Originals

Drug use in pregnancy: a comparative appraisal of data collecting methods

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Summary. We have compared the reliability of the information about drug therapy and pregnancy retrieved by interviewing patients with that distilled from pharmacy records. In the initial phase of each interview we used the internationally accepted open-ended technique, and extended this with an indication-oriented set of questions and then a set of specific drug-oriented questions. These data were then compared with those from pharmacy records on dispensing for the same patients during their pregnancy.

The results suggest that if drug consumption during pregnancy is evaluated by interview, one should not restrict oneself to open-ended questions but should include indication-oriented and, when appropriate, drug-oriented questions. Such specific questions offer the opportunity of detecting the use of over-the-counter medication and of constructing drug use/complaint profiles. By contrast, pharmacy records will give better information in case of long recall periods and in patients with multiple and/or repeated drug use. Investigators should use the complementary elements of both techniques where appropriate.

Key words: Drug use, Complaint profiles, Pregnancy; pharmacoepidemiology, pharmacy records

There have been many studies of drug use during pregnancy [1–9]. In such studies information is obtained either from the patient or from the health professionals who have prescribed or dispensed the drugs. Since medical records are only partly concerned with drug therapy and since the step between prescribing and dispensing may be subject to non-compliance, there is reason to believe that pharmacy records are relatively more reliable for this purpose. This is particularly likely to be the case when – as in the Netherlands – reimbursement regulations require accurate recording of pharmacy data.

In this study we have compared the reliability of the information retrieved by interviewing patients with that distilled from pharmacy records. In the initial phase of each interview we used the open-ended technique dictated by the WHO-initiated International Cooperative Drug Utilization Study in Pregnancy [10]. However, the interview continued with an indication-oriented set of questions and then a set of specific drug-oriented questions. Furthermore, we tried to establish and to analyse compliance and non-compliance rates on the basis of these data. In a subsequent phase of the study, the data were compared with those from the pharmacy records for the same patients during their pregnancy.

Materials and methods

Study population

The study was carried out in a mixed urban and rural population in the North of the Netherlands. Women living in this area who had delivered a live baby between 1 February and 15 June 1990, either at home or in hospital, were invited directly after birth to participate. Mothers of still-born babies (estimated as 0.6 % of all births) were not included. The women were approached indirectly, through a letter from either the nurses attached to the Green Cross organization devoted to home care (involved in home and outpatient deliveries), or from the hospital nursing staff (for hospital deliveries). They were asked to respond directly to the Department of Pharmacy and Society at the University of Groningen.

Interviews

Within 2 weeks after delivery, the women were interviewed at home by a trained interviewer, who strictly followed the open-ended ap-

Table 1. Indication-oriented questions

Have you used any medication or treatment during pregnancy for any of the following complaints?		
Anaemia	Asthma	Anorexia or vomiting
Cold and flu	Cough	Dermatological disorders
Diabetes mellitus	Diarrhoea	Epilepsy
Fatigue or malaise	Fever	Haemorrhoids
Headache	Heartburn	Hypertension
Imminent abortion	Insomnia	Nervousness or stress
Constipation	Oedema	Pain
Urinary tract infection	Vaginal infection	Other infections

Table 2. Numbers (%) of users, numbers (%) of drugs, both prescribed and OTC, and the mean numbers of drugs per user according to the different type of questions

	International questionnaire	International questionnaire + indication-oriented	International questionnaire + indication-oriented + drug-oriented
Users (%)	233 (79%)	252 (85%)	260 (88%)
Drugs (%)	534 (100%)	644 (121%)	732 (137%)
Drugs on prescription	419 (100%)	489 (117%)	506 (121%)
Self-medication (OTC)	115 (100%)	155 (135%)	226 (197%)
Mean number of drugs/user	2.3	2.6	2.8

proach of the International Cooperative Drug Utilization Study in Pregnancy questionnaire [10].

After the open-ended questioning, the women were asked whether they had suffered from any from a list of 24 disorders that commonly occur during pregnancy (Table 1), and whether they had used drugs for them. They were then shown a list of 25 vitamin A, vitamin B, and vitamin D formulations and 16 laxatives and were asked whether they had taken any of the drugs on the list.

All drugs concerned were classified according to the Anatomic Therapeutic Chemical classification code (ATC) [11]. The total number of drugs used was regarded as the number of occasions on which a drug was either dispensed or was purchased for the purpose of self-medication in the population studied. When a particular drug was issued to (or bought by) a woman on more than one occasion during a given trimester of pregnancy it was counted only once; if a drug was used in different trimesters of pregnancy, it was counted separately for each trimester.

The duration of pregnancy was calculated from the first day of the last menstrual period, as provided in the interview, and from the date of delivery.

Compliance

For obvious reasons, traditional methods for studying compliance, such as tablet counts and plasma/urine determinations, were not appropriate in this study. The interview contained structured questions concerned with compliance, such as:
• if a drug was prescribed, did you follow the treatment according to the instructions?
• if you did not follow the instructions,
a. did you discard the drug dispensed?
b. did you use the drug more briefly than had been recommended or for a longer period than recommended?
c. did you use the drug in a lower daily dose or in a higher daily dose than recommended?
• if you did not follow the instructions, what was the reason for your non-compliance?
• did you have any reservations about using any particular drug because of your pregnancy?
It was realized that the use of this questionnaire technique may have led to an overestimation of compliance.

Pharmacy records

Full information on drug use by the patients who gave informed consent to our consulting the pharmacy records relating to their pregnancy was obtained from the pharmacies or dispensing GPs concerned. The information related only to prescribed drugs, since the supply of over-the-counter (OTC) drugs is not recorded in the Netherlands. Drugs given in hospital during the perinatal period were also not included, since these drugs were not delivered by the community pharmacy or dispensing GPs and were not known to them.

Statistics

Group differences were tested using either Student's t-test or the χ^2 test; they were considered to be significant if P was below 0.05. Kappa values were calculated as a measure of agreement between interview data and pharmacy record data [12]; values above 0.75 reflect excellent agreement; values between 0.40 and 0.75 reflect fair to good agreement; values below 0.4 reflect poor agreement [13].

Results

Compared with the total number of babies that had been born in the area under study during the period concerned the average response was low (28%). It was slightly higher than average among women who delivered at home and slightly lower among those who delivered in hospital. Important reasons for this poor response may be the indirect and non-iterative approach; it may have been that not all the letters were dispatched, or that women were reluctant to assist an investigator whom they did not know. Again, the timing of the interview, which was determined in accordance with the International Study, may not have suited the women. Nevertheless, the sample responding was representative of the population of pregnant women in the Netherlands with respect to age, parity, number of antenatal consultations [14, 15], duration of gestation, birth weight of the baby, mode of delivery, congenital malformations, and breast-feeding [16, 17].

In all, 295 women [mean (SD) age 29.2 (4.4) y] entered the study. They had delivered 303 liveborn babies, of whom 144 (47.5%) were first-born children. Thirty-seven % of the women delivered at home, 12% in an outpatient clinic, and 51% in hospital. These proportions are consistent with Dutch population data.

The responses to the questionnaire are summarized in Table 2. 233 (79%) of the women admitted to using at least one drug during pregnancy, and this number rose to 85% after the addition of the indication-oriented questions and then to 88% after putting the drug-oriented questions. As a consequence of adding these two types of questions, the proportion of women originally not considered to have used any drug was nearly halved, falling from 21% to 12%. Figures for the numbers of drugs used rose likewise after the addition of the two supplementary sets of questions. Not surprisingly, the most prominent rise was observed for the OTC

Table 3. Numbers (%) of users, numbers (%) of drugs, and the mean numbers of drugs per user of the listed vitamins and laxatives in relation to the questionnaire design

	International questionnaire	International questionnaire + indication-oriented	International questionnaire + indication-oriented + drug-oriented
Users	30 (10%)	34 (12%)	91 (31%)
Drugs	33 (100%)	41 (124%)	125 (379%)
Mean number of drugs/user	1.1	1.2	1.4

Table 4. Numbers (%) of users, numbers (% increase) of drugs, and the mean numbers of drugs per user for one of the 24 listed indications (Table 1) in relation to the questionnaire design

	International questionnaire	International questionnaire + indication-oriented	International questionnaire + indication-oriented + drug-oriented
Users	224 (76%)	241 (82%)	244 (83%)
Drugs	469 (100%)	576 (123%)	592 (126%)
Mean number of drugs/user	2.1	2.4	2.4

drugs after the second set of queries, since vitamins and most laxatives belong in this category. However, the self-medication group increased disproportionally after adding only the indication-oriented questions (χ^2: $P < 0.01$).

The use of laxatives and vitamins was reported by only 10% of the women in response to the open-ended questions. This percentage increased threefold after the specific drug-oriented questions were added and so the number of drugs used also rose (Table 3).

Both observations confirm that self-medication plays an important role in the pattern of drug use in pregnancy, a role which is not fully detected by open-ended questions.

On the other hand, the number of drugs used (as registered when using the International Study Questionnaire) for any of the 24 disorders listed increased by 23% when the indication-oriented set of questions was added (Table 4). It may thus be concluded that the addition of indication-oriented questions to the open-ended questionnaire considerably improved the response rate.

Additionally, the supplementary set of 24 indication-oriented questions allowed us to draw up drug use/complaint rate profiles (Fig. 1). Such profiles could be of great interest in international cross-sectional studies.

None of the increases observed was either related to a particular trimester sequence, or (in the case of prescribed drugs) to the profession of the prescriber (midwife, general practitioner, obstetrician) (χ^2: $P > 0.2$).

Table 2 shows that the 295 participating women used in total 732 drugs; in addition, 7 drugs were reported to have been prescribed but not taken. After discounting the OTC drugs (226), it was possible to examine compliance with 513 (506 + 7) prescriptions. No data were available in 2.7% of cases, while in 74.9% the drugs were said to have been used according to the instructions. In the remaining 22.4% (114 drugs used by 93 women), corresponding to 39.1% of those for whom a drug had been prescribed, the prescription was not used according to the instructions (see Methods). Extrapola-

tion of the data revealed that information pointing to inadequate use would have been missed for 19 prescriptions (15 women) had only the open-ended questionnaire been used.

The reasons for poor compliance were variously adverse effects ($n = 26$), fear of fetal damage ($n = 24$), spontaneous remission of symptoms ($n = 14$), or lack of effect of the drug ($n = 10$).

The non-compliance rate varied among drug classes, probably depending on the perceived need for the drug: poor compliance was lowest in drug classes with the highest drug use/complaint ratio (Fig. 1).

Nine of the 295 women refused to have their pharmacy records used for further study; in another 4 consent was inadequate; 3 women could not remember the name of their pharmacy. In 62 cases the records of the pharmacies concerned were incomplete because of computerization problems. Thus, pharmacy record data from 217 women could be compared with concomitant interview data. According to the pharmacy records these 217 women received in total 409 prescribed drugs versus a figure of 374 drugs obtained from the interview data
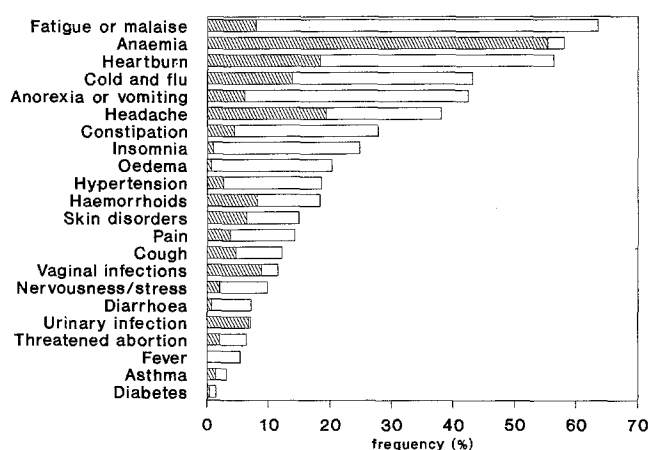

Fig. 1. Percentages of women with reported disorders (*full bars*) and with reported drug treatment during pregnancy (*hatched bars*)

Table 5. Comparison of drug use data as derived from interviews (I) or from pharmacy records (Ph), subdivided into different ATC main groups (*upper panel*) and subgroups (*lower panel*) of 217 women in The Netherlands (1990). The percentage agreement and the Kappa values are given

ATC main group	ATC code	Users [%]				Kappa value
		Ph + /I +	Ph-/I-	Ph + /I-	Ph-/I +	
Anti-inflammatory						
drugs	M	1.8	96.8	0.5	1	0.80
Bloodforming drugs	B	48	36.9	6.5	8.8	0.69
Gynaecological drugs	G	13.4	75.1	9.2	2.8	0.61
Gastrointestinal drugs						
+ vitamins	A	13.8	70.0	7.4	8.8	0.53
Antibiotics	J	7.8	81.6	6.5	4.1	0.52
Cardiovascular drugs	C	2.3	90.3	2.8	4.6	0.36
Respiratory drugs	R	4.6	82.5	9.2	3.7	0.35
Eye and ear drugs	S	0.5	97.2	1.8	0.5	0.33
Non-official drugs	Y	1.0	94.0	1	4.1	0.29
Dermatological drugs	D	2.8	84.8	9.2	3.2	0.25
Central nervous system	N	2.3	83.4	4.1	10.1	0.18
All drugs		74.2	10.1	7.4	8.3	0.45
ATC subgroup						
Vaginal infections	G01	9.7	85.3	4.1	1	0.76
Antacids	A02	10.6	83.9	3.2	2.3	0.74
Iron	B03 A	47.5	37.8	6.0	8.8	0.70
Antibiotics	J01	7.4	85.7	4.1	2.8	0.63
Cold and cough	R05	2.3	91.7	4.6	1.4	0.40
Antihaemorrhoids	C05	1.8	93	2.8	2.3	0.38
Vitamins	A11	1	91.2	1.4	6.5	0.11
Analgesics	N02	1	89.4	3.2	6.5	0.10

Ph + , users according to pharmacy records; Ph-, non-users according to pharmacy records; I + , users according to interview data; I-, non-users according to interview data

(including the two supplementary sets of questions). However, figures on the proportion of women using one or more drugs differed when using the two methods; the interview data provided a figure of 83%, the pharmacy records 82%. Nor did reported drug use per woman differ significantly between the two sources of information: the average (SD) was 1.7 (1.4) for the interview data and 1.9 (1.7) for the pharmacy records, though the pharmacy records pointed to a higher proportion of women using more than four drugs: 8.3 vs 3.7% ($P < 0.001$). Agreement between the two sources for ever/never use was 84%, with a Kappa value of 0.45. Perfect agreement concerning the numbers of drugs used was found in 92 women (42.6%) and a difference of one drug in 78 (36%). In the remaining 21% there was a larger difference between the interview data and the pharmacy data. In these women ($n = 125$) the data did not entirely correspond: 51% had received more drugs according to the interview and 49% according to the pharmacy records. At first sight, therefore, interview and pharmacy data seem to correspond quite well. However, a breakdown according to the various ATC drug classes shows considerable differences among these classes (Table 5), with Kappa values ranging from 0.80 (anti-inflammatory drugs) to 0.18 (central nervous system drugs).

A further breakdown of the most frequently used drugs (Table 5, lower panel) roughly corresponded with the ATC main group breakdown, but also seemed to suggest that agreement between the two systems is best for the more essential drugs, the use of which is most likely to be recalled.

Discussion

The aim of this study was to analyse two different data collecting systems on drug use in pregnant women and to compare their validity. Although the response was low, the sample of women studied was representative of the population of Dutch pregnant women, although it clearly may not correspond to populations in other countries: elsewhere in Europe, for example, home deliveries are (in contrast to the Netherlands) more the exception than the rule. Patterns of drug use may reflect that difference.

The interviews were held very soon after the baby was born: this may have helped to improve recall, which may have been poor in other studies (18–21). Seventy-nine percent of the women interviewed reported the use of one of more drugs during pregnancy (mean 2.3) when answering the open-ended questions. There was a considerable increase in this figure after adding two sets of questions. In a cross-over study the relative contribution of each set could have been analysed, but apart from the small subgroups that would have thus resulted, the investigational goals did not ask for such a design, and the more logical and practice-oriented sequential technique (i.e. first the indication-oriented questions, then the specific drug-oriented set) was preferred.

Adding the questions on the use of laxatives and vitamins showed that many women do not seem to consider OTC drugs as real drugs. Mitchell [22] observed a proportional increase after additional drug-oriented

questions for both prescribed and OTC drugs, comparable with our results. In our study 45% of the women reported the use of one or more OTC drugs, considerably more than in other studies using open-ended questions: Rubin [8] found 9%, Eskes [6] showed a decrease from about 11% in 1974–75 to about 7% in 1978–79. In contrast, in the prospective Eurocat study [23] the figure was 58%. We may conclude that information from open-ended questionnaires on the use of OTC drugs in pregnancy is bound to be incomplete. This could be important: although in the Netherlands OTC drugs are generally considered to be "innocent", international standards may differ, as may cultural opinions as to what constitutes a drug and what does not. This may render international comparisons difficult. A closely similar pattern was observed for compliance: the less urgently needed drugs were used in a less regular way, and women seemed to differ from the medical profession in their perceptions of fetal risk: a large proportion of the non-compliers did so out of fear of possible fetal damage. Again cultural differences internationally may lead to different results.

While specific drug-oriented questions will be useful only for particular purposes, the supplementation of the open-ended questionnaire with questions about the 24 most frequent disorders in pregnancy should certainly be recommended. Not only will the number of women recalling drug use (and particularly the use of prescribed drugs) increase, but the answers will also enable us to construct drug use/complaint profiles. Such profiles may add to the impact of international studies, since they give information about cultural differences in pattern of in complaints and concomitant responses in terms of medication.

Gross comparisons between the extended interview data and the pharmacy records did not reveal major differences, but ATC (sub)class comparisons showed considerable variation in agreement. The smallest Kappa values, i.e. the poorest correspondences, seem to be related to the less essential drugs. For such drugs pharmacy records most probably give the most reliable information. Payer also considered interview data inferior in that respect, since it was not always clear what was considered to be a drug [24]. Multiple drug use (more than 4) was also better registered by the pharmacy records, probably because of poor recall by the patient [25]. Poor recall is an important disadvantage of interview-based studies [22, 26]; in particular a long time interval between interview and drug use may invalidate reliability [18, 20, 21]. The early interview approach, though perhaps less acceptable to the patients, has great advantages. Though it is appreciated that the interview technique has its disadvantages, the use of self-medication and (some) estimate of compliance can only be analysed in this way. What is more a very important linkage with diagnostic data can be obtained.

In conclusion, we suggest that an interview data-collecting system should include indication-oriented questions (and in special cases drug-oriented questions); these questions should be formulated in such a way as to detect the use of OTC medication as far as possible.

Such interview data will outweigh data from pharmacy records as far as problems related to self-medication, compliance, and disease are concerned. By contrast, pharmacy records will give better information in case of long recall periods and in patients with multiple and/or repeated drug use. Investigators should use the complementary elements of both techniques where appropriate.

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