Roloff et al. J Fam Med Dis Prev 2015, 1:3
ISSN: 2469-5793

Journal of
Family Medicine and Disease Prevention

Original Article: Open Access

Methamphetamine use Increases Chances of Preeclampsia

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Abstract

Objective: To study the effect of methamphetamine use during pregnancy on the chance of developing preeclampsia, and the morbidity due to preeclampsia.

Study design: A single center, retrospective study was performed over an eighteen month period (January 2012 - June 2013) at a county hospital in San Bernardino, California. Methamphetamine use was defined as self-reported use or a positive urine drug screen (UDS) at admission for delivery. Preeclampsia was defined using the American College of Obstetricians and Gynecologists (ACOG) Task Force definition. 1 The incidence of preeclampsia among methamphetamine users was compared to non-users using inferential statistics. A composite outcome of morbidity due to preeclampsia was developed using abruption, eclampsia, HELLP (hemolysis elevated liver enzymes and low platelets) syndrome, elevated aspartate aminotransferase (AST) or alanine transaminase (ALT), thrombocytopenia, intensive care unit (ICU) admission, use of intravenous (IV) antihypertensive agent(s) for blood pressure control, or use of magnesium sulfate for seizure prophylaxis. This composite outcome was compared between methamphetamine users and non-users with preeclampsia.

Results: 3,721 patients were included. During the study, 200 (5.4%) cases of preeclampsia were identified. Ninety-nine (2.6%) patients had positive urine drug screen tests for methamphetamine and/or self-reported methamphetamine use during pregnancy. Methamphetamine users were more likely to develop preeclampsia (n = 34, 34.3%) than non-users (n = 166, 4.6%) (OR 10.89, CI 6.99-16.96; $p < 0.001$). Methamphetamine users were also more likely to deliver prematurely (n = 169 (4.5%) prematurity non-users; 31 (31%) prematurity methamphetamine users) (OR 9.84, CI 6.25-15.48; $p < 0.001$). There was no difference in composite adverse outcomes in patients with preeclampsia who used or did not use methamphetamine (2.4 ± 1.3 non-users, 2.5 ± 1.0 users, $p = 0.563$, unpaired t-test).

Conclusion: Methamphetamine use during pregnancy significantly increases the chance of developing preeclampsia, but does not increase morbidity due to preeclampsia.

Keywords

Methamphetamine, Substance abuse, Preeclampsia, Pregnancy, Hypertension

Abbreviations

ACOG: American College of Obstetricians and Gynecologists, UDS: urine drug screen, ARMC: Arrowhead Regional Medical Center, HELLP: hemolysis, elevated liver enzymes, low platelets, AST: aspartate aminotransferase, ALT: alanine transaminase, ICU: intensive care unit, IV: intravenous, mmHg: millimeters of mercury, OR: Odds ratio

Introduction

Substance abuse in pregnancy is multifactorial problem, with implications for both mother and baby. Current trends show that the most commonly used illicit substance in pregnancy is methamphetamine [1,2]. Nearly a quarter of pregnant women admitted for substance abuse treatment programs in the United States indicate their primary substance of abuse is methamphetamine [3]. The reported incidence of methamphetamine use in pregnancy is varied. National epidemiological studies suggest 7.2% of pregnant women report using methamphetamine during pregnancy, compared to 7.1% of non-pregnant reproductive aged women [4]. Estimates from the Infant Development, Environment and Lifestyle (IDEAL) study, a multi-center, multi-state study, suggest that approximately 5-6% of women use methamphetamine during pregnancy [5,6]. However, a review of linked mother-infant datasets from California Vital Statistics showed only 0.4% of pregnancies were complicated by methamphetamine use [7].

Methamphetamine, in part, causes release of norepinephrine [8], which leads to increased vascular tone (alpha mediated vasospasm) and hypertension. Preeclampsia is also thought to be a disease of excess catecholamine (the fight or flight hormones – adrenaline and norepinephrine) [9]. Thus, there is biological plausibility that methamphetamine use in pregnancy can trigger preeclampsia.

Preeclampsia occurs in up to 10% of pregnancies, and is one of the leading causes of perinatal morbidity and mortality [1]. Preeclampsia is a disease unique to pregnancy that leads to high blood pressure and proteinuria. If the patient with preeclampsia is left undelivered she may develop kidney or liver failure, seizures, or stroke. In extreme cases, her baby may die. Preeclampsia has four forms, including: (1) mild preeclampsia, which is characterized by mild elevations in blood pressure and slight protein in the urine; (2) severe preeclampsia, identified when systolic blood pressure exceeds 160 mmHg, or diastolic blood pressure exceeds 105 mmHg, there are laboratory abnormalities of the blood that suggest end-organ damage of the kidney or liver, and/or signs/symptoms of cerebrovascular involvement such as a severe headache or a seizure; (3) gestational hypertension, the same a mild preeclampsia but without proteinuria; and (4) superimposed preeclampsia, which occurs when a pregnant mother with an underlying chronic hypertensive disorder develops preeclampsia of any of the above types.

Because methamphetamine causes norepinephrine release [8],

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Citation: Roloff KA, Stepanyan G, Valenzuela G (2015) Methamphetamine use Increases Chances of Preeclampsia. J Fam Med Dis Prev 1:011

Received: August 26, 2015: **Accepted:** September 16, 2015: **Published:** September 19, 2015

and norepinephrine is implicated in the pathogenesis of preeclampsia [2], and because acute methamphetamine toxicity is associated with severe hypertension, hypertensive crisis, cerebrovascular accident and intracranial hemorrhage [10,11], the current study examined the relationship between methamphetamine use in pregnancy and preeclampsia. We quantified the incidence of preeclampsia in methamphetamine users and non-users, using updated diagnostic criteria as set forth by the American College of Obstetricians and Gynecologists (ACOG) Task Force on hypertension in pregnancy in 2013 [1]. We also examined a composite marker for severity of preeclampsia to determine if any differences exist in morbidity due to preeclampsia between methamphetamine users and non-users.

Materials and Methods

This is a single center, retrospective review of consecutive deliveries between January 2012 and June 2013 at Arrowhead Regional Medical Center (ARMC), a tertiary care county hospital in San Bernardino, California. This study was conducted with approval from the Arrowhead Regional Medical Center Institutional Review Board.

Local data highlights that this area is known to have a high prevalence of methamphetamine abuse [3,6,5,12]. Methamphetamine use was defined as self-reported use or providing a positive urine drug screen (UDS) at any point during pregnancy. UDS was performed using a Roche Cobas system with sensitivity to detect urinary methamphetamine concentrations greater than 1000 ng/ml. Methamphetamine is rapidly cleared via urine, and repetitive methamphetamine ingestion can result in detectable urine concentrations for up to 7 days [13]. Due to the limitations in UDS for detecting methamphetamine use, patients who reported methamphetamine use at any point in pregnancy were included in the user cohort. UDS testing was done voluntarily, and prior to initiation of anti-hypertensive therapy. All patients were screened at the first prenatal visit using the 4P's Plus© Screen for Substance Use in Pregnancy, a validated screening instrument developed specifically for assessing risk of alcohol or drug use in pregnant women [14]. Patients were screened again during the routine history/physical examination conducted at admission for delivery. Patients who did not self-report methamphetamine use and had a negative UDS or no UDS were categorized as non-users.

Preeclampsia was defined according to the ACOG Task Force on hypertension in pregnancy [1]. Patients were classified as having mild preeclampsia if they were diagnosed as having a new onset of hypertension (systolic blood pressure > 140 mmHg, or diastolic > 90 mmHg) on two separate occasions more than 4 hours apart, with a random urine protein to creatinine ratio of greater than 0.3, or urine dipstick test with 1+ proteinuria, or atypical features of preeclampsia. Patients were classified as severe preeclampsia if they had systolic blood pressure in excess of 160 mmHg or diastolic blood pressure in excess of 105 mmHg, or evidence of end organ involvement such as a severe headache, laboratory abnormalities, oliguria (low urine output), or seizure. Patients were considered to have superimposed preeclampsia if they were diagnosed with hypertension prior to 20 weeks of gestation, and had hypertensive urgency leading to delivery, worsening proteinuria, and/or other signs of severe preeclampsia. Gestational hypertension was diagnosed when the patient had new onset abnormal blood pressure as in mild preeclampsia without proteinuria.

To measure morbidity due to preeclampsia we developed a composite measure which included the presence of any of the following: abruption, eclampsia, HELLP (hemolysis elevated liver enzymes and low platelets) syndrome, elevated aspartate aminotransferase (AST), elevated alanine transaminase (ALT), thrombocytopenia, intensive care unit (ICU) admission, use of intravenous (IV) antihypertensive agent(s) for blood pressure control, or the use of magnesium sulfate for seizure prophylaxis.

Demographic characteristics and incidence of preeclampsia were compared between methamphetamine users and non-users for the whole cohort. Student t-test and Fisher's exact test were used to compare continuous and categorical variables respectively. An alpha level of < 0.05 was used for all statistical tests. Confidence intervals were reported at the ninety-fifth percentile. All analyses were performed using IBM SPSS Statistics, v22.0.0.0.

Table 1: Demographic characteristics and incidence of preeclampsia compared between non-users and methamphetamine users. Values are mean ± standard deviation or n (%).

	Non-Users	Methamphetamine-Users	p
n	3622 (97.3)	99 (2.7)	
Age (years)	26.4 ± 6.3	28.6 ± 6.0	< 0.001
Gravidity	2.9 ± 1.9	4.5 ± 2.8	< 0.001
Parity	1.4 ± 1.5	2.5 ± 2.2	< 0.001
Ethnicity[a]			
Caucasian	384 (10.6)	32 (32.3)	
Hispanic	2659 (73.4)	57 (57.6)	
Black	427 (11.8)	8 (8.1)	< 0.001
Asian	54 (1.5)	0 (0)	
Other	68 (1.9)	1 (1.0)	
Preeclampsia	166 (4.6)	34 (34.3)	< 0.001
Mild	55 (33)	11 (32)	
Severe	37 (23)	8 (24)	0.339
Gestational	49 (28)	6 (18)	
Superimposed	25 (16)	9 (27)	
Gestational age	38.9 ± 3.2	37.4 ± 2.9	< 0.001
Preterm birth	169 (4.5)	31 (31)	< 0.001
Birth weight	3013 ± 725	3043 ± 804	0.832

[a]Missing data in 30 non-users, missing data in 1 methamphetamine user

Table 2: Logistic regression analysis of preeclampsia with known contributing variables as well as methamphetamine use

Variable	Significance (p)	95% confidence interval	
		Lower	Upper
Methamphetamine	.026	.166	.893
Advanced maternal age	.414	.351	12.8
Previous preeclampsia	.310	.138	508
Nulliparity	.128	.762	8.7
Obesity	.093	.850	8.2
Diabetes	.634	.004	27.5
Hypertension	.116	.423	2514
Smoking	.092	.021	1.3

Results

We reviewed 3,721 consecutive deliveries. Two hundred (5.4%) cases of preeclampsia were identified. Ninety-nine (2.6%) patients tested positive for methamphetamine using UDSs or self-reported methamphetamine use during pregnancy. UDS was collected in 2,419 (65%) of patients. Methamphetamine users were more likely to be older, multigravid and multiparous (see Table 1 for participant demographics). There were more Caucasian methamphetamine users, and fewer Hispanic and Black methamphetamine users, but the distribution of ethnicity between methamphetamine users and non-users was not statistically different.

Methamphetamine users were more likely to develop preeclampsia (n = 34, 34.3%) than non-users (n = 166, 4.6%) (OR 10.89, CI 6.99-16.96; $p < 0.001$). Methamphetamine users were also more likely to deliver prematurely (n = 169 (4.5%) prematurity non-users; 31 (31%) prematurity methamphetamine users) (OR 9.84, CI 6.25-15.48; $p < 0.001$) (Table 1).

Multivariate binary logistic regression was performed to determine the impact of methamphetamine use on preeclampsia controlling for known risk factors. Control variables included age, history of preeclampsia in a prior pregnancy, nulliparity, obesity, pre-existing diabetes, and chronic hypertension, and smoking (smoking has been shown to be protective against preeclampsia). Table 2 shows the results of the logistic regression model. The model has a -2 Log likelihood of 80.796, with $\chi^2 = 81.401$, suggesting goodness of fit. There

Table 3: Risk factors for preeclampsia and markers of severity of preeclampsia compared between non-users and methamphetamine users. Values are mean ± standard deviation or n (%).

	Non-Users	Meth-Users	
N	**166**	**34**	**p**
Advanced maternal age	29 (18)	12 (35)	0.033
Nulliparous	75 (45)	10 (29)	0.127
Preterm Birth	53 (32)	15 (44)	0.122
Pre-existing diabetes	3 (4)	1 (5)	0.560
Chronic hypertension	21 (21)	7 (33)	0.255
Previous pregnancy with preeclampsia	6 (7)	5 (26)	0.027
Smoker	10 (6)	9 (27)	0.001
Other drugs			
Cannaboids	6 (3.6)	5 (14.7)	
Alcohol	2 (1.2)	1 (2.9)	0.018
Opiates	6 (3.6)	0	
Heroine	2 (1.2)	0	
Body-Mass-Index (kg/m2)	34.7 ± 7.1	34.4 ± 7.5	0.853
Obese (Body-Mass-Index > 30kg/m^2)	73 (75)	14 (75)	1
Peak systolic blood pressure	159 ± 14	168 ± 23	0.004
Peak diastolic blood pressure	96 ± 10	100 ± 14	0.030
Peak AST[a] (mg/dL)	33 ± 55	53 ± 147	0.190
Peak ALT[b] (mg/dL)	27 ± 47	47 ± 130	0.150
Platelet nadir (x100,000)	193 ± 57	230 ± 74	0.002
Composite Morbidity	**2.4 ± 1.3**	**2.5 ± 1.0**	**0.563**

[a] AST=aspartate aminotransferase, [b]ALT=alanine transaminase

was no significant interaction effect between methamphetamine use and any of the variables controlled for. Results show that advanced maternal age was significantly correlated with pre-existing diabetes and chronic hypertension (p = 0.027, and p = 0.033, respectively). Obesity was also significantly correlated with chronic hypertension (p = 0.013). Methamphetamine use was the only variable significantly associated with preeclampsia (p = 0.026, CI 0.166 - 0.893) (Table 2).

As shown in Table 3, there were no differences in health morbidity outcomes as a result of preeclampsia between methamphetamine users and non-users. There was no difference in composite adverse outcomes in patients with preeclampsia who used or did not use methamphetamine (2.4 ± 1.3 non-users, 2.5 ± 1.0 methamphetamine users, p = 0.563, unpaired t-test). Methamphetamine users were more likely to have had a prior pregnancy with preeclampsia (p = 0.027), to be smokers (p = 0.001), and had higher peak systolic blood pressures (159 non-users; 160 methamphetamine users; p = 0.004), and diastolic blood pressures (96 non-users; 100 methamphetamine-users; p = 0.030). However the difference in both peak systolic and peak diastolic blood pressure is minimal, hence unlikely to be of any clinical significance (Table 3).

Discussion

This study shows that methamphetamine use in pregnancy is associated with a significant increase in the incidence of preeclampsia. This is of particular importance given that methamphetamine use is increasing in the United States [3,14], and up to 7.2% of women may use methamphetamine at some point in pregnancy [4].

Methamphetamine use is a known risk factor for preterm delivery [2]. In this study, we noted a significant risk of preterm birth among methamphetamine users. In fact, about one third of methamphetamine users developed preeclampsia, and one third delivered prematurely. This study was not designed to determine the reasons for premature delivery among methamphetamine users, but we speculate that preeclampsia may be a significant contributor to the higher number of infants born prematurely. Further research is needed to determine if there is a causal relationship between methamphetamine use and preeclampsia as a reason for preterm birth.

Methamphetamine users in this study were older than controls. This was a surprising finding in comparison to the extant literature, which suggests that an age of less than 20 years to be a prominent risk factor for methamphetamine use [5]. Perhaps demographics of methamphetamine users vary by geography. The rate of methamphetamine use in our study population was slightly less reported by others [6,3,4], but more than captured when California Vital Statistics data was reviewed [7]. However, these differences may be due to the mechanism for defining or screening for methamphetamine use.

One limitation of this study was that UDS was not performed on all patients. Only methamphetamine use up to one week prior to testing is detected by a UDS [13]. Therefore, we included self-reported methamphetamine use along with UDS positive screening, with the reasoning that it would be uncommon for a patient to falsely admit to illegal activity [15]. Our rate of methamphetamine use is comparable to other reports for expected use in this area [5,3,12]. Since patients are likely to under-report methamphetamine use [15], we suspect we have underestimated the number of methamphetamine users and would therefore only have underestimated the incidence of preeclampsia in users. In addition, we are unable to quantify the dose and duration of methamphetamine exposure as we relied on self-reported use or urine drug screening to define methamphetamine use. It is possible that some users had heavy use, and others had minimal use. Further research would be necessary to determine if heavier methamphetamine use, i.e. a higher dose of methamphetamine, would results in a dose related effect on the incidence of preeclampsia [16].

Despite the increased incidence of preeclampsia in methamphetamine users, results did not indicate any differences in morbidity due to preeclampsia among methamphetamine users versus non-users. However, methamphetamine users with preeclampsia had a slightly higher peak systolic and diastolic blood pressure than non-users with preeclampsia.

Methamphetamine is a powerful central nervous stimulant and sympathomimetic, and is associated with intrauterine growth restriction, preterm birth, and childhood behavioral problems [2,5]. The results of this study indicate we should add preeclampsia to the list of complications of methamphetamine use in pregnancy. Blood pressure monitoring and a low index of suspicion for preeclampsia may be of particular importance in women who admit to methamphetamine use during pregnancy, and active methamphetamine use should prompt initiation of bi-weekly antenatal surveillance (non-stress testing with amniotic fluid index) and blood pressure checks in the third trimester.

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