Morbidity and drugs in pregnancy

The influence of illness and drugs on the aetiology of congenital malformations

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SUMMARY. In a prospective study involving 9,000 pregnant women, no cause-and-effect relationships have been established between morbidity recorded or drugs taken during early pregnancy and subsequent congenital malformations. The relationships that have been identified are largely explained by the influence of a history of a previous abnormal outcome of pregnancy (including abortion) and, to a lesser extent, by the influence of maternal anxiety on the diagnosis of doubtful malformations. It is also very unlikely that any drug in common use in 1964 had even a minor influence on congenital malformations recognisable in the first six weeks of life.

Introduction

In 1964, the College of General Practitioners undertook a study to investigate the possible roles of maternal morbidity and its therapy in the aetiology of congenital malformations. This paper describes 9,147 pregnancies in patients who reported a last menstrual period (LMP) between December 1963 and January 1965. Data were provided by 170 general practitioners in various parts of the United Kingdom. A similar, but separate and larger, study was launched in Scotland shortly afterwards. A model of some of the causal relationships in the aetiology of congenital malformations is outlined in figure 1. In this conventional model the assumption is made that in early pregnancy either morbid processes in the pregnant woman or drugs taken by her may influence the likelihood of malformation in her baby. The two main alternative versions of this hypothesis are outlined in the same figure. The design of the study described here and the preliminary programmes for analysing the data were all based on the assumption inherent in this conventional model.

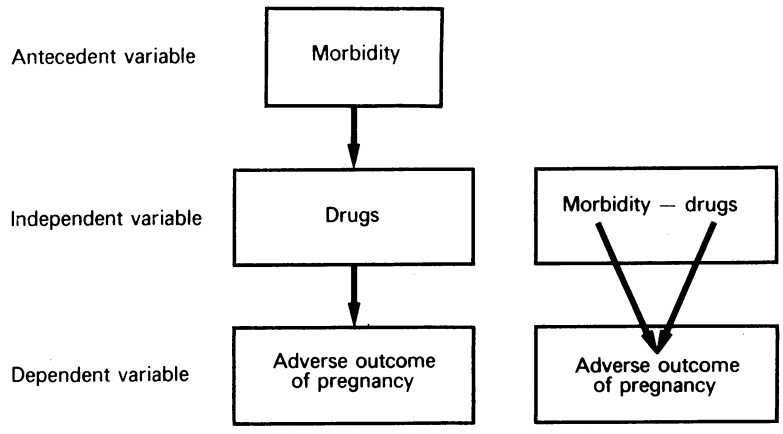


Figure 1
Conventional model showing relationship between morbidity, drugs, and outcome of pregnancy.

Method

Details of the pregnancies were recorded by the general practitioners as they occurred and progressed; the Research Unit of the Royal College of General Practitioners in Birmingham collected information at three stages:

(1) Immediately after the practitioner reported suspicion of pregnancy in a patient.

(2) After 22 weeks duration of pregnancy (or its earlier refutation or termination).

(3) Outcome details at six weeks after birth.

Records were made on a three-part antenatal card similar in format to antenatal co-operation cards in common use. *Part A* recorded retrospective information of obstetric history, chronic illness, morbidity experienced by the mother or other members of the household in the interval between the date of initial consultation and six weeks before the last menstrual period.

Drug therapy, whether self-administered or prescribed, was recorded by date, name of preparation, dose, and the total quantity prescribed. *Part B* contained similar records for drugs and morbidity up to week 22 of pregnancy (dating from the LMP) and the usual antenatal records of blood pressure, weight, and urinalysis. *Part C* contained information on the outcome of each pregnancy.

The records so obtained were coded numerically for mechanical analysis. All the data presented in this paper relate to pregnancies lasting more than 28 weeks from the last menstrual period and have been categorised as follows:

(1) *Normal outcome*—including normal multiple births.

(2) *Lethal malformation*—malformation causing stillbirth or death of a liveborn infant within six weeks of delivery.

(3) *Unequivocal malformation*—malformation diagnosed unequivocally in a baby living more than six weeks.

(4) *Doubtful malformation*—malformation of doubtful diagnostic significance occurring in a liveborn infant. This category includes ' malformations ' which were: almost certainly the result of obstetric birth injury; qualified or equivocal diagnoses such as ' mild ' talipes or; diagnoses which the recording doctor had prefixed by a question mark.

The conditions of umbilical hernia, congenital dislocation of hip(s)/' clicking hip(s) ' and pyloric stenosis were included in this group because uniform diagnostic criteria were not satisfactorily established for these conditions.

(5) *Rhesus incompatibility*—live or stillborn infant reported to be affected by rhesus incompatibility.

(6) *Other stillbirth*—not included in the above categories.

Morbidity was coded using the Royal College of General Practitioners' modification of the *International Classification of Disease* (1963). A drug code was prepared for the study, classifying drugs into broad groups according to chemical or therapeutic similarity and in greater detail according to the distribution of prescriptions issued to the first 500 women. Congenital malformations were coded using the Royal College of General Practitioners' classification of fetal malformations (Slater, Watson, and McDonald, 1964).

The main analyses relate the outcome of pregnancy to each drug prescribed and morbidity episode experienced.

Results

Population surveyed (*table* 1)

The total population surveyed is shown in table 1, as the number of patients in each

outcome category and the percentage distribution of those pregnancies of more than 28 weeks duration. The combined incidence of lethal and unequivocal malformation is 3·0 per cent (245 in 8,255 pregnancies lasting more than 28 weeks) and with the addition of the doubtful group 4·7 per cent (385 in 8,255). A total of 7,733 pregnancies ended in normal outcome and this figure includes 70 out of a total of 83 sets of twins.

TABLE 1
TOTAL OUTCOME OF STUDY POPULATION

Pregnancies less than 28 weeks			892
Pregnancies more than 28 weeks	*Number*	*Per cent*	
Normal outcome	7,733	*93·7*	
Lethal malformation	46	*0·6*	
Unequivocal malformation	199	*2·4*	
Doubtful malformation	140	*1·7*	
Rhesus ' malformation '	37	*0·4*	
Other stillbirth	100	*1·2*	
	8,255	*100%*	8,255
			9,147
Refutations			327
Total women studied			9,474

The influence of morbidity and drugs on outcome (*table* 2)

In table 2a data are presented about the outcome of pregnancy in women in relation to whether or not they received any drugs and/or experienced morbidity in the study period (six weeks before LMP to 22 weeks after it). The information in this table concerning the normal outcome group is based on the experience of a sample 500, obtained by systematically sampling a computer print-out of all normals.

Each abnormal outcome distribution was compared in turn with the distribution for the normal sample. The only difference which was significant at the five per cent level was that between the distribution for the ' doubtful malformation ' group and the normal sample ($\chi^2 = 8 \cdot 8$; 3 degrees of freedom; $\cdot 025 < p < \cdot 05$). The principal contributions to this difference were:

(1) The excess of women in the group who reported morbidity and received drugs.

(2) A deficit of women in the group who received drugs, but had no morbidity recorded.

The separate effects of drugs and morbidity are shown in table 2b which shows the number of women in each category of outcome who have experienced morbidity or received prescriptions for one or more drugs. In table 2c, the episodes of morbidity experienced and the drugs received by women in the various outcome categories are expressed as mean rates per pregnant woman.

The relevant observations that may be made from these tables are:

(a) *Morbidity episodes.* In the doubtful malformation category there were significantly more ($p < \cdot 001$) women who reported morbidity (71 per cent) than in the normal sample (57 per cent). There was a consistent trend in the other categories of abnormal outcome towards an increased proportion of women reporting morbidity episodes, though the individual values do not achieve statistical significance at the five per cent level when compared with that for the normal sample.

TABLE 2

PATIENTS REPORTED TO HAVE RECEIVED ANY DRUGS AND/OR SUFFERED ANY MORBIDITY IN RELATION TO THE OUTCOME OF THEIR PREGNANCY (PERCENTAGE FIGURES IN PARENTHESIS)

Drug morbidity status *Table 2a*	*Normal sample*	*Lethal malformation*	*Unequivocal malformation*	*Doubtful malformation*	*Rhesus incompatibility*	*Other stillbirth*
Drugs and morbidity	277 (*55*)	29 (*63*)	120 (*60*)	96 (*69*)	26 (*70*)	62 (*62*)
Morbidity but no drugs	9 (*2*)	0 (*0*)	8 (*4*)	4 (*3*)	0 (*0*)	3 (*3*)
Drugs but no morbidity	132 (*26*)	10 (*22*)	38 (*19*)	24 (*17*)	4 (*11*)	25 (*25*)
No drugs and no morbidity	82 (*16*)	7 (*15*)	33 (*17*)	16 (*11*)	7 (*19*)	10 (*10*)
TOTAL	500 (*100*)	46 (*100*)	199 (*100*)	140 (*100*)	37 (*100*)	100 (*100*)
Table 2b						
TOTAL women with recorded morbidity	286 (*57*)	29 (*63*)	128 (*64*)	100 (*71*)	26 (*70*)	65 (*65*)
TOTAL women with recorded drugs	409 (*82*)	39 (*85*)	158 (*79*)	120 (*86*)	30 (*81*)	87 (*87*)
Table 2c MEAN RATES PER PREGNANCY CORRECTED TO FIRST DECIMAL PLACE						
TOTAL morbidity episodes	1·0	1·0	1·1	1·4	1·2	1·2
TOTAL drug prescriptions	1·9	2·1	2·0	2·4	2·2	2·4

TABLE 3. NUMBER OF MORBIDITY EPISODES (IN GROUPS) EXPERIENCED BY WOMEN IN EACH CATEGORY OF OUTCOME

College classification number	*Category*	*Normal sample*	*Lethal malformation*		*Unequivocal malformation*		*Doubtful malformation*		*Rhesus incompatibility*		*Other stillbirth*	
		Observed	*obs.*	*exp.*	*obs.*	*exp.*	*obs.*	*exp.*	*obs.*	*exp.*	*obs.*	*exp.*
1	Communicable diseases	7	—	1	5	3	3	2	—	1	1	1
2	Neoplasms	4	—	0	—	1	—	1	—	0	1	0
3	Allergic, endocrine system metabolic and nutritional diseases	12	1	1	9	5	4	3	2	1	2	2
4	Diseases of blood and blood-forming organs	11	2	1	6	4	7	3	—	1	5	2
5	Mental, psychoneurotic, and personality disorders	35	2	3	17	14	18	10	2	3	14	7
6	Diseases of nervous system and sense organs	16	1	1	7	6	4	5	2	1	3	3
7	Diseases of circulatory system	7	1	1	5	3	6	2	1	1	1	1
8	Diseases of respiratory system	111	12	10	55	44	36	31	10	8	20	22
9	Diseases of digestive system	65	5	6	19	26	17	18	9	5	21	13
10	Diseases of genito-urinary system	57	9	5	25	23	21	16	3	4	18	11
11	Diseases and complications of pregnancy	79	7	7	41	31	32	22	8	6	16	16
12	Diseases of skin and cellular tissue	10	1	1	7	4	7	3	1	1	2	2
13	Diseases of bones and organs of movement	25	3	2	8	10	6	7	1	2	9	5
14	Congenital malformations	—	—	—	—	—	1	—	—	–	—	—
16	Symptoms and ill-defined conditions	50	1	5	12	20	23	14	5	4	9	10
17	Accidents, poisoning and violence	5	—	0	3	2	6	1	—	0	1	1
18	Prophylactic procedures	6	—	1	3	2	—	2	—	0	1	1
	TOTAL	498	45	46	222	198	191	139	44	37	124	100
	Mothers	500	46		199		140		37		100	
	Morbidity episodes per woman	1·0	1·0		1·1		1·4		1·2		1·2	

$$\text{Expected number in an outcome category} = \text{Observed number in sample} \times \frac{\text{Number of women in that outcome category}}{\text{Number of women in the sample}}$$

TABLE 4. NUMBER OF DRUGS (IN CONSOLIDATED GROUPS) PRESCRIBED TO WOMEN IN EACH OUTCOME CATEGORY

Drug code number	*Description*	*Normal sample*	*Lethal malformation*		*Unequivocal malformation*		*Doubtful malformation*		*Rhesus incompatibility*		*Other stillbirth*	
		Observed	*obs.*	*exp.*	*obs.*	*exp.*	*obs.*	*exp.*	*obs.*	*exp.*	*obs.*	*exp.*
100–129	Antacids	24	2	2	12	10	10	7	4	2	5	5
150–159	Laxatives	25	1	2	6	10	4	7	3	2	6	5
230–239	Ergotamine group (migraine drugs)	2	—	0	1	1	1	1	—	0	—	0
240–289	Cough preparations	33	3	3	13	13	11	9	6	2	9	7
300–319	Barbiturates	32	3	3	21	13	18	9	4	2	14	6
330–349	Antihistamines/anti-emetics	119	8	11	43	47	47	33	9	9	15	24
350–369	Major phenothiazines	31	—	3	7	12	7	9	2	2	11	6
370–379	Amphetamines	5	1	0	4	2	2	1	—	0	—	1
380–389	Other psychotropic drugs	16	2	1	4	6	7	4	1	1	4	3
390–397	Anticonvulsants	3	—	0	1	1	—	1	—	0	—	1
420–449	Iron	282	25	26	110	112	69	79	19	21	64	56
460–479 (ex. 470)	Vitamin preparations	29	8	3	16	12	25	8	4	2	9	6
470	Folic acid	15	1	1	4	6	3	4	—	1	2	3
500–516	Penicillins	25	4	2	10	10	7	7	3	2	5	5
530–539	Tetracyclines	8	—	1	8	3	4	2	1	1	3	2
550–569	Sulphonamides	26	4	2	14	10	9	7	2	2	13	5
584	Metronidazole	5	2	0	1	2	5	1	—	0	1	1
586	Nitrofurantoin	6	2	1	1	2	2	2	—	0	1	1
600–639	Non-corticosteroid hormones	28	6	3	9	11	12	8	4	2	9	6
750	Potassium/Sodium citrate	9	—	1	7	4	1	3	—	1	2	2
866–890	Analgesics (prescribed)	77	4	7	28	31	24	22	7	6	24	15
950–964	Self-medicated analgesics	31	5	3	14	12	10	9	2	2	3	6
900–999 (ex. 950–964)	Other self-medicated preparations	17	5	2	12	7	25	5	1	1	8	3
	All other drugs	115	9	11	44	46	37	32	9	9	28	23
	TOTAL	963	95	89	390	383	340	269	81	71	236	193
	Mothers	500	46		199		140		37		100	
	Drugs per woman	1·9	2·1		2·0		2·4		2·2		2·4	

$$\text{Expected number in an outcome category} = \text{Observed number in sample} \times \frac{\text{Number of women in that outcome category}}{\text{Number of women in the sample}}$$

(b) *Drugs.* The proportion of women who received prescriptions for drugs is similar for all categories of abnormal outcome to that for the normal sample (82 per cent). However, the mean rates of drugs issued per pregnant woman vary between the outcome categories, being maximal in the doubtful malformation and other stillbirth categories.

Analysis of morbidity—table 3

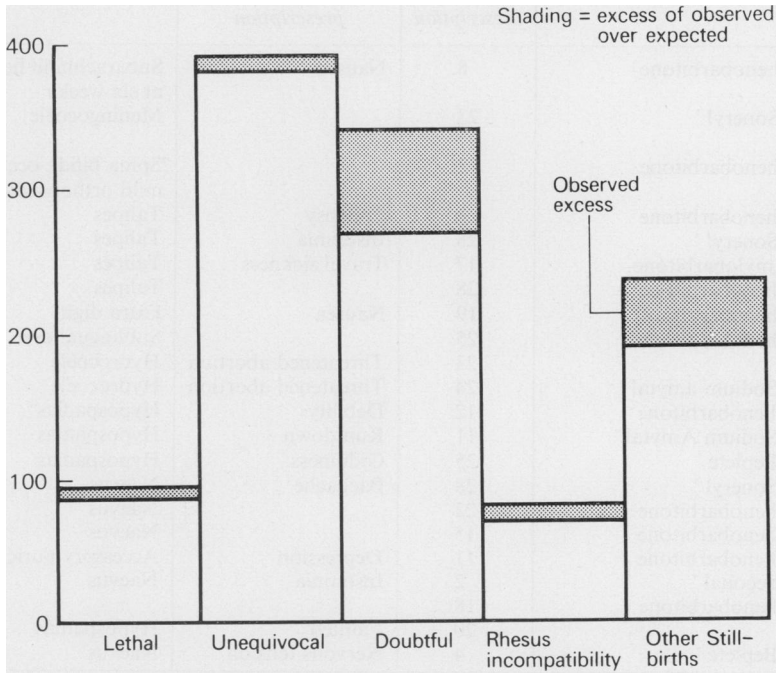
For table 3 the morbidity episodes reported are classified into the 18 main categories of the Royal College of General Practitioners' classification of the *International Classification of Disease* and detailed according to category of outcome. Against each observed value an expected figure is presented. This figure is calculated from the equivalent number of morbidity episodes reported in the normal sample.

The excess reported morbidity in the doubtful malformation category is shown to be widely distributed throughout several morbidity groups including ' mental, psychoneurotic, or personality disorders ', ' diseases and complications of pregnancy ' and ' symptoms and ill-defined conditions '. A similar pattern is observed for the ' other stillbirth ' outcome category.

Analysis of drugs—table 4

In table 4 data are presented about the various drugs prescribed for the women in each category of outcome. Observed values are calculated as described for morbidity episodes.

The information about the total number of drugs issued to each outcome category is also presented as a histogram (histogram 1) where the excess of observed over expected in the doubtful malformation and other stillbirth categories is clearly shown. The excess in the doubtful malformation category (340 compared with 269 which is equivalent



Histogram 1
The observed and calculated expected numbers of prescriptions issued to the abnormal outcome categories.

to 26 per cent) is most evident in ' barbiturates ', ' antihistamines/anti-emetics', 'vitamin preparations ', ' other self-medicated drugs ' and ' all other drugs ' groups. By contrast there are less iron preparations than expected in this category.

The excess in the ' other stillbirth ' category (236 compared with 193 which is equivalent to 22 per cent) is not localised to any individual groups of drugs; on the other hand there are only 15 anti-emetic preparations compared with 24 expected.

More detailed analyses of the influence of individual drugs by examining the outcome distribution for each drug have been made. Anomalies have then been investigated from source records and no cause-and-effect relationships have been established. Such analyses take into account the precise malformation and maturity of the pregnancy at the time of the prescriptions. Examples of some of these drugs include:

(a) *Barbiturates.* The marginal excess of barbiturate prescriptions in the category of unequivocal malformation required further examination because of the previous references to this association (Crombie *et al.*, 1970; Nelson and Forfar, 1971). Detailed analysis of the record cards (appendix A) identifying the nature of the malformation, the barbiturate prescribed, and the maturity of the pregnancy when prescribed showed no suggestion of a cause-and-effect relationship. The malformations so described in the children of the women in this category are in many cases similar to those which are classified as doubtful, if a question mark or descriptive limitation such as ' mild ' was attached to the ' diagnosis '. Among those which were undoubtedly unequivocal malformations there was a disproportionate number of minor skin malformations.

APPENDIX A. BARBITURATE PRESCRIPTIONS ISSUED IN CATEGORY OF UNEQUIVOCALLY MALFORMED OUTCOME

Patient number	*Drug*	*Coded week of prescription*	*Stated reason prescription*	*Malformation*
2223	Phenobarbitone	8	Nausea	Subarachnoid haemorrhage at six weeks
5932	' Soneryl '	23 27		Meningocoele
*12699	Phenobarbitone	12		?Spina bifida occulta and mild orthopaedic flexures
2298	Phenobarbitone	6	Epilepsy	Talipes
10834	' Soneryl '	28	Insomnia	Talipes
12022	Amylobarbitone	17	Travel sickness	Talipes
12341	Phenobarbitone	28		Talipes
13117	Phenobarbitone	19	Nausea	Extra digit
4682	Phenobarbitone	25		Sublingual cyst
3796		23	Threatened abortion	Hydrocoele
4116	' Sodium amytal '	24	Threatened abortion	Hydrocoele
10449	Phenobarbitone	12	Debility	Hypospadias
12042	' Sodium Amytal '	11	Run down	Hypospadias
15546	' Beplete '	25	Giddiness	Hypospadias
3462	' Soneryl '	28	Backache	Naevus
4719	Phenobarbitone	22		Naevus
5154	Phenobarbitone	15		Naevus
9128	Phenobarbitone	11	Depression	Accessory auricle
12332	' Seconal '	2	Insomnia	Naevus
12896	Phenobarbitone	18 20	Fainted	Hypospadias
12989	' Beplete '	4	Nervous tension	Naevus

*Case 12699 is included as an unequivocal malformation because two separate doubtful malformations are described in this patient.

Week of LMP=week 6.

(b) *Anticonvulsants.* There were 18 prescriptions for anticonvulsants issued to mothers who subsequently experienced a normal outcome to their pregnancies and one to a mother experiencing a malformed outcome (talipes) (South, 1972).

(c) *Tricyclic anti depressants.* The use of tricyclic antidepressive drugs was examined and the suspicion of teratogenic properties refuted (Crombie, Pinsent, and Fleming, 1972).

It is also necessary to identify source records because of the limitations of tests of statistical significance. In an investigation of a set of results which contains many subsets, and where differences between these are tested for significance at the five per cent level, then out of every 20 cases in which there is no real difference, one ' difference ' will be incorrectly reported.

The influence of previous pregnancies (*tables* 5 *and* 6)

Notwithstanding the localisation of these excesses of reported morbidity and drug use in general to the women who gave birth to doubtfully malformed or stillborn children, there are some unsatisfactory features. The most important of the anomalies has been the impossibility of localising the correlation to any subgroup of total morbidity or drugs. No matter how morbidity or drugs are partitioned, the same marginal excesses remain evident.

There are only two alternative explanations where variations cannot be localised to some subgroups of a group of variables such as morbidity or drugs. The first is that the effect is diffused over every item of morbidity and every drug, a hypothesis that finds little support from other knowledge of the teratogenic process. The second is that the association is spurious and the true casual relationship is with a third independent variable to which the hypothetical causal variables (morbidity and drugs, figure 1) are in fact dependent variables with the other already identified dependent variables (abnormal outcomes).

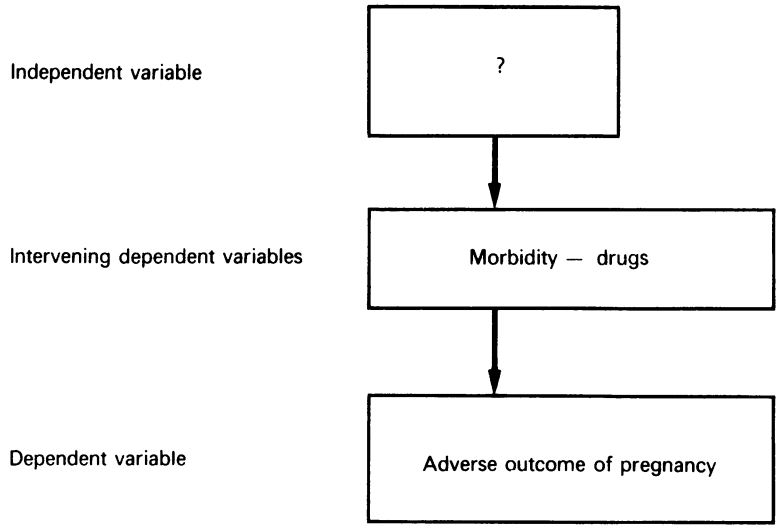


Figure 2
Alternative model showing relationship between morbidity, drugs, and outcome of pregnancy.

The anomalous results of this study prompted the conjecture of alternative models of causal relationships to the type outlined in figure 2, including a search for other

possible independent variables available in the data (or which would be inferred from it), but not included in the preliminary analyses. In this search two variables were identified which fulfilled the criteria for independence (Susser, 1973), when tested against the available data. These were: a previous pregnancy with an abnormal outcome and maternal anxiety, both of which probably also produce a degree of doctor anxiety! The relationship between these two independent variables is outlined in figure 3.

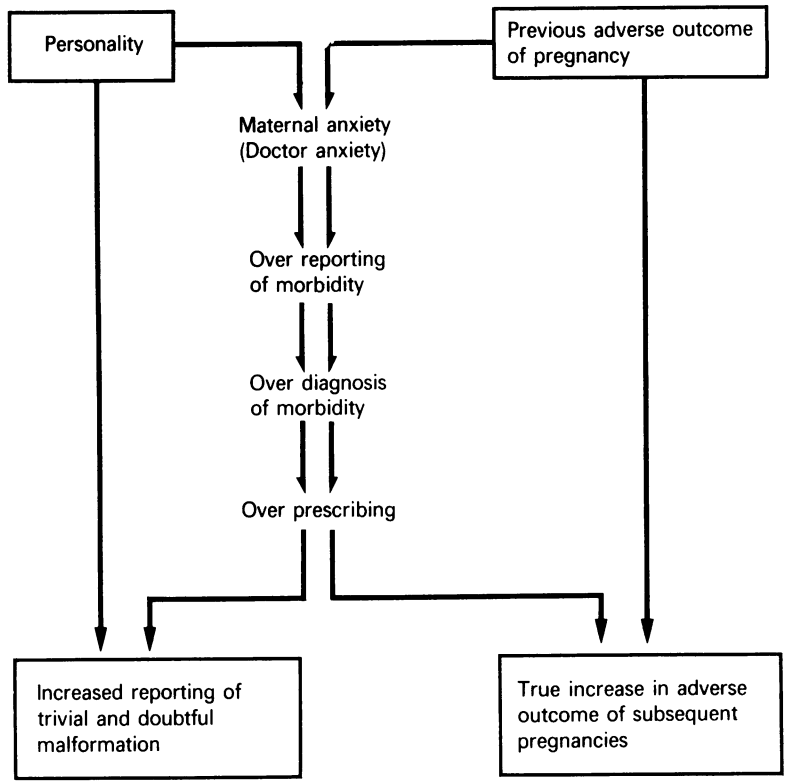


Figure 3
Model displaying the relationship between morbidity, drugs, and outcome of pregnancy as described in the text.

In table 5, data are presented about the women with a record of a previous abnormal outcome of pregnancy (including abortion) for each outcome category. In table 6, the

TABLE 5. THE NUMBERS (AND PERCENTAGES) OF WOMEN WITH A PREVIOUS HISTORY OF ABNORMAL OUTCOME OF PREGNANCY IN RELATION TO OUTCOME OF PREGNANCY UNDER STUDY

Number of women	*Normal sample*		*Lethal malformation*		*Unequivocal malformation*		*Doubtful malformation*		*Rhesus incompatibility*		*Other stillbirth*	
Previous abnormal outcome of pregnancy (including abortion)	104	(*21*)	14	(*30*)	47	(*24*)	30	(*21*)	17	(*46*)	26	(*26*)
Remainder	396	(*79*)	32	(*70*)	152	(*76*)	110	(*79*)	20	(*54*)	74	(*74*)
TOTAL	500	(*100*)	46	(*100*)	199	(*100*)	140	(*100*)	37	(*100*)	100	(*100*)

TABLE 6

RECORDED MORBIDITY EPISODES AND DRUGS ISSUED IN RELATION TO OUTCOME CATEGORY AND REPRODUCTIVE HISTORY

		Normal sample		*Lethal malformation*		*Unequivocal malformation*	
		Number	*Mean rate per pregnancy*	*Number*	*Mean rate per pregnancy*	*Number*	*Mean rate per pregnancy*
Morbidity episodes	Previous abnormal outcome of pregnancy	142	1·4	14	1·0	61	1·3
	Remainder	356	0·9	31	1·0	161	1·1
	Total	498	1·0	45	1·0	222	1·1
Total drugs prescribed	Previous abnormal outcome of pregnancy	226	2·2	28	2·0	98	2·0
	Remainder	737	1·9	67	2·1	292	1·9
	Total	963	1·9	95	2·1	390	2·0

		Doubtful malformation		*Rhesus incompatibility*		*Other stillbirth*	
		Number	*Mean rate per pregnancy*	*Number*	*Mean rate per pregnancy*	*Number*	*Mean rate per pregnancy*
Morbidity episodes	Previous abnormal outcome of pregnancy	58	1·9	22	1·3	52	2·0
	Remainder	133	1·2	22	1·1	71	1·0
	Total	191	1·4	44	1·2	123	1·2
Total drugs prescribed	Previous abnormal outcome of pregnancy	96	3·2	36	2·1	92	3·5
	Remainder	244	2·2	45	2·3	145	2·0
	Total	340	2·4	81	2·2	237	2·4

numbers and rates per pregnancy of morbidity episodes and drugs prescribed are presented for each outcome category separately according to the previous history. The observations that may be made from these tables are:

(a) The proportion of women in the ' doubtful malformation ' category (table 5) who have experienced a previous abnormal outcome to their pregnancy is the same as that in the normal sample (21 per cent). In all other abnormal outcome categories the proportion with adverse history is greater and though the increase is statistically significant ($p<\cdot001$) for the rhesus group only, the uniformity assumes its own significance.

(b) The morbidity episode rate of 1·4 per patient for those women in the normal sample with a previous history of abnormal outcome exceeds the rate of 0·9 for

those with no such history. This difference is greater than any of the differences between the total rates for each outcome category and that for the normal sample.

(c) The excess rate for morbidity episodes and drugs prescribed for ' doubtful malformations ' and ' other stillbirth ' outcome categories is shown to be particularly evident in those women who had previously experienced an abnormal outcome of pregnancy.

(d) Where there is no previous history of abnormal outcome, the rates for reported morbidity and drugs prescribed for those in the lethal or unequivocal malformation or other stillbirth groups are all similar to the women in the normal outcome group.

(e) There are no material differences with regard to morbidity and drug use between those women who had a normal baby and those who gave birth to a baby with either a lethal or unequivocal malformation.

The pattern of similarities and differences presented in these two tables and focused on the previous history is consistent with the model presented in figure 3. In particular the pattern is consistent with the general hypothesis that women who are anxious for any reason are more likely to report morbidity, to be prescribed drugs, and to notice and report any abnormality of their baby, however trivial, than mothers who are not anxious. Two main sources or types of maternal anxiety are identified. The first is that specifically associated with a previous pregnancy with an abnormal outcome. The second is a non-specific anxiety in predisposed women.

Discussion

Although many congenital malformations are genetically determined, the role of environmental influences must not be overlooked (Edwards, 1958). The interpretation of data about such influences is difficult because there may be many factors responsible for the aetiology of any specific malformation (Leck, 1965; Lowe, 1972). Even where drugs or morbidity have a malevolent influence on oncogenic processes they seldom achieve the high rate and devastating effects of thalidomide or rubella. Many aspects of the environment have been studied in relation to embryopathy. Seasonal and geographical factors, social class distribution, birth rate, and maternal age have all been linked to the incidence of congenital malformation (Slater *et al.*, 1964; Stevenson *et al.*, 1966).

This paper is particularly concerned with the total contribution of drugs in the doses used in clinical medicine (and to a lesser extent, morbidity) to the incidence of congenital malformation. Nelson and Forfar (1971) reported the results of a retrospective enquiry in which various associations between drugs and malformations were identified. In a preliminary communication of the results of this study we reported a six per cent excess (911 observed, 856 expected) of prescriptions issued to women who gave birth to malformed children.

In this report we have reported total drug usage during 28 weeks studied (six weeks before to 22 weeks after the LMP). The opportunity has been taken to examine data about individual drugs with particular reference to the gestational age. The results of this exercise have been essentially negative, though the restrictions that must be placed on data involving small numbers are inherent, even in a study involving over 9,000 pregnancies.

In this, as in other reports, malformations are grouped together and not considered individually. While it seems unlikely that an individual drug or group of drugs has such diffuse teratogenic properties that any random malformation may result, this possibility has not been eliminated. McCredie (1974) has suggested in connection with the aetiology of malformations after exposure to thalidomide the hypothesis that localised neurological disturbancies may produce multiple and various malformations.

In considering the presented data about groups of drugs, groups of malformations and a 28 weeks study period, rather than the respective specific sub-group units, the similarity between observed and expected makes it unlikely that an association linking drugs or morbidity could exist within any of the sub-groups.

(1) *Lethal and unequivocal malformations*

The lack of association between any drug use and the lethal and unequivocal malformation categories is reassuring. We find it difficult to believe that there were any drugs in common use in 1964–65 which had any teratogenic effect and at the same time allowed the pregnancy to progress to term.

(2) *Doubtful malformation*

The prescribing excess in the doubtful malformation category was further investigated by analysing the types of malformation in this miscellaneous category. A 100 of them could be classified as follows:

Pyloric stenosis—21.

Recorded as doubtful orthopaedic malformations—19.

Obstetric birth injury—19.

Umbilical hernia—18.

Recorded as doubtful cardiovascular lesions—12.

Recorded as clicking hip(s) or congenitally dislocated hip(s)—11.

The 40 remaining were not capable of aggregation into large groups; they included diagnoses such as ' blocked tear duct ', ' tongue tie ', ' very small hydrocoele ' and ' ? fibrocystic disease.' Whilst some variations in prescribing patterns in these categories have been observed, none is large enough to account for the significant excess in the whole group. The total list of diagnoses which were included in this category is available on request.

A previous history of abnormal outcome is shown to be associated with higher reported morbidity and prescribing rates. It is likely that a reduced tolerance to perceived illness and hence increased reporting of morbidity by pregnant women with such a history accounts for this observation. It is known that on average only one perceived aberration from normal health in four is reported to a doctor (Horder and Horder, E., 1954).

In the doubtful malformation category, the influence of a previous history of abnormal outcome is apparent as in the other abnormal outcome categories. It may be that women in this group are basically more anxious and less tolerant than pregnant women generally, and this view is supported by the following observations from the data presented:

(a) More women with a history of previously normal as well as previously abnormal outcome have reported morbidity in this outcome category than in the normal sample.

(b) The increased morbidity experienced was particularly apparent in psychiatric groups, pregnancy disturbances, and non-specific illness groups (table 3, groups 5, 11, 16).

(c) There was evidence of an increased use of self-medication by those women (25 observed compared with six expected, table 4).

(d) They were more likely to be prescribed antihistamine anti-emetic, and psychotropic drugs.

Further, many of the ' diagnoses ' included in this category are not generally

regarded as malformations and the diagnostic uncertainty is increased where the recording doctor has inserted qualifications, such as a question mark or terms such as ' mild ' or ' treatable '. The fact that iron prescriptions were the only large group of drugs not associated with an increase in the doubtfully malformed outcome category accords with the practice that iron is routinely prescribed to pregnant women and is not selectively prescribed by doctors to particular types of women who consult frequently.

(3) *Rhesus incompatibility*

The increased prescribing and morbidity rates observed in this category can be explained by the marked influence of previous abnormal outcome which is reflected in increased anxiety, increased doctor-patient contact, increased reported morbidity, and increased drug use.

(4) *Other stillbirths*

The influence in this category of a previous abnormal outcome on the rates for reporting morbidity and receiving prescriptions is particularly apparent and is likely to account for the excess prescriptions. Though the excess is widely scattered throughout many drug groups, the contrasting deficit of observed anti-emetic prescriptions compared with the expected is particularly interesting. It accords with the view that nausea of pregnancy is associated with a good prognosis for the fetus. There is no evidence from the study that the use of anti-emetics is harmful to the baby.

Conclusions

In this survey of over 9,000 pregnancies studied prospectively no direct aetiological relationship was established between drug prescriptions issued and morbidity experienced in early pregnancy and malformed outcome. The particular influence of a previous abnormal outcome on the reporting of morbidity and the issue of prescriptions is shown. This and the sub-division of malformations into categories of lethal, unequivocal, and doubtful has provided an explanation for reported morbidity and prescription excesses.

In particular, the results from partitioning the data in this way are compatible with the hypothesis that maternal anxiety leads to an increased reporting of morbidity and hence to an increased prescription of drugs also. The anxiety is manifest at two levels. The information emphasises the need to interpret the results of retrospective studies with caution and to verify them, wherever possible, from prospective data.

Notwithstanding the general conclusion that there is no evidence that drugs in common use with early pregnancy as a whole have any correlation with subsequent malformations in the child, adverse effects from rarely prescribed drugs cannot be ruled out.

The study is about malformation diagnoses made at approximately six weeks of age and conclusions relating to malformations diagnosed later cannot be made.

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REFERENCES

College of General Practitioners (1963). The Records and Statistical Unit: Research Committee of Council. *Journal of the College of General Practitioners*, **6**, 204–216.
Crombie, D. L., Pinsent, R. J. F. H. & Fleming, D. M. (1972). *British Medical Journal*, **1**, 745.
Crombie, D. L., Pinsent, R. J. F. H., Slater, B. C. S., Fleming, D. M. & Cross, K. W. (1970). *British Medical Journal*, **4**, 178–179.
Edwards, J. H. (1958). *British Journal of Preventive and Social Medicine*, **12**, 115–130.
Horder, J. & Horder, E. (1954). *Practitioner*, **173**, 177–187.
Leck, I. (1965). *New England Journal of Medicine*, **273**, 864–866.
Lowe, C. R. (1972). *British Medical Journal*, **3**, 515–520.
McCredie, J. (1974). *Medical Journal of Australia*, **1**, 159–163.
Nelson, M. M. & Forfar, J. O. (1971). *British Medical Journal*, **1**, 523–527.
Slater, B. C. S., Watson, G. I. & McDonald, J. C. (1964). *British Journal of Preventive and Social Medicine*, **18**, 1–7.
South, J. (1972). *Lancet*, **2**, 1154.
Stevenson, A. C., Johnston, H. A., Stewart, M. I. P. & Golding, D. R. (1966). *Bulletin of the World Health Organisation*, **34**, Suppl., 9–127.
Susser, M. (1973). *Causal Thinking in the Health Sciences*. P. 50. Oxford: Oxford Medical Publications.

REFLECTIONS ON HOSPITAL CARE

There is another communication gap which is even less excusable. This is the failure to take into account that the hospital gates provide access to a strange and frightening new world—a cloistered world with its own peculiar language and customs, which appear to defy all reason and decency; and a world where every orifice in the body has been cunningly provided with a device to assault it, either for the benefit of the ' voyeur ' or for a two-way traffic in mysterious fluids.

This is definitely a situation for which we do not adequately prepare the new immigrants. They must endure the sufferings of the 13-year-old being packed off to boarding school, a parallel heightened by the fact that we treat patients like children, label them and remove any remaining semblance of dignity as we remove their clothes, bath them, feed them, and put them into dormitories.

The consultant, consciously or unconsciously, plays the part of the Victorian parent—does he ever wonder why the house officer always knows so much more about his patients' problems, and the sister even more than the house officer.

Often on doing a ward round, the patient I have just seen will call the sister back to seek further information. Where have I failed? Why did she not ask me while I was at the bedside? Are we still considered to be unapproachable?

Is this the reason why with ever-increasing frequency these days I leave the onus on my senior registrar of informing the worried husband that his worst fears for his wife have been confirmed, using lack of time as the excuse for failing in my duty? Or is there something deeper? " Thus conscience doth make cowards of us all."

REFERENCE

Rawlings, E. E. (1975). *British Medical Journal*, **2**, 86.