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The role of preterm birth in the association between opioid maintenance therapy and neonatal abstinence syndrome

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Abstract

Background—Pregnant women treated with methadone as opioid maintenance therapy are more likely than women treated with buprenorphine to deliver preterm. Preterm birth is associated with less risk of neonatal abstinence syndrome (NAS). We sought to assess the role of preterm birth as a mediator of the relationship between in utero exposure to methadone and NAS compared with buprenorphine.

Methods—We studied 716 women receiving methadone or buprenorphine and delivering live-born infants at Magee-Womens Hospital, Pittsburgh, Pennsylvania (2013-2015). We implemented inverse probability weighted marginal structural models to isolate the role of preterm birth (<37 weeks' gestation). Weights accounted for confounding by maternal age, race, insurance, parity, delivery year, marital, employment, hepatitis C, and smoking status.

Results—Approximately 57% of the cohort were treated with methadone. Preterm birth was more common in methadone exposed pregnancies (25% versus 14%). The incidence of NAS treatment was higher in methadone-compared with buprenorphine-exposed infants (65% versus 49%), and term compared with preterm births (64% versus 36%). For every 100 infants live-born to mothers treated for opioid dependence, there were 13 excess cases of NAS among infants exposed to methadone compared with buprenorphine (adjusted risk difference [RD] 13.3, 95% confidence interval [CI] 5.7, 20.9). Among term births, this increased to 17 excess cases of NAS in methadone- compared with buprenorphine-exposed (RD 16.7, 95% CI 9.3, 24.0).

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Conclusion—The further increased risk of NAS associated with methadone use versus buprenorphine in term deliveries emphasises the utility of buprenorphine in clinical settings aimed at decreasing NAS.

Keywords

buprenorphine; methadone; neonatal abstinence syndrome; preterm birth; mediation analysis

Introduction

Neonatal abstinence syndrome (NAS), or postnatal opioid withdrawal, affected nearly 6 of every 1000 live-born US infants in 2012[1] — a five-fold increase since 2000.[2] NAS is associated with long-term physical and behavioral complications[3], and cost the US health system an estimated $1.5 billion in 2012 alone.[1] The marked increase in NAS parallels increases in opioid use dependence in pregnancy,[4] and the two recommended opioid maintenance therapies, buprenorphine and methadone.[5] Determining which treatment regimen will maternal and infant outcomes, including reducing risk of NAS, is a public health priority.

Buprenorphine is associated with improved perinatal outcomes compared with methadone, most notably reporting less NAS and shorter duration of neonatal treatment.[6-9] Though the majority of extant studies are in agreement, methadone remains the mainstay of care in the US,[10] and barriers to access buprenorphine treatment persist.[11] Prescription of buprenorphine as opioid maintenance therapy in an outpatient setting requires that the physician obtain a waiver from the Controlled Substances Act.[12] In 2012, only 2.2% of all US physicians applied for and received the waiver and were therefore able to treat patients with buprenorphine.[13]

Inherent biases in prescribing preferences, access to treatment options, and necessity of tailoring treatment to the individual beyond risk of NAS, have continued to fuel the debate on optimal treatment in pregnancy. The role of gestational age in these associations, however, has not been investigated - a problem frequently encountered in perinatal epidemiologic studies.[14] Gestational age is often adjusted in regression models, when treated as a confounder, or excluded from the model, thereby assessing the total association. Such approaches ignore the complexities of this relationship. When evaluating the relationship between opioid maintenance therapy and NAS, the interplay among treatment, NAS and gestational age is important. Methadone treatment has been associated with an increased risk of preterm birth compared with buprenorphine treatment or no treatment,[7,15-18] and preterm infants exhibit a lower incidence and reduced severity of NAS compared with term infants.[19-21] If preterm birth is a mediator of this relation, the estimated increased risk of NAS associated with methadone compared with buprenorphine may be an underestimate among term infants.

We aimed to estimate the association between opioid maintenance therapy and NAS, independent of the effect of opioid maintenance therapy on preterm birth. We hypothesised that the increased risk of NAS associated with methadone exposure compared with buprenorphine would be stronger among term than preterm births. If true, these results will

support the expansion of buprenorphine use and access in pregnancy, making more treatment options available to individualize treatment.

Methods

Data source

Magee-Womens Hospital is one of the largest maternity hospitals in Pennsylvania with approximately 10 000 deliveries annually. Pregnant women initiating new opioid maintenance therapy at Magee-Womens Hospital can self-select treatment with methadone or buprenorphine in accordance with the American Congress of Obstetricians and Gynecologists recommendations provided they meet prescribing requirements for both.[5] Women who conceive while receiving opioid maintenance therapy are normally maintained on their medication regimen.

Study cohort

The study cohort consisted of all live-born, singleton deliveries to women exposed to methadone or buprenorphine as opioid maintenance therapy on the day of delivery at Magee-Womens Hospital from 2013-2015. Using *International Classification of Diseases*, Ninth and Tenth Revision codes for drug- dependent (ICD-9 64831) or drug- complicated delivery (ICD-10 O99324) we identified 872 drug-dependent pregnancies (Figure 1). Of these, 745 had documentation of opioid maintenance therapy with either buprenorphine or methadone on the day of delivery. We restricted the cohort further to live-born, singleton pregnancies and therefore excluded 6 fetal deaths and 9 pairs of twins. Twins were excluded due to known differences in gestational ages and the dearth of information on NAS in twin pregnancies. We retained 716 pregnancies (691 women) in the final analytic sample. The Institutional Review Board at the University of Pittsburgh approved this study.

Opioid maintenance medications

We determined maternal exposure to opioid maintenance therapy with pharmacy billing claims, then extracted dosing information directly from the medical chart. Women treated with Subutex® (buprenorphine, n=299; Reckitt Benckiser Pharmaceuticals Inc., VA) or Suboxone® (buprenorphine + naloxone, n=10; Reckitt Benckiser Pharmaceuticals Inc., VA) were considered buprenorphine-treated. In utero exposure to buprenorphine was the referent in all analyses. We selected treatment on the day of delivery as the exposure of interest and used this as a surrogate of pregnancy exposure as opioid exposure closest to the time of delivery is thought to have the highest impact on NAS risk[22] and we lacked data on entire treatment trajectories.

Neonatal abstinence syndrome

We identified cases of NAS using pharmacy-billing codes indicating infant pharmacologic treatment with morphine. Therefore, our analysis only accounts for NAS cases that were severe enough to be treated, using treatment as a surrogate of NAS. At Magee-Womens Hospital all infants with known exposure to opioids, both illicit and maintenance, remain in the hospital for five to seven days post-delivery for continuous monitoring for NAS. Infants are scored using the Finnegan Neonatal Abstinence Scoring Tool[23] every 3 to 4 hours; those

with an average score of eight or greater for three consecutive assessments receive treatment with morphine. In our cohort, receipt of morphine was highly correlated with ICD code indicating “Drug Withdrawal Syndrome in Newborn” (kappa>0.99).

Preterm birth

Preterm birth was the mediator in each analysis. For consistency with the literature, we defined preterm birth as live-born delivery prior to 37 weeks’ gestation documented in the pharmacy billing records.[24] We were unable to discern between spontaneous and induced labor and therefore considered both in our definition of preterm birth. Gestational age was determined using the best obstetric estimate from ultrasound or last menstrual period when ultrasound was unavailable. All pregnancies had documented gestational age from 20 to 42 weeks at delivery.

Preterm birth meets the criteria as a potential mediator of the association between opioid maintenance therapy and NAS as (i) methadone has been shown to be associated with preterm birth both in comparison to buprenorphine[7,17,18] and to no opioid maintenance therapy;[15,16] and (ii) preterm infants develop less, or less severe, NAS compared with term infants after exposure to methadone.[19-21,25]

Covariates

We obtained data on medication use, maternal characteristics and pregnancy outcomes from electronic pharmacy records at Magee-Womens Hospital. Information missing from electronic pharmacy records was informed directly from patient charts and birth certificates. Data were therefore a combination of clinical billing codes, documentation by a health professional, and self-report.

Maternal characteristics in the cohort included maternal age, race (Black, White, or other), education (less than high school, high school graduate or equivalent, some college, or college graduate), marital status (yes or no), employment status (employed or unemployed), type of insurance (private or public), and prepregnancy body mass index (BMI, kg/m^2). BMI was calculated as prepregnancy weight in kilograms divided by height in meters squared and was categorised as underweight (BMI <18.5), normal weight (BMI 18.5-24), overweight (BMI 25-29), or obese (BMI ≥30).[26] Data pertinent to the pregnancy included parity, hepatitis c status (positive or negative), smoking status (smoked at any time in pregnancy), birthweight, congenital anomalies, and year of delivery.

Statistical analysis

The analytic strategy was to assess the total adjusted association between opioid maintenance therapy and NAS treatment, then to define the controlled direct effect of opioid therapy on NAS treatment by removing the effect of preterm birth.[27] The difference between these associations represented the effect of preterm birth. Causal diagrams were used to identify potential confounders of the overall relationship between opioid maintenance therapy and NAS, and of the preterm birth-NAS association.[28,29] Variables identified as potential confounders of the opioid maintenance therapy-NAS total association included maternal age, race, marital status, employment status, type of insurance, parity, hepatitis c

status, smoking status, and year of delivery. Final models of the preterm birth- NAS association were adjusted for parity, maternal race, age, smoking status, and marital status.

We first assessed interactions between treatment and preterm birth. Log-binomial models regressing NAS against treatment (methadone versus buprenorphine) were performed with and without the treatment and an interaction term for treatment-by-preterm birth. Because the risk ratio changed by less than 10% with the inclusion of the interaction term, interaction between exposure and mediator was considered insignificant and was not included in the final models.

The primary analysis evaluating mediation by preterm birth adjusted for confounders marginally using inverse probability weighting.[27] This approach can estimate the direct effects in the presence or absence of exposure-induced mediator-outcome confounding. To execute this analytic approach, we used two log-binomial regression models weighted by stabilised inverse probability weights. The weights were generated from modelling methadone exposure then preterm birth as a mediator. Weights were calculated as:

$$sw = \begin{cases} \frac{P(X=1)}{P(X=1|Cxy)} \times \frac{P(M=1)}{P(M=1|Cmy)}, \text{ if } X=M=1 \\ \frac{P(X=0)}{P(X=0|Cxy)} \times \frac{P(M=1)}{P(M=1|Cmy)}, \text{ if } X=0 \text{ and } M=1 \\ \frac{P(X=1)}{P(X=1|Cxy)} \times \frac{P(M=0)}{P(M=0|Cmy)}, \text{ if } X=1 \text{ and } M=0 \\ \frac{P(X=0)}{P(X=0|Cxy)} \times \frac{P(M=0)}{P(M=0|Cmy)}, \text{ if } X=M=0 \end{cases}$$

where X denotes treatment (X=1 if methadone or X=0 if buprenorphine), M represents preterm birth (M=1 if term birth or M=0 if preterm birth), and C represents potential confounders included in the model (described above). In the models, Y indicated NAS (Y=1 if infant treated for NAS or Y=0 no treatment for NAS). The numerators represent the predicted probabilities from logistic regression models of treatment and preterm birth and the denominators replicate this model but adjusted for the confounding variables. All stabilised weights had a mean of one with no extreme values.

Weights were then incorporated into two log-Binomial regression models: (i) modelling the total effect of methadone treatment on NAS compared with buprenorphine; (ii) the controlled direct effect of methadone on NAS among term births. Results were reported on both the risk difference (RD) and risk ratio (RR) scale. Standard errors were obtained using robust variance estimators, which accounts for pseudo-clustering induced by the inverse probability weights, and the correlation within women with multiple pregnancies.[30] Finally, the proportion increase in the association in term births was calculated as the absolute value of: [(Total effect−Controlled Direct Effect)/Total effect] × 100.[31]

To confirm the results, we implemented a mediation analysis conditionally adjusting for the same variables using the generalised product method.[32] While this approach can accommodate exposure-mediator interactions, it cannot account for mediator-outcome confounders affected by the exposure. However, as demonstrated in our causal diagrams, we suspected that no such mediator-outcome confounders were present, and the analyses

suggested no exposure-mediator interactions with the available, measured confounders. If these assumptions are true, the generalised product method should yield results identical to the inverse probability weighted approach.

Sensitivity analysis

We previously demonstrated minimal impact from unmeasured confounding by severity of addiction on the total association between opioid maintenance therapy and NAS[33]; however, we undertook a sensitivity analysis to evaluate the role of unmeasured confounding by prepregnancy BMI on the Controlled Direct Effect. We implemented an approach developed by VanderWeele et al[34] that addresses unmeasured confounding, and used this to simultaneously address the impact of missing data for maternal prepregnancy BMI. We classified BMI as obese (BMI≥30 kg/m^2) vs not obese (BMI<30 kg/m^2). Classification of missing data and thereby prevalence of obesity by opioid maintenance therapy and preterm birth were varied for evaluation. Analyses were first conducted assuming all missing maternal weights were obese (Supporting Information: Sensitivity Analysis 1 and 3), then conducted once again assuming all women with missing weights were not obese (Supporting Information: Sensitivity Analyses 2 and 4). Next, because the degree of missing BMI may vary by preterm birth status, we considered different values for the prevalence of obesity based on preterm birth status (Supporting Information: Sensitivity Analyses 3a-4b).

Results

In the cohort, 57% (n=407) women were treated with methadone and the remaining 43% (n=309) with buprenorphine on the day of delivery. Nearly 20% of the final sample was born preterm, and 58% developed NAS. Women with a preterm birth were more likely than women with a term delivery to have less than a high school education, smoke during pregnancy, have a higher parity (Table 1). Race, maternal age, measured prepregnancy BMI, marital, employment, and hepatitis C status were not different between groups. The preterm infants were lighter at birth and more often had a birth defect than infants delivered at term. The incidence of NAS treatment was higher in methadone compared with buprenorphine-exposed infants (65% vs. 49%), and term infants compared with preterm infants [64% (363/570) versus 36% (52/146); Table 2]. Rates of preterm birth were also higher in methadone versus buprenorphine treated women [25% (103/407) versus 14% (43/309)].

Associations between type of opioid maintenance treatment and NAS are displayed in Table 3. On the absolute risk scale, for every 100 live-born infants exposed to opioid maintenance therapy in utero, there were 13 more cases of NAS among infants exposed to methadone compared with buprenorphine (RD 13.3, 95% CI 5.7, 20.9). When the mediating role of preterm birth was accounted for, the RD increased to 16.7 (95% CI 9.3, 24.0). These findings suggested an estimated 25% increase in the association among term births.

Assessing the associations on a relative scale resulted in a total increased relative risk of NAS of 1.26 (95% CI 1.10, 1.45) for women treated with methadone compared with buprenorphine. When the mediating role of preterm birth was accounted for, the relative risk of NAS increased to 1.34 (95% CI 1.17, 1.53). The results on the relative scale support the findings of an increased risk of NAS with methadone compared with buprenorphine that was

stronger among term births. Results were not meaningfully different when the generalised product method was used to assess mediation (proportion explained on RD scale=24.8% vs. 24.9%; supplemental Table 2).

Sensitivity analysis for unmeasured confounding

Bias estimates ranged from 0.99 to 1.02 depending on classification of missing BMI suggesting that the true association for the Controlled Direct Effect lies between 1.31 to 1.35. This demonstrates that, under our bias-analysis specifications, the potential confounding due to unmeasured BMI is minimal (Supporting Information). Results were not meaning different when the prevalence of obesity was varied based on preterm birth status.

Comment

Principal findings

Results from this study support earlier findings that risk of NAS is decreased in buprenorphine- compared with methadone-exposed infants. We advanced this research by further decomposing the association between methadone treatment and NAS compared with buprenorphine and finding that the association was stronger among term births compared with preterm births. As prolongation of pregnancy to term delivery is preferable when possible, this conclusion supports expanded use of, and access to, buprenorphine in women eligible for this therapy. Sensitivity analyses results suggest these findings are subject to minimal bias from unmeasured confounding and missing prepregnancy BMI.

Interpretation

This study expands upon previous work arguing the need to properly address gestational age in studying the association between opioid maintenance therapy and NAS,[35] by being the first to describe the role of preterm birth and to quantify to what extent it may influence the association. Regression adjustment for gestational age, an approach often implemented in the literature,[8,364] is inappropriate. Due to temporality, gestational age at delivery is a potential *result* of opioid maintenance therapy- and cannot be a *predictor* of treatment type.

Strengths of the study

Despite these limitations, our approach is characterised by several strengths. First, we found the same results using inverse probability weighted regression and the generalised product method, which suggests that our findings are robust to model misspecification. Second, we performed an empirically informed sensitivity analysis that simultaneously evaluated the extent to which unmeasured confounding by prepregnancy BMI impacted our results and the role of differential missingness of this variable. Results demonstrated little to no effect from such biases. We relied on pharmacy records only for identification of women receiving opioid maintenance therapy; each treatment type and dose was confirmed by extraction directly from the chart for all 716 women. Finally, to date, this is the largest study comparing these opioid maintenance therapies in actively treated pregnant women at one institution in the US.

Limitations of the data

As with all studies using observational data, interpreting the associations causally require assumptions of positivity, no interference, exchangeability, and counterfactual consistency.[37] In this work, positivity and no interference pose little to no threats to the validity of the inferences. Positivity requires the presence of both exposed and unexposed term and preterm infants in all confounder strata. This assumption is verifiable, and held in the setting, as evidenced by the distribution of our stabilised inverse probability weights. No interference requires that the outcome of any given infant is not affected by the opioid maintenance therapy or preterm birth status of any other infant, and is a reasonable assumption to make. Exchangeability requires no uncontrolled information, selection, or confounding bias. As with other studies, we were unable to control for the prescribing preference for methadone versus buprenorphine. However, we have previously reported that unmeasured confounding by severity of addiction had little impact on the association between methadone and NAS compared with buprenorphine.[33]

We also lacked data on treatment trajectories, urine toxicology data, and gestational age at initiation and therefore assumed that treatment remained constant throughout pregnancy. Though this could introduce immortal time bias if women receiving opioid maintenance therapy were not converted to treatment until after 37 weeks,[38] a detailed chart review we undertook in a subset of this cohort (n=200) found that no women were initiated on treatment after 36 weeks.[33] The absence of trajectories also prohibited the presentation of true ‘directed’ acyclic graphs. We were unable to establish temporality of certain associations. For example, it is reasonable to assume that lack of insurance could influence treatment type if a woman cannot afford certain treatments. Conversely, it is also reasonable to assume that a woman receiving methadone may be less likely to be employed and therefore have no insurance. Finally, a lack of treatment history also prevented the evaluation of cumulative exposure. If NAS is influenced by a cumulative effect or sensitive exposure window we were unable to asses this. We chose to utilize the day of delivery as our exposure of interest as complete pregnancy treatment data were unavailable and because this is thought to be the most strongly associated with NAS.[22]

A noteworthy limitation of this work is our assumption that the relationships between opioid maintenance therapy-preterm birth and preterm birth-NAS are causal. Though a large body of work supports the notion that methadone affects preterm birth,[7,15-18] research devoted to better understanding the mechanisms by which gestational age influences NAS is needed. Information on this relationship is limited as the pathophysiologic response associated with NAS is not fully understood. Therefore, it remains unknown whether the association between gestational age and NAS is attributable to a bias existing as Finnegan Scores were developed for term infants alone and symptoms in preterm may vary, or if a true difference in response to opioid exposure exists. This complication jeopardizes the validity of the counterfactual consistency assumption, an assumption that is commonly violated with measures of gestational age and preterm birth.[39] There are many potential biologic mechanisms explaining why preterm infants may experience less NAS, including opioid receptor network immaturity, differential development of neurotransmitters, increased placental transfer of the opioid as pregnancy progresses, less fatty tissues available for

methadone distribution in preterm infants, and/or less cumulative exposure to opioids.[40] Lastly, we did not have data specifying if preterm births were spontaneous or induced, nor conditions associated with each (e.g. preeclampsia).

Conclusions

Buprenorphine is not the ideal treatment for all women seeking care; numerous social, behavioral, and biological factors must be considered when initiating opioid maintenance therapy. Nevertheless, our study emphasizes that it is crucial to accurately assess the risk of NAS associated with each treatment, while appropriately accounting for gestational age, in order to inform clinical practice and guide treatment decisions for pregnant women initiating care. Though previous research has established less risk of NAS associated with buprenorphine, we found that the increased risk of NAS after methadone exposure in utero compared with buprenorphine was stronger among a population of term than preterm births. These results support expanded use of buprenorphine as opioid maintenance therapy with the aim of decreasing NAS, adding additional incentive to providers and insurance companies to expand access through prescribing availability and medication coverage. Future work is needed to assess the impact of gestational age on additional maternal and infant outcomes known to be associated with opioid maintenance therapy as NAS is not the only outcome influencing treatment decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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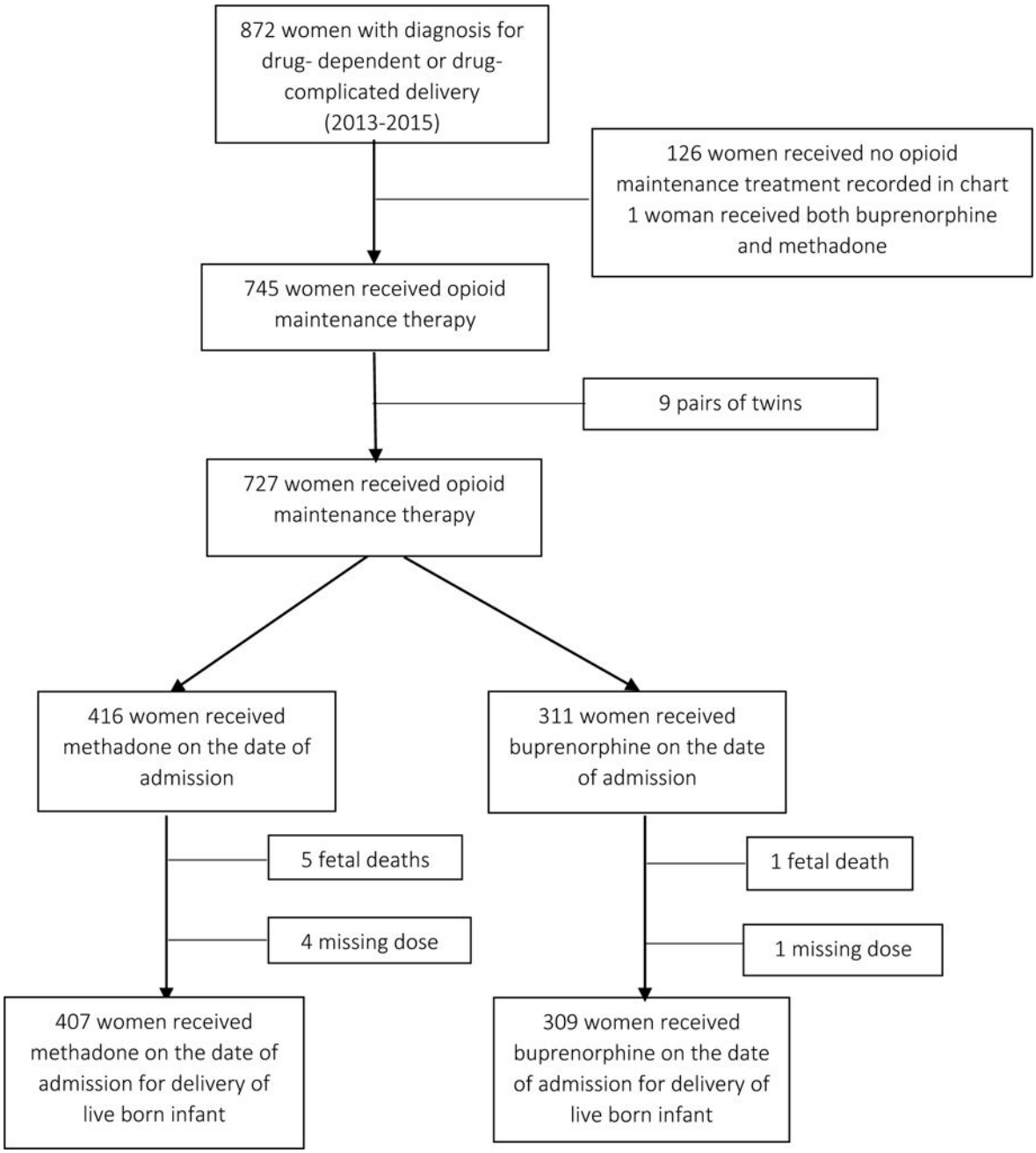

Figure 1.
Flow diagram describing sample population (n=716, 2013-2015*Note: 25 women with 2 pregnancies).

Table 1

Demographic characteristics of women diagnosed with drug-dependent deliveries of singletons based on preterm birth status at Magee-Women Hospital in Pittsburgh, Pennsylvania (2013-2015, n=716)

Characteristic	Preterm birth n (%)	Term birth n (%)
Total number of births	146	570
Opioid maintenance therapy		
Buprenorphine	43 (29.5)	266 (46.7)
Methadone	103 (70.5)	304 (53.3)
Race		
White	136 (93.2)	539 (94.6)
Black	7 (4.8)	20 (3.5)
Other/Unknown	3 (2.0)	11 (1.9)
Mother's age [Mean (SD)]	29.2 (4.7)	28.7 (4.8)
Mother's education		
Less than high school	35 (24.0)	93 (16.3)
High school graduate or GED completed	52 (35.6)	252 (44.2)
Some college credit	34 (23.3)	112 (19.7)
College graduate	20 (13.7)	100 (17.5)
Unknown	5 (3.4)	13 (2.3)
Prepregnancy BMI [Mean (SD)][a]	24.6 (6.5)	24.4 (5.5)
BMI category[a,b]		
Underweight	5 (7.8)	23 (7.9)
Normal weight	38 (59.4)	172 (58.9)
Overweight	21 (32.8)	97 (33.2)
Obese	8 (5.5)	45 (7.9)
Married	19 (13.0)	74 (13.0)
Employed	52 (35.6)	222 (39.0)
Smoked during pregnancy	129 (88.4)	456 (80.0)
Parity		
Nulliparous	43 (29.5)	181 (31.8)
1-2 previous pregnancies	67 (45.9)	292 (51.2)
Greater than 2 pregnancies	36 (24.6)	97 (17.0)
Hepatitis C positive	15 (10.3)	77 (13.5)
Birthweight [Mean (SD)]	2091 (588)	3043 (459)
Gestational age at delivery [Mean (SD)]	33.6 (3.0)	39.0 (1.2)
Diagnosed with congenital anomaly	21 (14.4)	56 (9.8)

SD=standard deviation; GED=general educational development; BMI=body mass index

[a]Prepregnancy BMI based on n=356.

[b]Prepregnancy BMI defined as underweight (<18.5 kg/m^2), normal weight (18.5-24 kg/m^2), overweight (25-29 kg/m^2), or obese (≥30 kg/m^2).

Table 2

Risk of neonatal abstinence syndrome (NAS) by opioid maintenance treatment and preterm birth status

Treatment	Term births		Preterm births		Total births
	With NAS	Without NAS	With NAS	Without NAS	
Methadone, n (%)	223 (55)	81 (20)	40 (10)	63 (15)	407 (100)
Buprenorphine, n (%)	140 (45)	126 (41)	12 (4)	31 (10)	309 (100)
Total	363 (51)	207 (29)	52 (7)	94 (13)	716 (100)

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Table 3

Opioid maintenance therapy (OMT) and neonatal abstinence syndrome (NAS) association and OMT-NAS association not attributable to preterm birth in women exposed to opioid maintenance therapy at Magee-Womens Hospital, 2013 to 2015 using inverse probability weighted marginal structural models (n=716)

	Events (n)	Population at risk (n)	Risk (%)	Risk difference (%) (95% confidence interval)		Risk ratio (95% confidence interval)		Proportion explained on risk difference scale
				Total association	Association not attributed to preterm birth	Total association	Association not attributed to preterm birth	Proportion of total avoided by preterm birth
Methadone	263	407	64.6	13.3 (5.7, 20.9)	16.7 (9.3, 24.0)	1.26 (1.10, 1.45)	1.34 (1.17, 1.53)	24.9%
Buprenorphine	152	309	49.2	0.0 (Reference)	0.0 (Reference)	1.00 (Reference)	1.00 (Reference)	

[a] Linear risk models adjusted for parity, maternal race, age, employment status, smoking status, marital status, hepatitis c status, private versus public insurance, and year of delivery

[b] Poisson regression models adjusted for parity, maternal race, age, employment status, smoking status, marital status, hepatitis c status, private versus public insurance, and year of delivery