INVESTIGATING DRUG USE IN PREGNANCY
METHODOLOGICAL PROBLEMS AND PERSPECTIVES

ABSTRACT

In this study the use of prescribed drugs before, during and after pregnancy is described. The study is based on data obtained from pharmacy records of 1,948 women who delivered a live-born infant. Different measures to evaluate drug exposure are used. During the nine months of pregnancy 86 percent of the women used on average 4.2 prescriptions. During the course of pregnancy the use of gastro-intestinal and blood-forming drugs increased, whereas the use of cardiovascular, antiphlogistic and central nervous system drugs decreased. Antiemetics were predominantly used in the first trimester, and antacids in the last trimester, whereas laxatives were especially used after delivery. The percentage of women who used a treatment for vaginal infections increased from 2 to 7 during pregnancy. Most of the women (73%) received one or more iron prescriptions during the course of pregnancy, however the prescribed daily dose was low (prescribed daily dose/defined daily dose = 0.6). At least 1 percent of the women filled a new prescription for anticonceptives in the first trimester of pregnancy. Most likely, our data reflect the general prescribing pattern for Dutch pregnant women who delivered a live-born baby. Therefore, they form a good and detailed base for further studies, for instance on the exposure to drugs with known or suspected risks or on the use of drugs in patients with chronic concomitant diseases. Such studies may lead to recommendations that may improve prescribing behaviour.

INTRODUCTION

Both the public and the medical profession have become increasingly aware of the potential risks of drug use during pregnancy. However, hard data on risks and benefits of most of the drugs commonly used during pregnancy is still limited. It is at present recommended that drugs should be avoided during pregnancy as much as possible. As a consequence, sometimes pregnancy will be terminated unnecessarily when drugs whose embryotoxicity is doubtful have been used. On the other hand, underutilization of drugs, needed for the health of the mother, may occur because of an unjustified fear for foetal side-effects

The majority of studies concerned with drug use in pregnancy have been published in the seventies and eighties and differ widely in the approaches used. Although study-population, method of data collection, studied period and kind of drugs studied differ largely, these studies indicate that drug use in pregnancy is common; 50-90% of the women received one or more prescriptions during pregnancy. Most studies provide information about a selected group of pregnant women such as Medicaid patients (a fairly homogeneous population of low-income, predominantly urban patients) or hospitalised patients. In others, interviews were used as the only source of information on drug exposure; thus reliability and validity of this type of data is entirely dependent on accuracy of recall and type of interrogation. Frequently, changes in the pattern of drug use during pregnancy can not be evaluated, since information on the use of drugs in the pre-conception period and in the post-partum period is lacking. Finally, the pattern of drug prescribing in pregnancy may change rapidly, as a consequence of changes on the pharmaceutical market.
For all these reasons, we initiated this study, which describes the pattern of drug use before, during and after pregnancy, in order to evaluate the changes in drug prescription as a consequence of the pregnant condition.

**METHODS**

This article presents dispensing data of prescribed drugs from 10 computerized community pharmacies, covering nearly the total population of 4 cities from 15,000 to 45,000 inhabitants in the north of The Netherlands (total population ± 100,000). In all pharmacies a uniform computer system (Pharmacom) is in use for prescription processing, medication surveillance and various administrative functions. The pharmacy records cover health fund patients as well as privately insured patients. Health fund patients are obligatory registered at one single pharmacy, that keeps a complete file of their prescriptions. Although private patients have freedom of choice, they will most likely visit the pharmacist closest by. If they fill their prescription in another pharmacy, that prescription still will be included in our analysis since all pharmacies in a single city are included in this study. All women who delivered between July 1st, 1987 and December 31st, 1988 were included in the study. Health fund patients could be detected because their liveborn babies are registered at the pharmacy as new patients shortly after birth. Privately insured mothers could only be found if their babies were for some reason registered in the pharmacy records. The drug histories of the mothers were studied from the pharmacy records during the period from 15 months before childbirth till three months thereafter. The drug histories of 1,948 mothers aged 27.9 (± 4.5) years on average are included in the analysis. Pregnancy was considered to begin, on average, 270 days prior to the birthday of the child. In this way, information was obtained about drug use during the 6 months (day-450/day-270) before the estimated conception (designated period -2 and -1), during the estimated 9 months (day-270/day0) of pregnancy (period 1, 2 and 3), and during the 3 months (day0/day90) after delivery (period 4) (Table 1).

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In the prescription file all drugs, including extemporaneous and locally standardized preparations, were identified by their Pharmacom® preparation name. For each prescription dispensed, data on patients’ age, name of the drug, date of dispensing, prescribed daily dose (PDD), total amount of the drug dispensed, route of administration and prescriber were collected. In case of non specified use, the usually daily dose was taken as PDD. Drugs were coded by hand according to the Anatomical Therapeutical Chemical (ATC) Classification; the number of defined daily dose (DDDs) per 1,000 women per day were calculated to indicate the amount of drugs used.15-17

In order to protect the privacy of patients and prescribers, their anonymity was strictly preserved.

Five measures of drug utilization have been used:

- **Prescription rate**: number of women per 1,000 who received one (or more) prescriptions for a given drug or class of drugs within one trimester;
- **Exposure rate**: number of women per 1,000 to whom the drug or class of drugs is available in theory, i.e. those who received a prescription in one trimester which was extended into the next trimester, are counted for both trimesters in which they had access to the drug;
- **Number of DDDs**: number of DDDs per 1,000 women per day available in theory per trimester. For those who received a prescription within one trimester lasting into next, the exact number of DDDs available is calculated per trimester;
- **Duration of drug use**: the mean number of days per user to indicate the duration of treatment per trimester;
- **PDD/DDD**: the prescribed daily dose expressed versus defined daily dose, used to indicate daily exposure of the users.

Prescription rate indicates the prescription behaviour of the medical profession, while the exposure rate and the number of DDDs are important in terms of possible risks. Student’s paired t-test is used for testing the significance of the differences between the mean number of DDDs of a given period as compared to period -1. Differences were considered to be significant if the p-value was < 0.05.

**RESULTS**

**Overall drug use.**

The prescription rate of all drugs increased from 358 and 347 per 1,000 before conception respectively in period -2 and -1 to 714 per 1,000 in the last trimester of pregnancy and 743 per 1,000 after delivery (Fig. 1). When taking the three trimesters of pregnancy together, 86% of the mothers received at least one prescription with a mean (±SD) of 4.2 (±3.6) prescriptions per user during the entire pregnancy. The prescription rate of iron supplements during the entire pregnancy is 73 percent (730/1,000 women). When iron preparations and vitamins were excluded the prescription rate was 352 and 341 per 1,000 respectively in the 2 periods before
conception to 465 per 1,000 in the last trimester of pregnancy and 690 per 1,000 after delivery (Fig. 1). If these iron preparations and vitamins were not taken into account, 68% of the mothers received at least one prescription during the whole pregnancy with a mean (±SD) of 2.4 (±3.2) prescription per user.

**Drug use in the ATC groups.**

Besides this information on drug use in general, more detailed data on the prescription rate (line) for most of the main groups of the ATC classification per trimester, is given in 2. Comparing the individual ATC groups, a different trend of drug use is visible. An increase of the prescription rate during the course of pregnancy was seen in the group of the gastro-intestinal drugs (group A, exclusive A11), the vitamins (group A11), the blood-forming drugs (group B) and to a lesser degree the respiratory drugs (group R). In contrast, the prescription rate of other drug groups decreased during the course of pregnancy (especially in period 1 and 2). This held true for the cardiovascular drugs (group C), the gynaecological drugs (group G), the anti-inflammatory drugs (group M) and the group of the central nervous system drugs (group N). After delivery, the prescription rate of some drugs such as the cardiovascular, anti-infective, anti-inflammatory drugs and central nervous system drugs clearly increased compared with the pregnancy periods, even to numbers higher than before conception.
Figure 2  Prescription rate (line), exposure rate (dark bars) both expressed as women/1,000 (left y axis) per trimester and number of DDDs (light bars) per 1,000 women per day (DDD/1,000/day) (right y axis) for drugs in some therapeutical groups according to the ATC classification. Note that the figures on the y axes are different among the various drug groups; the ratio of the y axis at the left (women/1,000) to y axis at the right (DDD/1,000/day) is the same for all ATC groups: namely 3. For explanation of the rate measures see text.
A more accurate evaluation of drug exposure showed that the data on exposure rate (hatched bars in Fig. 2) followed a similar pattern as the prescription rate. As could be expected, the prescription rate was consistently lower than the exposure rate. In the case of drugs used for short period of time, such as the anti-infective drugs (mean days <10) the difference was small, compared to drugs used for a longer period of time, such as the vitamins (mean days 23–39) and the blood-forming drugs (mean days 28–64). In the case of the blood-forming drugs, the prescription rate decreased between period 3 and 4 from 520 to 250 per 1,000 women while the exposure rate decreased much less steeply from 600/1,000 in period 3 to 500/1,000 in period 4. This is also illustrated in figure 3 with respect to the contraceptives (ATC: G03A): while the prescription rate decreased between period -1 and period 1, the exposure rate was still high, due to the fact that contraceptives are usually prescribed for a duration of 6 months.

![Figure 3](image-url)  
**Figure 3** Prescription rate (line) and exposure rate (bars) per 1,000 per trimester for contraceptive drugs (ATC: G03A). For explanation of the rate measures see text.

Additional information can be obtained from the data on the number of DDDs (stippled bars). In general, this parameter followed a similar course as the exposure rate. For the ATC groups in which the exposure rate increased, the number of DDDs also rose and if the exposure rate fell, the number of DDDs also decreased. The number of DDDs significantly increased during period 2 and 3 for the gastrointestinal drugs (both p<0.001) and the vitamins (both p<0.05), and during period 1, 2 and 3 for the blood-forming drugs (all p<0.001). The number of DDDs significantly decreased during period 1, 2 and 3 for the gynaecologicals (all p<0.001), the anti-infective drugs (all p<0.05) and the anti-inflammatory drugs (all p<0.05). However, the ratio between the two measures (the exposure rate and the number
of DDDs) varied in the different groups: in case of drugs for short time use such as the anti-infective drugs the exposure rate is high, while the number of DDDs is relatively low. On the other hand, the number of DDDs was relatively high for chronically used drugs such as the vitamins and the blood-forming drugs.

![Figure 4](image)

**Figure 4**  Prescription rate (women/1,000) per trimester of dermatologicals (D) (---), eye and ear drugs (S) (--), non-official drugs (Y) (-----) and anti-haemorrhoid drugs (C05) (----). For explanation of the rate measures see text.

The duration of drug use is plotted at the bottom of the charts of figure 2 as the mean number of days per user. The anti-infective drugs were prescribed for approximately 7-9 days, whereas the blood-forming drugs were used for approximately 30-60 days per trimester. In most ATC groups the number of days hardly changed during the period studied. Only in case of the blood-forming drugs the number of days doubled at the end of the pregnancy and fell sharply again after delivery. The duration of treatment also increased in the group of the gastro-intestinal drugs.

The data on PDD/DDD finally may enable us to see whether for a single prescription the prescribed daily dose during the course of pregnancy changed. If vitamins were prescribed, the daily dose generally was higher than the defined daily dose, whereas in case of the blood-forming drugs the reverse was true. This prescribing behaviour however, was stable during the follow up. Distinct changes were only observed for the cardiovascular drugs: at the end of the pregnancy and after delivery a higher daily dose was prescribed than before.

Because precise information about daily use of dermatologicals (group D), eye and ear medication (group S), antihaemorrhoid drugs (group C05) and non-official drugs (group Y) is not available, only the prescription rates of these ATC groups are given in figure 4. The prescription rate of dermatologicals and antihaemorrhoid
drugs increased during the course of pregnancy and after delivery whereas the prescription rate of non-official drugs and eye and ear medication did not change.
Figure 7  Exposure rate (women/1,000) per trimester of oxytocics (G02A) ( ), prolactin inhibitors (G02CB) ( ), contraceptives (G03A) ( ) and drugs against vaginal infections (G01A) ( ). For explanation of the rate measures see text.

**Drug use within ATC groups.**

It is interesting to look to some therapeutic sub-groups in more detail: the gastrointestinal drugs, blood-forming drugs and the gynaecological drugs. When we study the drug utilization in the group of gastro-intestinal drugs (Fig. 5), the slight increase in exposure rate during the first trimester of pregnancy appeared to be due to an increase in antiemetic drug use (group A04); the drug use of this drug group in the last trimester of pregnancy was almost fully due to the use of antacids (A02A), whereas the laxatives (A06A) were mostly responsible for the increase in drug use in the period after delivery. These data are presented more in detail, showing the exposure rate per day, in figure 5. As could be expected, the increased exposure rate in the group of blood-forming drugs (group B) was due to the use of iron supplements and to a lesser degree to that of folic acid (Fig. 6). The increased exposure rate in the group of gynecologicals (group G) in the trimester after delivery was caused by the use of contraceptives and to a lesser degree to the use of oxytocics and prolactin inhibitors. The use of agents against vaginal infections increased in the second and third trimester of pregnancy (Fig. 7).

**DISCUSSION**

This study describes the drug prescription pattern in a group of 1,948 women before, during and after pregnancy. Since the 6-months period before pregnancy is included, we are able to evaluate trends in the change of drug use as a consequence
of pregnancy. Since drug dose and duration of prescription were also registered, the number of women using a specific drug in relation to duration of use and daily dose could be accurately documented. In other words, real exposure to a certain drug could be measured.

The overall drug exposure increased during pregnancy; 86% of the mothers received one or more prescriptions during the course of pregnancy. This increase was mainly due to the use of iron supplements, folic acid, antacids, antiemetics, laxatives and drugs for vaginal infections. One could wonder whether the use of these drugs is warranted. It seems to be routine practice to give iron supplements: 73% of our study group received one or more iron prescriptions during the whole period of pregnancy. Our data differ markedly from those of Piper et al. who used a comparable study design as we did. In our Dutch patients iron was used ten times more frequently than in their American patients. We consider that in The Netherlands iron supplements seem to be overused in pregnancy, since an indication for iron supplements is only present in 10 percent of the pregnant population.

Piper et al. observed that the use of gastro-intestinal drugs was higher in the first trimester of pregnancy (due to the anti-emetics), whereas in the last trimester of pregnancy only approximately 2 percent of their patients used drugs from this therapeutic category. This is in sharp contrast with the 20 percent of women receiving gastro-intestinal drugs in the third trimester in our study (Fig. 4), which was mainly due to the use of antacids. Although the use of vitamins increased sharply pregnancy and remained elevated after delivery, the consumption was still fairly low (less than 4 percent) as compared to the American women (45 percent). One explanation could be that in The Netherlands vitamins are usually sold over the counter, whereas the low-income Medicaid population of the Piper study received these drugs as prescription drugs.

In contrast to this increase in the use of some drug groups during pregnancy, the use of others distinctly decreased. This appeared to be particularly true for the anti-inflammatory drugs, which were used by 34 and 39 per 1,000 women respectively during the two periods prior to conception and only by approximately 10 per 1,000 women during the second and third trimester of pregnancy. This decrease is not compensated by a shift to antipyretic analgesics, but may be explained by a decreased need, by an awareness of patient or/and physician that these drugs are better avoided during pregnancy, or by a shift to over-the-counter anti-inflammatory drugs.

The prescription rate, defined as the number of women who received a prescription in a given trimester is a fair estimate of prescribing behaviour. In terms of risks for the unborn child however, the exposure rate gives a more realistic picture because the duration of the prescription is taken into account. The different effects of presenting results in terms of either prescription rate or exposure rate are convincingly illustrated in the case of the blood-forming drugs: in period 4 the prescription rate is half the exposure rate i.e. the preparations are given for a longer period. In general, one may expect that in the prescription pattern of drugs or drug groups that are prescribed for relatively short periods of time, prescription rate
and exposure rate run fairly parallel, as is demonstrated for the anti-infective group in our study. In contrast, there is a discrepancy for the contraceptives: it is likely that most or all women will cease to take their contraceptives, once they realize that they are pregnant. The exposure rates given in the figures thus certainly overestimate the actual level of use of contraceptives. Nevertheless, the prescription rate of contraceptives in the first trimester of pregnancy was still 10.8 per 1,000. This suggests that even during early pregnancy new prescriptions for contraceptives were still filled (Fig. 3). The above findings illustrate the necessary of the consistent choice of measures; the prescription rate reflects the physicians prescribing behaviour whereas the exposure rate reflects the measure of risk which may be run by the patient.

Pharmacy records give the opportunity to document the changes of exposure in terms of duration of treatment and daily dose and additionally by the number of DDDs. Although, in all ATC groups the number of DDDs followed the same trend as the exposure rate, the ratio between these measures varied for the different ATC groups. Both duration of treatment (mean days) and prescribed daily dose (PDD/DDD) contribute to these differences. In case of drugs used for a short period of time, such as the anti-infective drugs, anti-inflammatory drugs and central nervous system drugs, the exposure rate is high while the number of DDDs is relatively low. The number of DDDs compared to the exposure rate is high for chronically used drugs. In case of the vitamins this is due to the prescription duration (varying from 23 to 39 days) as well as to the prescribed daily dose (PDD/DDD is 1.2–1.6), whereas in case of the blood-forming drugs only the duration of treatment attributed to the high number of DDDs because the prescribed daily dose (PDD/DDD) in fact is low (all periods 0.6).

The method used, does not allow us to include data on drug use in women whose pregnancies resulted in a miscarriage and induced abortion or in a still-born infant. The percentage of pregnancies resulting in abortion is not exactly known; the percentage of still-born infancy in The Netherlands is shown to be less than 1%. We may therefore conclude that our results reflect the drug prescribing pattern in Dutch women who delivered a live-born baby. Since privately insured patients constitute approximately one third of the Dutch population and data on differences in drug prescribing in pregnant privately insured patients, compared to health fund patients, are lacking, this category may have biased our results. The free choice of pharmacy services for privately insured patients may have caused some of them to visit incidentally a pharmacy outside the area under investigation, although most likely this will happen only sporadically. More important is the fact that babies from privately insured women are not automatically registered after their birth at a given pharmacy. In that case, the mother (and her prescribing pattern) will also not be detected, which may have led to some distortions of the figures. Babies from privately insured mothers will only be registered if they are drug users themselves; whether that is related to a different pattern of use in their mothers compared to other pregnant women is not known. The present study could usefully be complemented by investigations of drug use during hospital stay and studies that give information
about over-the-counter drugs. Such complementary data would naturally result in a higher for drug exposure than that emerging from the present study. Hospital admissions are quantitatively of importance only during delivery. In the area of this study approximately 50% of the women deliver at hospital; more than half of them stay in hospital only for one day.21

A further adjustment in the figures presented here can be applied in the light of compliance with drug therapy during pregnancy. The figures in the present article indicate the number of exposed women which would result if the patient started taking the product at the date of dispensing and continued until the supply was exhausted. However, it is not sure that prescriptions actually filled, are actually consumed; in all methods relating to drug use non-compliance is a well-known interfering factor.22

We conclude that the use of pharmacy records is a feasible data base to get reliable epidemiological information on drug use during pregnancy. It shows that prescribed drug use during pregnancy is frequent but that drugs suspected of adversely affecting foetal outcome are prescribed in decreasing frequency.23 Such data are necessary before prescribing behaviour can be adjusted.

REFERENCES