

## Research letters

## Congenital anomalies after prenatal ecstasy exposure

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Prospective follow-up of 136 babies exposed to ecstasy in utero indicated that the drug may be associated with a significantly increased risk of congenital defects (15.4% [95% CI 8.2–25.4]). Cardiovascular anomalies (26 per 1000 livebirths [3.0–90.0]) and musculoskeletal anomalies (38 per 1000 [8.0–109.0]) were predominant.

The illicit use of ecstasy (methylenedioxyamphetamine) has increased during the past decade and there is growing concern about its potential toxicity.<sup>1</sup> There are few data on the effects of ecstasy exposure in human pregnancy,<sup>2–4</sup> and no published teratological studies in animals. Whereas amphetamines and related compounds have been associated with an increased risk of structural malformations of the heart and great vessels in various species, studies on the teratogenicity of amphetamines in human pregnancy have produced conflicting results on both the overall risk of malformations and the risk of any specific birth defect.<sup>5</sup>

The UK National Teratology Information Service (NTIS) collected prospective follow-up data on the outcome of 136 pregnancies (one pair of twins), in which exposure to ecstasy occurred between January, 1989, and June, 1998. Within this period there were 302 enquiries involving ecstasy. 31 (10%) of these pregnancies are not yet completed and 135 (45%) were lost to follow-up because the enquiring health professional (in most cases the patient's general practitioner) could no longer identify the patient, or the patient did not return to the surgery.

In each case the enquirer was asked to provide information on drug exposure, both prescribed and non-prescribed, at the time of the enquiry, together with the mother's expected date of delivery. Follow-up was done by contacting the enquirer, after the expected date of delivery. Where necessary, information was then sought from other clinical specialists.

Drug exposure	Anomalies
<b>Ecstasy</b>	
4 weeks	Left 4th toe underlying the 3rd toe
6–12 weeks	Right-sided plagiocephaly
4–5 weeks	Unilateral talipes
First trimester	Unilateral talipes
6 and 9 weeks	Bilateral talipes
First trimester	Pyloric stenosis
First trimester	Absent upper limbs, left scapula, clavicles, and hypoplasticity of the first rib pair; pregnancy terminated at 22 weeks.
<b>Ecstasy, amphetamine and gamma hydroxybutyric acid</b>	
0–7 weeks	Ventricular septal defect (possibly atrio and ventricular), bilateral hydronephrosis, and bilateral clinodactyly
<b>Ecstasy and alcohol</b>	
6 weeks	Ventricular septal defect
<b>Ecstasy and amphetamine</b>	
0–12 weeks	One of twins born at 25 weeks, intrauterine growth retardation hydrocephalus, ambiguous sex
<b>Ecstasy and alcohol</b>	
17 weeks	Ptosis of the left eye
First trimester	Pigmentation of the right thigh
<b>Ecstasy and amphetamine</b>	
First trimester	Clicking hips

#### Malformations reported after exposure of fetus to ecstasy and other drugs of abuse

74 pregnant women reported taking ecstasy only and 62 took ecstasy with other drugs of abuse (ecstasy and amphetamine 37 women; ecstasy and cocaine 20; ecstasy and cannabis 16; ecstasy and alcohol 13; ecstasy and LSD nine; ecstasy and other drugs of abuse 13). Acute toxicity from ecstasy was reported in only two of the mothers. The maternal age at the time of exposure was obtained for 82 (60%) women: 26 women were aged 16–20 years; 31 21–25 years, 20 26–31 years, and five 31–36 years.

127 women (71 exposed to ecstasy alone and 56 exposed to ecstasy and other drugs of abuse) were exposed in the first trimester, two in the first and second trimesters, two in the second trimester, and one in the third trimester. Four women were exposed to several drugs of abuse throughout pregnancy.

11 pregnancies resulted in miscarriage, 48 women had elective terminations (one after prenatal diagnosis of malformations). No necropsy data were available on any of the other aborted fetuses. The rate of miscarriage was 8%, within the expected range; but the rate of elective terminations was 35%; higher than the UK average.

There were 78 liveborn infants; 66 were normal. 12 had congenital anomalies (15.4% [95% CI 8.2–25.4]), which is significantly higher than the expected incidence of 2–3% (table).

Eight infants were born prematurely between 25 and 36 weeks of gestation (including one pair of twins born at 25 weeks of gestation). There were two cases of fetal distress among those born prematurely that were thought not to be related to ecstasy. One neonatal death occurred in an infant without apparent abnormalities at birth who was born to a mother who had taken ecstasy, heroin, and methadone throughout pregnancy. No necropsy data are available.

No adverse effects were observed in the sex ratio. Birthweights were within the expected range for term infants (>37 weeks), with only three infants weighing less than 2.5 kg.

There were three female infants with talipes (rate of 38 per 1000 [95% CI 8–109] vs expected rate of 1 per 1000). Idiopathic talipes equinovarus has a male predominance of three to one in the UK.

The spontaneous incidence of congenital heart disease (CHD) is 5–10 per 1000 livebirths. Of infants with CHD, 24–34% have ventricular septal defects, 7% atrial septal defects, and 3% atrial and ventricular septal defects. In this case series there were two infants with CHD (one with ventricular septal defects, one with ventricular septal defects or possible atrial and ventricular septal defects) among the 78 livebirths (26 per 1000 [95% CI 3.0–90.0]). We are aware of one other case of CHD after exposure to ecstasy.<sup>3,4</sup> Although this small case series has insufficient statistical power to confirm a causal relation with any particular congenital anomaly, we consider that these initial data are important.

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## Aetiological parallel between tonsillar and anogenital squamous-cell carcinomas

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Patients with human papillomavirus (HPV)-associated anogenital cancers had a 4.3-fold increased risk of tonsillar squamous-cell carcinoma. These cancer types also have histopathological and molecular biological similarities. Thus HPV may be aetiological important in tonsillar carcinogenesis.

Similarities between mucosal linings at anogenital and oral sites make plausible a role for human papillomaviruses (HPV) in oral carcinogenesis. HPV are found in most anogenital squamous-cell carcinomas (SCC), but usually in less than 20% of oral cancers. Tonsillar SCC, however, is more likely than other oral cancers to be HPV positive.<sup>1</sup> We studied patients with HPV-associated anogenital SCC to test the hypothesis that these patients are at increased risk of tonsillar SCC.

Using Surveillance, Epidemiology, and End Results data from 1973 to 1994, we identified 72 066 individuals whose first cancer was an HPV-associated anogenital SCC (or cervical SCC in situ) and 422 023 with invasive HPV-unrelated first cancers of the colon, stomach, or breast (table 1). Person-years were counted from 1 month after the initial diagnosis until a diagnosis of one of the studied invasive SCC (tonsillar, other oral, cervical, vulvar/vaginal, or anal), death, or Jan 1, 1995, whichever came first. Population incidence rates for these SCC were calculated for strata of sex, race, and 5-year age and calendar periods. The expected number of a particular SCC was calculated as the sum of stratum-specific products of person-years and population incidence. Ratios of observed-to-expected SCC served as measures of relative risk. We compared relative risks of tonsillar SCC and of other oral SCC after anogenital SCC.<sup>2</sup>

Among patients with anogenital SCC, risks of SCCs at other anogenital sites were high (209 observed, relative risk 3.6 [95% CI 3.1-4.1]; table 2). The risk of tonsillar SCC was similarly increased. All three cases of tonsillar SCC after anal SCC were in men (relative risk 12.0 [2.4-35.1]).

Other oral SCC also occurred in excess, though the relative risk (2.3 [1.7-3.0]) was significantly lower than that for tonsillar SCC ( $p=0.013$ , one-sided). Among patients with HPV-unrelated cancers, relative risks were close to 1.0, although slightly low for cervical SCC.

This study suggests a strong link between tonsillar and anogenital SCC. HPV may be a common aetiological factor. Tobacco, a major risk factor for oral cancers, is also linked aetiological to anogenital SCC and may have contributed to the association. However, the finding that the relative risk was significantly higher for tonsillar SCC than for other oral SCC supports a role for HPV in the aetiology of tonsillar SCC. Although based on small numbers, the highest relative risk for tonsillar SCC was in patients with anal SCC, a cancer common among homosexual men. All three tonsillar cancers after anal SCC were in unmarried or divorced men. Unprotected orogenital sex with an infected partner may result in transmission of HPV to the oral cavity. There are no specific published data on sexual behaviours of patients with tonsillar cancer, but one study suggested an association between active oral sex and risk of oral cancer positive for HPV-16 DNA, of which tonsillar SCC was the most common type.<sup>3</sup> The role of the immune system in tonsillar carcinogenesis is unknown. Other HPV-associated cancers occur in excess among patients with HIV infection and AIDS and among patients with transplantation-related immunosuppression. Tonsillar SCC has been reported in young transplant patients.<sup>4</sup> The increasing incidence of tonsillar SCC in young US men, but not women (unpublished) may reflect an association with HIV-related immunosuppression.

The tonsillar crypt epithelium, believed to favour the capture and processing of antigens, may facilitate viral access to basal mucosal cells. This idea accords with the suggestion that HPV-associated tonsillar SCCs originate from the crypts, whereas HPV-unrelated SCC emerge from the tonsillar surface.<sup>5</sup>

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Initial cancer	ICD-O2 code topography + histology	Number of patients	Median age (years)	Person-years of follow-up
<b>HPV-associated anogenital SCC</b>				
Cervical SCC	C530-C539 + 80503-80763	18 586	50	120 535
Cervical SCC in situ	C530-C539 + 80502-80762	46 093	31	341 713
Vulvar/vaginal SCC	C510-C529 + 80503-80763	4155	70	21 907
Anal SCC*	C209-C218 + 80503-80763, 80943, 81203-80243	3232	63	16 522
Total		72 066		500 677
<b>HPV-unrelated cancer</b>				
Colon cancer*	C180-C189 + any	145 994	71	668 614
Stomach cancer*	C160-C169 + any	37 104	69	78 915
Breast cancer (women)	C500-C509 + any	238 925	62	1 490 875
Total		422 023		2 238 404

ICD-O2=International Classification of Diseases for Oncology, 2nd edn, 1990.

\*Proportions of women were 66%, 53%, and 39% among patients with initial anal SCC, colon cancer, and stomach cancer, respectively.

Table 1: Cohorts of patients followed up for tonsillar SCC, other oral SCC, and anogenital SCC after initial HPV-associated and HPV-unrelated cancers, SEER 1973-94