

Outcomes in pregnancies complicated by methamphetamine use

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OBJECTIVE: Methamphetamine use is widespread. Our goal was to examine the effects of methamphetamine use on various maternal and neonatal outcomes.

STUDY DESIGN: We conducted a retrospective cohort study looking at all pregnancies between 2005 and 2008 in the state of California that were associated with a diagnosis of methamphetamine use. Outcomes examined included gestational hypertension, preeclampsia, preterm birth, small for gestational age, birthweight, abruption, intrauterine fetal death, neonatal death, infant death, jaundice, and gestational diabetes mellitus. Statistical analysis included chi-squared tests and multivariable logistic regression analyses.

RESULTS: After adjustment for multiple confounding variables on multivariable regression analysis, results indicated that compared with control subjects, methamphetamine users had greater odds of

gestational hypertension (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.6–2.0), preeclampsia (OR, 2.7; 95% CI, 2.4–3.0), intrauterine fetal death (OR, 5.1; 95% CI, 3.7–7.2), and abruption (OR, 5.5; 95% CI, 4.9–6.3). Additionally, these patients had higher odds of preterm birth (OR, 2.9; 95% CI, 2.7–3.1), neonatal death (OR, 3.1; 95% CI, 2.3–4.2), and infant death (OR, 2.5; 95% CI, 1.7–3.7).

CONCLUSION: Methamphetamine use in pregnancy was found to be associated with specific patterns of increased maternal and fetal morbidity and death. With these results in mind, further work can be done to improve the care of pregnancies that are complicated by methamphetamine use in hopes of reducing these complications.

Key words: amphetamine, maternal, methamphetamine, neonatal, pregnancy, substance abuse

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Methamphetamine use was once considered an illicit drug use phenomenon endemic to the west coast of the United States. Unfortunately, this geographic divide no longer holds true. Although many of the highest use areas indeed remain in the western states, the use of methamphetamine has spread to reach all 4 corners of the country. According to the United States Drug Enforcement Administration's National Clandestine Laboratory Register, there are known methamphetamine laboratories

in all 50 states, which implies production, sales, and use in each state.¹

According to the National Survey on Drug Use and Health 2012, women 12-44 years old who reported having ever used stimulants, including methamphetamine, represented 7.2% among pregnant women vs 7.1% among non-pregnant women.² In many western and midwestern states, methamphetamine is now the third most commonly abused substance, after alcohol and marijuana, respectively, and an estimated 5.2% of pregnant women in the highest use areas of the United States use the drug at some point during pregnancy according to the Infant Development, Environment and Lifestyle study in 2006.³ Furthermore, in 2006, based on data from the Treatment Episode Data Set, which is a nationwide data system that is maintained by the University of Michigan that tracks admissions into substance treatment facilities that receive federal funding in all 50 states, it was reported that, among pregnant women who sought drug abuse treatment, 1 in 4 reported methamphetamine as their primary drug of abuse.⁴

Effects of the drug on the user are well-established. Furthermore, amphetamines cross the placenta and have been found in fetal organs after in utero exposure.⁵⁻⁷ Early reports suggested an association with an increase in various fetal anomalies⁸⁻¹⁰; however, case control and prospective analyses have not confirmed these associations.¹¹⁻¹³ Moreover, in an assessment of the risk of fetal anomalies after exposure to methamphetamine, the Teratogen Information System (University of Washington, Seattle, WA) database has deemed this unlikely, based on fair-to-good data.¹⁴ Existing research has demonstrated an association between maternal methamphetamine use and an increased risk for intrauterine growth restriction, low birthweight, or small-for-gestational-age neonates.^{13,15-22} Two small studies that evaluated the effects of methamphetamine use among pregnant women have found a statistically significant decrease in birthweight and head circumference among neonates who were born to methamphetamine-abusing mothers, compared with control subjects and after adjustment for gestational age at

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birth.^{13,23} However, many of these studies were small and evaluated limited outcomes. The largest study to date, which was published in 2010 and examined 276 pregnant methamphetamine users, reported a positive association with preterm delivery, low Apgar scores, cesarean delivery, and neonatal death.²⁴

Given this background that includes the wide use of methamphetamines in pregnancy and the relatively small number of studies, we sought to better characterize the associations between methamphetamine use in pregnancy and adverse maternal and neonatal outcomes.

MATERIALS AND METHODS

We conducted a retrospective cohort study that included all pregnancies from 2005 through 2008 in the state of California. The data for these calculations were derived from linked mother-infant datasets from the California Vital Statistics Birth Certificate Data, Vital Statistics Death Certificate Data, California Patient Discharge Data, and Vital Statistics Fetal Death File. Data linkage is performed by the California Office of Statewide Health Planning and Development Healthcare Information Resource Center, under the California Health and Human Services Agency, with the use of a unique record linkage number specific to the mother-infant pair. The state of California maintains these linked datasets that include health information from maternal antepartum and postpartum hospital records for the 9 months before delivery and 1 year after delivery, as well as birth records and all infant admissions that occur within the first year of life. We obtained human subjects approval from the Institutional Review Board at Oregon Health & Science University, the California Office of Statewide Health Planning and Development, and the Committee for the Protection of Human Subjects. The linked dataset did not contain potential patient privacy/identification information, so informed consent was exempted.

Our primary exposure of interest was a diagnosis of methamphetamine use during the pregnancy; we identified 8542 women with pregnancies that were associated with methamphetamine use

with the use of the following *International Classification of Diseases, 9th Revision* (ICD-9) codes: 304.4, 304.40 (dependence, unspecified use), 304.41 (dependence, continuous use), 304.42 (dependence, episodic use), 305.70 (nondependent abuse, unspecified use), 305.71 (nondependent abuse, continuous use), 305.72 (nondependent abuse, episodic use), and 969.72 (poisoning by amphetamines). These 8542 cases were compared with 2,031,328 control pregnancies. To avoid the confounding of complications linked to multifetal gestations and congenital anomalies, we excluded these pregnancies for both the case group and the control group. Analyses were conducted with Stata software (version 12; StataCorp, College Station, TX) and R software (version 2.13.1; R Foundation for Statistical Computing, Vienna, Austria).

Outcomes of interest that we examined were also determined retrospectively through the use of ICD-9 codes and included gestational hypertension, preeclampsia, pregnancy-associated hypertension (defined as gestational hypertension or preeclampsia), severe preeclampsia, severe preeclampsia among those with pregnancy-associated hypertension, eclampsia, abruptio, intrauterine fetal death, preterm delivery (<37 weeks 0 days), very preterm delivery (<32 weeks 0 days), small for gestational age, birthweight <2500 g, birthweight >4000 g, gestational diabetes mellitus, neonatal death, infant death, and neonatal jaundice among those born preterm. Statistical comparisons of categorical variables were made with chi-squared tests. Potential confounders that included maternal age (≥ 35 and <20 years old), maternal education (>12 vs ≤ 12 years), insurance status (private insurance vs public insurance or no insurance), race/ethnicity, parity, diabetes mellitus, chronic hypertension, gestational diabetes mellitus, tobacco use, and alcohol use were controlled for with the use of multivariable logistic regression analyses and excluded those variables that were used as the outcome of interest when appropriate. For example, we did not adjust for gestational diabetes mellitus when we evaluated gestational

diabetes mellitus as an outcome. Those women with exposure to cocaine, opioids, and/or cannabis were also excluded from analysis. Statistical significance was determined by a probability value of $< .05$ and/or 95% confidence intervals (CIs).

RESULTS

With the use of methods described earlier, 8542 pregnancies (0.4%) that were linked to a diagnosis of methamphetamine use were identified and compared with 2,031,328 control pregnancies. Demographic data for the 2 groups is listed in Table 1. In unadjusted analysis (Table 2), there was a statistically significant increase in hypertensive diseases of pregnancy associated with methamphetamine use. Compared with control pregnancies, methamphetamine users had a greater frequency of pregnancy-associated hypertension (11.6% vs 5.8%; $P < .001$), gestational hypertension (5.6% vs 3.2%; $P < .001$), preeclampsia (6.8% vs 2.9%; $P < .001$), severe preeclampsia (2.5% vs 0.8%; $P < .001$), and eclampsia (0.3% vs 0.1%; $P < .001$). Furthermore, among those women who were diagnosed with pregnancy-associated hypertension, the percentage who went on to experience severe preeclampsia was 21.6% among methamphetamine users vs 13.5% among control subjects ($P < .001$).

Gestational age at delivery was also associated with the use of methamphetamine. Preterm birth, which was defined as delivery at <37 weeks 0 days of gestation (23.4% vs 8.9%; $P < .001$), and very preterm birth, which was defined as delivery at <32 weeks 0 days of gestation (5.3% vs 1.2%; $P < .001$), both were increased significantly among methamphetamine users when compared with control subjects.

Methamphetamine use was associated with increased incidence of small-for-gestational-age neonates, when compared with control subjects (18.2% vs 10.6%; $P < .001$), and birthweight <2500 g (17.2% vs 5.0%; $P < .001$).

Methamphetamine users were found to have a higher incidence of abruptio (5.2% vs 0.8%; $P < .001$) and intrauterine fetal death (1.4% vs 0.3%; $P < .001$). Neonatal death was increased among neonates who were born to

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