Drug utilization studies in pregnancy
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Chapter 4

DRUG USE IN PREGNANCY
A VALIDATION OF PHARMACY RECORD DATA


This chapter has been submitted to the European Journal of Clinical Pharmacology.
ABSTRACT

Information on drug use in pregnancy can be obtained either by studying pharmacy/medical records or by interviewing women. Both methods have their own characteristics and shortcomings. In this study regarding overall drug use during pregnancy, we compared data from pharmacy records with data obtained from interviews of the mother. In the interview we also evaluated compliance to drug treatment. After excluding the reported self-medication drugs from the interview data, there is no difference between the two sources (pharmacy and interview data) with respect to the mean number of drugs used per woman (1.7±1.4 and 1.8±1.8 respectively). Agreement with respect to the exact number of drugs received per woman was very low (42% with a kappa value of 0.28). Poor agreement was related to a higher percentage of users according to interview data in case of analgesics, vitamins and non-official drugs whereas in case of dermatological, respiratory and eye/ear drugs a higher percentage of consumers was found in the pharmacy data. Good agreement was found for the antacids, iron preparations, antibiotics and drugs for vaginal infections. At least one quarter of all prescriptions was not used according to the instructions and 4 out of 10 women admitted not to have followed the instructions adequately. We conclude that the two methods of data collecting are clearly complementary to each other. Information on compliance and on the use of self-medication drugs needs personal interview, whereas incidental and topical drug use may be more reliably obtained from pharmacy record data.

INTRODUCTION

Information on drug use in pregnancy can be obtained either from pharmacy or medical records or by interviewing women. All methods have their own characteristics. It may well be that the information obtained with the one method is different from the information obtained using the other. One can argue that interview data will detect the actual drug use (non-compliance excluded), while pharmacy record data represent amounts dispensed i.e. intended drug use (including non-compliance).

Interviews may indicate higher figures for drug use than pharmacy record data in several circumstances, namely:

- when self-medication or over-the-counter drug sales are included in interviews since these are not reflected in pharmacy records
- when a woman has received drugs from a different pharmacy than her usual one
- when she has received drugs during hospital admittance
- when she continued the use of the drug prescribed prior to pregnancy

On the other hand pharmacy records may show higher drug use figures than interviews:

- when recall by the woman is insufficient (the opposite is also possible)
- when she has used a drug, but did not recognize it as a “drug” (for example nose drops or dermatological preparations)
- when she has filled a prescription during pregnancy, but did not start using the
drug until pregnancy has ended, and finally
when she has received the prescription drug but did not take it or took it only in part (non-compliance).

Although both methods thus have their potential shortcomings, few studies have sought to determine whether the two could be complementary to each other. Although some studies comparing interview data with data derived from medical records showed poor agreement between the two sources, such studies only focused on the use of one single drug and frequently involved long recall periods. To our knowledge no study on overall drug use during the nine months of pregnancy, comparing data from pharmacy records on dispensed drugs with data obtained via interview with specific questions, has so far been published. We recently submitted a interview study on drug use in pregnancy in The Netherlands (Chapter 3). Of the women who participated in this study we also obtained data on drug use from pharmacy records and evaluated compliance with drug treatment. Pharmacy records are uniquely complete in The Netherlands since medication surveillance as well as reimbursement regulations require detailed data on the drug that are actually dispensed to the patient. Therefore we can compare the data obtained from pharmacy records with those obtained from interview.

METHODS

We recently studied the drug use in pregnancy of 295 women by means of an extended questionnaire conducted shortly after delivery. The details of the methodology and the results of the interviews have been published in Chapter 3.

Comparison of interview with pharmacy record data

At the end of the interview the women were asked whether they would allow their pharmacy records to be studied as regards to the drugs dispensed during their pregnancy. The exact duration of the pregnancy was determined from the date of the last menstruation or, if necessary in combination with the results of echography. Sixteen of the 295 women either refused to give informed consent, or could not provide correct information as to the pharmacy or pharmacies to which they went with their prescriptions. The records of the pharmacies which had supplied drugs to 62 of the 279 remaining women, were incomplete because of computerization problems. Data from 217 women (= 74%) were thus available for the present analysis. The mean age of these 217 women was 29.3 (±4.3) years. The 217 pregnancies resulted in 222 liveborn children (three twins and one triplet); 45.5% of the liveborn children were the first child; 36.4% delivered at home, 12.4% in an out-patient clinic and 51.2% in hospital. This group is comparable with the 295 women.

In both the interview study and the pharmacy record study we recorded the type of drug, the duration of use of that drug and the prescriber involved. Drugs were classified according to the Anatomic Therapeutic Chemical (ATC) classification.
scheme. If a woman had received multiple prescriptions for the same drug during pregnancy, she was recorded as having received one drug. In the present analysis the data obtained from the interviews comprise the data obtained from open-ended questions in combination with more specific questions i.e. indication-oriented and drug-oriented (Chapter 3).

Correspondence between the data sources was analysed by two-way tables and by calculation the proportion of agreement over and above chance (i.e. kappa statistic) for the main ATC groups and the most frequently used classes of drugs. According to Landis and Koch a kappa greater than 0.75 represents excellent agreement beyond chance, values between 0.40 and 0.75 represent fair to good agreement beyond chance and values below 0.40 represent poor agreement.

Compliance with drug use
In the interview study we also tried to estimate compliance by asking the women the following questions:

1. If a drug was prescribed, did you follow the treatment according to the instructions?
2. If you did not follow the instructions,
   a. did you discard the dispensed drugs?
   b. did you use the drug shorter than advised, or for a longer period than advised?
   c. did you use the drug in a lower daily dose or in a higher daily dose than recommended?
3. If you did not follow the instructions, what was the reason for your non-compliance?
4. Did you have any reserves to use any particular drug because of your pregnancy?

The interviewer strictly followed the sequence and wording of the questions. Compliance was tested per woman and per drug, thus offering information on how many women were compliant and how many prescriptions were adequately followed. We also sought to establish whether compliance varied for different drugs. For obvious reasons, traditional compliance controls such as pill counts and plasma/urine determinations were not appropriate in this study. An overestimation of compliance due to the wish to give acceptable answers can therefore not be excluded.

RESULTS

Comparison between interview and pharmacy record data
According to the interview data the 217 women whose pharmacy records were available, used overall 525 drugs of which 151 were reported self-medication drugs and 374 were prescribed drugs. According to the pharmacy records these 217 women received overall 409 drugs. In the present analysis the data obtained from the interviews comprise the data obtained from three types of questions taken to-
together, as described in Chapter 3. Since pharmacy records provide no information on the sale of self-medication drugs, we will confine ourselves to the prescribed drugs for the comparison between data from interviews and data from pharmacy records. (Thus we excluded the reported self-medication drugs from the interview data). Figure 1 shows the distribution of the total number of prescribed drugs used per woman according to the interview data and the pharmacy record data. According to the interview data 83% of the women used one or more prescription drugs during pregnancy. This percentage is hardly different from the pharmacy record data, which showed 82% of the women as having used one or more drugs. There is no statistically significant difference between the two sources in the mean number of drugs received per woman with 1.7±1.4 drugs per woman according to the interview data and 1.9±1.7 drugs per woman according to the pharmacy record data.

Interestingly, the pharmacy record data yielded statistically significant higher results for the percentage of women who used more than 4 drugs during pregnancy (8.3 versus 3.7%, p<0.001). Agreement between interview drug use data and pharmacy records was 84% (= 74%+10%) with a kappa value of 0.45 for ever/never using any drug during pregnancy. The number of drugs received corresponded exactly in 92 women (=42.4%) between the two sources while in 78 women (36%) the two sources yielded a difference of one drug. We found a difference of two drugs between both sources in 29 women (=13%) and a difference of more than two drugs in 18 (=8%) of the women. The kappa value is 0.28 for the exact number of drugs per women used during pregnancy. Of the 125 women with a disagreement...
as to the total number of drugs used between both sources, 51% had received more
drugs according to the interview and 49% had received more drugs according to
the pharmacy records.

Table 1  Comparison of drug use data as derived from interviews (I) or from pharmacy records (Ph)
subdivided in different ATC groups of 217 women in The Netherlands (1990). The percent-
age agreement and the kappa value are given. (See under methods for explanation).

<table>
<thead>
<tr>
<th>ATC main group</th>
<th>ATC-code</th>
<th>% users</th>
<th>agreement</th>
<th>kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ph+/I+</td>
<td>Ph-/I-</td>
<td>Ph+/I-</td>
<td>Ph-/I+</td>
</tr>
<tr>
<td>Anti-inflammatory drugs</td>
<td>M</td>
<td>1.8</td>
<td>96.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Bloodforming drugs</td>
<td>B</td>
<td>48</td>
<td>36.9</td>
<td>6.5</td>
</tr>
<tr>
<td>Gynecological drugs</td>
<td>G</td>
<td>13.4</td>
<td>75.1</td>
<td>9.2</td>
</tr>
<tr>
<td>Gastrointestinal drugs</td>
<td>A</td>
<td>13.8</td>
<td>70.0</td>
<td>7.4</td>
</tr>
<tr>
<td>+ vitamins</td>
<td>J</td>
<td>7.8</td>
<td>81.6</td>
<td>6.5</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>C</td>
<td>2.3</td>
<td>90.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>R</td>
<td>4.6</td>
<td>82.5</td>
<td>9.2</td>
</tr>
<tr>
<td>Respiratory drugs</td>
<td>S</td>
<td>0.5</td>
<td>97.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Eye- and ear drugs</td>
<td>Y</td>
<td>1.0</td>
<td>94.0</td>
<td>1</td>
</tr>
<tr>
<td>Non-official drugs</td>
<td>D</td>
<td>2.8</td>
<td>84.8</td>
<td>9.2</td>
</tr>
<tr>
<td>Dermatologic drugs</td>
<td>N</td>
<td>2.3</td>
<td>83.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td>74.2</td>
<td>10.1</td>
<td>7.4</td>
</tr>
</tbody>
</table>

Ph+/Ph- : users/non-users according to pharmacy records
I+/I- : users/non-users according to interview data

We next sought to determine whether these differences are dependent upon the
type of drug used; the question was examined both for the main ATC groups and
for the most frequently used individual classes of drugs. Table 1 shows the percent-
age of users of drugs in the various main ATC-groups, according to interviews and
to pharmacy record data, as well as the agreement between both sources and the
kappa value. The degree of agreement varies from 84% for the ATC group A (gas-
trointestinal drugs and vitamins) to 99% for the group M drugs (anti-inflammatory
drugs). More discriminative is the kappa value for the various drug groups, with
kappa values ranging from 0.80 for group M drugs (anti-inflammatory drugs) to
0.18 for group N (central nervous system). A fair or good degree of correspon-
dence between both sources (kappa >0.40) was found in the drug groups A (gas-
trointestinal drugs and vitamins), B (blood forming drugs), G (gynaecologic drugs)
and M (anti-inflammatory drugs). Poor agreement between the two sources (kappa
<0.40) was found in the ATC groups C (cardiovascular drugs), D (dermatological
drugs), N (central nervous system drugs), R (respiratory), S (eye and ear drugs) and
Y (non-official drugs). This poor agreement between the two sources was related to a higher percentage of users according to the interview data in case of the group C (cardiovasculars), N (central nervous system) and Y (non-official drugs) whereas in case of the D (dermatological), R (respiratory) and S (eye and ear) drugs use was found to be higher in the pharmacy record data. Correspondence of the most commonly used ATC subgroups is shown in Table 2. The vitamins and analgesics had the lowest degree of correspondence (kappa 0.11 and 0.10 respectively); as mentioned before they refer only to the prescribed vitamins and analgesics. For these ATC subgroups the percentage of users is according to the interview approximately two- to three-fold of that emerging from the pharmacy record data. The degree of correspondence is on the other hand the highest for the group of antacids, iron, drugs for vaginal infections and antibiotics.

<table>
<thead>
<tr>
<th>ATC subgroup</th>
<th>ATC-code</th>
<th>% users</th>
<th>agreement</th>
<th>kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>vag infections</td>
<td>G01</td>
<td>9.7</td>
<td>85.3</td>
<td>4.1</td>
</tr>
<tr>
<td>antacids</td>
<td>A02</td>
<td>10.6</td>
<td>83.9</td>
<td>3.2</td>
</tr>
<tr>
<td>iron</td>
<td>B03A</td>
<td>47.5</td>
<td>37.8</td>
<td>6.0</td>
</tr>
<tr>
<td>antibiotics</td>
<td>J01</td>
<td>7.4</td>
<td>85.7</td>
<td>4.1</td>
</tr>
<tr>
<td>cold and cough</td>
<td>R05</td>
<td>2.3</td>
<td>91.7</td>
<td>4.6</td>
</tr>
<tr>
<td>antihaemorhoids</td>
<td>C05</td>
<td>1.8</td>
<td>93</td>
<td>2.8</td>
</tr>
<tr>
<td>vitamins</td>
<td>A11</td>
<td>1</td>
<td>91.2</td>
<td>1.4</td>
</tr>
<tr>
<td>analgesics</td>
<td>N02</td>
<td>1</td>
<td>89.4</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Ph+/I+ : users/non-users according to pharmacy records
I+/I- : users/non-users according to interview data

Compliance
The 295 women participating in the interviews reported having used 732 drugs during pregnancy. In addition 7 drugs were reported to have been prescribed but not consumed, bringing the total to 739. Since our compliance interview technique did not apply to self-medication drugs, we excluded the 226 drugs that were reported as self-medication, thus leaving 513 drugs prescribed by a physician or a midwife. The drugs were said to have been used according to the instructions in 74.9% (Table 3). In 2.7% no information on compliance could be obtained. In the remaining 114 (=22.4%) prescriptions concerning 93 women, the prescription was not used according to the instructions. Non-compliance included: too short duration of use, taking too small dosages, a combination of the two, non-use, or over-use...
Of all women who received one or more prescriptions (n=238) 39.1% thus reported non-compliance. Reasons given for not having followed the instructions included: hesitation to use the drug during pregnancy (24×), the experience that the drug caused side effects (26×), disappearance of the complaints for which the drug was prescribed (14×), or the fact that the complaint persisted notwithstanding drug therapy (10×). Women were asked about their reserves on drug use in pregnancy. In those who expressed hesitation, non-compliance was more frequently observed (36.8%) than in women who had no reserves about their drug use (16.8%). The degree of non-compliance was dependent upon the type of drug: it involved 34.6% of the prescriptions for the respiratory drugs (ATC: R-group), 32.6% for the gastro-intestinal drugs and vitamins (ATC: A-group) and 26.3% for the central nervous system drugs (ATC: N-group). Non-compliance was much lower for the gynecological preparations (ATC G-group), the blood-forming drugs (ATC: B-group) and the anti-infective drugs (group J) with percentages of 19.2, 18.9 and 11.8%, respectively.

**Table 3** Compliance and reasons for non-compliance with 511 prescriptions of 295 women in The Netherlands (1990).

<table>
<thead>
<tr>
<th>Reason for non-compliance</th>
<th>Prescriptions</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use according to instructions</td>
<td>385</td>
<td>74.9</td>
</tr>
<tr>
<td>Compliance not known</td>
<td>14</td>
<td>2.7</td>
</tr>
<tr>
<td>• shorter duration of use</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>• lower daily dose</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>• shorter duration and lower dose</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>• non-use</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>• longer use or higher dose</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Not according instructions:</td>
<td>114</td>
<td>22.4</td>
</tr>
<tr>
<td>Total</td>
<td>513</td>
<td>100</td>
</tr>
</tbody>
</table>

**DISCUSSION**

At first glimpse there appears to be a good correlation between the data on drug consumption obtained in the interview study and in the study of the pharmacy records with 83 and 82% of the women respectively reported to have used one or more drugs, the agreement between the methods with respect to ever/never using a drug being 84%. We also found no difference between the methods as regards
the mean number of drugs received per women. On closer examination, however, the methods reveal clearly different results. The difference was not systematically in favour of higher scores with either of the two methods. With regard to the total number of drugs used, one half of the 125 women with disagreement had received more drugs according to the pharmacy data while the other half had used more drugs according to the interview.

The pharmacy record data, firstly, yielded higher figures for drug use in the situation where more than 4 drugs were received during pregnancy. This could be explained by an insufficient recall when so many drugs have been used. Others also have shown that insufficient recall clearly hampers the reliability of interview studies. Secondly, the pharmacy records showed higher figures for drug use in the case of the dermatological, eye and ear drugs and respiratory drugs such as drugs for cold and cough. One possible explanation for this discrepancy between the two methods may be that such drugs for topical application were not regarded as drugs by the women interviewed; drugs for topical application may not be considered as “real” drugs. Payer similarly concluded that collecting data by interviews may be insufficient since it is not always clear what one considers to be a drug. Also, short duration of drug treatment for every-day illnesses may be not considered as “real” use and therefore forgotten. Thirdly, pharmacy record data will inevitably suggest higher drug use figures than interview data because they fail to reveal inadequate compliance to the prescription.

Although our study indicates that compliance is far from optimal only 7 prescriptions were not used at all. At least one quarter of all prescriptions was not used according to the instructions, and four out of the ten women admitted not having followed the instructions adequately. This insufficient compliance was reported to be predominantly due to hesitation to use drugs during gestation. If a woman hesitated to use a drug during pregnancy failure to follow the instructions was twice as frequent as when she did not hesitate. This suggests that the women valued possible risks differently compared to the medical profession. Another frequently used justification for deviating from instructions was the idea that the drug had induced side effects, such as anorexia, heart burn, diarrhea or constipation. Naturally one cannot conclude from the present data whether these indeed were side effects of the drug, or whether these complaints were independent of drug use. Compliance was poorest for the use of respiratory and central nervous system drugs and vitamins, whereas it was the best for gynecological, blood forming and anti-infective drugs. These differences may well relate to the perceived need to use these drugs; the indication for the latter group of drugs may well have been more strict than that for the former group. We would hesitate to draw firm conclusions from this study as regard compliance since in view of the manner in which the data were collected some over-estimation of the figures is possible. However, non-compliance clearly is a reason for over-estimation of actual drug use when we only look at pharmacy records.

We also found that in half of the women the interviews registered higher drug use figures than the pharmacy record data. Figures for overall drug use were naturally
higher in the interview study, since self-medication drugs are included in the interviews; 31% (226/732) of the drugs reported in the interviews were reported to be self-medication drugs. These drugs are left out of the comparison between pharmacy record data and interview data. Even after the omission of these self-medication drugs, however, drug use scores in the interview study were still found to be higher for the analgesics, the non-official (or alternative) drugs and for the vitamins. We suggest that the higher scores for these drugs in the interview study may reflect a perception by women that these drugs, which in our country belong to the limited group that can also be bought without prescription, had been recommended by the physician, and were thus reported as having been prescribed, which was not actually the case. Figures for the cardiovascular drugs were also found higher in the interview study. This difference may be due to the fact that these drugs might be prescribed during a hospital stay, for example shortly before childbirth, and were therefore not in the records of the community pharmacy.

Other studies\textsuperscript{1,3,4} found poor agreement between questionnaire data and medical record data. This lack of correspondence is related to the recall period which ranged from nine months to 30 years. Complete agreement, by contrast, was found in the study regarding drug use during delivery where the recall period was only three weeks and where the questions were associated with an important event, childbirth.\textsuperscript{3} An almost perfect agreement, on the other hand was found for labor-related drugs, such as ermetrine or oxytocin. Poor agreement was found for the use of tranquillizers at the time of labour, but the authors attributed this to a failure to ask more specific questions.\textsuperscript{11,12}

In conclusion, drug use data derived from pharmacy records are frequently rather different from data obtained via interviews. Since in about half of the cases studied the one method records a higher level of drug use while in the other half the alternative method produces the higher figure, we cannot conclude that either method is superior to the other. The two methods however are clearly complementary to each other. Data on the use of self-medication drugs and on compliance with the prescription can be obtained only via personal interview, whereas data on drug use in women who receive a drug more than incidentally and data on the use of drugs for topical application may be more reliably obtained from pharmacy records. Further studies should take such specific considerations into account.

REFERENCES

6 De Jong-van den Berg,.... het andere artikel