Teratology

BIAS AGAINST THE NULL HYPOTHESIS: THE REPRODUCTIVE HAZARDS OF COCAINE

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Summary To examine whether studies showing no adverse effects of cocaine in pregnancy have a different likelihood of being accepted for presentation by a large scientific meeting, all abstracts submitted to the Society of Pediatric Research between 1980 and 1989 were analysed. There were 58 abstracts on fetal outcome after gestational exposure to cocaine. Of the 9 negative abstracts (showing no adverse effect) only 1 (11%) was accepted, whereas 28 of the 49 positive abstracts were accepted (57%). This difference was significant. Negative studies tended to verify cocaine use more often and to have more cocaine and control cases. Of the 8 rejected negative studies and the 21 rejected positive studies, significantly more negative studies verified cocaine use, and predominantly reported cocaine use rather than use of other drugs. This bias against the null hypothesis may lead to distorted estimation of the teratogenic risk of cocaine and thus cause women to terminate their pregnancy unjustifiably.

INTRODUCTION

IN biomedical research it can be hard to publish negative results in peer reviewed journals. Although such studies may be perceived as "not news", how can we quantify this impression when the data languish unpublished? Under-reporting of safe use of drugs and chemicals in pregnancy may be detrimental. Pregnant women exposed to non-teratogens perceive their teratogenic risk to be in the range of 25%, which is similar to that of thalidomide.[1] After the Chernobyl disaster it was estimated that half of the pregnant women in Greece terminated their pregnancy due to erroneous perception of teratogenic risk.[2]

TABLE I—FETAL OUTCOME MEASUREMENTS*

Outcome measurement	No of studies	Outcome measurement	No of studies
Birth weight and/or length	24	Necrotising enterocolitis	3
Gestational age	20	Apgar score	3
Head circumference	11	Cardiovascular changes	2
Malformations	9	Auditory response	2
Intracranial haemorrhage	8	Spontaneous abortions	2
Neonatal neurobehavioural examination	6	Pneumogram pattern	2
		Apnoea	2
SIDS	6	Sepsis	2
Neurological abnormalities	5	Death	2
Bayley scale of infants development	3	Obstetric complications	2

*A study could report on more than one variable.
Placental haemorrhage, fetal breathing, neonatal withdrawal, eye vascularity, caesarean section, meconium staining, central-nervous-system structural damage, urinary tract infection, increased cerebral blood flow, pneumothorax, and hyaline membrane disease—1 each.
SIDS = sudden infant death syndrome.

Because young fecund adults are the greatest recreational users of cocaine, the drug's hazards to the fetus are of concern. The extent and potential severity of such adverse effects are controversial. Intrauterine growth retardation,[3,4] abruptio placenta,[5,6] prematurity,[7,3] sudden infant death syndrome,[8] and neonatal behavioural abnormalities[6,9] have been reported. Interpretation of these results is hampered by clustering of other risk factors in pregnant women who use cocaine, such as use of other drugs of abuse, cigarettes, and alcohol and socioeconomic status.

When counselling pregnant women who have used cocaine we often reveal an unrealistically high perception of teratogenic risk, which often leads to requests for termination. Whilst many of our patients "know" that cocaine use is a serious risk to pregnancy, they are not aware of the controversy and of the many negative reports. We have investigated whether studies showing no adverse effects of cocaine in pregnancy have a different likelihood of being reported by a large scientific organisation than do studies showing adverse effects.

METHODS

All abstracts submitted to the annual meeting of the Society for Pediatric Research are published in the April issue of *Pediatric Research*. Unaccepted abstracts are also published, with those selected for presentation marked with a symbol. We identified all abstracts on cocaine in pregnancy submitted to the meeting between

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TABLE II—ABSTRACTS ON FETAL OUTCOME AFTER COCAINE EXPOSURE IN PREGNANCY

Fetal outcome	Accepted	Not accepted	Totals
Adverse	28	21	49
Not adverse	1	8	9
Total	29	29	58

TABLE III—COMPARISON OF ABSTRACTS SHOWING ADVERSE OUTCOME WITH THOSE SHOWING NO ADVERSE OUTCOME

—	Adverse (n=49)	Non-adverse (n=9)
Cocaine users		
Predominantly cocaine use	42 *(86%)*	9 *(100%)*
Verification of cocaine use	19 *(39%)*	6 *(67%)*
Sample size	105·5 (288·8)*	199·2 (184·7)
Controls		
Used controls	39 *(80%)*	8 *(89%)*
Matched for variables	17 *(35%)*	2 *(22%)*
Sample size	91·1 (198·4)	1767·6 (3622·9)†

*Mean (SD).
†1 abstract contained 8235 controls; without this abstract the mean sample size and standard deviation for the control non-adverse group would be 150·6 and 269·2, respectively.

1980 and 1989. The abstracts were evaluated by a reader who was blinded to the title and to the acceptance symbol. Abstracts that omitted measurements of pregnancy outcome were excluded.

The following items were extracted from each abstract: no effect or adverse pregnancy outcome; verification of cocaine use by history and/or urine analysis; involvement of polydrug users compared with cocaine users only; and inclusion of comparison groups and their size. Accepted and rejected abstracts showing adverse effects (positive) were compared with those showing no adverse effects (negative) by Fisher's exact or *t* tests for unpaired results as appropriate.

RESULTS

No abstracts on cocaine in pregnancy were submitted before 1985. From a total of 68 abstracts on cocaine use during pregnancy 10 did not report pregnancy outcome measurements (4 were epidemiological, 4 were animal studies, and 2 were analytical). The 58 studies reported various end-points (table I). 49 abstracts were positive and 9 were negative. 28 of the positive abstracts (57%) but only 1 of the negative abstracts (11%) were accepted (p=0·013) (table II).

To examine whether the quality of the negative abstracts was poorer, thus leading to more frequent rejection, we compared them with the positive abstracts (table III). The two groups did not differ significantly in involvement of polydrug users, inclusion of control groups or matched controls, and inclusion of socioeconomic status. Negative studies tended to verify cocaine use in pregnancy more often, although not significantly so. Similarly such studies tended to have more cocaine and control cases.

We also compared the 8 rejected negative with the 21 rejected positive abstracts (table IV). Significantly more negative studies verified cocaine use (p=0·01). The negative studies tended to be larger in numbers of cocaine-exposed patients, although not significantly so. Similarly almost all negative studies (7/8) had control groups whereas only 14/21 of the positive rejected studies were controlled (not significant).

TABLE IV—COMPARISON OF POSITIVE AND NEGATIVE ABSTRACTS NOT ACCEPTED

—	Adverse (n=21)	Non-adverse (n=8)
Cocaine users		
Predominantly cocaine use	16 *(76%)*	8 *(100%)**
Verification of cocaine use	4 *(19%)*	6 *(75%)*†
Sample size	69·5 (148 4)	222·9 (269·0)
Controls		
Used controls	14 *(67%)*	7 *(88%)*
Matched for variables	7 *(33%)*	2 *(25%)*
Sample size	68·8 (124·5)	270 (25·9)‡

Adverse *vs* non-adverse: *p=0 08, †p=0·01, and ‡p<0·001.

DISCUSSION

Cocaine has gained a wide public reputation of being an "evil drug", because of its link with many illegal activities. The drug is almost "expected" to have adverse effects on the fetus. Indeed, published studies have stressed various adverse fetal outcome measurements.[3-9] However, these effects occurred in women dependent on cocaine and who had a cluster of risk factors, including use of other illicit drugs, heavy alcohol and cigarette consumption, and poor medical follow-up. Attempts to control for these factors are difficult because cocaine users tend to consume more cigarettes and alcohol than those who abuse other drugs.[10,11] Findings from this group have been widely publicised as being applicable to the mild, recreational user of cocaine, who often discontinues use during pregnancy. For example, a newspaper article in Toronto warned women that even one dose of cocaine in pregnancy can harm the baby.[12] Counselling women exposed to cocaine in early pregnancy in Greater Toronto led us to suspect that there is substantial distortion of medical information, which has led many women to terminations even when they were exposed briefly and mildly in early pregnancy.

In the present study we used the rare opportunity created by the Society for Pediatric Research, which publishes not only accepted but also rejected abstracts. Our analysis revealed that the likelihood of a negative study being selected for presentation was negligible, whereas a positive study was likely to be accepted in 57% of cases. It is generally assumed that studies are selected for presentation or publication based on objective scientific criteria. In selecting criteria for this assessment we tried to identify those elements in an abstract that reviewers are likely to use. The data indicated that negative abstracts were similar to or better than positive abstracts. In particular negative abstracts tended to verify cocaine use more frequently, which is probably the most important independent variable in such studies.

The positive abstracts, being a substantially larger group than the negative, are likely to include both scientifically sound and flawed papers. In a comparison of the 21 rejected positive with the 8 rejected negative abstracts, we found the negative studies to be superior in almost every variable studied. This strengthens the suggestion that most negative studies were not rejected because of scientific flaws, but rather because of bias against their non-adverse message. The subconscious message may be that if a study did not detect an adverse effect of cocaine when the common knowledge is that this is a "bad drug", then the study must be flawed.

To study the impact of this bias, consider the association between cocaine use and SIDS. There are published studies to suggest higher rates of SIDS with gestational use of cocaine,[8] although some investigators could not detect such a relation.[13] We found 6 abstracts on SIDS; 3 claimed association with cocaine use and 3 did not. 2 of the positive

abstracts but none of the negative abstracts were accepted for presentation.

We were recently consulted about a case that highlighted a detrimental effect of this reporting bias. Foster parents brought to the Motherisk Clinic a baby exposed in utero to cocaine, to find out whether he needs to continue to be monitored for apnoea. At birth the attending physician told the natural mother, who was unmarried but wished to keep the child, that there is a high risk for SIDS and therefore the baby should be monitored during sleep for apnoea. Neighbours had complained to a childrens' aid group that the "monitor goes on too frequently", and the child was taken from the natural mother against her will. The history revealed that the child had never had apnoea and was healthy. 1 of the negative abstracts had actually detected a lower frequency of respiratory distress syndrome in children exposed in utero to cocaine than in controls.[14] This paper was not accepted for presentation.

Bias by journals, scientific societies, and funding agencies against negative results may have far-reaching detrimental effects: scientists, realising their slim chance of having such data acknowledged, may be thus discouraged from submitting negative results. Rosenthal[15] identified a tendency of psychology journals to publish only significant findings—the file drawer problem. Even more alarming, this bias may lead scientists to massage or misrepresent data to obtain positive results.[16]

It is the duty of editorial boards, scientific committees, and funding agencies to acknowledge this serious bias and to indicate clearly that research results are not more important if they are positive. Rather importance should be dictated by the relevance of the scientific questions and by the ways they are answered.

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Screening

ANTENATAL TESTING FOR HUMAN IMMUNODEFICIENCY VIRUS

Results from the Royal College of Obstetricians and Gynaecologists' National Study of HIV Infection in Pregnancy

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Summary Current policies on antenatal testing for human immunodeficiency virus (HIV) in the main obstetric units of the United Kingdom and the Republic of Ireland were surveyed by postal questionnaire; 294 of 299 units responded. HIV testing was available at 192 (65%) of the 294 units that responded. 414 HIV-positive pregnancies in 386 women were reported from 74 (25%) units. Most were from Scotland, the four Thames Regions, and Ireland. In 46% of the HIV-positive women the infection was identified by antenatal testing; the remainder had been tested previously and knew that they were infected. The findings support the view that selective antenatal testing should be established in areas where no testing is offered at present and possibly that testing should be offered to all pregnant women in high-prevalence areas.

INTRODUCTION

BY July, 1989, in the United Kingdom 82 cases of acquired immunodeficiency syndrome (AIDS) in women had been reported to the Communicable Disease Surveillance Centre or Communicable Diseases (Scotland) Unit, and there had been 1087 laboratory reports of women seropositive for human immunodeficiency virus (HIV).[1] However, it is not known how many of these women were pregnant at the time of reporting. In addition, 316 children under 15 years were known to be positive for HIV antibody by July, 1989.[1] 126 were children of infected mothers; since at least 99 of the children were younger than 18 months, the number infected remains unknown because maternal antibody can persist until this age.[2]

Of 558 cases of AIDS in children reported from the European Community, Finland, Sweden, and Switzerland to the World Health Organisation AIDS centre in Paris, 76% had acquired infection from their mothers. Of these 426 women, 48% were intravenous drug users, 33% were partners of HIV-positive men, 3% were blood transfusion recipients, and the risk category for transmission in the remainder was either a combination of the above or unknown.[3]

This study was set up under the auspices of the Royal College of Obstetricians and Gynaecologists (RCOG) to collect confidential information on the numbers and geographical distribution of HIV-positive pregnant women seen antenatally and to record antenatal testing policies.

METHODS

299 obstetric units in the UK and the Republic of Ireland were identified from the Joint Planning Advisory Committee Census,