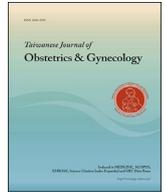




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Original Article

Maternal characteristics and pregnancy outcomes among illicit drug-using women in an urban setting

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ABSTRACT

Objective: To identify characteristics and pregnancy outcomes among pregnant illicit drug users living in an urban area, and to describe trends in drug use over an 8-year period.

Materials and methods: Data on pregnant women living in the Bangkok Metropolitan Region who delivered at our institution during 2008–2015 were studied. Women with drug use (n = 197) and women without drug use (n = 787) were compared in terms of maternal characteristics and pregnancy outcomes.

Results: The pregnant drug user rate markedly rose from 0.46% in 2008 to 1.28% in 2015. All pregnant drug users consumed amphetamine-type stimulants (ATS). The most important factor related to drug use was smoking (adjusted odds ratio [aOR] 41.03, 95% confidence interval [CI] 18.90–89.04). Other significant characteristics were teenage pregnancy (aOR 1.78, 95% CI 1.01–3.18), low level of education (aOR 4.97, 95% CI 1.18–20.90 for secondary school and aOR 5.61, 95% CI 1.28–24.49 for primary school or lower), and inadequate number of antenatal visits (aOR 2.20, 95% CI 1.16–4.17 for 1–3 visits and aOR 14.05, 95% CI 7.54–26.16 for no visit). Women of non-Thai ethnicity were less likely to use drugs (aOR 0.15, 95% CI 0.04–0.54). Pregnant drug users had a significantly higher risk of anemia (aOR 1.73, 95% CI 1.05–2.85), preterm delivery (aOR 2.35, 95% CI 1.29–4.29), low birth weight (aOR 2.26, 95% CI 1.23–4.17) and small for gestational age infants (aOR 3.19, 95% CI 1.39–7.33), but lower risk of cesarean section (aOR 0.43, 95% CI 0.21–0.86) than non-drug users.

Conclusion: Compared to urban pregnant women without drug use, women who consumed drugs were younger, had lower level of education, poorer self-care and poorer pregnancy outcomes. ATS was the single most commonly used drug.

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Introduction

Illicit drugs are drugs that are prohibited for non-medical use by international law [1]. These drugs include heroin and other opioids, amphetamine-type stimulants (ATS), marijuana and cocaine [1]. According to the World Drug Report 2016 [2], the global number of illicit drug users aged 15–64 years went up from 208 million people in 2006 to 247 million people in 2014 with a net increase of 18.8%. A remarkable increase in global illicit drug consumption and production is due mainly to rapid industrialization and population growth in developing countries [2–4].

An urban area is a human settlement typically consisting of a large population with social, cultural, economic and ethnic diversity. Urban inhabitants were reported to have higher prevalence rates of drug use than those living in rural environments [5,6]. Moreover, urban drug-using pregnant women were found to present with more severe drug use resulting in poorer pregnancy outcomes compared to rural ones [7]. Several reasons have been proposed to explain an increase of drug use among urban population. These include higher financial capacity and easier drug accessibility [8,9]. Other reasons are more peer pressure among urban adolescents, stressful urban lifestyle, and unhealthy family relationships [8,10].

Drug-using women of childbearing age were found to be at increased risk of unplanned pregnancy [7,11,12], which then increases the risk of prenatal drug exposure. One option to improve the pregnancy outcomes of these women, especially in urban ones

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who tend to have severe degree of drug use, is to identify their particular characteristics, so a proactive early detection and specialized treatment program could be directly applied to this specific group. Several authors reported characteristics of pregnant women living in urban areas who consumed illicit drugs [13–15]. However, these studies did not exclude women with a short-term stay who might not be regarded as actual urban inhabitants. In addition, results from previous reports showed the inconsistencies in findings associated with the teratogenic effects of some drug types including ATS and cocaine [16,17].

The aim of this study was to determine characteristics associated with illicit drug use during pregnancy and related pregnancy outcomes among urban pregnant women. Eight-year trends in prevalence and types of drug use were also evaluated.

Materials and methods

This retrospective matched cohort study included pregnant women who had lived in the Bangkok Metropolitan Region (BMR) for at least five years and delivered at our institution between January 1, 2008 and December 31, 2015. The cohort subjects were chosen in two steps. Firstly, women who reported use of illicit drug(s) during pregnancy with a positive urine drug screen were identified as study subjects. Then, each study subject was matched to four control women who had no record of drug use, according to parity and date of delivery. Exclusion criteria were multiple pregnancies, known medical diseases that may affect the outcomes of pregnancy (e.g. chronic hypertension, overt diabetes, renal disease, etc.), history of spontaneous preterm delivery, fetal chromosomal anomalies and incomplete medical records. The research protocol was reviewed and approved by the Vajira Institutional Review Board (approval number 51/2558).

Data on maternal characteristics and pregnancy outcomes were obtained from medical charts and the hospital's electronic database. Maternal characteristic features included age, ethnicity, level of education, marital status, occupation, parity, pre-pregnancy weight, weight at delivery, gestational weight gain (GWG), number of antenatal visits, history of smoking and alcohol consumption during pregnancy, presence or absence of sexually transmitted infections (particularly HIV, syphilis and hepatitis B), and type of illicit drug use in study subjects. Ages of the women were classified into three categories: <20 years (teen age); 20–34 years (normal age); and ≥35 years (advanced age). Numbers of antenatal visits were also divided into three groups: ≥4 (adequate number); 1–3 (low number); and 0 (no visit). Low number and no visit were considered to be an inadequate number of antenatal visits.

Pregnancy outcomes were obstetric and neonatal outcomes. Obstetric data included: gestational age (GA) at delivery; mode of delivery and adverse maternal outcomes, including anemia at admission for delivery; preterm delivery; premature rupture of the membranes (PROM); preeclampsia; placental abruption; and postpartum hemorrhage. Neonatal data were neonatal birth weight, adverse neonatal outcomes comprising low birth weight (LBW), small for GA (SGA), Apgar score less than 7 at 1- and 5 min, congenital anomalies and neonatal death. GA was calculated based on last menstrual period and/or by ultrasound confirmation. A diagnosis of SGA was made using a Thai infant birth weight nomogram [18].

Statistical analysis was performed with the IBM SPSS Statistics version 22.0 (IBM corporation, Armonk, NY, USA). Student *t* test was used to compare continuous variables. Univariate and multivariate analyses were used to determine significant maternal characteristics and pregnancy outcomes associated with illicit drug use during pregnancy. Data were presented as crude and adjusted odds ratios

(ORs) with 95% confidence intervals (CIs). All statistical analyses used two-sided tests with an overall significance level of $\alpha = 0.05$.

Results

A total of 17,555 women who had lived in the BMR for at least five years gave birth at our institution during an 8-year period, 199 (1.13%) of whom reported use of illicit drug(s) during pregnancy. These 199 drug users (study subjects) were matched to 796 non-users (controls). Of these, one control had multiple pregnancy, seven (one study subject and six controls) had underlying medical diseases and three (one study subject and two controls) had a history of spontaneous preterm delivery. Hence, 197 study subjects and 787 controls remained for analysis.

Mean ages of women in the study group and control group were 25.1 ± 6.6 years and 27.2 ± 6.6 years ($P < 0.001$), respectively. Study subjects had a significantly lower number of antenatal visits than controls (2.9 ± 3.6 times vs. 8.5 ± 3.9 times, $P < 0.001$). Further characteristic features of women in the study group and control group are presented in Table 1. In univariate analysis, age, ethnicity, level of education, marital status, occupation, number of antenatal visits, smoking and alcohol intake were significantly associated with drug use during pregnancy. After controlling for potential confounders, smoking was identified as the greatest risk factor associated with illicit drug use (adjusted OR [aOR] 41.03, 95% CI 18.90–89.04). Other positive risk factors were teenage pregnancy, low level of education (secondary school or lower) and inadequate number of antenatal visits. On the contrary, women of non-Thai ethnicity were less likely to use illicit drugs.

Obstetric outcomes of women in both groups are summarized in Table 2. The mean GA at delivery of the study group was significantly shorter than that of the control group: 37.0 ± 2.3 weeks vs. 38.3 ± 1.4 weeks, $P < 0.001$. Moreover, the study group was found to be at significantly higher risk for being anemic at admission for delivery, preterm delivery and PROM but lower risk for cesarean section than the control group. These outcomes, except PROM, remained significant after adjustment for potential confounding factors. The aORs of anemia, preterm delivery and cesarean section in the study group were 1.73 (95% CI 1.05–2.85), 2.35 (95% CI 1.29–4.29) and 0.43 (95% CI 0.21–0.86), respectively.

Table 3 shows neonatal outcomes of the study group and control group. Neither congenital anomalies nor neonatal death was observed in all 984 infants. Univariate analysis demonstrated that study subjects had a significantly higher risk of LBW, SGA and low 1-min Apgar score than control subjects. In multivariate analysis, only risks of LBW and SGA remained significant: 2.26-fold (95% CI, 1.23–4.17) and 3.19-fold (95% CI, 1.39–7.33), respectively.

We further evaluated trends in drug use among urban pregnant women over the study period. The prevalence rates of drug used by year from 2008 to 2015 are shown in Table 4. The highest use rate was 2.26% in 2013 and the lowest use rate was 0.32% in 2009. All of the 199 pregnant drug users consumed ATS; however, with different numbers and routes of administration. The most commonly used ATS was methamphetamine oral tablet. The majority (89.45%) of drug users consumed a single type of ATS while the remaining 10.55% used both oral tablet and inhaled crystalline methamphetamine.

Discussion

Illicit drug use is a big global public health problem. Although evidence suggests that treatment for illicit drug use can reduce the risk of morbidity and mortality [19], identification of drug users, particularly pregnant drug users, is often overlooked.

Table 1
Comparison of characteristic features between the study group and control group^a.

Characteristic	Study group (n = 197)	Control group (n = 787)	Crude OR (95% CI)	P value	Adjusted OR ^b (95% CI)	P value
Age, y						
<20	51 (25.9)	95 (12.1)	2.37 (1.61–3.50)	<0.001	1.78 (1.01–3.18)	0.049
20–34 ^c	129 (65.5)	570 (72.4)	1.00	–	1.00	–
≥35	17 (8.6)	122 (15.5)	0.62 (0.36–1.06)	0.077	0.60 (0.26–1.36)	0.597
Ethnicity						
Thai ^c	193 (98.0)	717 (91.1)	1.00	–	1.00	–
Others	4 (2.0)	70 (8.9)	0.21 (0.08–0.59)	0.001	0.15 (0.04–0.54)	0.004
Level of education						
University or higher ^c	3 (1.5)	119 (15.1)	1.00	–	1.00	–
Secondary school	114 (57.9)	480 (61.0)	9.42 (2.94–30.17)	<0.001	4.97 (1.18–20.90)	0.029
Primary school or lower	80 (40.6)	188 (23.9)	16.88 (5.21–54.67)	<0.001	5.61 (1.28–24.49)	0.022
Marital status						
Married ^c	134 (68.0)	673 (85.5)	1.00	–	1.00	–
Widowed	0 (0)	0 (0)	–	–	–	–
Separated/divorced	6 (3.1)	8 (1.0)	3.77 (1.29–11.03)	0.010	1.37 (0.18–10.18)	0.761
Single	57 (28.9)	106 (13.5)	2.70 (1.86–3.92)	<0.001	1.41 (0.78–2.53)	0.256
Occupation						
Government official ^c	13 (6.6)	90 (11.4)	1.00	–	1.00	–
Employee	52 (26.4)	374 (47.5)	0.96 (0.50–1.84)	0.908	0.96 (0.26–3.62)	0.957
Student	112 (56.9)	284 (36.1)	2.73 (1.47–5.08)	0.001	1.26 (0.52–3.06)	0.604
Unemployed	20 (10.1)	39 (5.0)	3.55 (1.61–7.85)	0.001	1.70 (0.72–3.98)	0.224
Parity						
Nulliparity ^c	61 (31.0)	243 (30.9)	1.00	–	–	–
Multiparity	136 (69.0)	544 (69.1)	0.99 (0.71–1.40)	0.981	–	–
Prepregnancy weight, kg	53.6 (10.2)	55.6 (11.6)	–	0.031	–	–
Weight at delivery, kg	62.0 (11.1)	67.5 (12.3)	–	<0.001	–	–
Gestational weight gain, kg	8.4 (4.7)	11.9 (6.0)	–	<0.001	–	–
Number of antenatal visits						
≥4 ^c	71 (36.0)	690 (87.7)	1.00	–	1.00	–
1–3	41 (20.8)	67 (8.5)	5.95 (3.76–9.41)	<0.001	2.20 (1.16–4.17)	0.016
0	85 (43.2)	30 (3.8)	27.54 (16.99–44.62)	<0.001	14.05 (7.54–26.16)	<0.001
Smoking						
No ^c	91 (46.2)	777 (98.7)	1.00	–	1.00	–
Yes	106 (53.8)	10 (1.3)	90.51 (45.68–179.33)	<0.001	41.03 (18.90–89.04)	<0.001
Alcohol drinking						
No ^c	182 (92.4)	784 (99.6)	1.00	–	1.00	–
Yes	15 (7.6)	3 (0.4)	21.54 (6.17–75.18)	<0.001	3.04 (0.50–18.66)	0.230
HIV infection						
No ^c	192 (97.5)	780 (99.1)	1.00	–	–	–
Yes	5 (2.5)	7 (0.9)	2.90 (0.91–9.24)	0.059	–	–
Syphilis infection						
No ^c	195 (99.0)	784 (99.6)	1.00	–	–	–
Yes	2 (1.0)	3 (0.4)	2.68 (0.44–16.13)	0.264	–	–
Hepatitis B infection						
No ^c	194 (98.5)	776 (98.6)	1.00	–	–	–
Yes	3 (1.5)	11 (1.4)	1.09 (0.30–3.95)	0.894	–	–

CI, confidence interval; OR, odds ratio.

^a Values are given as mean ± standard deviation or number (percentage).^b Adjusted for the other variables in the column.^c Reference group.

This study focused on characteristics of drug-using pregnant women who had lived in an urban setting. The duration of at least five years stay was required to homogenize subjects with urban behavior. Our findings showed that teenage pregnancy, Thai ethnicity, low level of education, inadequate number of antenatal visits and smoking were characteristic features associated with illicit drug use during pregnancy. Other studies which included women who had lived in urban areas for unspecified durations also reported characteristics of pregnant drug users [13–15]. Ho et al. [13] who conducted a study in Toronto, Canada found that drug-using pregnant women were significantly younger, more likely to be single, and had more episodes of alcohol drinking and smoking during pregnancy compared to non drug-using women. The other two studies conducted in urban areas of the United States reported that pregnant women who consumed drugs had significantly higher rates of no partner, no antenatal care, alcohol drinking and smoking, but were older, than women who did not use drugs [14,15]. The collective findings among our study and these three

studies suggested that the use of illicit drugs among urban pregnant women might be because of peer pressure and unhealthy family relationships as these women had lower level of education and poor self-care. Aside from these common observations, our study also identified Thai ethnicity as a significant factor associated with drug use. Since the majority (87%) of population who had lived in the BMR was Thai [20], this may lead to such a finding. Furthermore, over 50% of non-Thai inhabitants were migrant workers with lower average income leading to lower financial capacity to buy drugs than Thai population [20]. To be noted, rates of sexually transmitted infections including HIV, syphilis and hepatitis B were not significantly increased in our pregnant drug users. This might be because routes of drug administration among these women were oral and inhaled routes, not intravenous injection.

Similar to previous reports [21,22], we found that pregnant drug users, specifically ATS users, were at increased risk of being anemic and preterm delivery, but had a lower risk of cesarean section. The plausible explanation of anemia is that pregnant drug users have

Table 2
Comparison of obstetric outcomes between the study group and control group^a.

Characteristic	Study group	Control group	Crude OR	P value	Adjusted OR ^b	P value
	(n = 197)	(n = 787)	(95% CI)		(95% CI)	
GA at delivery, wk	37.0 (2.3)	38.3 (1.4)	–	<0.001	–	–
Mode of delivery						
Normal delivery ^c	168 (85.3)	541 (68.7)	1.00	–	1.00	–
Operative vaginal delivery	6 (3.0)	25 (3.2)	0.77 (0.31–1.92)	0.577	0.55 (0.15–2.01)	0.367
Caesarean section	23 (11.7)	221 (28.1)	0.34 (0.21–0.53)	<0.001	0.43 (0.21–0.86)	0.017
Anemia at admission						
No ^c	98 (49.7)	622 (79.0)	1.00	–	1.00	–
Yes	99 (50.3)	165 (21.0)	3.81 (2.74–5.29)	<0.001	1.73 (1.05–2.85)	0.033
Preterm delivery						
No ^c	133 (67.5)	722 (91.7)	1.00	–	1.00	–
Yes	64 (32.5)	65 (8.3)	5.35 (3.61–7.91)	<0.001	2.35 (1.29–4.29)	0.005
PROM						
No ^c	143 (72.6)	681 (86.5)	1.00	–	1.00	–
Yes	54 (27.4)	106 (13.5)	2.43 (1.67–3.53)	<0.001	1.39 (0.79–2.48)	0.257
Preeclampsia						
No ^c	187 (94.9)	764 (97.1)	1.00	–	–	–
Yes	10 (5.1)	23 (2.9)	1.78 (0.83–3.80)	0.133	–	–
Placental abruption						
No ^c	195 (99.0)	786 (99.9)	1.00	–	–	–
Yes	2 (1.0)	1 (0.1)	8.06 (0.73–89.36)	0.043	–	–
Postpartum haemorrhage						
No ^c	194 (98.5)	774 (98.3)	1.00	–	–	–
Yes	3 (1.5)	13 (1.7)	0.92 (0.26–3.26)	0.898	–	–

CI, confidence interval; GA, gestational age; OR, odds ratio; PROM, premature rupture of the membranes.

^a Values are given as mean ± standard deviation or number (percentage).

^b Adjusted for age, ethnicity, level of education, number of antenatal visits, smoking, alcohol drinking and the other variables in the column.

^c Reference group.

Table 3
Comparison of neonatal outcomes between the study group and control group^a.

Characteristic	Study group	Control group	Crude OR	P value	Adjusted OR ^b	P value
	(n = 197)	(n = 787)	(95% CI)		(95% CI)	
Birth weight	2797.8 (467.6)	3076.0 (435.0)	–	<0.001	–	–
LBW						
No ^c	152 (77.2)	730 (92.8)	1.00	–	1.00	–
Yes	45 (22.8)	57 (7.2)	3.79 (2.47–5.82)	<0.001	2.26 (1.23–4.17)	0.009
SGA infant						
No ^c	174 (88.3)	764 (97.1)	1.00	–	1.00	–
Yes	23 (11.7)	23 (2.9)	4.39 (2.41–8.01)	<0.001	3.19 (1.39–7.33)	0.006
Apgar score less than 7 at 1 min						
No ^c	186 (94.4)	770 (97.8)	1.00	–	1.00	–
Yes	11 (5.6)	17 (2.2)	2.69 (1.23–5.82)	0.010	1.64 (0.52–5.16)	0.398
Apgar score less than 7 at 5 min						
No ^c	193 (98.0)	787 (100)	1.00	–	1.00	–
Yes	4 (2.0)	0 (0)	– ^d	–	– ^d	–

CI, confidence interval; LBW, low birth weight; OR, odds ratio; SGA, small for gestational age.

^a Values are given as mean ± standard deviation or number (percentage).

^b Adjusted for age, ethnicity, level of education, number of antenatal visits, smoking and alcohol drinking.

^c Reference group.

^d OR with 95% CI could not be determined because the value in one cell is 0.

Table 4
Prevalence rates and types of ATS used by year, 2008–2015.

Year	Delivery cases ^a (n)	Type of ATS use (%)			
		All	Methamphetamine tablet	Crystalline methamphetamine	Ecstasy
2008	2805	13 (0.46)	12 (0.43)	1 (0.03)	0 (0)
2009	2848	9 (0.32)	8 (0.28)	1 (0.04)	0 (0)
2010	2343	17 (0.73) ^b	15 (0.64)	4 (0.17)	0 (0)
2011	2100	27 (1.29) ^b	22 (1.05)	8 (0.38)	1 (0.05)
2012	2251	32 (1.42) ^b	18 (0.80)	15 (0.67)	1 (0.04)
2013	1987	45 (2.26) ^b	36 (1.81)	14 (0.70)	0 (0)
2014	1810	38 (2.10) ^b	25 (1.38)	21 (1.16)	0 (0)
2015	1411	18 (1.28)	11 (0.78)	7 (0.50)	0 (0)
All	17,555	199 (1.13) ^b	147 (0.84)	71 (0.40)	2 (0.01)

ATS, amphetamine-type stimulants.

^a Only women living in the Bangkok Metropolitan Region for at least five years were included.

^b More than one woman used both oral methamphetamine tablet and inhaled crystalline methamphetamine.

poor self-care, resulting in inadequate dietary and iron intakes [23]. This was supported by our study's findings of a higher rate of no antenatal care and a lower mean of GWG in pregnant drug users than non-users. Poor maternal nutritional status can lead to spontaneous preterm delivery, thereby resulting in vaginal birth rather than cesarean delivery by reason of a small infant. Regarding other obstetric outcomes, Cox et al. [24] and Gorman et al. [25] showed increased risks of several maternal complications including PROM, preeclampsia and placental abruption among drug-using women. However, the studies of Shah et al. [14] and Wright et al. [26], as well as our study did not confirm these findings. The differences among these studies might lie in dissimilar population backgrounds with various types, routes, amounts and durations of drug use. In our study, pregnant women consumed oral and/or inhaled ATS while women in other studies used ATS but with unknown route of administration.

With regard to neonatal outcomes, we found a 2.26-fold increased risk of LBW and 3.19-fold increased risk of SGA infants in pregnant drug users compared to non-drug users. This was in agreement with the finding of Smith et al. [27] who observed a 3.5-fold increased risk of SGA infants in ATS exposed pregnancies compared to control subjects. The possible mechanism by which ATS causes SGA is that ATS can cross the placenta [28], leading to vasoconstriction and restriction of oxygen and nutrients to the fetus [14]. Other issues of concern are congenital anomalies and neonatal death. Elliott et al. [29] conducted a case-control study on 71 pregnant women and reported that fetal gastroschisis was associated with maternal ATS use. However, the limitations of such a study were that it had a small sample size and was unable to assess the timing of ATS exposure with respect to the pregnancy [29]. In another retrospective study conducted by Good et al. [15], the rate of neonatal death was found to be higher in pregnant ATS users than non-users. It is noteworthy, however, that the study by Good et al. [15] did not exclude or control for confounding factors such as maternal age, GA at delivery, and obstetric or medical comorbidities; hence, this might affect the results of the study. In contrast to the studies of Elliott et al. [29] and Good et al. [26], our study and another large population-based study [14] did not find an increased risk of congenital anomalies and neonatal death in ATS-using pregnant women. In the same way, the Teratogen Information System reported that the risk of teratogenicity after exposure to ATS is unlikely based on fair to good data [16].

Focusing on trends in prevalence and types of drug use, our results showed that ATS was the single most commonly used drug among pregnant women living in an urban setting over eight years. Moreover, our finding of a 2.78-fold increase in pregnant drug user rates from 2008 to 2015 suggested a growing ATS epidemic in urban settings. Aside from our data, McCabe et al. [30] who evaluated an eleven-year trend in drug use among American women reported that pregnant women were more likely to use marijuana as well as ATS and cocaine. The growing trend toward the use of ATS among urban pregnant women in both eastern and western countries indicates an urgent need for policymakers to strengthen prevention and treatment programs.

This is the first study to evaluate the nearly one decade-old trend in increasing prevalence and types of drug use among urban pregnant women. The strength of our study was that it had a large number of pregnant drug users. In addition, it included control subjects and used multivariate analysis to adjust for confounding variables, therefore providing more accurate results than a descriptive analysis. Nevertheless, some limitations were observed. As this was a retrospective study, data on total amount of ATS used were not available. Additionally, without a national or institutional policy, a urine drug screen at each prenatal visit and maternal drug concentration testing for fetal anomalies or neonatal

death were not routinely performed and could not be assessed in this study. Another limitation was the developmental outcome of infants born to drug-using mothers. Although short-term behavioral disorders were not observed among ATS-exposed neonates, we lacked data on long-term mental and behavioral development as these infants did not attend our pediatric outpatient clinic during their childhood period. Similarly, each pregnant drug user was referred to attend a national/regional drug treatment and rehabilitation center after hospital discharge. So, data on treatment outcomes were limited. Lastly, the reported prevalence of pregnant drug users might be underestimated as some women might report false-negative information.

Our study demonstrated significant characteristics associated with illicit drug use among urban pregnant women. This information would aid in identifying pregnant drug users, leading to appropriate intervention programs for this selected group of women. As drug-using pregnant women are at greater risk for anemia, preterm delivery, LBW and SGA, further studies are needed to evaluate whether amount and duration of drug use during pregnancy are positively correlated with these unfavorable outcomes.

Conflict of interest

The authors report no conflicts of interest.

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