significantly higher for methadone but not for buprenorphine when results were stratified by maternal smoking status.

Similar to the current study, Norgaard et al.[26] observed a greater frequency of current cigarette smokers among the pregnant women treated with buprenorphine and methadone as compared to the general population. In this Swedish study, the prevalence of smoking was not statistically different between the buprenorphine and methadone groups, but in the Danish study, the prevalence of smoking was greater in the methadone group.[26] Smoking may have contributed to some of the increased frequencies of adverse birth outcomes observed in the current study. Smoking has been shown to increase adverse birth outcomes, particularly SGA and preterm birth,[33] and women with OUD were more likely to be smokers.[34] While smoking was not adjusted for in the current analysis, results from the Danish study indicated that adjusting for smoking explained only a small portion of the outcome relationships observed with methadone.

Differences in maternal age could account for some of the differences in adverse birth outcomes observed between the general population and the treated groups. Women treated with buprenorphine were, on average, younger than those in the methadone group. Duration of OUD was not available to analyze in this study, but previous studies have reported longer duration of OUD in methadone-treated pregnant women as compared to those treated with buprenorphine.[19] Older maternal age is a risk factor for adverse birth outcomes, such as congenital malformations, SGA, C-section, preterm birth, and low Apgar scores.[35,36] The higher proportion of women aged more than 35 years treated with methadone could account for some of the increased frequencies of congenital malformations, C-section, and preterm birth observed as compared to buprenorphine-treated women and the general population.

There was no consistent pattern in the distribution of malformations by organ system observed in this study, which is

similar to other studies that assessed malformations in infants of women treated with buprenorphine and methadone.[20,21,24] Some of the malformations observed in this study were also observed in other studies. In a retrospective cohort study of 609 women treated with buprenorphine or methadone, two infants had congenital malformations, a cleft palate with exposure to buprenorphine, and an absent hand with exposure to methadone.[21] The significantly higher frequency of infants with any congenital malformation among Swedish women treated with methadone compared to the general Swedish population was consistent with two other studies that demonstrated a significant elevation in congenital malformations with methadone treatment.[26,37] In a population-based study of 114 infants exposed to methadone in utero in Ireland, three infants were malformed, one each with cardiovascular malformation, trigonocephaly, and congenital melanocytic nevus.[37] In the Danish population-based study, atrial and ventricular septal defects accounted for almost one-third of the congenital malformations observed.[26]

While cardiovascular malformations are among the most common types of malformation in the general population, the frequencies observed for buprenorphine (2.8%) and methadone (5.7%) in this Swedish analysis were higher than would be expected compared to population-based rates using European Surveillance of Congenital Anomalies data (0.72%) and other published population-based studies in Sweden (0.14%).[38] The high proportion of cardiovascular malformations may be related to factors other than treatment with buprenorphine or methadone. OUD itself may be an independent risk factor for cardiovascular malformations, as results from a retrospective cohort study of 85 women who abused illicit drugs demonstrated that 71% (5/7) of the fetal malformations observed were cardiovascular.[7] Additionally, in the current Swedish study, 94% of the women were treated during pregnancy with other prescription drugs, including antidepressants and antipsychotics, some of which have been associated with cardiovascular malformations.[39,40] Finally, older maternal age is a risk factor for fetal cardiovascular malformations[41] and could explain some of the high proportion of cardiovascular malformations as the majority of methadone-treated women (6/8) with an affected infant were over 35 years.

The finding that NAS developed less frequently in infants born to mothers treated with buprenorphine as compared to infants of mothers taking methadone was consistent with other published studies, although no direct comparison was made and the confidence intervals overlap.[18,19,23,42] The frequency of NAS was also generally consistent with other studies in which the NAS frequency ranged between 26% and 77%.[15,42–44]

Although this study was based on a large population-based sample for which information was obtained by interviews in early pregnancy and linked national health register data, the results of this preliminary analysis must be viewed in the context of the study limitations. First, the sample sizes of the groups treated with buprenorphine and methadone in this analysis were relatively small. Statistical comparisons of birth outcomes by maternal treatment with buprenorphine or methadone were not performed, as the statistical power was low when comparing across groups. The sample size limited the ability to perform rigorous multivariate analyses, and hence thorough examination of available confounding factors within this dataset was not possible. The unadjusted effect size is often biased (artificially high) as a result of confounding and will decrease when measured confounders are adjusted for, although potential residual confounding from unmeasured or unknown confounders may remain. The absence of information on several relevant confounding factors also limited the interpretation of the data. Second, the data used in this analysis did not allow for differentiation between buprenorphine and methadone prescribed for analgesia and for OMAT. Women prescribed OMAT for OUD may have different risk factors for adverse birth outcomes than women prescribed opioids for analgesia. Potential confounding could also occur in assessing adverse outcomes of buprenorphine compared to methadone because maternal characteristics that influence the choice of OMAT may also affect pregnancy outcomes. For example, differences in the severity of maternal opioid dependence and maternal social conditions that may influence clinical prescribing could not be accounted for in this analysis. Finally, in addition to differences in lifestyle factors and severity of maternal opioid dependence among the buprenorphine and methadone groups, additional factors that could not be examined in this analysis may have influenced study findings. In previous studies, women receiving methadone as compared to buprenorphine reported greater use of other illicit substances including cannabis, heroin, and cocaine[20] as well as other prescription drugs like benzodiazepines and amphetamines[45] that could not be examined in this study. Employment status was another factor that has been demonstrated to differ among methadone and buprenorphine users that could not be measured here.[45]

Conclusions

This population-based, linked health-care database analysis did not identify any of the selected adverse birth outcomes with statistically significant greater frequency in pregnant women treated with buprenorphine as compared to the general population of Sweden, except for NAS. The results of this preliminary descriptive analysis suggested that maternal use of methadone may be associated with a significantly higher frequency of preterm birth and congenital malformations as well as NAS. However, differences also may be partly explained by older average maternal age in the methadone group and differences in other confounders between the treatment groups and the general population, such as a higher proportion of cigarette smokers, delayed onset of prenatal care, lifestyle factors, and other unmeasured confounders, eg, exposure to other substances of abuse (including illicit opioids) and medications during pregnancy. As more exposure data are accumulated, additional analyses should be

conducted that include adjustment for possible confounders using multivariable modeling approaches, as statistically appropriate for the sample size available, to confirm these findings.

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Author Contributions

Conceived and designed the experiments: The original study was designed to respond to a European post-marketing safety commitment of the sponsor and this secondary analysis of those results was conceived and designed by KEW, ELM, BKZ, and ARJ. Analyzed the data: KEW, ARJ. Wrote the first draft of the manuscript: KEW. Contributed to the writing of the manuscript: KEW, BKZ, ARJ, MS, ELM. Agree with manuscript results and conclusions: KEW, BKZ, ARJ, MS, ELM. Jointly developed the structure and arguments for the paper: KEW, BKZ, ARJ, MS, ELM. Made critical revisions and approved final version: KEW, BKZ, ARJ, MS, ELM. All authors reviewed and approved of the final manuscript.

Abbreviations

C-section: cesarean section
CI: confidence interval
ICD: International Classification of Disease
OMAT: opioid agonist medication-assisted treatment
SMBR: Swedish Medical Birth Register
NAS: neonatal abstinence syndrome
PAR: Patient Register
PDR: Prescribed Drug Register
PR: prevalence ratio
SGA: small for gestational age

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