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Maternal drug histories and congenital malformations: limb reduction defects and oral clefts

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SUMMARY In a case control study, prescription data were examined for the three months before the last menstrual period and for the first trimester of pregnancy in *(a)* 115 mothers of children with limb reduction defects, *(b)* 676 mothers of children with oral cleft, and *(c)* an equal number of control mothers of normal babies from the same doctor's practice for each case. In the limb reduction study, the study mothers were prescribed more drugs generally although this did not reach statistical significance, nor were there significant differences between study and control mothers for individual groups of drugs. In the oral cleft study, significantly more drugs were prescribed to study mothers in the three months before the last menstrual period, and a similar trend, which did not reach statistical significance, was observed in the first trimester. Anticonvulsant drugs were prescribed significantly more frequently to study mothers during the whole period of the study. A significant association was also demonstrated between oral contraceptives taken in the three months before the last menstrual period and oral cleft, but doubt must remain concerning this relationship; the risk is not well understood and is likely to be nonspecific. A number of other significant associations were identified, although their importance in practice is uncertain in view of the confounding factors that may affect a study of this kind.

Certain congenital malformations are known to be related to the use of drugs in early pregnancy, the best known examples being the limb reduction (and other) defects caused by thalidomide and the relation of oral clefts to anticonvulsants.[1–4] However, the evidence for teratogenicity of other commonly used drugs, such as steroid hormones and antinauseants, is more controversial.[5–12] The present study, the fourth in a series carried out jointly by the Committee on Safety of Medicines (CSM) and the Office of Population Censuses and Surveys (OPCS), was therefore undertaken to see whether the use of drugs commonly prescribed around the time of conception, or in the first trimester, was associated with subsequent limb reduction defects or oral cleft in the babies. These are both congenital abnormalities known to be drug related in some instances and are readily diagnosed at birth.[1–4]

Subjects and methods

The selection of subjects and method of study were similar to those in previous investigations.[6 13] The study population consisted of all infants born with oral cleft and/or major limb reduction defects during the 12 month period from 1 October 1983 and notified to the OPCS congenital malformation surveillance system. Each infant was matched with a control, the next normal infant born in the same general practice as the abnormal child within three months of the latter's birth. This design was chosen to minimise the effect of any change in prescribing habits by the family practitioner as a result of the birth of a malformed baby in the practice. The family practitioner in each case was identified with permission from the District Health Authorities and was visited by one of the CSM's part time medical officers who obtained from the written practice records the available details of the mother's personal and family history of congenital malformations (in first cousins or closer), her obstetric history, and the drugs prescribed during the three months before the last menstrual period (PLMP) and during the first trimester (FT) of the pregnancy resulting in the malformed child. The presence and nature of the malformation as notified were confirmed with the practitioner's records, and a control was selected and documented in the same way as for the study case.

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Odds ratios (OR) and 95% confidence limits (CL) were calculated using matched pair analysis.[14 15] Where age adjustment was necessary, the matching was broken, and a summary OR was obtained using the Mantel-Haenszel procedure.

Results

LIMB REDUCTION DEFECTS

One hundred and seventy four pairs were admitted to the study, but 59 (33·9%) were excluded; in 40 cases this was because the child's condition was either dwarfism, arthrogryphosis or achondroplasia rather than a limb reduction defect. Of the remainder, 10 were excluded because of inability to trace the family, inability of the family practitioner to cooperate in six cases, and no part time medical officer being available for three cases, leaving 115 for analysis.

The pairs were well matched for age, social status, and previous live/stillbirths. There was a significant difference between the two groups in the distribution of miscarriages (including terminations), which were commoner in the study group ($p<0·01$), and the expected excess of prematurity, stillbirths, and early deaths was seen in the malformed children themselves. A family history of malformations was five times more frequent in the study population.

Maternal drug histories

Although more mothers in the study group were prescribed medication in both the PLMP and FT periods than controls, this difference was not statistically significant. Table 1 shows the most frequently prescribed groups of drugs in the two periods under study with associated odds ratios and confidence limits.

Mothers in the study group were prescribed more hormonal steroids and analgesics in both periods, but the difference was not statistically significant. In fact the only significant finding was a lower risk to study mothers who were prescribed penicillin in the PLMP. The numbers were, however, very small: three study mothers and 11 controls (OR 0·3, CL 0·1–0·8).

ORAL CLEFT

Seven hundred and eighty eight study/control pairs were admitted, of which 112 (14·2%) were excluded for various reasons, leaving 676 pairs for analysis (table 2).

There were significant differences between the study and control mothers with regard to age and social class distribution, the study group containing more very young (under 25) and older (35 and over) women ($p<0·01$) and more from the manual class, as assessed by the general practitioner ($p<0·01$). There was no difference between the groups in previous live/stillbirths, but previous miscarriages (including terminations) were significantly more common in the study group (141 study, 108 control mothers, $p<0·01$).

The malformed babies showed the expected excess of stillbirths, prematurity, and early deaths (183 study and 70 control babies). The sex and cleft distribution

Table 1 *Limb reduction defects: groups of drugs commonly prescribed in 115 study/control pairs*

	3 months before last menstrual period					*First trimester of pregnancy*				
Drug group	*Study mother*	*Control mother*	*Both*	*Neither*	*OR (CL)*	*Study mother*	*Control mother*	*Both*	*Neither*	*OR (CL)*
All steroid hormones	17	9	4	85	1·9 (0·9–4·2)	7	2	2	104	3.5 (0·8–15·3)
Oral contraceptives	13	7	4	91	1·9 (0·8–4·6)	4	0	2	109	—
Progestationals and fertility	4	2	0	109	2·0 (0·4–10·6)	3	2	0	110	1·5 (0·3–8·9)
Antibacterials	10	14	1	90	0·7 (0·3–1·6)	13	10	1	91	1·3 (0·6–3·0)
Analgesics	6	2	0	107	3·0 (0·7–13·8)	3	5	0	107	0·6 (0·1–2·5)
Antihistamines	5	2	0	108	2·5 (0·5–12·2)	4	7	1	103	0·6 (0·2–1·9)
Antinauseants	5	2	0	108	2·5 (0·5–12·2)	4	3	0	108	1·3 (0·3–5·9)
Antispasmodics and antidiarrhoeals	5	2	0	108	2·5 (0·5–12·2)	2	1	0	112	2·0 (0·2–21·0)
Antifungals (oral)	3	1	0	111	3·0 (0·3–25·8)	3	5	1	106	0·6 (0·1–2·5)
Corticosteroids (topical)	3	3	0	109	1·0	2	3	0	110	0·7 (0·1–3·9)
Hypnotics and tranquilisers	3	0	0	112	—	2	1	0	112	2.0 (0·2–21·0)
Anticonvulsants	1	1	0	113	1·0	1	1	0	113	—
All drugs prescribed	31	20	24	40	1·6 (0·9–2·7)	34	29	19	33	1·2 (0·7–1·9)

Table 2 *Oral cleft—exclusions*

Number admitted to study		788
Exclusions		112
No malformation, or malformation not oral cleft	19	
Patient moved, not traced	21	
No records available	20	
Family doctor unable to cooperate	24	
Records incomplete at close of intake	17	
No part time medical officer available	8	
Other	3	
Remaining for analysis		676

corresponded with that described in the literature (male preponderance, 218 cleft palate, 303 cleft lip and palate, 155 cleft lip, 183 with other malformations as well). A family history of malformations was three times more frequent in the study group, especially of oral cleft, which was present in 10% of the study population, corresponding to the usual pattern. The study population was thus a representative sample of clefts. Two infants had neural tube defects (spina bifida) and 25 (13 female, 12 male) were reported to have chromosomal abnormalities, but of these only nine had mothers who had been prescribed medicines: seven being oral contraceptives (see below).

Maternal drug histories

3 months before LMP There was a significant excess of study mothers prescribed medication (OR 1·4, CL 1·1–1·7), although the number of visits by them to their general practitioner was less than the number made by controls (153 study and 162 controls). Table 3 shows the groups of drugs most frequently prescribed during this period. Most commonly prescribed were steroid sex hormones, mainly oral contraceptives (OC), and the study group was significantly more likely to have used these. Adjusting for differences in maternal age distribution between cases and controls

Table 3 *Oral cleft: groups of drugs commonly prescribed in 676 study/control pairs during the 3 months before last menstrual period*

Drug group	*Study mother only*	*Control mother only*	*Both*	*Neither*	*Total*	*OR (CL)*
All steroid hormones	94	61	21	500	676	1·5** (1·1– 2·1)
Oral contraceptives	87	53	20	516	676	1·6** (1·2– 2·3)
Progestationals and fertility	9	9	0	658	676	1·0
Antibacterials	68	64	14	530	676	1·1 (0·8– 1·5)
Penicillins	38	31	5	602	676	1·2 (0·8– 2·0)
Sulpha and trimethoprim	19	8	1	648	676	2·4** (1·1– 5·3)
Analgesics	50	34	1	591	676	1·5 (0·9– 2·3)
Antihistamines	23	22	0	631	676	1·0 (0·6– 1·9)
Hypnotics and tranquilisers	21	12	0	643	676	1·8 (0·9– 3·5)
Anticonvulsants	16	3	0	657	676	5·3** (1·8–16·0)
Antinauseants	11	15	0	650	676	0·7 (0·3– 1·6)
Corticosteroids topical	16	19	0	641	676	0·8 (0·4– 1·6)
Corticosteroids oral	3	1	0	672	676	3·0 (0·3–25·8)
Non-steroidal anti-inflammatory agents	19	13	0	644	676	1·5 (0·7– 2·9)
Antifungals (oral)	14	20	1	641	676	0·7 (0·4– 1·4)
Antispasmodics and antidiarrhoeals	10	5	0	661	676	2·0 (0·7– 5·7)
Neuroleptics and antidepressants	6	1	0	669	676	6·0 (0·9–38·5)
Vitamins	13	9	2	652	676	1·4 (0·6– 3·4)
Folic acid	8	6	0	662	676	1·3 (0·5– 3·8)
All drugs prescribed	168	123	142	243	676	1·4** (1·1–1·7)

**Significant

made little difference (OR unmatched and adjusted for age 1·4, CL 1·04–1·9).

In view of the importance of the time relation between stopping OCs and conception, and the known difficulty of determining the date of conception in ex-OC users, a further analysis attempted to separate out those where there was reasonable certainty that OCs had been stopped before conception, but within the three months before the LMP. In this group, where dates were reasonably certain, there was a significant excess of study mothers. No significant difference was found between the groups where OCs had been used about the time of conception or where details of the dates of prescribing or stopping OCs were not certain, but the differences were in the same direction (table 4).

We also examined what additional drugs mothers on OCs had been taking on the assumption that, for instance, enzyme inducers or antifolate agents including anticonvulsants might have contributed to adverse effects. This was not found to be the case. Although study mothers on OCs were prescribed more additional drugs, this only reflected the general pattern in the PLMP period, and none was on anticonvulsants.

On the supposition that chromosomal defects rather than OCs may have produced the cleft, we excluded the seven mothers on OCs in the PLMP (one continuing into pregnancy) whose infants had accompanying chromosomal abnormalities but this did not affect the result (OR 1·5, CL1·1–2·1).

Table 3 also shows that antibacterials were frequently prescribed, but, of all these, members of the sulphonamide/trimethoprim group were the only ones to be significantly more frequently prescribed to study mothers. Since these two drugs were taken together in all but two study and one control case, it proved impossible to apportion relative importance.

The most striking finding was the risk associated with anticonvulsants, in particular phenobarbitone (10 study, 1 control: OR 10·1, CL 1·9–53·7) and phenytoin (9 study, 2 controls: OR 4·6, CL 1·1–18·5).

Since it is possible that an inherited tendency to delayed midline closure might have enhanced the effect of anticonvulsants as a risk factor, we examined this possibility: however, none of the mothers on anticonvulsants gave birth to infants with neural tube defects.

Analgesics, especially paracetamol and codeine preparations and also benzodiazepines, showed a non-significant excess in the study mothers. None of the other groups of drugs prescribed showed any difference between study and control groups.

First trimester of pregnancy No significant difference was found between the two groups with regard to total prescribing, although study mothers made more visits to their general practitioner (699 compared with 619 controls). Drugs prescribed during this period are shown in table 5. Antibacterials were the most commonly prescribed but showed no difference between the groups, and this applied to the sulphonamides/trimethoprim, although the numbers here were very small. Anticonvulsants continued to be significantly more commonly prescribed among study mothers, and since they are usually given continuously, one cannot separate the PLMP from the FT period. Thirteen study and nine control mothers were prescribed OCs in the FT period, a non-significant difference.

Adjusting these figures to include the women shown in table 4 who may also have used OCs at the time of conception or in early pregnancy continued to result in a non-significant difference (OR 1·3, CL 0·8–2·3).

A significant difference was found for codeine preparations (20 study, 9 controls: OR 2·3, CL 1·0–4·9). Steroids, nearly all topical, as a group showed no difference between cases and controls. However, when individual derivatives were examined,

Table 4 *Oral cleft: OC use in relation to time of conception in 107 study and 73 control mothers*

Time relation	*Study mother only*	*Control mother only*	*Both*	*Neither*	*Total*	*OR (CL)*
Date of stopping OCs known	38	30	7	601	676	—
Date of prescribing and quantity of OCs known	28	12	1	635	676	—
Subtotal known to have stopped in the 3 months prior to LMP	66	42	8	560	676	1·6** (1·1– 2·3)
OCs used about time of conception	15	12	0	649	676	1·3 (0·6– 2·7)
Continued OCs into pregnancy	4	0	0	672	676	—
OCs prescribed, exact timing not certain	12	9	2	653	676	—
Total†	97	63	10	506	676	—

**Significant
†Although total number of mothers is the same as in table 3 the pairs under "both" did not fall into the same groups when analysed by time relation.

Table 5 *Oral cleft: groups of drugs commonly prescribed in 676 study/control pairs during first trimester of pregnancy*

Drug group	*Study mother only*	*Control mother only*	*Both*	*Neither*	*Total*	*OR (CL)*
Antibacterials	63	48	7	558	676	1·3 (0·9– 1·9)
Penicillins	36	31	4	605	676	1·2 (0·7– 1·9)
Sulpha and trimethoprim	8	6	0	662	676	1·3 (0·5– 3·8)
Analgesics	35	28	1	612	676	1·3 (0·8– 2·1)
Antihistamines	26	28	2	620	676	0·9 (0·5–1·6)
Antinauseants	12	23	1	640	676	0·5 (0·3– 1·0)
All steroid sex hormones	19	15	1	641	676	1·3 (0·6– 2·5)
Oral contraceptives	13	9	0	654	676	1·4 (0·6– 3·4)
Progestationals	7	7	0	662	676	1·0
Anticonvulsants	17	2	0	657	676	8·5** (2·5–28·8)
Antifungals (oral)	17	20	1	638	676	0·9 (0·4– 1·6)
Antispasmodics and antidiarrhoeals	17	14	0	645	676	0·8 (0·6– 2·5)
Corticosteroids topical	15	18	1	642	676	1·7 (0·4– 1·7)
Non-steroidal anti-inflammatory agents	10	6	0	660	676	1·7 (0·6– 4·5)
Hypnotics and tranquilisers	7	6	0	663	676	1·2 (0·4– 3·5)
Neuroleptics and antidepressants	3	0	0	676	676	—
Immunisations	4	1	0	671	676	4·0 (0·5–30·3)
Vitamins	37	40	21	578	676	0·9 (0·6– 1·4)
Folic acid	90	82	112	392	676	1·1 (0·8– 1·5)
All drugs prescribed	134	118	239	185	676	1·1 (0·9– 1·5)

**Significant

beclomethasone and betamethasone, both topical, were prescribed significantly more often in the study group although the numbers were small (8 study, 1 control: OR 8·1, CL 1·4–46·5). No differences emerged for any of the other drugs, including antinauseants, particularly doxylamine. Vitamins and folic acid had no apparent protective effect.

Discussion

Although we believe that the cases finally included in the limb reduction defect study were a representative sample of major limb reduction defects, the study lacked power because of the small numbers. Accordingly, the discussion here concentrates on the results of the oral cleft study.

The study population was a representative sample of the abnormality with distribution of clefting, sex, and family history corresponding to that usually described.

The design of the study is, however, open to criticism. Information was obtained solely from the family practitioners' records, and thus no information was available on medicines bought 'over the counter' or any others prescribed elsewhere but not communicated to the practitioner, nor is it known whether the medicines prescribed were all taken. Nothing was known of maternal smoking habits, though oral clefting has sometimes been shown to have a relation to smoking.[16 17] However, the findings on anticonvulsants are in line with published work and suggest that some reliance can be placed on the methodology employed. There was a significant degree of mismatch between the populations with regard to maternal age, but this may have been a reflection of the known relation between increased maternal age and oral clefts,[18 19] and a greater incidence of congenital defects in women under 25 years has also been noted in a previous study.[13] The excess of prematurity, stillbirths, and early deaths in

the study infants agrees with the findings of other authors and is considered to be directly associated with the presence of malformations.[20–22] It should be noted that malformed terminations and miscarriages were not taken into account in this study and might have influenced the results.

The drugs that stood out above all others as a risk factor were the anticonvulsants, in particular phenobarbitone and phenytoin. These drugs have repeatedly been shown to be teratogens associated with oral cleft and nail and digital reduction defects (which we did not consider here) and cardiac abnormalities.[6 22–24]

Although phenobarbitone and phenytoin are particularly implicated, all anticonvulsants are under suspicion.[4 22–24] This was confirmed in the present study: the risk associated with the group as a whole was highly significant, but sufficient numbers for statistical analysis were available only for phenobarbitone and phenytoin. Anticonvulsants are known enzyme inducers[25] making OC failure more likely, and they also have antifolate activity.[3] There is therefore a need for more careful supervision of epileptics of childbearing age, with advice on contraception and, during pregnancy, possibly folate supplements.

No evidence was found in this study that an inherited tendency to delayed midline closure may predispose to oral clefting. Only two infants with neutral tube defects were reported in the study as a whole, and neither was born to a mother on anticonvulsants (or any other medication).

Steroid sex hormones, especially OCs, were also prescribed significantly more frequently to the study mothers in the PLMP period. This effect was also apparent in the periconceptual period but did not reach statistical significance, possibly due to the small numbers exposed. We examined the possibility that other drugs, such as anticonvulsants, might have contributed to the result, but this was not found to be the case; the pattern of additional drugs prescribed reflected the pattern of prescribing in the study as a whole, and no mother on OCs was taking anticonvulsants. Adjusting for age differences between cases and controls did not affect the result, and the distribution of clefts and of family histories followed that of the study population as a whole; no particular risk group was identified.

Nor was there any evidence that chromosomal abnormalities influenced the effect of oral contraceptives.

Our findings have to be viewed in the context of published work, which shows a considerable divergence of opinion on the possible teratogenic effects of steroid sex hormones. On the one hand, a number of very large cohort studies, each involving several thousand women, have shown no increased risk of congenital malformation in ex-OC users.[7 26–28] On the other hand, several case control studies, which are more likely to show up rare events, have shown significant associations between the use of steroid sex hormones and OCs and a number of malformations such as cardiovascular defects[29 30] and limb reduction defects, with or without cardiac and other abnormalities.[5 10 11] There are only a few studies which specifically note the relation of OCs to oral cleft: Greenberg *et al*[6] and also Brogan[31] noted a significant relation between hormonal pregnancy tests and oral cleft, and Harlap *et al*[30] noted a small risk of oral cleft following the use of oestrogen and progesterone in early pregnancy. However, Savolainen *et al*,[32] in a study of 3000 mothers of malformed children, could not demonstrate a link between exposure to OCs and 170 cases of oral cleft. Similar results were obtained by Lammer,[33] although his method of using as controls children with other malformations may be questionable. The whole subject is fully reviewed by Schardein,[34] and it is clear that, although a number of studies have shown an association between steroid sex hormones and various congenital defects, the findings have varied. Considerable doubt therefore remains about the relation between oral clefts and exposure to OCs; the risk is not clearly understood but is likely to be small and nonspecific.

It has been suggested that OC use may reduce the frequency of miscarriage and therefore the expulsion of abnormal embryos rather than acting as a teratogen, but the present study was not designed to answer this question. Reporting of congenital malformations to the OPCS surveillance system is restricted to stillbirths and the first week of life, so only previous miscarriages among the study pairs could be ascertained from the family practitioner's notes.

Unexpected findings in this study were the associations between malformations and sulphonamide/trimethoprim preparations, codeine derivatives, and the topical steroids betamethasone and beclomethasone. Saxen[20] noted a close association between oral cleft and penicillin, but not sulphonamides. In our study, it was not possible to separate the effects of sulphonamides from those of trimethoprim, since they were almost always given together. It is possible that trimethoprim rather than sulphonamides is the problem, which could explain the difference between our findings and those of Saxen, which are otherwise difficult to reconcile.

An association between oral cleft and analgesics and opiates has also been shown by Saxen,[20] lending some support to the present findings on codeine in early pregnancy. Since many codeine preparations are available 'over the counter' and are said to represent 12.9% of drugs administered in early pregnancy,[35] this

association could, if confirmed, be important.

Corticosteroids administered to animals in early pregnancy are known to produce oral clefts,[36 37] but this has never been shown in man. The number of women exposed to betamethasone and beclomethasone in this study was very small, and the importance of the association with oral cleft must therefore remain doubtful.

In conclusion, the study shows generally increased prescribing in the periconceptual period in mothers of children with oral cleft. The most striking association was with anticonvulsant drugs, but the practical importance of a number of significant associations with other prescribed drugs is uncertain, and some of the associations may simply be due to chance.

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