Periconceptional Use of Opioids and the Risk of Neural Tube Defects

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OBJECTIVE: Opioid medications are among the most effective analgesics. However, the consequences of opioid exposure to the developing human offspring are not known. We assessed whether maternal opioid use in the periconceptional period was associated with the risk of neural tube defects in the offspring.

METHODS: We used data from 1998 to 2010 from the Slone Epidemiology Center Birth Defects Study, an ongoing case–control study. Mothers were interviewed by telephone within 6 months of delivery about sociodemographic factors and exposures during pregnancy including detailed questions on type and timing of medication use. Mothers of 305 offsprings with neural tube defect were compared with mothers of 7,125 offsprings in the nonmalformed control group and 13,405 offsprings in the malformed control group. Periconceptional opioid use was defined as any reported use in the 2 months after the last menstrual period. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for study center.

RESULTS: A higher percentage of mothers of offsprings with neural tube defects (3.9%) reported using an opioid medication than mothers of offsprings in the nonmalformed control group (1.6%) and offsprings in the malformed control group (2.0%) with adjusted ORs of 2.2 (95% CI 1.2 −4.2) and 1.9 (95% CI 1.0 −3.4), respectively. When offsprings were restricted to those with spina bifida, the adjusted ORs were 2.5 (95% CI 1.3–5.0) and 2.2 (95% CI 1.1–4.1), respectively.

CONCLUSION: A 2.2-fold increase in risk would translate to a neural tube defect prevalence of 5.9 per 10,000 live births among women who use opioids. Overall, opioid use in the periconceptional period appeared to be associated with a modest increased risk of neural tube defects.

(Obstet Gynecol 2013;122:838–44)

DOI: 10.1097/AOG.0b013e3182a6643c

LEVEL OF EVIDENCE: II

Opioid medications are effective analgesics and are among the most commonly prescribed drugs in the United States.[1–3] Estimates of the prevalence of opioid use among women of reproductive age range widely, from 1.5% to 23%, but exposure appears to be increasing over time.[4–7] The prevalence of use is similar among pregnant women and ranges from 2% to 20%.[7,8] When temporal trends of first-trimester use among pregnant women were examined, the prevalence more than doubled from 8.6% in 1995 to 20.1% in 2009.[8]

Opioids cross the placenta[9] and have been detected in the umbilical cord, placenta, and meconium,[10,11] but the effects of opioid exposure on the developing human fetus are not known.[10,11] In animal studies, exposure to codeine, heroin, hydromorphone, meperidine,

From the Slone Epidemiology Center at Boston University, Boston, Massachusetts; and the National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

Supported by the Centers for Disease Control and Prevention (DD000697).

The authors thank Dawn Jacobs, RN, MPH, Fiona Rice, MPH, Rita Krolak, RN, Kathleen Sheehan, RN, Moira Quinn, RN, Clare Coughlin, RN, Laurie Cincotta, RN, Mary Thibeault, RN, Nancy Rodriquez-Sheridan, Ileana Gatica, Laine Catlin Fletcher, Carolina Meyers, Joan Shander, Julia Venanzi, Mark Abcede, and Judy Jean, RN, for their assistance in data collection; Katherine Kelley, RPh, for assistance in classifying of medications; and Nastia Dynkin for computer programming.

Presented as a poster at the 7th International Conference on Neural Tube Defects, November 6–9, 2011, Austin, Texas.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Financial Disclosure

Dr. Werler is on advisory boards of manufacturer-sponsored studies that evaluate pregnancy outcomes among women treated with medications for rheumatoid arthritis. Dr. Mitchell owned stock (until August 2012) in Johnson & Johnson, which markets various analgesics; he also serves on the advisory committee of the Biogen-Idec, Tysabri Pregnancy Registry. The other authors did not report any potential conflicts of interest.

ISSN: 0029-7844/13

methadone, morphine, and propoxyphene during critical periods of gestation can lead to anomalies of the central nervous system.[12–15] Two epidemiologic studies also suggest that there may be an association between opioids as a class and central nervous system anomalies, specifically neural tube defects, with odds ratio (ORs) ranging from 1.7 to 2.9.[7,16] Few studies had sufficient numbers of exposed cases to examine individual opioids, but those that have observed an increased risk of neural tube defects with codeine and hydrocodone.[7,17]

The objective of our study was to examine whether the risks of neural tube defects were increased among mothers with opioid use in the periconceptional period, the gestational time of neural tube defect development, and whether risks were higher for subgroups of opioid medications.

MATERIALS AND METHODS

The Birth Defects Study (also known as the Pregnancy Health Interview Study) is an ongoing case–control study conducted by the Slone Epidemiology Center at Boston University. The study began in 1976 and the methods have been previously described in detail.[18–20] For the present analysis, cases were ascertained from birth hospitals and tertiary care centers in the greater metropolitan areas of Boston, Massachusetts; Philadelphia, Pennsylvania; Toronto, Canada; San Diego County, California; and from birth defect registries in Massachusetts and New York state. For the hospital-based centers, study staff identified cases from clinical and surgical logs, discharge lists, and newborn nurseries. The study has been approved by the institutional review board at Boston University and other institutions, as appropriate, and is in compliance with the Health Insurance Portability and Accountability Act. For this analysis, the data were restricted to the years 1998–2010.

Cases included liveborn offsprings, terminations, and fetal deaths after 20 weeks of gestation, although the latter two groups were not routinely ascertained. For the present analysis, cases consisted of infants with anencephaly, encephalocele, or spina bifida. Excluded were conjoined twins and infants affected by chromosomal anomalies, Mendelian-inherited disorders, known syndromes, amniotic bands, or body wall defects. Offsprings in the case group were considered "isolated" if they had no other major structural malformation. Liveborn offsprings with no major malformations were selected for the control group (nonmalformed group) from the same birth hospitals as offsprings in the case group or from a random sample of statewide birth records (Massachusetts only). Telephone interviews were conducted within 6 months of delivery by trained study nurses. The computer-assisted interview included questions on demographic information, reproductive history, parental occupations, behavioral factors during pregnancy (eg, cigarette smoking, alcohol and caffeine consumption), dietary history, illness history, and details of medication and vitamin use. In the medication section, mothers were specifically asked if they had taken any medications for "migraine," "headache," "backache," "joint or muscle pain, sprains, or injury," "other pains," "any other drugs (cocaine, crack, marijuana, or any others)," and "other indications." No specific prompts were used to identify use of illicit opioids (eg, heroin). The Slone Drug Dictionary[4] was used to identify which of the medications reported were opioids, defined as a substance that binds to the opioid receptors in the body. Exposure was defined as reported use of an opioid in the periconceptional period–that is, in the two 28-day months after the mother's last menstrual period. Women who were uncertain of their exposure dates or only reported opioid use outside the periconceptional period were not included in the analysis.

The distribution of opioid exposures was compared between mothers of offsprings in the case group and those in the control group, and logistic regression models were used to estimate ORs and 95% confidence intervals (CIs). Sociodemographic factors that were considered as potential confounders included study center (Boston, Philadelphia, Toronto, San Diego, New York), maternal race or ethnicity (non-Hispanic white, non-Hispanic African American, Hispanic, Asian, other), maternal age (younger than 20, 20–24, 25–29, 30–34, 35–39, 40 years or older), maternal education (less than 12 years, 12 years, 12 years or more), prepregnancy body mass index (calculated as weight (kg)/[height (m)]^2; less than 18.5, 18.5 to less than 25, 25 to less than 30, 30 or greater), pregnancy intention (intended or unintended), gestational diabetes (yes or no), smoking (yes or no), use of folic acid-containing multivitamins (no use, consistent use, inconsistent use), illicit street drugs (yes or no), and concomitant medications for pain (yes or no). Each factor was added into the model one at a time and if the OR for opioid use changed by more than 10%, the factor was included in the final model. As a result of the small number of anencephaly and encephalocele cases, only spina bifida cases were assessed separately. Given previously reported associations with codeine, we separately considered codeine-containing products and noncodeine-containing opioids. The number of exposed cases was insufficient to permit risk estimation for specific opioids.

Case–control studies of birth defects are often thought to be subject to recall bias. This concern arises over suspicion that mothers with malformed offsprings may under- or overreport their exposures, possibly out of guilt or enhanced recall, respectively. There is little evidence to suggest this is the case,[21] but to assess the possibility of such a bias, we used a second control group consisting of mothers of infants with a wide range of malformations other than neural tube defects. Mothers in this control group are assumed to have similar reporting accuracy as mothers of offsprings in the case group. All analyses were conducted separately for offsprings in the nonmalformed control group and offsprings in the malformed control group.

A sensitivity analysis was conducted in which nonneural tube defect birth defects that had previously been associated with opioid use were removed from the malformed control group. Based on the Broussard et al study, which examined opioid use and a wide range of birth defects,[7] birth defects with an adjusted OR greater than 1.3 were removed from the malformed control group for this analysis.

Two additional sensitivity analyses were performed to assess the possibility of selection bias. The first was prompted by the lack of an appropriate control group for cases that ended in terminations and the underascertainment of terminations, stillbirths, and neonatal deaths. In our study, terminations of offsprings with no birth defects were not ascertained. Even if they had been, these women would not necessarily be the optimal control group because women who terminate for reasons other than a birth defect may differ in various characteristics. Therefore, the first sensitivity analysis restricted the cases and both control groups to only liveborn offsprings. The second analysis was prompted by the fact that a nonmalformed offsprings in the control group could come from a study hospital from which we had no neural tube defect cases; in such a situation, it would be possible that the control population would not represent the base population that gave rise to cases, which could introduce selection bias. The sensitivity analysis was thus restricted to cases and nonmalformed controls from the same birth hospitals. All analyses were performed using SAS 9.1 software.

RESULTS

Of the mothers contacted by telephone, 65% of nonmalformed offsprings in the control group and 68% of offsprings in the case group with any major malformation provided consent and participated in the interview. A total of 305 offsprings with neural tube defects were identified, of which 220 had spina bifida, 51 had anencephaly, 30 had encephalocele, three had both spina bifida and encephalocele, and one had both spina bifida and anencephaly. The nonmalformed group and the malformed control group consisted of 7,125 offsprings and 13,405 offsprings, respectively. Maternal demographic and behavioral characteristics are presented in Table 1. A small proportion of women were excluded as a result of uncertain dates of exposures (0.5% of offsprings in the nonmalformed control group and 0.6% of offsprings in the malformed control group) or reporting opioid use only outside the periconceptional period (4.1% of case offsprings, 4.6% of nonmalformed controls, and 4.7% of malformed controls). Fifteen different opioids (codeine, oxycodone, hydrocodone, morphine, propoxyphene, meperidine, methadone, tramadol, hydromorphone, butorphanol, heroin, fentanyl, buprenorphine, nalbuphine, and diphenoxylate) were reported as having been used in the periconceptional period exposure window. For each outcome group, the most commonly reported specific agents were codeine, oxycodone, and hydrocodone.

Maternal report of indications for opioid use in the periconceptional period varied and were grouped into the following categories: pain (joint or muscle pain, sprains, injury, backache, arthritis, cramps, menstrual problems, or other unspecified pains), headache (migraine or headache), infections (cold, flu, cough, bronchitis, pneumonia, sinusitis, sinus infection, congestion, strep throat, ear infection, stomach flu, or urinary tract infection), dental (toothache, tooth abscess, or dental procedure), medical procedures (gynecologic, infertility, hospitalization, or other unspecified medical procedures), other (allergies, asthma, seizures, high blood pressure, sleeping problems, nausea and vomiting, stomach problems, vaginal bleeding, yeast or vaginal infections, or not otherwise specified conditions), and abuse (or its treatment). The last indication included reports of heroin, methadone, and buprenorphine as well as oxycodone and hydrocodone when the mother's volunteered response suggested abuse. As a result of acetaminophen with codeine being readily available over the counter in Canada, some indications that are not typically treated with opioids (eg, stomach flu, yeast infections) were reported by mothers. The most frequently reported reason for using an opioid among all mothers was pain followed by headache (Table 2).

Mothers of offsprings with neural tube defects reported more opioid use during the periconceptional period (3.9%) than mothers of offsprings in the nonmalformed (1.6%) and malformed control groups (2.0%)

Table 1. Maternal Demographic and Behavioral Characteristics of Cases and Controls, Birth Defects Study, 1998–2010

Characteristic	Neural Tube Defects	Nonmalformed Control Group	Malformed Control Group
Total	305 (100)	7,125 (100)	13,405 (100)
Maternal race or ethnicity			
White, non-Hispanic	182 (59.7)	4,980 (69.9)	8,576 (64.0)
African American, non-Hispanic	35 (11.5)	556 (7.8)	1,277 (9.5)
Hispanic	60 (19.7)	1,033 (14.5)	2,314 (17.3)
Asian	23 (7.5)	400 (5.6)	847 (6.3)
Other	5 (1.6)	150 (2.1)	365 (2.7)
Missing data	0 (0.0)	6 (0.1)	26 (0.2)
Maternal age at conception (y)			
Younger than 20	21 (6.9)	515 (7.2)	1,100 (8.2)
20–24	48 (15.7)	994 (14.0)	2,118 (15.8)
25–29	103 (33.8)	1,857 (26.1)	3,318 (24.8)
30–34	84 (27.5)	2,418 (33.9)	4,056 (30.3)
35–39	45 (14.8)	1,149 (16.1)	2,231 (16.6)
40 or older	4 (1.3)	171 (2.4)	569 (4.2)
Missing data	0 (0.0)	21 (0.3)	13 (0.1)
Maternal education (y)			
Fewer than 12	41 (13.4)	660 (9.3)	1,696 (12.7)
12	68 (22.3)	1,294 (18.2)	2,863 (21.4)
More than 12	196 (64.3)	5,165 (72.5)	8,826 (65.8)
Missing data	0 (0.0)	6 (0.1)	20 (0.1)
Birth status			
Liveborn	205 (67.2)	7,118 (99.9)	12,654 (94.4)
Terminations	76 (24.9)	0 (0.0)	333 (2.5)
Stillborn	1 (0.3)	1 (0.0)	17 (0.1)
Neonatal death	23 (7.5)	5 (0.1)	338 (2.5)
Infant death	0 (0.0)	1 (0.0)	63 (0.5)
Diabetes			
Gestational diabetes	16 (5.2)	327 (4.6)	854 (6.4)
No report of gestational diabetes	289 (94.8)	6,798 (95.4)	12,551 (93.6)
Periconceptional vitamin use*			
No use	88 (28.9)	1,515 (21.3)	3,187 (23.8)
Consistent use	127 (41.6)	3,063 (43.0)	5,321 (39.7)
Inconsistent use	90 (29.5)	2,547 (35.7)	4,897 (36.5)
Maternal smoking in the first lunar month of pregnancy			
Never or former smoker	248 (81.3)	5,996 (84.2)	10,953 (81.7)
Smoked during pregnancy	57 (18.7)	1,128 (15.8)	2,452 (18.3)
Unknown	0 (0.0)	1 (0.0)	0 (0.0)
Study center			
Boston	42 (13.8)	3,718 (52.2)	3,266 (24.4)
Philadelphia	99 (32.5)	1,448 (20.3)	4,404 (32.9)
Toronto	90 (29.5)	649 (9.1)	2,422 (18.1)
San Diego	44 (14.4)	946 (13.3)	2,094 (15.6)
New York	30 (9.8)	364 (5.1)	1,219 (9.1)
Maternal BMI (kg/m^2)			
Lower than 18.5	17 (5.6)	418 (5.9)	734 (5.5)
18.5 to less than 25	155 (50.8)	4,406 (61.8)	7,516 (56.1)
25 to less than 30	65 (21.3)	1,357 (19.0)	2,779 (20.7)
30 or higher	53 (17.4)	785 (11.0)	1,973 (14.7)
Missing data	15 (4.9)	159 (2.2)	403 (3.0)

BMI, body mass index.
Data are n (%).
* Periconceptional use included the 2 lunar mo before or 1 mo after the last menstrual period.

Table 2. Reported Opioid Use in the Periconceptional Period by Indication, Birth Defects Study, 1998–2010

Indication	Neural Tube Defects	Nonmalformed Control Group	Malformed Control Group
Pain	6 (2.0)	59 (0.8)	115 (0.9)
Infection	2 (0.7)	4 (0.1)	39 (0.3)
Headache	2 (0.7)	21 (0.3)	63 (0.5)
Dental	1 (0.3)	13 (0.2)	39 (0.3)
Illicit use	1 (0.3)	6 (0.1)	18 (0.1)
Medical procedure	0 (0.0)	9 (0.1)	10 (0.1)
Other*	1 (0.3)	11 (0.2)	22 (0.2)

Data are n (%).
* Other indications included: allergies, asthma, nausea or vomiting, seizures, high blood pressure, stomach problems, sleeping problems, vaginal infections, or not otherwise specified conditions.

(Table 3). The mean duration of opioid use reported by mothers was 87.4, 84.8, and 89.3 days for offsprings with neural tube defects, offsprings in the nonmalformed control group, and offsprings in the malformed control group, respectively. Only study center met the criterion for confounding and was included in the final model; of note, folic acid did not confound our associations although folic acid has been found to reduce the risk of spina bifida. When the nonmalformed control group was used, the adjusted OR for mothers who reported any opioid medication in the periconceptional period was 2.2 (95% CI 1.2–4.2). When the data were restricted to offsprings with spina bifida, the adjusted OR was 2.5 (95% CI 1.3–5.0). When opioids were subgrouped according to codeine or noncodeine opioids, the ORs for neural tube defects were not materially different, although a somewhat higher risk for spina bifida was observed for noncodeine opioids (OR 2.8, 95% CI 1.3–6.3). When opioid use was restricted to only those who reported it for pain, the most commonly reported indication for use, the estimates remained elevated with adjusted ORs of 2.0 (95% CI 0.8–4.8) and 2.2 (95% CI 0.9–5.7) for neural tube defects and spina bifida, respectively, although the CIs included 1.0. Among the 162 offsprings with spina bifida considered isolated, mothers of seven (4.3%) reported opioid use in the periconceptional period, and ORs did not change substantially (data not shown).

The observed pattern of results held when malformed controls were used, although the estimates were slightly attenuated (Table 3). When previously associated nonneural tube defect birth defects were removed from the malformed control groups, the prevalence of opioid use remained the same among the malformed

Table 3. Associations Between Opioid Medications and Neural Tube Defects, Birth Defects Study, 1998–2010

	Case Group	Nonmalformed Control Group			Malformed Control Group		
	n (%)	n (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)	n (%)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Any opioids							
All neural tube defects	12 (3.9)	114 (1.6)	2.5(1.4–4.6)	2.2 (1.2–4.2)	281 (2.0)	1.9 (1.1–3.4)	1.9 (1.0–3.4)†
Spina bifida	10 (4.5)	114 (1.6)	2.9 (1.5–5.6)	2.5 (1.3–5.0)	281 (2.0)	2.2 (1.2–4.2)	2.2 (1.1–4.1)†
Codeine‡							
All neural tube defects	6 (2.0)	36 (0.5)	4.0 (1.7–9.5)	2.5 (1.0–6.3)	109 (0.8)	2.5 (1.1–5.7)	2.0 (0.9–4.7)
Spina bifida	4 (1.8)	36 (0.5)	3.6 (1.3–10.3)	2.5 (0.9–7.4)	109 (0.8)	2.3 (0.8–6.2)	2.0 (0.7–5.5)
Non-codeine‡							
All neural tube defects	7 (2.3)	83 (1.1)	2.0 (0.9–4.4)	2.2 (1.0–4.9)§	181 (1.4)	1.7 (0.8–3.7)	1.9 (0.9–4.1)†
Spina bifida	7 (3.1)	83 (1.1)	2.8 (1.3–6.0)	2.8 (1.3–6.3) §	181 (1.4)	2.4 (1.1–5.1)	2.5 (1.1–5.4)†

OR, odds ratio; CI, confidence interval.
* Controlling for study center (referent: Boston).
† No confounders met 10% criteria, but study center included for consistency.
‡ One case, five offsprings in the nonmalformed control group, and 13 offsprings in the malformed control group reported using both a codeine and noncodeine medication and are included in both categories.

control group (1.9%) and adjusted estimates did not change substantially: 2.1 (95% CI 1.1–3.8) and 2.4 (95% CI 1.3–4.7) for neural tube defects and spina bifida, respectively.

When the data were restricted to only liveborn offsprings, ORs were 2.4 (95% CI 1.2–4.9) with the nonmalformed control group and 2.2 (95% CI 1.1–4.3) with the malformed control group. Odds ratios also remained elevated when offsprings in the case group and offsprings in the nonmalformed control group were restricted to those from the same birth hospital: 2.0 (95% CI 1.0 −4.1) and 2.4 (95% CI 1.1 −5.2) for neural tube defects and spina bifida, respectively.

DISCUSSION

Overall, our data support a modestly increased risk of neural tube defects associated with maternal periconceptional opioid use. Based on the most recent prevalence for neural tube defects in the United States,[22] a 2.2-fold increase in risk would translate to a neural tube defect prevalence of 5.9 per 10,000 live births among women who use opioids.

Our results are consistent with other epidemiologic studies of this topic. The National Birth Defects Prevention Study also used a case–control design and reported ORs of 2.0 and 1.7 for spina bifida and anencephaly, respectively, for first-trimester opioid use and stronger associations for hydrocodone but a more modest association for codeine.[7] Bracken and colleagues[16] reported an OR of 2.9 for first-trimester narcotic use and central nervous system anomalies, which included spina bifida. First-trimester codeine use was not associated with central nervous system defects[17] or neural tube defects[23] in two other studies. We observed higher estimates for codeine use, but all the studies had small numbers of exposed women and wide CIs. To better assess individual opioids, larger studies will be needed.

Animal studies showed prenatal opioid exposure can lead to central nervous system malformations,[12] kinking of the spinal cord,[13,14] a reduction in neural tube volume and thickness,[15,24] and inhibited growth of the brain and nervous system.[25,26] Furthermore, opioids cross the blood–brain barrier and are detectable in fetal tissue[26–29] with the highest concentrations in the fetal nervous system.[30] Endogenous opioids and opioid receptors are known to play a role in cell proliferation in the developing brain, organogenesis, DNA synthesis, and are also thought to act as a negative growth regulator.[31,32] Thus, if our observed associations reflect causality, they may reflect an interaction of exogenous opioids with endogenous opioids and their receptors during development, leading to a malformation of the neural tube.[33]

There were limitations to our study. First, numbers of exposed mothers for some analyses were small and the resulting estimates were unstable with CIs that included 1.0. Small numbers also limited our ability to explore associations with specific opioids. In addition, we conducted multiple analyses and cannot rule out the possibility of chance associations. We did not have information on dosage and were not able to assess a dose response. Furthermore, our interview inquired about indications that frequently involve treatment with opioids, not specific opioids, although prompts were thorough and it is likely mothers would recall using an opioid when prompted with various indications.

The prevalence of periconceptional opioid use in our study was 3.9% for offsprings in the case group, 1.6% for offsprings in the nonmalformed control group, and 2.0% for offsprings in the malformed control group. Previous studies report varying prevalences of opioid use in early pregnancy. Broussard and colleagues[7] reported first-trimester opioid use ranging from 2% to 2.6%. Another study using Tennessee Medicaid data reported 14.5% of mothers filled a prescription for an opioid in their first trimester.[8] Neither of these studies included illicit opioid use and although we included reports of opioid abuse, it is likely underreported because we did not explicitly ask about drug abuse.

We cannot rule out the possibility that the observed increased risk for opioid use is the result of the underlying indication. However, multiple and diverse indications were reported by mothers, reducing the likelihood of such confounding.

Another limitation is the possibility of selection bias related to underascertainment of case terminations or fetal losses. Such bias is unlikely to account for our findings, because restricting cases and controls to liveborn offsprings did not change our results. However, if terminations were associated with opioid use, our results may only be generalizable to liveborn offsprings and not all neural tube defects. Similarly, analysis restricted to cases and control mothers from the same hospitals did not materially alter our findings. Selection bias arising from differential participation according to opioid use and case–control status is also a possibility. However, we would expect this differential to be between mothers with and without a malformed child. The similar results observed for both the nonmalformed and malformed control groups suggest participation bias does not account for the observed associations.

These assessments for possible selection bias are among our study's strengths as was the use of a malformed control group to assess the possibility of recall bias. In addition, the short interval between delivery

and interview (6 months or less) reduced concerns of incomplete recall. The medication information collected in the interview was detailed with respect to gestational timing and allowed us to identify use during the relatively narrow window for exposures that may affect neural tube development.

In conclusion, our findings support and extend previous research demonstrating an approximately twofold higher risk for neural tube defects, and particularly spina bifida, with maternal periconceptional opioid use.

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