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Substance misuse in early pregnancy and relationship to fetal outcome

Abstract To establish the frequency of substance misuse in early pregnancy in an urban UK population, 807 consecutive positive pregnancy test urine samples were screened for a range of drugs, including cotinine as an indicator of maternal smoking habits. A positive test for cannabinoids was found in 117 (14.5%) samples. Smaller numbers of samples were positive for other drugs:- opiates (11), benzodiazepines (4), cocaine (3) and one each for amphetamines and methadone. Polydrug use was detected in nine individuals. Only two samples tested positive for ethanol. The proportion with a urine cotinine level indicative of active smoking was 34.3%. The outcome of the pregnancy was traced for 288 subjects. Cannabis use was associated with a lower gestational age at delivery ($P < 0.005$), an increased risk of prematurity ($P < 0.02$) and reduction in birth weight ($P < 0.002$). Whilst maternal smoking was associated with a reduction in infant birth weight ($P < 0.05$), this was less pronounced than the effect of other substance misuse.

Conclusion This study suggests that one in six women in South London are using drugs in early pregnancy and that cannabinoid use is associated with a poorer pregnancy outcome.

Key words Cannabis · Cotinine · Prematurity · Low birth weight

Introduction

Substance misuse during early pregnancy is associated with adverse pregnancy outcome [1, 3]. Cocaine use has been linked to an increased incidence of spontaneous abortion, renal and limb abnormalities, prematurity and low birth weight [15, 17, 23]. Behavioural abnormalities in infants exposed to cocaine in-utero have also been described [4]. Intra-uterine growth retardation, craniofacial abnormalities and developmental delay are features of the fetal alcohol syndrome [13, 14, 22]. Data on the effect of opiates and marijuana use during pregnancy are less common and are complicated by concomitant use of cocaine or nicotine [5, 19, 25].

From studies on the prevalence of substance misuse during pregnancy in the United States, rates of cocaine use as high as 31% have been reported based on toxicological screening of meconium at birth [20]. Screening of urine samples during pregnancy in Boston showed that 28% of urine samples tested positive for marijuana and 17% for cocaine or its metabolites [9]. More typical are figures obtained from an urban area in Florida where 14.8% of urine samples collected at the first prenatal visit had positive drug screens, with cannabis use predominating (11.9%) [6]. Very few surveys have been carried out in the United Kingdom, although one recent study in an urban area of East London found 10.6% of urines tested positive for illicit drugs on anonymous testing (approximately 3 months post-conception) [7];

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cannabis use predominated with cocaine being detected in only 1.1% of samples.

The majority of studies which used urine samples for identifying drug use in pregnancy employed samples obtained from women enrolling for prenatal care, typically around 12 weeks gestation. This is likely to result in an underestimate, as knowledge of certain pregnancy may modify the women's behaviour. We have, therefore, screened 807 consecutive urine samples with positive pregnancy tests submitted to our laboratory by family practitioners, to determine the frequency of substance misuse in the first trimester of pregnancy and where possible determine the outcome of the pregnancy and relate this to substance misuse.

Subjects and methods

Subjects

Urine samples submitted to King's College Hospital, London for pregnancy testing in the 6 months from November 1994 to May 1995 were included in the study. Consecutive samples with positive pregnancy tests (807) were tested for ethanol, cotinine, cannabis, opiates, methadone, benzodiazepines, cocaine and amphetamines. Samples were assigned a code number and were tested anonymously. To ascertain if substance misuse in early pregnancy affected pregnancy outcome, the labour ward and paediatric records in 1995/6 were searched for data on the outcome of the pregnancy for 807 subjects. All stillbirths as well as live births were routinely delivered on the labour ward. Matches were found against 288 subjects and the obstetric/paediatric information was assigned to the subjects code number. A paediatrician who was unaware of the result of the urinary drug tests then examined the paediatric records to determine the infant's gestational age, birth weight and 5 min Apgar score. Gestational age had been determined from the mother's last menstrual period and ultrasound scan prior to 21 weeks of gestation. Intra-uterine growth retardation was defined as a birth weight less than the 10th percentile for gestational age. All babies had been routinely examined prior to discharge by a paediatrician who recorded the results on a standard form. From that record all congenital abnormalities were noted. Information regarding pregnancy complications was obtained from the computerized record of antenatal events which was routinely transferred to the neonatal notes.

The data were then analysed by linking the code numbers, by an individual (RAS) who did not have access to any of the subjects names. Care was therefore taken to ensure that anonymity was preserved. The study was approved by the Research Ethics Committee of King's Healthcare Trust.

Analytical methodology

Urine samples positive for human chorionic gonadotrophin (200 IU/L, Neo-Planotest, Organon Teknika) were aliquoted and then stored at −20°C until assayed. Initial screening of the urines was carried out with the EMIT II homogeneous immunoassays (Syva, Maidenhead, UK) on the Cobas Mira (Roche Diagnostics, Welwyn Garden City, UK) for cannabinoids, opiates, amphetamines, methadone, cocaine and benzodiazepines. The cut-off concentrations used to determine positivity were as recommended by the manufacturer (cannabinoids 20 μg/l, opiates 300 μg/l, amphetamines 1000 μg/l, methadone 300 μg/l, cocaine 1000 μg/l and benzodiazepines 300 μg/l). All positive urines (except cannabinoids) were confirmed by gas chromatography. Urine ethanol was assayed by an enzymatic method (Sigma Chemical, Poole, UK) on the Cobas Mira. Urine cotinine was determined by gas chromatography [8]. The urine cotinine results were divided into four ranges; 0–20, 20–40, 40–200 and >200 μg/l. A urine cotinine in the range 20–40 μg/l may be due to occasional smoking, i.e. one cigarette/day, but may also be achieved from passive exposure to cigarette smoke in an enclosed environment. For the purposes of this study, the first two ranges were considered to be indicative of non-smokers.

Statistical analysis

Differences between groups of numerical data were assessed with the Mann Whitney Rank Test and between categorical variables using the chi-squared test. Data were analysed using the Astute medical statistics add-in for Excel 5.0 (University of Leeds, UK).

Results

Urine testing

There were 137 positive tests for substance misuse from 126 subjects in the 807 urine samples tested (Table 1). Multiple drug use was detected in nine subjects and in all such cases cannabis was present. Only two urines tested positive for ethanol. The urinary cotinine results are shown in Table 2. The overall percentage of smokers (urine cotinine >40 μg/l) was 34.3% (277/807). There was a significantly higher proportion of smokers, 98/126 (78%) in the drug positive compared to the drug negative group, 179/681 (26%, $P < 0.0001$).

Pregnancy outcome

The outcome of the pregnancy (that is either stillbirth or livebirth) could be traced in 288 cases. Of these, 36 (12.5%) had positive urine drug screens; 31 cannabis

Table 1 Drugs detected in urine samples for pregnancy testing

Drug(s)	Number of samples	% of total screened	% of positive results
Total screened	807		
Cannabis	117	14.5	79
Opiates	11	1.3	7.4
Benzodiazepines	4	0.5	2.7
Cocaine	3	0.4	2.0
Methadone	1	0.1	0.7
Amphetamines	1	0.1	0.7
Ethanol	2	0.2	1.4
Cannabis + additional illicit drugs	9	1.1	6.1

Table 2 Proportion of samples with different urinary cotinine concentrations in 807 positive pregnancy tests

Urinary cotinine concentration	*n*	%
0–20 μg/l	428	53.1%
20–40 μg/l	102	12.6%
40–200 μg/l	81	10.0%
>200 μg/l	196	24.3%

Table 3 Birth weights in relation to urinary drug or cotinine screens

	n	Mean ± SD	Birth weight (kg)	
			Median	Semi-quartile range
Negative urine drugs test	252	3.35 ± 0.58	3.39	2.65–4.02
Positive urine drugs test	36	2.92 ± 0.81*	3.10	1.46–3.86
Urine cotinine <40 μg/l	213	3.35 ± 0.62	3.40	2.70–4.00
Urine cotinine >40 μg/l	75	3.15 ± 0.63**	3.26	2.40–3.80

* Significantly different from drug negative group ($P < 0.002$)
** Significantly different from low cotinine group ($P < 0.05$)

only, 3 opiates only, 1 cannabis + opiates and 1 cannabis + benzodiazepines. There were 75 (26%) smokers in the 288 cases, 27 of the 36 with positive drug screens (75%) being smokers. The proportions of drug users and smokers in the cases in which pregnancy outcome was known, were not significantly different from those in the 807 samples originally screened.

Infants born to mothers with positive urine drug tests had lower birth weights ($P < 0.002$) than those with negative tests (Table 3). Infants born to drug test positive mothers were also born significantly earlier, mean gestational age 37.3 ± 4.6 weeks versus 39.2 ± 3.0 weeks for drug test negative mothers ($P < 0.005$). Analysis of the data for infants born to mothers using cannabis but no other drug ($n = 31$) showed that they had a mean gestational age of 37.0 ± 4.9 weeks and a mean birth weight of 2.87 ± 0.85 kg. This was not significantly different from the drug abusing group as a whole. In the combined drug positive and negative groups, infants born to mothers who smoked had lighter babies than those who did not ($P < 0.05$). No statistically significant difference in gestational age at birth was observed between the smoking and non-smoking groups. The birth weights and gestational age at birth of infants from drug and smoking positive mothers ($n = 27$) did not differ significantly from those positive for drugs but negative for smoking ($n = 6$). Of the 252 in the drug negative group, 17 (7%) and 8 of the 36 (22%) infants whose mothers had positive drug tests were born prematurely ($P < 0.02$). Two of the pregnancies resulting in premature deliveries in the maternal drug history positive group had placental abnormalities, placenta praevia and placenta abruptio.

There were four stillbirths in the maternal drug negative group (at 17, 20, 20 and 32 weeks respectively) and three in the drug positive group (at 21, 27 and 28 weeks respectively). The foetus stillborn at 21 weeks had chromosomal abnormalities. The three stillborn infants in the maternal drug positive group were all from mothers who used cannabis but were negative for cotinine and the four in the drug negative group were also born to non-smoking mothers.

No infant in the maternal drug history positive group had congenital anomalies, but one infant in the drug negative group had a gastroschisis and another a polycystic kidney. The proportion of infants with intrauterine growth retardation was similar in the drug positive and negative groups, 10/36 and 40/252 respectively. The 5 min Apgar scores did not differ significantly between the groups. There was also no significant difference between the frequency of ante-partum haemorrhage (5/36 vs 22/252) or pregnancy-induced hypertension (1/36 vs 19/252) between the groups.

Discussion

The frequency of positive urine drug screens in this study of pregnant women in South London (15.6%) is significantly higher than that previously reported in an inner city population in East London (10.6%) [7]. This may simply reflect differences in the populations of the two areas. London has a sociologically and ethnically diverse population and the pattern of illicit drug use may be expected to vary considerably from area to area. Alternatively, the differences in results may be related to the earlier timing of sampling in our study. A positive urine test for cannabinoids, which accounted for 85% of our positive results, may be found up to 10–14 days after use of cannabis. As our samples were taken from initial pregnancy tests it is possible that consumption of cannabis occurred before the women suspected they were pregnant.

By the time of the first antenatal clinic visit, it is possible that some women modify their behaviour resulting in the lower frequency observed at that time [6, 7]. The frequency of marijuana use was lower than the 32% reported from urban areas of the US [24]. The frequency of other drug use in our study was relatively low and similar to that in the East London study [7]. Positive urine tests for opiates must always be interpreted with caution as some non-prescription analgesic or anti-diarrhoeal preparations can produce positive results. Only two samples were positive for alcohol, but as alcohol can only be detected in urine for 12–18 h after consumption, abstention for the previous 24 h will result in a negative result. The proportion of women whose urine samples indicated they were smokers (34.3%) is

consistent with the prevalence of smoking in the age group for the population as a whole.

The outcome of the pregnancy was ascertained in 288 cases (36%). Although this might seem to be a low proportion, a combination of miscarriages, terminations of pregnancy, changes of name and the transient nature of much of our local population makes it less surprising. The frequency of drug test positivity and smoking, however, was similar for the sub-group versus the group screened initially, suggesting the sub-set was representative. Stillbirth or late spontaneous abortion occurred in seven cases, four in the drug negative group and three in the positive group. Cigarette smoking, but not marijuana usage, has been reported to be associated with an increased risk of spontaneous abortion [16, 21]. None of the seven mothers in the present study who had a late spontaneous abortion had positive urine cotinines and the three mothers in the drug positive group had urine samples positive for cannabis only; our sample size however, may have been insufficient to detect a significant association.

A dose-dependent relationship between cigarette smoking and birth weight reduction has been well established [18] but the evidence relating to marijuana is contradictory [2]. Cigarette smoking in our study was associated with an average reduction in birth weight of 200 g, consistent with previous findings [2]. Smoking did not, however, significantly affect gestational age, suggesting growth retardation rather than prematurity as the cause of the reduced birth weight. In contrast, drug use was associated with an average birth weight reduction of 400 g and a shortening of gestation of up to 2 weeks. This supports the findings of a number of studies on the effects of cannabis on birth weight and gestation [10, 11, 25], but contradicts others [12]. It could be argued that the effects of cannabis use on birth weight merely reflect the high concurrent consumption of cigarettes. In our study, however, the effect of drug use on birth weight and gestational age was much more pronounced than that due to smoking alone. Additionally, there was no difference in the magnitude of the effect between those who were using drugs and smoking and those using drugs alone.

From our data it would appear that illicit drug use, particularly cannabis, in pregnancy is associated with an increased risk of prematurity and a reduction in birth weight. Whilst heavy smoking may account for some of these effects, there appears to be an independent contribution from drug use on its own. With nearly one in six of the women in our study using drugs soon after conception, primary health care workers and obstetricians should be aware of the need to ensure adequate prenatal care in this particular subgroup of patients and preconception counselling.

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ANNOUNCEMENTS

World Association for Infant Heath (WAIMH): 7th World Congress

July 26–30, 2000
Montréal, Canada

The World Association for Infant Mental Health (WAIMH) will hold its 7th World Congress in Montréal between July 26–30, 2000. The topic of the Congress will be Diversity: Challenges and Opportunities in Infancy. The theme will be discussed within the context of brain-behaviour, developmental psychopathology, culture, environmental health, caregiving and special babies/special caregivers. This Congress is relevant for all individuals working with preschool children and their families. For further information please contact:

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7th Salzburg Weekend Seminar Oral Diseases in Children

October 23–24, 1999

Guest lecturer: Prof. Dr. C. Scully, Eastman Dental Institute, London

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