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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

**D. N. Bateman · P. R. McElhatton · D. Dickinson
C. Wren · J. N. S. Matthews · M. O'Keeffe
S. H. L. Thomas**

A case control study to examine the pharmacological factors underlying ventricular septal defects in the North of England

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Abstract *Background*: Amphetamine exposure is associated with congenital cardiac abnormalities in animals. We previously reported an association between recreational use of 2,4-methylenedioxymethamphetamine (ecstasy, MDMA) and ventricular septal defect in babies born to users. We have carried out a case control study to investigate risks in the occurrence of ventricular septal defect in a cohort of babies born in the North East of England.
Methods: Cases were identified from paediatric cardiology units in Newcastle upon Tyne and Leeds, and controls were recruited from the mothers of babies born in the same hospital as the index case. Research nurses carried out interviews using a structured questionnaire.
Results: A total of 296 case control pairs were studied. There was insufficient exposure to ecstasy to test the primary hypothesis. Increased risk of ventricular septal defect was found to be associated with consumption of cough and cold remedies [pre-conception OR 2.2, 95% CI 1.41, 3.51; pregnancy OR 5.1, 95% CI 2.56, 11.27; exposure in either OR 2.83, 95% CI 1.85, 4.45; $P < 0.005$] and in the case of non-steroidals for exposures in pregnancy (OR 4.2, 95% CI 1.54, 14.26; $P < 0.005$).
Conclusions: These findings suggest that ventricular septal defect is associated with consuming the medications identified. They are also compatible with the hypothesis that sympathomimetics (pseudoephedrine, phenylephrine and phenylpropanolamine) present in cough mixtures cause the increased risk, and with our original hypothesis that sympathomimetics and amphetamines are potentially cardiotoxic in utero.

D. N. Bateman (✉)
NPIS Edinburgh, Scottish Poisons Information Bureau,
Royal Infirmary of Edinburgh, 51 Little France Crescent,
Edinburgh, EH16 4SA, UK
E-mail: Nick.bateman@luht.scot.nhs.uk
Tel.: +44-131-2421383
Fax: +44-131-2421387

P. R. McElhatton · S. H. L. Thomas
Wolfson Unit, National Teratology Information Service,
Newcastle upon Tyne, UK

D. Dickinson
Department of Cardiology, Leeds General Infirmary,
Leeds, UK

C. Wren
Department of Cardiology, Freeman Hospital, Newcastle upon
Tyne, UK

J. N. S. Matthews · M. O'Keeffe
Department of Statistics, University of Newcastle,
Newcastle upon Tyne, UK

S. H. L. Thomas
Wolfson Unit, Regional Drug and Therapeutics Centre,
Newcastle upon Tyne, UK

Introduction

The aetiology of many congenital abnormalities is unknown [1, 2]. While genetic factors are responsible for some, the possibility that modifiable environmental factors, particularly drug exposure, may contribute to the risk of congenital abnormality is of particular concern to physicians. The link between birth defects and illicit drugs is particularly important because of their increasing use [3, 4] and because they have not been adequately tested for their teratogenic potential.

In 1999, we reported a series of cases in which it appeared that ventricular septal defects (VSDs) were occurring more frequently than expected in the offspring of women who had been exposed to 3,4-methylenedioxymethamphetamine (ecstasy, MDMA) during the first trimester of pregnancy [5]. The hypothesis that MDMA might be teratogenic was supported by data available from previous animal work suggesting that cardiac malformations are more frequent in animals exposed to those amphetamines that are chemically similar to MDMA [6, 7]. This is a potentially important association, since congenital VSD is common [8, 9].

We therefore designed a case control study to examine the hypothesis that the risk of VSD would be increased in children whose mothers had taken amphetamines or ecstasy during early pregnancy.

Methods

The study was based on a population of children attending two paediatric cardiac units in the North of England, which serve a population of approximately 6 million. These units are located in Newcastle upon Tyne and Leeds, and satellite clinics are also run from these hospitals, and records kept of cardiac malformations.

The study was designed as a case control study. A power calculation was carried out on the basis of a student survey [10] conducted in Newcastle upon Tyne in 1995, in which university students self reported rates of use of amphetamine of 3.5% per week and of ecstasy of 2.7% per week. Far higher rates were reported for less frequent exposure. With the knowledge that the use of these drugs was increasing, we designed a study powered to demonstrate a threefold relative risk of a ventricular septal defect assuming the exposure among controls would be around 2.5%. In this scenario, approximately 300 cases and controls would be sufficient to detect a threefold increase in risk with a power of 80%.

Ethics permission was obtained from a Multicentre Research Ethics Committee and from the Local Research Ethics Committees in the areas studied. Cases were identified over an 18-month period by the consultant paediatric cardiologists responsible for the babies' care, who approached the mothers of these babies for permission to be interviewed by a dedicated research nurse. Lesions were identified by the presence of an audible murmur and the diagnosis confirmed by ultrasound after the clinical suspicion had been raised. The lesions investigated in this study were simple VSDs not associated with other congenital cardiac syndromes.

Controls were identified from obstetric units in hospitals where the index cases were born. The next five babies born in that hospital after the index case were selected. Mothers of these babies were approached in sequence of birth order via their general practitioners. A letter seeking permission to approach them for interview was forwarded to them by their GP and, when they responded, an appointment was made for a face-to-face interview with the research nurse. A standard questionnaire was administered to all mothers. As a result of the methodology used, data on controls was collected some weeks after that on cases. Data was extracted from the reporting forms into a database from which subsequent analysis was performed. Information was specifically sought regarding exposure to a range of medicinal agents and to drugs of abuse (including alcohol and tobacco) during the 3 months prior to the mother's knowledge of pregnancy, the period before the first missed menstrual cycle, and during the first trimester of pregnancy, the period after the first missed menstrual loss.

Odds ratios were calculated for pre-conception and post-conception exposure to the agents of interest, with exposure classified as a binary variable, i.e. any exposure compared with exposure. Unadjusted odds ratios were calculated taking account of the matching. The associated P values and 95% CI were computed using the exact (binomial) distribution. A conditional logistic regression analysis was performed to calculate odds ratios adjusted for the effects of potential confounding variables.

Results

A total of 296 case control clusters were studied, 165 from Newcastle and 131 from Leeds. The mean age of the Newcastle mothers was 29 years (SD 5.35 years) and the age range was 16–52 years (Table 1).

Because of concerns raised by Local Research Ethics Committees in Yorkshire about the confidentiality of data collection, details of maternal age and babies' gestation, gender and weight were required to be stored separately from the main data file. A decision was made locally to hold this on paper to fulfil these requirements, but this data set was stolen with other items from its storage location, and a duplicate was not available. An initial analysis was therefore carried out only on the data sets collected in Newcastle in order to establish whether the missing variables from the Leeds data were likely to impact on its analysis. There was no evidence from the 165 matched pairs in Newcastle that maternal age, maturity at delivery, babies' gender and birth weights were related to risk of VSD (Table 2). However, it is possible that adjustment for these variables could have a material impact on the estimated odds ratios. Therefore, three analyses are presented for some exposures: (1) the unadjusted analysis for the Leeds and Newcastle data combined, (2) the unadjusted analysis of the Newcastle data and (3) the adjusted analysis for the Newcastle data. Discrepancies between analyses (2) and (3) can be attributed to the effect of various confounding variables,

Table 1 Outline demographic data of cases and controls

	Cases		Controls	
	Mean	SD	Mean	SD
Mother's age (years)	28.50	5.71	29.52	4.97
Gestational age (weeks)	38.99	1.87	39.37	2.04
Weight of baby (kg)	3.36	0.59	3.41	0.56
Sex of baby (male/female)	72/78		81/83	

Table 2 Relationships between maternal age (years), babies' gestational age (weeks), birth weight (kg), sex of baby and risk of VSD in data collected in Newcastle and surrounding areas

	Odds ratio	P	95% CI
Mother's age	0.97	0.13	0.93, 1.01
Maturity	0.89	0.12	0.76, 1.03
Sex of baby	0.94	0.78	0.59, 1.49
Weight of baby (kg)	1.18	0.52	0.72, 1.93

while discrepancies between analyses (1) and (2) will arise if there are differences between the data from Leeds and Newcastle. The numbers of cases and controls exposed to a variety of agents are shown in Table 3.

There were three instances of ecstasy exposure, both pre-pregnancy (one case and two controls) and three instances of amphetamine use pre-pregnancy (two cases and one control). Post-pregnancy one case indicated that they had taken amphetamines (Table 3). Because of this unexpectedly low exposure to ecstasy, the study lacked statistical power to test the primary hypothesis. The odds ratio for exposure to amphetamines and/or ecstasy from the Leeds and Newcastle data combined was 1.00 with 95% CI (0.07, 13.79).

The odds ratios and 95% CI for the other agents of interest are shown in Tables 4 and 5. No relationship between maternal smoking or cannabis use and VSD in the offspring was documented. Although odds ratios from the Newcastle data suggested reduced risk for pre-conception alcohol exposure, this was not sustained when these data were combined with those from Leeds.

In the unadjusted analysis using all data collected, medicinal drug groups significantly associated with an increased risk of VSD were non-steroidal anti-inflammatory agents (NSAIDs), and cough and cold remedies (Table 5). The effect of adjustment was limited and the highest odds ratios were found during pregnancy. A similar pattern was obtained for analgesics but the odds ratios were smaller.

It is arguable that the increased risk associated with NSAIDs and cough and cold remedies actually reflects the effects of viral infection rather than those of the

Table 3 Exposure status pre- and post-conception or both to specific factors in cases and controls. *NSAID* non-steroidal anti-inflammatory

Factor	Exposure status of case/control pairs			
	Both exposed	Case exposed/control unexposed	Case unexposed/control exposed	Both unexposed
Amphetamines				
Pre-conception	0	2	1	293
Pregnancy	0	1	0	295
Either	0	2	1	293
Ecstasy				
Pre-conception	0	1	2	293
Pregnancy	0	0	0	296
Either	0	1	2	293
Amphetamines and/or ecstasy				
Pre-conception	0	2	2	292
Pregnancy	0	1	0	295
Either	0	2	2	292
Alcohol				
Pre-conception	159	66	51	20
Pregnancy	102	74	67	53
Either	169	64	46	17
Smoking				
Pre-conception	19	53	56	168
Pregnancy	12	51	51	182
Either	21	53	55	167
Cannabis				
Pre-conception	0	8	9	279
Pregnancy	0	5	6	285
Either	0	8	9	279
Anti-infectives				
Pre-conception	2	18	26	250
Pregnancy	22	48	31	195
Either	31	48	41	176
Clotrimazole				
Pre-conception	0	4	3	289
Pregnancy	2	26	17	251
Either	2	28	19	247
Analgesics				
Pre-conception	162	63	40	31
Pregnancy	133	78	55	30
Either	202	46	35	13
NSAIDs				
Pre-conception	11	53	35	197
Pregnancy	0	21	5	270
Either	11	54	35	196
Cough and cold remedies				
Pre-conception	21	66	30	179
Pregnancy	14	51	10	221
Either	28	85	30	153

Table 4 Odds ratios and, for Newcastle data, adjusted odds ratios for factors of interest, drugs of abuse

Factor	Leeds/Newcastle unadjusted			Newcastle unadjusted			Newcastle adjusted[a]		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Amphetamines									
Pre-conception	2.00	0.10, 118.01	1.00	–	–	–	–	–	–
Pregnancy	–	–	–	–	–	–	–	–	–
Either	2.00	0.10, 118.01	1.00	–	–	–	–	–	–
Ecstasy									
Pre-conception	0.50	0.01, 9.60	1.00	–	–	–	–	–	–
Pregnancy	–	–	–	–	–	–	–	–	–
Either	0.50	0.01, 9.60	1.00	–	–	–	–	–	–
Amphetamines and/or Ecstasy									
Pre-conception	1.00	0.07, 13.79	1.00	–	–	–	–	–	–
Pregnancy	–	–	–	–	–	–	–	–	–
Either	1.00	0.07, 13.79	1.00	–	–	–	–	–	–
Alcohol									
Pre-conception	1.29	0.88, 1.90	0.20	0.49	0.26, 0.89	0.02	0.40	0.21, 0.77	0.01
Pregnancy	1.10	0.78, 1.56	0.61	0.61	0.37, 0.99	0.05	0.65	0.40, 1.08	0.10
Either	1.39	0.94, 2.08	0.10	0.50	0.25, 0.96	0.04	0.38	0.19, 0.77	0.01
Smoking									
Pre-conception	0.95	0.64, 1.40	0.85	1.09	0.66, 1.82	0.81	0.94	0.53, 1.66	0.80
Pregnancy	1.00	0.66, 1.50	1.00	1.03	0.61, 1.75	1.00	0.87	0.49, 1.55	0.63
Either	0.96	0.65, 1.43	0.92	1.13	0.68, 1.89	0.71	0.97	0.55, 1.73	0.93
Cannabis									
Pre-conception	0.89	0.30, 2.60	1.00	0.67	0.14, 2.81	0.75	0.65	0.17, 2.52	0.53
Pregnancy	0.83	0.20, 3.28	1.00	0.75	0.11, 4.43	1.00	0.82	0.16, 4.26	0.82
Either	0.89	0.30, 2.60	1.00	0.67	0.14, 2.81	0.75	0.65	0.17, 2.52	0.53

[a]Adjusted for mother's age and baby's gestational age, birth weight and sex. Newcastle data only (see text)

Table 5 Odds ratios, and for Newcastle data adjusted odds ratios for factors of interest, medicinal products. *NSAID* non-steroidal anti-inflammatory

Factor	Leeds/Newcastle unadjusted			Newcastle unadjusted			Newcastle adjusted[a]		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Anti-infectives									
Pre-conception	0.69	0.36, 1.31	0.29	0.82	0.38, 1.78	0.72	0.71	0.33, 1.54	0.39
Pregnancy	1.55	0.97, 2.52	0.07	1.18	0.69, 2.02	0.61	1.09	0.63, 1.89	0.75
Either	1.17	0.76, 1.82	0.53	1.00	0.59, 1.69	1.00	0.91	0.53, 1.56	0.74
Clotrimazole									
Pre-conception	1.33	0.23, 9.10	1.00	1.50	0.17, 17.96	1.00	2.18	0.31, 15.28	0.43
Pregnancy	1.53	0.80, 3.00	0.22	1.38	0.69, 2.80	0.42	1.64	0.82, 3.29	0.16
Either	1.47	0.79, 2.79	0.24	1.35	0.69, 2.70	0.43	1.62	0.82, 3.20	0.17
Analgesics									
Pre-conception	1.58	1.04, 2.40	0.03	1.12	0.63, 1.97	0.79	1.15	0.66, 2.02	0.62
Pregnancy	1.42	0.99, 2.04	0.06	1.26	0.79, 2.04	0.36	1.32	0.81, 2.13	0.26
Either	1.31	0.83, 2.10	0.27	0.82	0.41, 1.60	0.64	0.89	0.46, 1.70	0.72
NSAIDs									
Pre-conception	1.51	0.97, 2.39	0.07	1.44	0.76, 2.80	0.29	1.15	0.60, 2.21	0.68
Pregnancy	4.20	1.54, 14.26	<0.005	3.33	0.86, 18.85	0.09	3.29	0.88, 12.31	0.08
Either	1.54	0.99, 2.43	0.06	1.50	0.80, 2.89	0.23	1.19	0.63, 2.27	0.60
Cough and cold remedies									
Pre-conception	2.20	1.41, 3.51	<0.005	1.43	0.82, 2.56	0.23	1.33	0.73, 2.41	0.35
Pregnancy	5.10	2.56, 11.27	<0.005	3.25	1.43, 8.31	<0.005	4.16	1.67, 10.35	<0.005
Either	2.83	1.85, 4.45	<0.005	1.96	1.16, 3.39	0.01	1.88	1.09, 3.23	0.02

[a]Adjusted for mother's age and baby's gestational age, birth weight and sex. Newcastle data only (see text)

remedies per se. This is difficult to assess from our data: a partial investigation is to fit a conditional logistic regression to see whether the odds ratio is higher among those taking remedies containing pseudoephedrine, phenylephrine or phenylpropanolamine than when taking other forms of cold remedy. The odds ratio for those taking this kind of remedy is 2.41 times greater [with 95% CI (0.93, 6.30)] than for those taking remedies not containing these ingredients. However, the *P* value is 0.07, indicating that the evidence of a differential effect is weak.

The study also permits us to examine change in reported behaviour at the onset of pregnancy in a large

cohort of women. During pregnancy there was a small reported decrease in smoking but a larger decrease in alcohol consumption (Table 3). NSAID use, analgesic use, and the use of cough and cold remedies also decreased during pregnancy. Use of anti-infective agents, only available in the UK on prescription, increased in the first 3 months of pregnancy. The use of the anti-fungal agent clotrimazole also increased at this time (Table 3).

Discussion

Use of drugs such as MDMA during pregnancy raises a number of concerns. Ho and colleagues [4] have reported that use continues into pregnancy in the vast majority of users. Christophersen [11] indicated that usage is of the order of 1–5% across Europe in young adults. St Omer et al. [12] studied effects on pregnant rats and found little evidence of postnatal development toxicity but did see reduced maternal weight gain. As this was not a classical teratology study in which the foetuses were delivered prior to term to examine for congenital malformations and resorptions (miscarriages), no accurate assessment can be made of the effects of ecstasy on foetal development. Other workers have found cardiotoxicity in teratological studies using amphetamines [6, 7]. As VSD is a relatively common cardiac malformation, small increases in relative risk are important [13, 14].

The primary hypothesis of this study was not properly tested. This is because the reported exposure to ecstasy and amphetamine was so low in the populations that it was not possible to calculate an estimate of risk with any degree of accuracy. These data are in one sense reassuring because they suggest that the exposures of the average population of child-bearing women to drugs of this type in the north of England between 1999 and 2002 were relatively low, and certainly far lower than those suggested by the survey reported by Webb [10]. This is perhaps because nearly half the mothers were aged 30 years and older, while ecstasy use predominates in younger women [11]. We cannot exclude the possibility that some exposures were not reported by mothers.

Although there was no evidence from the 165 matched pairs that maternal age or sex of the baby were related to an increased risk of VSD, the number of subjects in this study is small. There are convincing data from other studies based on over 2000 cases that maternal age and parity may have an effect on the risk of VSD [15]. Pradat et al. reported a normal sex ratio for infants with VSD. There was also a higher risk of severe cardiac defects, but not septal defects, in children born to women aged 35 years or over. However, this may not be a specific age-related effect, but may reflect that this age group of pregnant women are considered to have high-risk pregnancies and their babies may be monitored more often; thus the likelihood of picking up the less severe CHD is increased.

It is well documented that high consumption of alcohol during pregnancy is associated with an increased risk not only of structural malformations, such as CHD, but also of long-term adverse effects on development, behaviour and subsequent health [8, 9, 16–20]. However, much less is known about the effects of mild-moderate alcohol consumption or occasional binge drinking. A study of VSD (156 cases and 756 controls) in Finland between 1982 and 1983 showed that maternal alcohol consumption during the first trimester was more common (47%) in the mothers of VSD infants than among those of controls (38%, $P < 0.05$) [16]. However, this study did not show an association between VSD and smoking, caffeine, aspirin or diazepam.

The present study also demonstrated that women alter their behaviour in terms of smoking, alcohol intake, and use of over the counter cough medicines before and after pregnancy. The numbers smoking and drinking alcohol were reduced in reported activity during pregnancy, and the numbers of non-prescription medications taken were reduced.

There are conflicting data between the association of certain CHDs and maternal smoking [21]. No effect of maternal smoking on the risk for VSD was observed in a prospective study of 311 cases (77 smokers, 235 non-smokers; OR 1.02, 95% CI 0.79, 1.79) [22]. The analysis of the results of several studies indicate that even if maternal smoking may be significantly associated with some type of CHD, it is unlikely to be a major risk factor for the majority of CHD.

Over the counter cough medicines reportedly taken by the women in this study contained two sympathomimetic agents, phenylpropanolamine and ephedrine. The apparent association between their use and VSD risk is a cause for concern. There are reports that exposure to some vasoactive substances including decongestants and cyclo-oxygenase inhibitors during pregnancy may cause an increased risk of gastroschisis and small gut atresia via a vascular mechanism [23, 24]. However, these studies have several methodological limitations and are subject to recall bias. No association between sympathomimetics and cardiovascular effects were found in the large prospective Collaborative Perinatal Project study in the US, but the number of exposures was relatively low (first trimester exposures to: phenylephrine 1,249; phenylpropanolamine 726 and pseudoephedrine 39) [25].

Similar comments apply to use of NSAIDs. When ascribing cause and effect in retrospective case control studies of this nature, there is always a concern that selective memory is more likely in women who have given birth to a child with an abnormality. It is also important to remember that association may not indicate cause. There are conflicting data reports on the potential teratogenic effects of aspirin and NSAIDs such as ibuprofen and naproxen [13, 23, 24, 26, 27]. A possible association with cardiovascular malformations was reported in three studies [13, 26, 28]. Such effects may be non-specific effects of NSAIDs, which are

cyclo-oxygenase inhibitors resulting in prostaglandin inhibition. However, drugs such as ibuprofen and aspirin are available over the counter to treat a number of conditions such as fever and pain and adverse pregnancy outcome may be related to the condition for which the NSAID was taken rather than a direct teratogenic effect of the drug.

In a case control study, 5,015 infants with cardiovascular system defects without known chromosome anomalies were compared with a control group of all infants (577,730) born in Sweden between 1 July 1995 and 1 July 2001 [28]. Of the 2,128 infants with VSD, 607 were exposed to different types of medication during the first trimester [OR 1.10, 95% CI (1.00, 1.21)]. Among this group, 24 of the children were exposed to naproxen in utero [24/1,679 OR 1.70, 95% CI (1.14, 2.54)]. There are no differences in effect in severe or less severe (e.g. VSD) cardiac defects. However, when all NSAID exposures were analysed together (80/7,698), no significant increase in risk for CHD was observed [OR 1.24, 95% CI (0.99, 1.55)].

Thus, as analgesics and cough and cold remedies are used to manage symptoms of disorders caused by viral infections, one possible hypothesis that we cannot exclude in this study is that the findings we have seen are related to virus exposure, not to the drugs ingested. We did not demonstrate a clear association between VSD risk and use of anti-infective agents, so the study provides no evidence that bacterial infections during pregnancy are a major cause of VSD. However, as antibiotics are often inappropriately prescribed for viral and bacterial infections secondary to viral infections, no clear conclusion can be drawn as to whether or not there is an association. Further work is required to confirm or refute these possible associations.

Overall, we were unable to confirm previous reports of an excess risk of VSD in female infants [8]. Similarly, in contrast to Wasserman et al. [29], who studied the effects of smoking on conotruncal heart abnormalities, but in common with Loffredo [9] who studied VSD in infants in the USA, and Tikkanen and Heinonen [16] who studied VSD in Finland, we did not identify smoking as a risk factor in this series. We were not able to show any association between VSD and alcohol or cannabis use.

In conclusion, we have shown a significant association between maternal ingestion of two drug groups during early pregnancy and risk of VSD in the offspring. There was insufficient exposure to amphetamine and ecstasy in the study to estimate excess risk. However, if overall levels of exposure have been correctly reported, then they are sufficiently low to suggest this is not a major aetiological factor for VSD in the North of England. The association with consumption of cough and cold preparations raises an important question, since those taken in the early phases of pregnancy contain sympathomimetics. This would be compatible with the hypothesis that amphetamine-like compounds are a risk factor for VSD in man.

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