Chapter 5

A STUDY OF DRUG UTILIZATION DURING PREGNANCY IN THE LIGHT OF KNOWN RISKS:
IS THERE ROOM FOR IMPROVEMENT?

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ABSTRACT

The prescription records of 1,948 Dutch women who delivered a live-born during an 18 month period in 1987 and 1988 were set against the Australian classification of drugs with respect to their known or suspected risk in pregnancy. During pregnancy the use of drugs with proven or anticipated fetal toxicity proves to decrease, indicating that the medical profession is relatively well aware of these potential side effects. In the case of antibiotics the fall in the use of potentially toxic drugs is due to a shift to relatively less toxic drugs whereas the decreased use of analgesics and some antirheumatic drugs is not accompanied by replacement by others. Prescriptions for hormonal contraceptives were sometimes actually filled in the first trimester of pregnancy, and the figures suggest that exposure to these products in early pregnancy may not be negligible. The present study shows that in spite of the generally favourable trends, 167.8 out of 1,000 women received during the course of pregnancy one or more prescriptions from the higher risk categories (D, C or B3) in the Australian system. By combining such utilization studies with data from registries of birth defects one will be able to develop the fund of knowledge and to ensure that the classification of drugs with respect to their risks in pregnancy is as accurate as it can reasonably be.

INTRODUCTION

The fact that certain drugs given in pregnancy may prove harmful to the unborn child is one of the classic problems in medical treatment; the benefit will sometimes outweigh any possible risk, but the fact that the risks are commonly so difficult to assess complicates the physician's task. Reproductive studies with drugs in animals can provide an indication of possible teratogenicity, but they do not reliably predict (or exclude) risks when these same drugs are given in human pregnancy. On the other hand the reporting of suspected teratogenic effects in human pregnancy continues to be very incomplete, the quantification of such data has as to the present been almost entirely lacking. For such reasons, drug risk assessment in pregnancy is in many cases fragmentary or disputed, and physicians may interpret it in different ways. It therefore becomes important to examine the pattern of drug use in pregnancy, and to see to what extent there may be room for improvement in the light of current knowledge.

We have recently undertaken a study of drug utilization in a population of nearly 2,000 women in a region in the northern part of The Netherlands. The methodology is described in detail in Chapter 2; the bulk of the drug utilization data were obtained from pharmacy records, which in the region studied are unusually complete as regards the dating of pregnancies and deliveries.

† Teratogenicity is a manifestation of development toxicity, representing a particular case of embryo/foetotoxicity by the induction or the increase of the frequency of structural or functional disorders in the progeny.
In the present analysis, we set the data emerging from our study alongside what is known as to the risks of the drugs concerned. The very uncertainty of data on this score means that one cannot simply classify drugs as “safe” or “dangerous” where pregnancy is concerned: one needs a more complex classification which will take into account the strength and nature of the evidence available. In several countries such systems of classification have been devised, but they have not all as yet been tested in practice. For the present purpose we used the classification system of the Australian Drug Evaluation Committee, which the Committee has employed to classify the bulk of drugs on sale in that country; the classification is virtually identical to that used in Sweden and is presented in Table 1. Other classifications do exist but they tend to be less complete or less completely applied to a wide range of drugs than the Australian system.

**Table 1** The Australian Risk Classification system 1989

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>Drugs which have been taken by a large number of pregnant women and women of child-bearing age without an increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>Drugs which have been taken by only a limited number of pregnant women and women of child-bearing age without an increase in the frequency of malformations or other direct or indirect harmful effects on the human foetus. As experience of effects of drugs in this category in humans is limited, results of toxicological studies to date (including reproduction studies in animals) are indicated by allocation to one of three subgroups:</td>
</tr>
<tr>
<td>1.</td>
<td>Studies in animals have not shown evidence of an increased occurrence of foetal damage.</td>
</tr>
<tr>
<td>2.</td>
<td>Studies in animals are inadequate and may be lacking, but available data show no evidence of an increased occurrence of foetal damage.</td>
</tr>
<tr>
<td>3.</td>
<td>Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>Drugs which have caused an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.</td>
</tr>
<tr>
<td><strong>X</strong></td>
<td>Drugs that have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.</td>
</tr>
</tbody>
</table>

**MATERIAL AND METHODS**

Information on the drug use of 1,948 mothers giving birth to live children were included in this study. These data were obtained from the records of 10 computerized...
pharmacies located in 4 cities (ranging in size from 15,000 to 45,000 inhabitants) in the north of the Netherlands. All mothers who delivered between July 1st 1987 and December 31st 1988 were involved in the study. As pointed out above, the methodology is published in detail in Chapter 2. Essentially records were collected of all drugs dispensed to each woman during a fifteen month period, comprising the 2 trimesters before the estimated conception (designated as periods -2 and -1), the 3 trimesters of pregnancy (periods 1,2 and 3), and the 3 months after delivery (period 4). For each prescription the drug name, its therapeutic classification according to the ATC code developed by the Nordic Council on Medicines, the date of dispensing, the total amount of the drug issued, the daily dose and the route of administration were recorded. With these data on file it was possible to examine the extent of population exposure to any individual drug or class of drug at the various periods of time in and around pregnancy. Our findings are presented in terms of the number of women per 1,000 who received one or more prescriptions for a given drug in a particular trimester. Where a woman received in one period a sufficient supply of a drug for treatment to continue into the next period she was regarded as having been exposed during both trimesters.

In the present study we correlated this analysis with the Australian classification of drugs with respect to their known or suspected risks in pregnancy. As will be seen from Table 1, the Australian system classifies drugs into five main categories, ranging from category A for those drugs which appear in the light of much experience to be safe for use in human pregnancy to category X which covers those medicines which carry such severe and established risks that they should not be used in pregnancy at all. It is clear that the real problems facing the physician are however those in the intermediate categories where the evidence may be open to question or efficacy/safety balance is still undetermined. For that reason we concentrated in our analysis on category B3 (where there is an increased risk from animal studies), C and D (where there is some evidence of human risk). This enabled us to set aside the large amount of data on record relating the use of substances and products generally regarded as entirely safe, including iron supplements, folic acid, antacids and mild laxatives.

Of the three categories which we examined, D may be most problematical for a prescriber, since it relates to drugs which have cause an increased incidence of human foetal malformations or irreversible damage; the difficulty is that some of these drugs are of considerable value even in pregnancy, notably certain antiepileptic drugs. category C drugs, for which human risks are suspected rather than documented, include some which are known to be very widely used although there is evidence of reversible pharmacological effects, e.g. the beta-blockers and the benzodiazepines. The evidence of risks in Australian category B3, since it relates only to animal studies may be less familiar to the physician; this category too includes some known to be widely used, such as trimethoprim.
Figure 1 a. The exposure rate to drugs in Categories D ( ), C ( ) and B3 ( ) per 1,000 women per three-month period is presented in absolute terms. b. The change in extent of use for each of these three categories D (— ); C ( — — ) and B3 ( . . . ) during the periods studied as a percentage shift from the exposure rate in period -1.

RESULTS

Figure 1a shows the rate of exposure to drugs in the three risk categories studied, i.e. D, C and B3; in category B3 the oral contraceptives are excluded; they will be discussed separately below. It will be seen that in all three risk categories the use of the drugs concerned decreased sharply during pregnancy and increased again after delivery. This was the most prominent for the drugs from category D. The pattern is even more clear in Fig 1b, where the use during and after pregnancy is plotted as a percentage of use during the immediate preconception period (period -1). Whereas the use in category D fell to less than 20 percent from the pre-conception value, the use of drugs from category C and B3 fell to nearly 40 percent of the preconception value.

The data for individual drugs in category D are presented separately in Table 2. In view of the human evidence of risk it is not surprising that the use of progestagens and tetracyclines decreased markedly during pregnancy. Only a few women used anticonvulsants, antirheumatics and central nervous system drugs falling within this category, and the use of these three therapeutic groups hardly changed during pregnancy. The only category D drug that was used more frequent during the pregnancy was coumarine.

The exposure rate to drugs in category C (i.e. those having pharmacological effects which could prove harmful) is analyzed in Table 3. The overall trend to decreased use of these drugs in pregnancy is also discernible for most of the indi-
The exposure rates per 1,000 women per trimester and during the entire pregnancy (last column) to the drugs belonging to Category D of the Australian risk classification system.

<table>
<thead>
<tr>
<th>Drug class/drug</th>
<th>ATC</th>
<th>Period</th>
<th>Preg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive system</td>
<td>G03D</td>
<td>6.7</td>
<td>11.3</td>
</tr>
<tr>
<td>Progestagens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>J01A</td>
<td>14.9</td>
<td>23.6</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>N03AA02</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>N03AD01</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>N03AX04</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Valproate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antirheumatics</td>
<td>M01C</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>M05AA</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Hydrokinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>N05AX01</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>B01A</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Coumarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>23.1</td>
<td>35.9</td>
<td>15.4</td>
</tr>
</tbody>
</table>

This is most evident for the antirheumatics and to a lesser extent for drugs affecting the central nervous system. However, the rate of exposure to benzodiazepines, which decreased in periods 1 and 2, rose again thereafter and in the third trimester of pregnancy it attained the same level as before pregnancy. The overall use of antihypertensives is fairly low. Whereas the use of beta-blocking agents and diuretics showed only minor changes during pregnancy, the use of other antihypertensives increased during the last trimester; this increase could totally be accounted for by the use of the alpha/beta blocker labetalol. The use of diuretics increased after delivery. With respect to the antibiotics, the use of sulfonamides decreased whereas nitrofurantoin was used somewhat more frequent. The high exposure rates to ergometrin after delivery is not unexpected.

For category B3 — the drugs for which foetal damage has been demonstrated in animal studies — our data are presented in Table 4. As pointed out above, the oral contraceptives were omitted from the representation of this category in Figure 1a, but they are listed individually in the Table. The contraceptive figures are surprising, though one must realize that the figures in this table indicate the total exposure which would result if the patient started taking the product at the date of dispensing and continued until the supply was exhausted; it is likely that most or all women will cease to take their contraceptives once they realize that they are pregnant, i.e. the supply (commonly intended fulfill 3 to 6 months needs) will remain largely unused in the medicine cabinet. The figures given thus almost certainly much overestimate
Table 3  Risk-group C

The exposure rates per 1,000 women per trimester and during the course of pregnancy (last column) to the drugs belonging to Category C of the Australian risk classification system.

<table>
<thead>
<tr>
<th>Drug class/drug</th>
<th>ATC</th>
<th>Period</th>
<th></th>
<th></th>
<th></th>
<th>Preg.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-2</td>
<td>-1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Antiinflammatory</td>
<td>M01A</td>
<td>28.8</td>
<td>32.3</td>
<td>8.7</td>
<td>2.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Antirheumatics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>antiphlogistics</td>
<td>N02A</td>
<td>1.0</td>
<td>0.0</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narcotic analgesics</td>
<td>N02BA</td>
<td>13.4</td>
<td>9.2</td>
<td>12.3</td>
<td>7.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Acetyl salicylic acid</td>
<td>N02C</td>
<td>3.6</td>
<td>3.1</td>
<td>0.5</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Ergotamine alkaloids</td>
<td>N05A</td>
<td>2.6</td>
<td>4.1</td>
<td>3.1</td>
<td>3.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>N05B/CD</td>
<td>14.9</td>
<td>19.0</td>
<td>13.9</td>
<td>10.3</td>
<td>18.5</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>N06</td>
<td>3.6</td>
<td>3.6</td>
<td>1.5</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocking agents</td>
<td>C07</td>
<td>2.6</td>
<td>4.6</td>
<td>1.5</td>
<td>1.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Diuretics</td>
<td>C03</td>
<td>3.1</td>
<td>1.5</td>
<td>2.1</td>
<td>1.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Other antihypertensives</td>
<td>C02</td>
<td>1.0</td>
<td>1.5</td>
<td>0.5</td>
<td>0.0</td>
<td>5.1</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>J03A/B</td>
<td>9.8</td>
<td>8.7</td>
<td>5.1</td>
<td>2.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>G04AC</td>
<td>3.6</td>
<td>7.2</td>
<td>6.7</td>
<td>9.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Oxytocics</td>
<td>G02AB</td>
<td>11.8</td>
<td>13.9</td>
<td>1.0</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>R06AD</td>
<td>6.2</td>
<td>8.7</td>
<td>9.2</td>
<td>5.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>H02AB</td>
<td>2.1</td>
<td>5.1</td>
<td>2.1</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>C01</td>
<td>1.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Antiarrythmic</td>
<td>A10B</td>
<td>0.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>95.9</td>
<td>106.2</td>
<td>64.1</td>
<td>42.1</td>
<td>54.4</td>
</tr>
</tbody>
</table>

the actual level of intake. All the same, it it remarkable that 44.6 of 1,000 women had a new prescription for a contraceptive filled in the last trimester before they became pregnant and 10.8 of 1,000 women did so in the first trimester of pregnancy. We would therefore suggest that even during pregnancy, especially during early organogenesis, exposure to contraceptives is not negligible. Drugs used to induce ovulation such as chlomiphene were, if one takes all the periods together, used by 13.3/1,000 women. The use of the anticonvulsant carbamazepine increased during pregnancy, which thus contrasts to the above-mentioned stable pattern of use of the anticonvulsants of Australian category D. The use of the other drugs in risk category B3 was reduced during the period of pregnancy.

Finally, one can seek to answer the key question as to the extent to which prescribing in pregnancy is influenced by knowledge of possible risks. Our data provide an opportunity to determine whether in a homogenous ATC group (such as for example the antibiotics/chemotherapeutics or the drugs affecting the central nervous system) the use of individual drugs shows differing trends correlating with their in-
The exposure rates per 1,000 women per trimester and the entire pregnancy (last column) to the drugs belonging to Category B3 of the Australian risk classification system.

<table>
<thead>
<tr>
<th>Drug class/drug</th>
<th>ATC</th>
<th>Period</th>
<th>Preg.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-2</td>
<td>-1</td>
</tr>
<tr>
<td>Reproductive system contraceptives</td>
<td>G03A</td>
<td>91.9</td>
<td>130.4</td>
</tr>
<tr>
<td>oestrogens</td>
<td>G03CA</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>ovulation inducers</td>
<td>G03G</td>
<td>4.1</td>
<td>9.2</td>
</tr>
<tr>
<td>cyproterone</td>
<td>G03H</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>carbamazepine</td>
<td>N03AX01</td>
<td>0.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Antimycotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ketoconazole</td>
<td>J02A</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>griseofulvin</td>
<td>D01BA01</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>tinidazole</td>
<td>G01AF03</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>trimethoprim</td>
<td>J01E</td>
<td>4.6</td>
<td>7.7</td>
</tr>
<tr>
<td>Micellaneous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>antiparkinson drugs</td>
<td>N04</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>antimalarials</td>
<td>P01B</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>mebendazole</td>
<td>P02X</td>
<td>3.6</td>
<td>4.6</td>
</tr>
<tr>
<td>loperamide</td>
<td>A07D</td>
<td>5.1</td>
<td>7.2</td>
</tr>
<tr>
<td>beclometasone</td>
<td>R03BA</td>
<td>1.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>112.3</td>
<td>162.1</td>
</tr>
</tbody>
</table>

Exclusion in a particular risk category in the Australian system. To some extent this indeed proves to be the case. Exposure to the most extensively used antibiotic and chemotherapeutic drugs is for example shown in Figure 2a; it will be seen that during pregnancy the overall level of use of these anti-infective drugs remained stable, with an increase after delivery. When we look to the individual drugs in the group, however, we see that the use of penicillins, known as a safe drug for use during pregnancy (category A) increased. The use of the tetracyclines (category D), the sulphonamides and cotrimoxazole (category C) and trimethoprim given alone (category B3) by contrast shows a decline during pregnancy and increases again after delivery, whereas the use of nitrofurantoin (category C) remains fairly stable during the entire period. These changes during pregnancy are plotted as a percent change from the preconception value in Figure 2b.

To examine the same question meaningfully for the drugs affecting the central nervous system drugs it is necessary to take separately the subgroups covering the anticonvulsants, the sedatives and the analgesics. Exposure to the anticonvulsants is shown in Figure 3. Overall exposure appears to increase during the pregnancy, due to the relatively greater use of carbamazepine (although still in category B3), but the use of the category D anticonvulsants hardly changes. With respect to the sedatives, we noted above that the benzodiazepines (Australian category C) were used...
The exposure rate to penicillines ( ), tetracyclines ( ), nitrofurantion ( ) and sulfon/triethoprim ( ) per 1,000 women per three-month period in absolute terms. 

The change in extent of use of each pen. ( - ), tetr. ( - - ), nitrof. ( - - - ) and sulf./trim. ( --- ) during the periods studied as a percentage shift from the exposure rate in period -1.

The exposure rate to all anticonvulsants (dark bar) and carbamazepin (light bar) per 1,000 women per three-month period in absolute terms.

somewhat less frequent during the first two trimesters of pregnancy, but that in the third trimester they were used as frequently as before pregnancy. In contrast to the
situation in the group of antibiotics and chemotherapeutics, one finds in this therapeutic group there was no increase in the use of the safer (category A) sedatives (the data for which are not illustrated here). Finally, the use of the antipyretic analgesics is shown in Figure 4, plotting the exposure rate of the category C analgesic acetylsalicylic acid alongside that of the category A analgesic paracetamol. The use of both drugs decreased in parallel during pregnancy and increased thereafter, i.e. there was no difference in usage trends between the category C and the category A drug.

We would add that we also discerned some trends to change in the routes of administration of drugs in pregnancy. This is evident in Figure 5 relating to the antiasthmatic drugs. Both the use of systemic corticosteroids and that of systemic sympathicomimetics decreased, whereas the tracheal administration of these drugs increased. The use of antimycotic drugs for vaginal infections shows a similar shift: during pregnancy systemic administration decreases whereas and the local application of these drugs increases (Fig. 6)

**DISCUSSION**

Our study provides in the first place evidence that, during pregnancy, the use of drugs with proven or anticipated fetal toxicity decreases. This indicates that the medical profession is relatively well aware of these potential side effects. Similar
Figure 5 a. The exposure rate to tracheal steroids (■), systemic steroids (▲), tracheal sympathetic-mimetics (□) and systemic sympathetic-mimetics (●) per 1,000 women per three-month period in absolute terms. b. The change in extent of use of each of these drugs tr. ster. (-----), syst. ster. ( - - ), tr. symp. (· · · ·) and syst. symp. (· - ·) during the periods studied as a percentage shift from the exposure rate in period -1.

Figure 6 a. The exposure rate to antmycotic drugs for vaginal infections (vag. application (dark bar) and systemic (light bar) per 1,000 women per three-month period in absolute terms. b. The change in extent of use (vag. (closed line) and syst. (broken line) during the periods studied as a percentage shift from the exposure rate in period -1.
results were also obtained by Piper et al in a Medicaid population in the United States. In essence we have extended their observations, by including more drugs in our study and by determining whether safer alternatives were used. For such a purpose the Australian risk classification system, which categorizes drugs according to the severity of the side effect, is an important tool. Category D drugs will present danger during the entire course of the pregnancy and particularly so in the first trimester during the period of organogenesis. Most of the drugs in category C probably present particular risks during the last trimester. As shown in Figure 1, the exposure to risk category D drugs decreases more markedly than does exposure to category C drugs, but no clear difference was observed in the trend as between the three trimesters of pregnancy.

Naturally, one should realize that there are some limits to the validity of these data. On the one hand the figures may be underestimated because the use of drugs during hospital admissions is not included. On the other hand some may be overestimated since we do not know to what extent drugs dispensed by the pharmacy are actually consumed and in some cases (as already pointed out with respect to the oral contraceptives) the overestimation may be considerable. It is quite evident that a woman who finds that she is pregnant may cease to take a medicine which has been prescribed for her earlier, and this will not be reflected in our data; that could lead in particular to an overestimate of exposure in the second trimester of pregnancy, by which time the pregnancy is unlikely to have remained unrecognized. Finally, the fact that even brief courses of treatment may cross the borderline between one trimester and the next, and thus be reflected in both, may somewhat mask the differences between trimesters, though our full methodological analysis shows that this source of distortion only applies to a small percentage of the women studied.

Despite such reservations however, and the evidence of an adjustment in prescribing during pregnancy, the fact remains that during their pregnancies 167.8 out of 1,000 women were exposed to one or more drugs in risk Categories D, C and B3 and that fact merits further study. Since we are not informed as to the severity of the illnesses which led to these prescriptions, we cannot argue that the use of these drugs was not justified. In such situations (as for example in women with epilepsy, severe asthma or severe psychiatric disorders) the benefits for the mother may well be considered to outweigh the risks for the child; in others they will not, e.g. where a drug is prescribed without being aware of the pregnancy, or when the prescriber is unaware that the drug could adversely affect the fetus, or where the indication is relatively trivial.

Decreases in the level of drug use in pregnancy can be traced to various factors, acting alone or in concert. They could merely reflect the fact that prior to pregnancy drug consumption has been unnecessarily high; this could explain the observed lesser consumption of sedatives and analgesics. Secondly, the decline could relate to prescribing for certain conditions which become less severe during pregnancy, such as for example rheumatoid arthritis; that might explain the decreased use of analgesics and antirheumatics which was noted. Thirdly, one could expect a general
reduction in prescribing in pregnancy reflecting caution on the part of prescribers but no special knowledge of particular drug risks. The fall in the use of potentially toxic drugs could be due to the fact that within a certain pharmacological subgroup relatively less toxic drugs are substituted (antibiotics and anticonvulsants), and one would also expect some shift from oral to local application of the same drug (anti-asthmatics or antimycotics for vaginal infections) in the hope of decreasing systemic and thus foetal exposure.

Some of these trends are indeed demonstrated by our findings, but the extent of change is sometimes less than one would hope to find. In the field of antibiotics and chemotherapy, it is noteworthy that the use of the (category D) tetracyclines, with their known skeletal and dental effects on the unborn child, fell sharply. However, in the first trimester of pregnancy 8.2 women per thousand nevertheless used tetracycline. This could reflect either unawareness of the pregnancy or not planned pregnancy, as discussed above, or the fact that some physicians regard the use of tetracyclines in the first trimester of pregnancy as safe (9). Since on the other hand tetracyclines even in early early pregnancy are reported to be hepatotoxic, one would wish to see them completely eliminated in all three trimesters, particularly since plenty of safe alternatives are available.

In the same field, we were surprised to find that the use of the (category C) drug nitrofurantoin did not change at all; during each period of the pregnancy 7 to 10 women per 1,000 used this chemotherapeutic agent, and 19.5 women per 1,000 used it in all three trimesters. This could be due to the fact that the medical profession is not aware of the potential side effects of this drug, notably haemolytic anaemia in the foetus. On the other hand one might also argue that the inclusion of this drug in risk category C is unjustified; if the risks in human pregnancy are really such as to justify its inclusion in this category, the extent of use evident from our study might lead one to expect many more reports of suspected second-generation injury than are in fact available, even bearing in mind the fact that only a limited proportion of adverse effects ever do find their way into print or into systems monitoring congenital anomalies.

In this connection we would, however, stress that our present study was not such as to lend itself to the study of side effects in the population concerned. For that purpose, and to decide optimally how a drug should be classified with regard to risks in pregnancy, one will need to correlate in-depth drug utilization studies with data available to registers of congenital anomalies. In a recent but separate study we indeed carried out this exercise, setting registry data alongside our utilization data, a prominent finding being that there was an association between the use of clomiphene and development disorders. That particular study leads us to suggest that clomiphene should be classified in Australian risk category D rather than in category B3. Conversely, if in a similar study on a sufficient scale no problems

†† European Registration of Congenital Anomalies and Twins (EUROCAT) and the International Clearinghouse for Birth Defects Monitoring Systems.
were detected with nitrofurantoin one could consider that nitrofurantoin should be included in category A rather than C.

With respect to the antiasthmatics, we showed a shift from systemic to local application, both for the corticosteroids and for the sympathicomimetic agents. At first glance this appears to be a logical response to the onset of pregnancy; as pointed out above it presumably reflects an attempt to avoid systemic (and foetal effects). However, one must doubt whether tracheal application indeed does eliminate systemic effects. Even after local application these drugs have been shown to be present in the plasma,\(^{15}\) and for some corticosteroids given by inhalation the total dose required is not dissimilar to that which would be given orally. Similarly, the use of antimycotics for vaginal infections using local instead of systemic application does not fully exclude the attainment of significant plasma concentrations of these potentially toxic substances.

Our present study shows that in the medical profession there is some recognition of the relative risks of particular drugs and classes of drug in pregnancy, and some attempt to take this into account when prescribing for pregnant women. Our findings show, however, that further adjustments are required; it is essential to avoid completely the use of potentially toxic drugs in pregnancy where they can easily replaced by safer products or where their use is not essential. Further work along these lines will no doubt demonstrate more clearly what adjustments are required, and may indicate how prescribers can best be guided towards optimal prescribing in pregnancy. By combining such utilization studies with data from registries of congenital abnormalities one will at the same time be able to develop our fund of knowledge and to ensure that the classification of drugs with respect to their risks in pregnancy is as accurate as it can reasonably be.

REFERENCES