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► To cite this version:

Bengt Källén, Emma Nilsson, Petra Otterblad Olausson. Antidepressant use during pregnancy: comparison of data obtained from a prescription register and from antenatal care records. *European Journal of Clinical Pharmacology*, 2011, 67 (8), pp.839-845. 10.1007/s00228-011-1021-8 . hal-00677629

HAL Id: hal-00677629

<https://hal.science/hal-00677629>

Submitted on 9 Mar 2012

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**Antidepressant use during pregnancy. Comparison of data obtained from a
prescription register and from antenatal care records.**

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Short title: Antidepressants during pregnancy:

Abstract

Purpose: To compare interview data on drug use during pregnancy with data identified from a register of prescriptions.

Materials: We compared information from the Swedish Prescribed Drug Register with the Swedish Medical Birth Register on antidepressant use. In order to evaluate the clinical significance of difference in ascertainment with the two methods, the rate of preterm births among singletons and of neonatal symptoms were studied.

Results: During the year before the last menstrual period, 1.5% of the women filled prescriptions for antidepressants each month. Already before the pregnancy was known, the rate of filled prescriptions decreased and reached 0.5% towards end of pregnancy. Twenty-two per cent of first trimester use of antidepressant was unidentified using interview data and prescriptions during 2nd and 3rd pregnancy months covered only 55% of actual use. When women who filled prescriptions one or three months before the last menstrual period were included, 17 and 43%, respectively, of women were included who probably did not use the drugs in the first trimester. Prescriptions gave a more complete ascertainment of drug use after the first trimester than data from antenatal care which seemed to over-estimate drug use.

Conclusions: Interview data seem to give the most valid results on early use. When interview data are not available, prescription data could be used but should not include prescriptions given earlier than one month before the last menstrual period. Studies of drug use later in pregnancy are best based on prescription data in absence of interview data.

Key words: Antidepressants, interview data, pharmacoepidemiology, prescription register,

Introduction

In pharmacoepidemiological studies of drug use during pregnancy, various techniques are used [1]. Some studies are based on cohorts of exposed women, often obtained from Teratology Information Services (e.g., antidepressant studies [2-4]). Such studies are usually limited in size and have therefore little power to detect anything but very strong effects of the drug. In order to get a larger study material, different approaches have been used. At present, a much used methodology is based on linkage between national or regional registers of prescriptions with registers of delivery outcomes. Such studies of antidepressants have been made for instance in Canada [5, 6], Finland [7], and Denmark [8, 9]. Timing of drug use during pregnancy is then made from the date of filling the prescription related to the week of pregnancy. ~~This methodology has so far not been validated.~~ There are two problems involved, the filling of a prescription does not necessarily mean that the patient took the drug, and the dating method may be less exact than thought. Often prescriptions filled during a period before the last menstrual period (LMP) have been used as indicating exposure during the first trimester, sometimes including one, sometimes three months before LMP. This obviously increases the uncertainty about if the women used the drugs during pregnancy. On the other hand, women may well use drugs during pregnancy which they have possessed for a long time.

[Two recent studies compared interview data with prescription data. In a study from Norway \[10\] prescription data were used as “golden standard” and the specificity and positive predictive values were calculated for various drug categories and the uncertainties in the use of prescription data were disregarded.](#)

[A Swedish study \[11\] made use of one year's data from the Swedish medical birth register and the prescribed drug register \(the same sources as in the present study\). There was no clear-cut distinction in the analysis between interview data referring to early pregnancy and antenatal information on drug prescriptions after the first trimester and in the comparison they included prescriptions filled 3 months before pregnancy..](#)

With the beginning on July 1, 1994, information on drug use during pregnancy has been included in the Swedish Medical Birth Register (MBR) [129]. Information on early use is based on interviews performed in early pregnancy and information on later use comes from antenatal care records. In a recent publication, these data were used for a study of antidepressant use and its effect in pregnancy [143].

From July 1st, 2005, a prescribed drug register exists in Sweden with individual identification of each patient [142]. This gives an opportunity to compare information from this register with that given by the woman and recorded on antenatal care records. We choose to analyze the use of antidepressants which represent a drug group often used for extended periods but where an uncertainty on the safety during pregnancy exists.

Material and Methods

Two sources of information was used. One was the prescribed drug register [142] which contains information on all filled prescriptions in Sweden since July 1st, 2005 with, among other things, patient identification, date of dispensing, and ATC (Anatomical, Therapeutic, Chemical) code.

The second source was the Medical Birth Register (MBR) [120]. This register was started in 1973 and contains information on antenatal care, delivery, and neonatal conditions, since 1982 based on copies of the original medical records. Information on drug use was included from July 1, 1994 [153]. Nearly all women attend the antenatal care system and the first visit usually takes place before the end of the first trimester, the majority between weeks 10 and 12. At this visit, the woman is interviewed by a midwife, among other things on which drugs she has taken since she became pregnant [13]. During the remaining antenatal care, information on prescribed and recommended drug use is available from copies of antenatal care records. This may be based on an information from the woman that she has begun to use the drugs with or without recommendations from the antenatal care. The woman may have got prescriptions from other sources than antenatal care which may not have been recorded.

Drug names are recorded in clear text and are later transferred to ATC codes in a semi-automatic process. Timing in pregnancy weeks of the filling of a prescription is based on the estimated last menstrual period date (LMP), calculated from the date of birth and the estimated pregnancy duration in days. The majority of estimates on pregnancy duration was based on second trimester sonography. [Information on gestational duration was missing in 200 women \(0.08%\).](#)

From MBR, information was obtained on maternal age, parity, smoking habits in early pregnancy, height, and prepregnancy weight (from which body mass index, BMI, was calculated). These variables were used together with year of delivery as co-variables in the calculation of adjusted odds ratios (OR) with 95% confidence intervals (95% CI) for preterm birth in singletons and for some neonatal conditions. The latter consisted of respiratory problems (ICD-10 codes P22-P28), jaundice (P59), hypoglycaemia (P70.4-P70.9), and low

Apgar score (<7 at 5 minutes). Estimates of the ORs were made using Mantel-Haenszel procedure and those of the 95% CIs with Miettinen's method.

The mean gestational week at the first antenatal care center was 12.1 (SD =5.7), the median 10 weeks. The mean number of antenatal care visits after the first visit was 9.0 (SD 4.0).

Linkage between the prescribed drugs register and MBR was made with the use of the unique personal identification number which everyone born in Sweden or immigrating to Sweden gets and which is widely used in society and in all health care.

Ethics: The study was performed within the responsibilities of the National Board of Health and Welfare and therefore no ethical approval from outside ethical committees was needed.

Results

Pattern of antidepressant prescription in relation to pregnancy

During the period July 1, 2006 to December 31, 2008 we identified 23 151 women (28 039 deliveries) who had a delivery registered in MBR with a known pregnancy duration and had received a prescription for an antidepressant between July 1st, 2005 and December 31, 2008.

The number of women "at risk" for each month was calculated from MBR, indicating how many women were included pregnant in that month of pregnancy.

Figure 1 shows the monthly percentage of women who had a prescription for an antidepressant during one year before LMP (-12 to-1) and during pregnancy (1-10). The monthly rate was thus about 1.5% before LMP – as prescriptions usually represent 3 months use, this would mean that about 4.5% of all pregnant women used antidepressants before LMP. After LMP, the rate started to decrease already during the first month – when the woman did not know that she was pregnant – and continued to decrease to about one third of the pre-LMP monthly use. The strongest decline was seen after the first trimester.

We identified 6 832 women who had got a prescription for an antidepressant any time during pregnancy. Table 1 shows the distribution per trimester (<12 weeks, 12-24 weeks, >24weeks after LMP). Seventy-seven per cent of the women had such a prescription during the first trimester, 46% during the second trimester, and 40% during the third trimester. In 23% the woman had the first prescription during pregnancy after the first trimester. Among those who had a prescription during the first trimester, 48% had no further prescription during pregnancy.

Prescriptions during the year before LMP occurred in 77% of the women who had got prescriptions during all three trimesters, slightly fewer in women who had prescriptions during the first trimester but not during the second or third trimester, while women who had the first prescriptions during pregnancy in the second and still more evident in the third trimester had less often had a prescription during the year before LMP.

Comparison of data obtained from prescriptions with data reported by the women in early pregnancy

The total number of women reporting use of antidepressants in early pregnancy (mainly 1st trimester) is 4 488. These women were compared with women who had got a prescription for antidepressants. This comparison was made with three different exposure windows according to the date of prescription (Table 2).

It is likely that the majority of women who got a prescription during months 2-3 of pregnancy used the drug in early pregnancy. This would mean that 22% of these women did not report the drug use or that the midwife did not record it ([Table 2](#)). Another explanation is that the woman used the drug after the first visit to the antenatal care, notably if that visit occurred early. Use of MBR thus identified 78% of the possible exposures while use of the prescription register only identified a little more than half of them.

For the period of one month before LMP to the end of the first trimester, 67% were identified from MBR and 85% from the prescription register. If we accept 22% as a likely estimate of under-registration in MBR, it means that the true number of users during early pregnancy is 1226 more than recorded in MBR but they explain only 56% (1226/2208) of the excess number of women who got prescriptions during this period without being recorded in MBR . The remaining 44% most likely did not use antidepressants in early pregnancy and 17% of all women identified from the prescription register by including prescriptions one month before LMP probably did not use the drugs in early pregnancy.

A similar calculation made for the window three months before LMP to the end of first trimester indicates that only 23% of the excess cases in the prescription register are explainable by non-recorded MBR cases and 43% of all women identified from the prescription register probably did not use antidepressants in early pregnancy.

A comparison of the specific drug in the prescription given during the first trimester and the drug name stated by the woman and recorded by the midwife in MBR shows to a large extent complete agreement (97%). Two types of discrepancies were found. In a total of 54 instances, the name in MBR was unspecified – the vast majority (51) referred to escitalopram (Cipralextm) or citalopram (Cipramiltm). In other instances, the name given in MBR differed from the name in the prescribed drugs register, again the most common combination was escitalopram and citalopram (n=18). The similarities in the two names (and also in the content of the drugs) can explain the discrepancies: the woman may only have recalled that the drug name began with Cipra.

Comparison of prescriptions given after the first trimester with drug use reported in MBR

From the prescription register, 4 294 women were identified who had got a prescription of an antidepressant more than 84 days after LMP. In the MBR, 3 096 women had a note indicating the use of an antidepressant after the first antenatal care visit. In 2 452 women, both a prescription and a MBR note existed. Thus in 79% of the women who had a MBR recommendation, a prescription was identified - in 21% a prescription after the first trimester was thus not identified. Either the woman had not filled the prescription obtained from the antenatal care or she had resumed using a drug which she had got earlier.

The total number of possible users after the first trimester is thus 4 978 (4 294 + 3 096 – 2 412). Among them the prescription register identified 86% and MBR only 62%. In 38% drug use probably occurred without a documentation in the antenatal care records.

Discrepancies between the type of drug in the prescription register and in MBR occurred in 144 cases (6%). In 47 of them, MBR noted an unspecified antidepressant (42 of them referred to escitalopram or citalopram). In 11 cases, the prescription register stated escitalopram and MBR citalopram, in 3 cases the opposite.

Effect on neonatal conditions after maternal use of antidepressants in late pregnancy

Table 3 shows the presence of preterm birth in singletons and of any one among certain neonatal symptoms in three groups of infants: those whose mothers had filled a prescription of an antidepressant after day 84 but had no such drug use noted in MBR after the first antenatal care visit, those had no prescription but MBR information on antidepressant use after the first antenatal visit, and those who had both.

The odds ratio for preterm birth or having a diagnosis is shown in Table 4, comparing the various sources of information on antidepressant use. Infants born of mothers who had prescriptions on antidepressants without a recording in MBR had a significantly higher rate of preterm births and of neonatal complications than infants born of mothers with only information from MBR. The latter had a significantly lower risk for preterm birth than infants born of women who had both a prescription identified and information in MBR on antidepressant use.

Absence of drug recording in MBR could be due to absence of records from the antenatal care after the first visit – possibly because of non-attendance. If women with no antenatal care records after the first visit were removed from the analysis, the OR for preterm birth among infants born of women with prescriptions for antidepressants after the first trimester but no

information in MBR about antidepressant use versus infants born of women without such prescriptions but with information on antidepressant use in MBR decreased slightly (OR=1.56, 95% CI 0.96-2.54, based on 1554 infants) and lost statistical significance – the corresponding OR for infants with certain neonatal symptoms also decreased slightly and lost statistical significance (OR=1.34, 95% CI 0.95-1.87, based on 1601 infants).

Discussion

The study has both strengths and weaknesses. The main strength lies in the relatively large number of cases and the possibility of reliable linkage between registers. The main weakness lies in the inexact timing of drug use in MBR. Early use means use before the first antenatal care visit, and if this occurs early, some drugs used during the first trimester may not be included. On the other hand, if the first visit occurs after the first trimester, some late drug use may be mistaken as first trimester use.

The reason to chose antidepressants for analysis was that even though the drugs are often used during extended periods, a concern for possible adverse effects when used during pregnancy can affect the patient's decision to use the drugs. This can be seen in Figure 1. A decline in the use of antidepressants (as evaluated from the prescription register) is seen already before the woman can know about her pregnancy, a period when pregnancy may be planned and therefore drugs avoided. The use of antidepressants then decreases markedly during the first trimester and for the rest of the pregnancy usage is only about 1/3 of that before pregnancy. This graph shows the filling of prescriptions, not the actual use of the drugs.

We have information from MBR on the use of drugs in early pregnancy as stated by the woman at the first antenatal visit. Most likely, if the woman stated that she had used an antidepressant she had actually used it – but the timing may be outside the period of organogenesis. Some women will have used the drugs without it being recorded, either because they did not report it or because the midwife did not record it adequately. This phenomenon may vary between different types of drugs, some may be more “sensitive” than others. In order to get an estimate of the amount of non-reported antidepressants, we analyzed women who had got a prescription for antidepressants during the 2nd and 3rd month of pregnancy (the main period of organogenesis) and compared them with women who had reported the use of such drugs in early pregnancy. It then appeared that 22% of the women with a prescription had no MBR information on drug use. There may be different reasons for that discrepancy, but the dominating one is probably that the use was not adequately recorded. This means that the unexposed comparison group will contain some individuals who were actually exposed but as they are few they will hardly affect the risk in the unexposed group and therefore not affect the risk ratio estimate.

We then used the estimate of unrecorded drug exposure to estimate how large proportion of women who got prescriptions before LMP used the drugs during early pregnancy. When the analysis included prescriptions filled during one month before LMP, 17% of the women may not have used the drug during early pregnancy, if prescriptions filled during a 3-month period before LMP were included, the corresponding percentage was 43%. Inclusion of unexposed cases in the exposed group will result in a reduction of the estimated risk.

This analysis demonstrates the effect of incomplete ascertainment of exposure or of misclassification. If all exposed infants are not identified, little effect on risk estimates are

usually obtained. If a misclassification of cases occurs so unexposed cases are regarded as exposed (e.g., a prescription of a drug is recorded but the woman never used it) it will result in a bias towards no effect. When both interview and prescription information is available, interview information is preferable but in absence of interview data, prescription data are acceptable with the understanding that some underestimate of risk may occur. Preferably prescriptions filled more than one month before LMP should not be included. In the context of the Swedish Medical Birth Register, exposures during early pregnancy should mainly be based on interview data, possibly supplemented with prescriptions filled during 2nd and 3rd month of pregnancy.

For exposure during later parts of pregnancy, it is clear that prescription data are more complete than data from antenatal care. Some women who are then regarded as exposed may not be so if she did not take the drug she had bought. In the absence of interview information, the size of this error cannot be estimated. It will bias risk estimates towards null. This phenomenon may explain why women with a recorded statement of the use of an antidepressant but without any identified prescription had a lower odds ratio for neonatal complications than when a prescription was identified, supposing that the effects on the neonatal conditions actually were caused by the drugs.

Concern has been expressed that interview data on drug use could lead to mistakes in drug identification [9]. Our comparison of discrepancies between the actual drug name according to the prescription and the name reported by the woman indicated that this problem is small but could be a specific problem for two drugs with similar proprietary names, Cipramil® (citalopram) and Ciprallex® (escitalopram).

Finally, it should be stressed that different drug categories may behave differently in this type of analysis. Examples are drugs for chronic diseases, e.g., anticonvulsant use in epilepsy which are usually taken for an extended period of time. On the other hand, anticonvulsants used as mood stabilizers at bipolar disease may behave like the antidepressants studied in the present paper. Other drugs like antibiotics are usually used only during a short period and the inclusion of drugs prescribed even within one month before LMP is probably not relevant for exposure during the organogenetic period.

In conclusion, we find that antidepressant drug exposure during early pregnancy (of interest in studies of teratogenicity) is best ascertained from prospective interview data. If prescription register data are used, inclusion of prescriptions earlier than one month before LMP increases the percentages of probable non-users considerably and should be avoided. For studies of effects of drug use later in pregnancy, the best source of information is the prescription register even though identification of drug use is then probably incomplete.

Acknowledgement: The study was supported by a grant from Evy and Gunnar Sandberg Foundation, Lund to BK. The authors declare that they have no conflict of interest

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Table 1: Distribution of prescriptions for antidepressants according to trimester when the prescription was filled. [Data from the Prescribed Drugs Register.](#)

Trimester 1	Trimester 2	Trimester 3	Number	%	Among them prescriptions 12 weeks before LMP	%
Yes	Yes	Yes	1481	22	1133	77
Yes	Yes	No	549	8	407	74
Yes	No	Yes	698	10	499	71
Yes	No	No	2538	37	1530	60
No	Yes	Yes	667	10	450	67
No	Yes	No	418	6	240	57
No	No	Yes	481	7	177	37

Table 2: Identity of women who reported use of antidepressants in early pregnancy (MBR) and women who [according to the Prescribed Drug Register](#) had prescriptions for antidepressants according to different definitions (PRESC).

Time window for PRESC	No. in PRESC	No. in MBR	Both in MBR and PRESC	Total identified	% in MBR	% in PRESC
3 months before LMP-week 12	9265	4 488	4 028	9725	46	97
1 month before LMP - week 12	5692	4 488	3 484	6696	67	85
Months 2-3 of pregnancy	3153	4 488	1 891	5750	78	55

Table 3: Presence of preterm birth or a neonatal diagnosis of respiratory problems, low Apgar score, intraventricular haemorrhage, hypoglycaemia, and/or jaundice according to source of information on maternal use of antidepressant after the first trimester. [Data from MBR and from the Prescribed Drug Register](#)

Prescribed Drug Register	MBR	Preterm births	Total ^a	%	Neonatal complications	Total	%
Yes	No	164	1785	9.2	286	1842	15.5
Yes	Yes	184	2416	7.6	343	2488	13.0
No	Yes	34	629	5.4	66	679	9.9

^aSingleton infants with known gestational duration

Table 4: Odds ratio (OR) with 95% confidence interval (95% CI) comparing groups of infants according to information of maternal use of antidepressant after the first trimester.

[“Prescription” refers to Prescribed Drug Register.](#)

Groups compared	Preterm birth		Neonatal complications	
	OR	95% CI	OR	95% CI
Prescription and no MBR vs. prescription and MBR	1.10	0.84-1.44	1.20	0.97-1.49
Prescription and no MBR vs. no prescription but MBR	1.65	1.03-2.66	1.40	1.00-1.96
No prescription but MBR vs. prescription and MBR	0.64	0.42-0.97	0.85	0.62-1.17

[Odds ratio \(OR\) estimated with Mantel-Haenszel technique with adjustment for year of delivery, maternal age, parity, smoking, and body mass index. Calculation of 95% confidence intervals \(95% CI\) with Miettinen’s method.](#)

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Figure Captions

Fig. 1: Diagram showing percentage of women who get a prescription for an antidepressant related to last menstrual period (LMP)

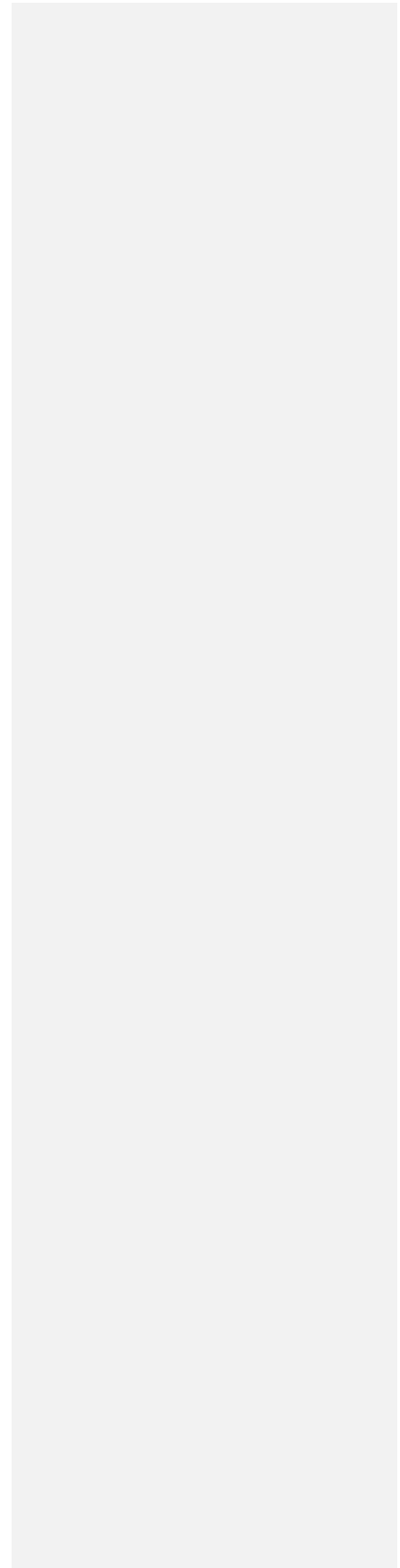


Fig. 1

