OBSTETRICS

Methadone and perinatal outcomes: a retrospective cohort study

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OBJECTIVE: The purpose of this study was to examine the relationship among methadone maintenance treatment, perinatal outcomes, and neonatal abstinence syndrome.

STUDY DESIGN: This was a retrospective cohort study of 61,030 singleton births at a large maternity hospital from 2000-2007.

RESULTS: There were 618 (1%) women on methadone at delivery. Methadone-exposed women were more likely to be younger, to book late for antenatal care, and to be smokers. Methadone exposure was associated with an increased risk of very preterm birth <32 weeks of gestation (adjusted odds ratio [aOR], 2.47; 95% confidence interval [CI], 1.40–4.34), being small for gestational age <10th percentile (aOR, 3.27; 95% CI, 2.49–4.28), admission to the neonatal unit (aOR, 9.14; 95% CI, 7.21–11.57), and diagnosis of a major congenital anomaly (aOR, 1.94; 95% CI, 1.10–3.43). There was a dose-response relationship between methadone and neonatal abstinence syndrome.

CONCLUSION: Methadone exposure is associated with an increased risk of adverse perinatal outcomes, even when known adverse sociodemographic factors have been accounted for. Methadone dose at delivery is 1 of the determinants of neonatal abstinence syndrome.

Key words: methadone, neonatal abstinence syndrome, perinatal outcome, pregnancy

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An estimated 30,000 pregnant women use illicit opiates each year in the European Union.[1] Methadone is the treatment of choice for the management of opioid dependence in pregnant women.[2,3] In the context of optimal care, methadone has been shown to improve engagement with antenatal services, improving perinatal outcomes compared with continued illicit drug use.[4,5] Despite these improvements, methadone-maintained women and their infants appear

★ EDITORS' CHOICE ★

to be at increased risk of adverse perinatal outcomes, compared with the total population. Previous cohort studies report markedly elevated rates of preterm birth of 29-45%[6,7] and admission of up to one-half of exposed neonates to the neonatal unit.[8] A metaanalysis showed a lower mean birthweight in methadone-exposed neonates, compared with control subjects.[9] Although it is known that methadone-exposed pregnancies are at greater risk of adverse outcomes, few population-based studies have quantified the likelihood of adverse perinatal outcomes, compared with unexposed pregnancies, accounting for the effect of confounding sociodemographic factors.

Neonatal abstinence syndrome (NAS) is another important consequence of methadone use in pregnancy that affects between 13% and 94% of exposed neonates.[10-12] Studies to date have had inconsistent findings about the existence of a relationship between maternal methadone dose and NAS.[8,13-16] A recent metaanalysis did not find consistent evidence for a dose-response relationship.[17] However, many studies on this topic had limited sample sizes with inadequate power to detect an association between methadone dose and the occurrence of NAS. It is important to determine whether this relationship exists to facilitate optimal dosing of methadone during pregnancy.

We used electronic records from a maternity hospital in Dublin, Ireland, to compare pregnancy outcomes for women who were exposed to methadone with the unexposed population over an

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8-year period. Our first objective was to establish population-based estimates of the risk of adverse perinatal outcomes that included preterm birth, intrauterine growth restriction, congenital anomalies, admission to the neonatal unit, and perinatal death in methadone-exposed and -unexposed pregnancies. A second objective was to explore the determinants of the incidence of NAS in methadone-exposed neonates.

Materials and Methods

A retrospective cohort study was conducted. The cohort included all singleton deliveries in the Coombe Women and Infants University Hospital between January 1, 2000, and December 31, 2007. This is a tertiary care maternity hospital that is located in a deprived inner-city area. The hospital serves a catchment area with a population of >500,000. All women have a booking interview with a midwife at the first antenatal visit. Comprehensive records are available routinely for all deliveries of >24 weeks' gestation or 500 g weight. This study was approved by the hospital's research ethics committee.

Maternal sociodemographic, medical and obstetric characteristics, and perinatal outcomes were recorded from electronic antenatal and delivery records. Information on the following maternal characteristics was extracted: age at delivery, socioeconomic group, nationality, marital status, parity, planned/unplanned pregnancy, booking gestation, receipt of publicly funded antenatal care, smoking during pregnancy, alcohol use before pregnancy, and serologic status. *Hepatitis B–positive serologic status* was defined as a current or past positive result for hepatitis B surface antigen, core antibody, E antigen, or E antibody; *hepatitis C* was defined as current or past positive result for hepatitis C antibody or viral RNA; and *human immunodeficiency virus* was defined as a positive result for human immunodeficiency virus antigen or antibody.

Opiate-dependent women are referred routinely to a Drug Liaison Midwife who coordinates the care, liaising between the addiction and obstetric services.[18] Multiple sources of ascertainment were used to identify women who were using methadone at the time of delivery, which included antenatal records, controlled drug registers, and prescription records. Methadone dose at delivery was recorded from controlled drug registers or prescription records. Controlled drug registers must be used to record all doses of methadone that are dispensed in the hospital. Women were categorized as methadone-exposed based on use at delivery.

Maternal and perinatal outcome measures included mode of delivery, gestational age at delivery, weight for gestational age, infant condition at birth (Apgar scores at 1 and 5 minutes and whether resuscitation was required), admission to neonatal special/intensive care, congenital anomalies, and perinatal death. Every woman had an ultrasound scan at the booking antenatal visit. Gestational age was estimated from the calculation based on first day of the last menstrual period; however, the booking ultrasound scan estimate was preferred if the dates were uncertain or there was a discrepancy of >7 days. *Preterm birth* was defined as the birth of a live baby at <37 weeks' gestation. *Very preterm birth* was defined as the birth of a live baby <32 weeks' gestation. Preterm births were further categorized according to whether preterm labor was spontaneous. Birthweight percentiles were calculated with the GROW-Centile calculator that yields percentiles that are customized for maternal height, weight, ethnicity, parity, infant sex, and delivery gestation.[19] Population mean maternal height and weight were used for percentile calculations where data were missing for any individual pregnancy. *Birthweights below the customized 10th percentile* were defined as small-for-gestational age. Further neonatal outcome information was available for neonates who were admitted to the neonatal unit, including the main reason for admission and congenital anomaly diagnoses. The perinatal death register was used for the ascertainment of stillbirths and neonatal deaths, along with electronic delivery suite records. *Stillbirth* was defined as delivery of a baby that showed no signs of life ≥24 weeks' gestation. *Neonatal death* was defined as the death of a baby within the first 7 days of life. Congenital anomalies were identified from records of a physical examination of all babies after delivery and from neonatal unit discharge records. Congenital anomalies were categorized as major, minor, or chromosomal based on the EUROCAT classification system (EUROCAT Central Registry, Newtownabbey, Northern Ireland).[20]

During the study period, neonates were monitored initially for NAS on the postnatal ward with the use of a 17-item scoring system that had been adapted from Finnegan and Ehrlich[21] by removing the moro reflex, sweating, and mottling items. Neonates with suspected NAS were admitted to the neonatal unit for assessment and treatment, if necessary. NAS was normally diagnosed if the neonate had ≥2 successive Finnegan scores of ≥8. Diagnosis of NAS was ascertained from multiple fields in the electronic neonatal discharge register, which included main diagnosis, central nervous system diagnosis, unresolved problems at discharge, other diagnoses, and discharge medications. Neonatal urine toxicologic screening for opiates (excluding methadone), benzodiazepines, cannabis, cocaine, amphetamines, and alcohol was performed when clinically indicated in the first days of life.

Basic descriptive statistics were used to describe maternal characteristics and perinatal outcomes for the exposed and unexposed groups. Differences in means were assessed with independent samples Student's *t* test. Univariable and multivariable logistic regression analyses were used to determine crude and adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the association between methadone exposure status and maternal characteristics, and between methadone exposure status and a range of perinatal outcomes. Only maternal characteristics that differed significantly between the exposed and unexposed groups were included in the final

TABLE 1
Maternal characteristics by methadone exposure status

Variable	Total, n	Exposed, n = 618 (1%)	Not exposed, n = 60,412 (99%)	Odds ratio	95% CI
Age at delivery, y	61,030				
<20		20 (3.2)	3052 (5.0)	0.35	0.22–0.56
20-24		211 (34.1)	8640 (14.3)	1.32	1.10–1.59
25-29		267 (43.2)	14,461 (23.9)	1	—
30-34		96 (15.5)	20,254 (33.5)	0.26	0.20–0.32
35-39		18 (2.9)	11,830 (19.6)	0.08	0.05–0.13
>40		6 (1.0)	2175 (3.6)	0.15	0.06–0.34
Socioeconomic group	60,995				
Home duties		43 (7.0)	12,833 (21.2)	1	—
Professional, manager, employer		5 (0.8)	13,945 (23.1)	0.11	0.04–0.27
Nonmanual		48 (7.8)	19,087 (31.6)	0.75	0.50–1.13
Manual		18 (2.9)	2447 (4.0)	2.19	1.26–3.81
Unemployed		449 (72.6)	8696 (14.4)	15.4	11.2–21.1
Not classifiable		55 (8.9)	3369 (5.6)	4.87	3.26–7.27
Nationality: Irish	59,582	556 (94.7)	46,687 (79.1)	4.73	3.29–6.79
Married	60,640	26 (4.3)	39,287 (65.4)	0.02	0.01–0.03
Nulliparous	61,027	187 (30.3)	25,275 (41.8)	0.60	0.51–0.72
Unplanned pregnancy	59,921	429 (70.9)	20,662 (34.8)	4.56	3.82–5.44
Booking gestation, wk	59,625				
<12		114 (19.7)	12,465 (21.1)	1.07	0.86–1.33
12-20		322 (55.5)	37,718 (63.9)	1	—
>20		144 (24.8)	8862 (15.0)	1.90	1.56–2.32
Publicly funded obstetric care	60,069	604 (99.8)	44,184 (74.3)	208.9	29.4–1485
Smoked during pregnancy	60,213	569 (93.7)	13,109 (22.0)	53.1	38.2–73.8
Alcohol use before pregnancy (units per wk)	60,246				
Never		202 (33.3)	11,235 (18.8)	1	—
Occasional		254 (41.8)	25,337 (42.5)	1.26	1.04–1.51
1-5		89 (14.6)	17,049 (28.6)	0.29	0.23–0.37
6-9		34 (5.6)	4626 (7.8)	0.41	0.28–0.59
10-14		8 (1.3)	1014 (1.7)	0.44	0.21–0.89
15-20		10 (1.6)	275 (0.5)	2.02	1.06–3.86
>20		10 (1.6)	103 (0.2)	5.40	2.78–10.49
Hepatitis B-positive serologic status[a]	31,972	20 (3.5)	326 (1.0)	3.47	2.19–5.49
Hepatitis C-positive serologic status[b]	31,973	275 (48.2)	193 (0.6)	150.2	120.9–186.6
Human immunodeficiency virus positive[c]	56,781	33 (5.8)	171 (0.3)	20.3	13.8–29.7

CI, confidence interval.

[a] Current or past hepatitis B surface antigen, core antibody, E antigen, or E antibody positive; [b] Current or past hepatitis C antibody or polymerase chain reaction positive; [c] Antigen or antibody positive.

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TABLE 2
Maternal and perinatal outcomes by methadone exposure status

Variable	n	Exposed, n = 618 (1%)	Not exposed, n = 60,412 (99%)	Odds ratio	95% CI	Adjusted odds ratio[a]	95% CI
Mode of delivery	60,832						
Spontaneous vaginal		431 (69.8)	38,535 (64.0)	1	—	1	—
Elective lower segment cesarean section		40 (6.5)	4713 (7.8)	0.76	0.55–1.05	1.72	1.20–2.48
Emergency lower segment cesarean section		71 (11.5)	7496 (12.4)	0.85	0.66–1.09	1.26	0.94–1.68
Forceps/ventouse		75 (12.1)	9471 (15.7)	0.71	0.55–0.90	1.45	1.10–1.91
Meconium-stained liquor	60,533	76 (12.6)	9076 (15.1)	0.81	0.63–1.03	0.68	0.52–0.88
Preterm birth <37 wk	60,978	126 (20.4)	3382 (5.6)	4.32	3.54–5.27	2.47	1.97–3.11
Spontaneous preterm labor		93 (15.1)	2036 (3.4)	5.08	4.06–6.36	2.68	2.06–3.49
Very preterm birth <32 wk	60,978	27 (4.4)	727 (1.2)	3.75	2.53–5.56	2.27	1.40–3.69
Spontaneous preterm labor		22 (3.6)	363 (0.6)	6.11	3.94–9.47	2.99	1.69–5.29
Small for gestational age <10th percentile[b]	59,877	268 (45.9)	8379 (14.1)	5.15	4.37–6.07	2.21	1.85–2.64
Apgar score							
<3 at 1 min	60,725	20 (3.3)	636 (1.1)	3.18	2.02–5.00	1.94	1.12–3.37
<7 at 5 min	60,668	22 (3.6)	680 (1.1)	3.28	2.13–5.06	2.07	1.23–3.48
Ventilation required at resuscitation	60,977	6 (1.0)	398 (0.7)	1.48	0.66–3.32	0.92	0.33–2.55
Admitted to neonatal unit	61,029	328 (53.1)	8735 (14.5)	6.69	5.70–7.85	6.15	5.14–7.36
Congenital anomaly	61,029						
Any		47 (7.61)	1778 (2.94)	2.71	2.01–3.67	2.20	1.54–3.14
Minor		22 (3.56)	842 (1.39)	2.61	1.70–4.02	2.12	1.26–3.56
Major		19 (3.07)	647 (1.07)	2.92	1.84–4.65	1.94	1.10–3.43
Chromosomal		1 (0.16)	150 (0.25)	0.65	0.09–4.66	1.48	0.19–11.4
Unclassified		5 (0.81)	101 (0.17)	4.87	1.98–12.0	7.26	2.58–20.4
Perinatal death[c]	61,030	15 (2.43)	491 (0.81)	3.04	1.80–5.11	1.70	0.87–3.30
Neonatal abstinence syndrome	61,029	247 (40.0)	39 (0.06)	1030	724–1466	426	249–728

CI, confidence interval.

[a] Adjusted for age at delivery (years), socioeconomic group, Irish nationality, marital status, nulliparity, planning of pregnancy, booking gestation (weeks), receipt of publicly funded health care, number of cigarettes per day (none, 1-9 a day, >10 a day), and units of alcohol used per week before pregnancy (none, 1-9 units, >10 units); [b] Birthweight percentiles were calculated with the use of GROW-Centile calculator, a customized weight percentile calculator; [c] Includes stillbirths and neonatal deaths. *Stillbirth* was defined as the delivery of a baby who showed no signs of life at ≥24 weeks' gestation. *Neonatal death* was defined as the death of a baby within the first 7 days of life.

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multivariable models. The analysis was repeated excluding women with diabetes mellitus during the pregnancy or a history of epilepsy. Separate univariable and multivariable logistic regression analyses were conducted to examine the determinants of NAS in methadone-exposed neonates. Variables that were found to have an impact on the incidence of NAS in the univariable analyses were included in the multivariable models. Likelihood ratio tests were used to test for evidence of interactions. Subgroup analyses were carried out examining the determinants of NAS excluding infants with urine toxicologic results that were positive for opiates, benzodiazepines, cannabis, or cocaine exposure. A logistic regression analysis with methadone dose group as an ordered categoric variable was used to test for a dose-response relationship between methadone and the occurrence of NAS.

TABLE 3
Major congenital anomaly subgroups in methadone-exposed neonates

Anomaly subgroup	Exposed, n = 618	Nonexposed, n = 60,412
Nervous system	2 (0.3)	105 (0.2)
Eye	0	8 (0)
Ear, face, and neck	1 (0.2)	43 (0.1)
Congenital heart disease	4 (0.6)	103 (0.2)
Respiratory	0	11 (0)
Orofacial clefts	3 (0.5)	54 (0.1)
Digestive system	0	45 (0.1)
Abdominal wall defects	0	33 (0.1)
Urinary	1 (0.2)	46 (0.1)
Genital	0	72 (0.1)
Limb	4 (0.6)	129 (0.2)
Musculoskeletal	0	23 (0)
Other malformations	0	6 (0)
Teratogenic syndromes with malformations	0	4 (0)
Genetic syndromes and microdeletions[a]	4 (0.6)	12 (0)

[a] Includes Pierre Robin sequence.

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STATA IC 10 (Stata Corp, College Station, TX) was used for all statistical analysis. The STATA command *xtmelogit* was used to carry out mixed effects logistic regression to generate odds ratios that were adjusted for the lack of independence in perinatal outcomes for women with >1 delivery in the study period. These regression models adjusted for the fact that some women may have had >1 infant in the cohort during the study period.

RESULTS

Of 61,030 singleton deliveries between 2000 and 2007, 618 women (1%) were receiving methadone at delivery. A further 13 women with a history of methadone use were excluded from the study because of unavailability of medical records.

Maternal characteristics are outlined in Table 1. The mean ages at delivery in the methadone-exposed and -unexposed groups were 26.1 and 30.0 years ($P < .0001$), respectively. Compared with women in the unexposed population, those women who were using methadone at delivery were more likely to be unemployed, Irish, parous, and smokers and to have an unplanned pregnancy and publicly funded obstetric care. Serologic evidence of viral bloodborne disease, particularly hepatitis C, was more likely in methadone-exposed women than in the nonexposed population.

Maternal and perinatal outcomes are described in Table 2. Methadone exposure was associated with preterm birth (aOR, 2.47; 95% CI, 1.97–3.11) and very preterm birth (<32 weeks' gestation; aOR, 2.27; 95% CI, 1.40–3.69). Methadone-exposed neonates were more likely to be small-for-gestational age (aOR, 2.21; 95% CI, 1.85–2.64). Admission to the neonatal unit was much more likely if the neonate had been exposed to methadone (aOR, 6.15; 95% CI, 5.14–7.36). Diagnosis of a major congenital anomaly was more likely in methadone-exposed neonates.

The occurrence of major congenital anomaly subgroups is compared in Table 3. After an examination of the individual major congenital anomalies, it was apparent that Pierre Robin sequence was overrepresented, with 4 cases among the 618 methadone-exposed neonates (1 in 155) and 8 cases in the unexposed group (1 in 7552).

Adjustment for interdependence of pregnancy outcomes in women with >1 delivery during the study period with the use of mixed-effects binary logistic regression resulted in marginal changes in the ORs for most outcomes, with the exception of preterm delivery, being small for gestational age and admission to the neonatal unit. For these outcomes, the following changes to the aORs were made: preterm birth at <37 weeks' gestation (aOR, 3.07; 95% CI, 2.28–4.14), spontaneous preterm birth at <37 weeks' gestation (aOR, 3.23; 95% CI, 2.32–4.50), very preterm birth at <32 weeks' gestation (aOR, 2.47; 95% CI, 1.40–4.34), spontaneous preterm birth at <32 weeks' gestation (aOR 3.19; 95% CI, 1.67–6.08), small-for-gestational age (aOR, 3.27; 95% CI, 2.49–4.28), and admission to the neonatal unit (aOR, 9.14; 95% CI, 7.21–11.57). No evidence of exposure-confounder interaction was found. Repeating the analysis excluding women with diabetes mellitus during the pregnancy or a history of epilepsy did not change the results materially.

The mean (standard deviation) methadone doses in mothers of neonates with and without a diagnosis of NAS were 62.0 ± 26.3 mg and 49.8 ± 24.5 mg, respectively ($P < .0001$). Compared with neonates who were born to women on very low doses (<21 mg), those neonates who were born to women on higher doses were more likely to have a recorded diagnosis of NAS with a clear dose-response relationship (Table 4). The rate of NAS ranged from 23.3% in the very low-dose group to 73.3% in the highest dose group (Figure). An NAS diagnosis was more likely among neonates who were born at <37 weeks' gestation or with a birthweight below the 10th percentile. The effect of methadone dose on the incidence of NAS was also present when neonates were dichotomized into low- and high-dose groups with 50 mg and 80 mg cutoff points, respectively. After adjustment for preterm birth and a birthweight <10th percentile, the ORs for NAS in neo-

TABLE 4
Determinants of neonatal abstinence syndrome in methadone-exposed neonates

Variable	n	Neonatal abstinence syndrome, n (%)	No neonatal abstinence syndrome, n (%)	Odds ratio	95% CI	Adjusted odds ratio	95% CI	Adjusted odds ratio[a]	95% CI
Preterm birth <37 wk	617	70 (55.6)	56 (44.4)	2.22	1.49–3.30	2.05[b]	1.37–3.08	2.19[b]	1.36–3.53
Very preterm birth <32 wk	617	12 (44.4)	15 (55.6)	1.21	0.56–2.63	1.04[b]	0.47–2.31	0.98[b]	0.39–2.41
Small for gestational age <10th percentile	584	121 (45.2)	147 (54.8)	1.56	1.12–2.18	1.50[b]	1.06–2.11	1.59[b]	1.06–2.39
Male	618	135 (41.8)	188 (58.2)	1.17	0.85–1.62	1.34[c]	0.94–1.90	1.39[c]	0.93–2.04
Methadone-dose band at delivery, mg	615								
<21		19 (23.8)	61 (76.2)	1	–	1[d]	–	1[d]	–
21-50		73 (33.3)	146 (66.7)	1.60	0.89–2.89	1.66	0.88–3.11	1.72	0.86–3.46
51-80		117 (47.4)	130 (52.6)	2.88	1.63–5.12	2.95	1.59–5.47	3.22	1.59–6.53
81-100		26 (48.1)	28 (51.8)	2.98	1.42–6.26	2.90	1.32–6.34	3.12	1.30–7.50
>100		11 (73.3)	4 (26.7)	8.83	2.52–30.97	9.04	2.49–32.83	10.91	2.48–48.04
Maternal smoking during pregnancy	608								
None		11 (28.2)	28 (71.8)	1	–	1[c]	–	1[c]	–
1-10/d		103 (37.1)	175 (62.9)	1.50	0.72–3.14	1.16	0.52–2.60	1.14	0.48–2.74
>10/d		128 (44.0)	163 (56.0)	2.00	0.96–4.17	1.40	0.63–3.11	1.38	0.58–3.30
Alcohol use before pregnancy	607								
None		86 (42.6)	116 (57.4)	1	–	1[c]	–	1[c]	–
Light (≤9 units/wk)		144 (38.2)	233 (61.8)	0.83	0.59–1.18	0.84	0.58–1.22	0.83	0.55–1.25
Moderate/heavy (≥10 units/wk)		12 (42.9)	16 (57.1)	1.01	0.45–2.25	0.92	0.38–2.23	0.86	0.32–2.31

CI, confidence interval.

[a] Mixed effects logistic regression was used to adjust for the interdependence of outcomes for women who delivered more than once during the study period; [b] Adjusted for methadone-dose band at delivery; [c] Adjusted for methadone-dose band at delivery, being small for gestational age (<10th percentile) and preterm birth (<37 weeks' gestation); [d] Adjusted for being small for gestational age (<10th percentile) and preterm birth (<37 weeks' gestation).

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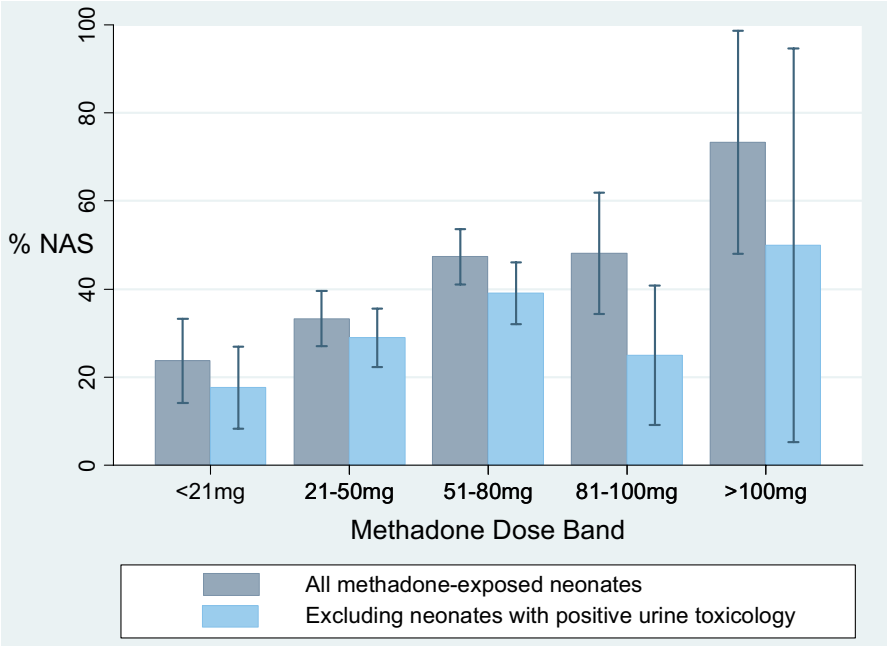
nates who were born to women on doses above and below 50 mg and 80 mg were 2.10 (95% CI, 1.49–2.98) and 1.73 (95% CI, 1.04–2.87), respectively. Maternal smoking and alcohol use were not associated with NAS. Neonatal urine toxicologic results were available for 254 of the methadone-exposed neonates (41.1%). Of these, 79 neonates (31.1%) were opiate positive; 72 neonates (28.3%) were benzodiazepine positive; 15 neonates (5.9%) were cannabis positive, and 5 neonates (2.0%) were cocaine positive. A relationship between the maternal methadone dose at delivery and occurrence of NAS was still evident with doses above and below 50 mg in subgroup analyses that excluded neonates with urine toxicologic results that were positive for opiates, benzodiazepines, cannabis, or cocaine (≤50 mg compared with >50 mg; aOR, 1.71; 95% CI, 1.13–2.55; ≤80 mg compared with >80 mg; aOR, 0.76; 95% CI, 0.37–1.58). Tests for trend in the occurrence of NAS with the use of logistic regression analyses found evidence of a dose-response effect when all the methadone-exposed neonates were included in the analysis ($P < .001$) and when neonates with positive urine toxicologic results were excluded ($P = .02$).

Comment

Maternal methadone use during pregnancy was associated with a range of adverse perinatal outcomes, even after known sociodemographic risk factors were accounted for. Adverse outcomes included preterm and very preterm

FIGURE
Neonatal abstinence syndrome (*NAS*) by methadone dose band at delivery



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birth, being small for gestational age, low Apgar scores, neonatal unit admission, and diagnosis of a major congenital anomaly. The incidence of NAS was related to maternal methadone dose at delivery.

This study examined perinatal outcomes in a geographic cohort of women who delivered in a large maternity hospital. The hospital's catchment area includes areas of inner-city deprivation with relatively high rates of illicit drug use, which facilitated the identification of a large cohort of methadone-exposed pregnancies. Multiple sources of ascertainment were used to ensure as complete identification of methadone-exposed pregnancies as possible. The large sample size facilitated an assessment of the effect of methadone on perinatal outcomes and the incidence of NAS that may be missed in smaller studies.

Because this retrospective study used routinely collected electronic records, not all information that was relevant to the research questions was available. Limited information was available on maternal nutrition, which may account for some of the adverse perinatal outcomes. Also, there were limited data on neonatal urine toxicologic status and no data on maternal toxicologic testing or prescription medication use, which limited the ability to adjust for the effect of concomitant licit and illicit drug exposure on perinatal outcomes. It is possible that there is residual confounding relating to socioeconomic differences between the 2 groups of women that could contribute to the findings. Ascertainment of congenital anomalies was not complete, because information was available only on anomalies that were diagnosed before first hospital discharge. Some of the effect of methadone on adverse perinatal outcomes may be explained by detection bias, with a greater detection of some study outcomes in the methadone-exposed group because of a higher rate of admission to the neonatal unit.

Rates of adverse perinatal outcomes (such as preterm birth, lower birthweight and admission to the neonatal unit) are higher in methadone-exposed pregnancies than in the overall population.[6,8,9,14] Our 20.4% estimate of the incidence of preterm birth is in agreement with the 20.3% rate that was reported by Dryden et al[8] for a similar cohort in Glasgow, although other studies have reported higher rates.[7] Serologic evidence of hepatitis C infection was also quite common in the Dryden et al[8] study. Our study shows that, after adjustment for a variety of maternal characteristics that may affect the risk of preterm birth adversely, methadone treatment was associated independently with preterm and very preterm delivery. This effect was also present when spontaneous delivery before 37 and 32 weeks' gestation was considered as the outcome. Almario et al[6] found that the risk of preterm birth rose with the number of supplemental drugs that were used by the mother in addition to methadone.

Other adverse perinatal outcomes (such as growth restriction and low Apgar scores) were also more likely with exposure to methadone. Previous reports have demonstrated lower birthweights in this population.[9,22] As with previous studies, neonatal unit admission was common for methadone-exposed neonates.[8] This has important consequences for health system resources, with long durations of hospitalization reported in a variety of settings.[7,8]

Methadone generally is not considered to be teratogenic.[23,24] The present analysis found that methadone exposure increased the likelihood of a major congenital anomaly diagnosis. Many previous studies in this area did not report congenital anomalies systematically as a study outcome. Small sample sizes also limit the potential to examine rare outcomes such as congenital anomalies. Unexpectedly, we found that there was an elevated rate of Pierre Robin sequence in the methadone-exposed group. The rate in the unexposed group was similar to rates reported internationally of 1 in 8500 and 1 in 14,000.[25,26] This incidental finding is not sufficient to link methadone causally to Pierre Robin sequence. Future studies are required to verify or reject this finding.

Many previous studies have examined the relationship between methadone and NAS. In agreement with some studies, this study finds that there is a relationship between maternal methadone dose

at delivery and NAS.[7,8,13,18,27] Other authors have not reported such a relationship.[14-16,28,29] The dose-response effect could be explained by greater concomitant illicit drug use in women who receive higher methadone doses, but the effect persisted in subgroup analyses, which excluded neonates with definite illicit drug exposure. It is possible that studies with smaller sample size might miss a true dose-response effect, or perhaps some studies with high mean methadone doses missed a dose-response relationship because of a ceiling effect. Some authors have demonstrated a relationship between maternal smoking and the severity or duration of NAS.[30,31] Smoking was not associated with NAS in this study, although the CIs for the ORs were wide because most of the methadone-exposed women smoked.

Methadone's beneficial effects of minimizing illicit drug use and fostering engagement with antenatal care may outweigh the risks of adverse perinatal outcomes that were found in this study. The increased incidence of very preterm birth and low Apgar scores has important implications because they are associated with adverse consequences in the short and long term. The incidence of congenital anomalies in methadone-exposed neonates should be assessed routinely and reported in future studies. Although we report an association between methadone dose and the incidence of NAS, it is important not to view NAS in isolation. NAS is a short-term, treatable condition. Although it is an important outcome, it is not the only one to consider when decisions are being made about optimal methadone doses in pregnancy. Continued stability or cessation of drug use and associated risk behaviors currently take precedence over endeavors to minimize NAS. It is possible that there is a subgroup of motivated, stable women within this population for whom careful, supervised dose reductions may reduce the likelihood of NAS, but this potential benefit must be balanced against the risk of decreased methadone doses leading to relapse of illicit drug use.

In conclusion, methadone exposure in pregnancy is associated with a range of adverse perinatal outcomes, even after accounting for the effects of maternal sociodemographic risk factors. This vulnerable group of women and their neonates require dedicated, well-resourced, multidisciplinary care to improve perinatal and long-term outcomes. ■

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