ORIGINAL RESEARCH ARTICLE

Drug Saf 2010; 33 (7): 593-604
0114-5916/10/0007-0593/$49.95/0

Drugs Dispensed in Primary Care During Pregnancy

A Record-Linkage Analysis in Tayside, Scotland

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Abstract

Background: For many regularly used drugs, evidence for safe use in pregnancy has not been established. Despite this, international studies have identified high levels of drug prescribing among pregnant women.

Objective: To investigate the patterns of prescribing of drugs to women who gave birth in Tayside, Scotland, in 2007.

Methods: Scottish maternity records were linked to dispensed prescribing data for all women who gave birth in Tayside in 2007. Drugs prescribed were coded according to the US FDA classification for risks of drugs in pregnancy. Patterns of prescribing were investigated during the 3 trimesters of pregnancy and the 3 months prior to conception.

Results: Prescribing in pregnancy was common, with 21 093 prescriptions dispensed to 3356 (85.2%) of the 3937 women. The most frequently prescribed drugs were antacids, antibacterials, oral iron, folic acid preparations and analgesics. Category A drugs (positive evidence of safety in pregnancy) and Category B drugs (some evidence of safety in pregnancy) accounted for 19.6% and 26.9% of all prescriptions dispensed, respectively.

Prescribing of Category X drugs (evidence of risk to the fetus; use contraindicated in women who are or may become pregnant) during pregnancy was rare, with 112 prescriptions dispensed to 68 women (1.7%). Most of these were oral contraceptives or sex hormones. Prescribing of Category X drugs fell markedly during the first trimester and remained very low thereafter. Category D drugs (evidence of risk to the fetus but benefits of therapy may outweigh the potential risk) [432] were dispensed to 166 women (4.2%) during pregnancy. The most commonly prescribed Category D drugs were anxiolytics, nicotine replacement therapy and antiepileptic drugs. The frequency of prescribing of Category D drugs reduced in the third trimester. Prescribing of Category C drugs (insufficient evidence to know whether they are harmful) was common. Thirty percent of women received a total of 3641 Category C

prescriptions, which accounted for 17.3% of all prescriptions issued during pregnancy. Prescribing of Category C drugs showed only a very modest decline during pregnancy. No FDA code was available for 4035 prescriptions issued (87 different items), the majority of which were for antacids and preparations for indigestion. More than 40% of women received such medications.

Conclusions: Prescribing of drugs during pregnancy was very common, but the levels of prescribing of drugs that are known to be harmful were low. Much of the prescribing was for drugs related to the pregnancy. While this study provides some evidence that primary-care prescribers in Tayside are prescribing potentially harmful drugs appropriately and with caution during pregnancy, safety data during pregnancy are unavailable for many drugs that are commonly prescribed.

Background

Despite the fear of abnormal fetal development when medications are taken during pregnancy, recent international studies have identified high levels of prescribing among pregnant women.[1-8] Clinicians are advised to prescribe the lowest effective doses possible during pregnancy.[9,10] Although the number of drugs known to be teratogenic is low,[11,12] for many regularly used drugs evidence for safe use in pregnancy has not been established.[13,14] Calls have been made to develop an effective system to identify and quantify the risks associated with drugs taken during pregnancy.[14] This poses a major challenge given that data on safety are often not based on human studies as clinical trials do not include pregnant women and animal models may not reflect the effects on the human fetus.[10,12] Observational evidence in humans may also be lacking.

There have been few studies in the UK on drug prescribing during pregnancy. However, the development of record-linkage techniques in Scotland has provided an opportunity for us to examine primary-care dispensed prescribing to women who gave birth in Tayside, Scotland, in 2007. The detailed patient-specific data available have enabled us to investigate not only the dispensing of potentially harmful drugs but also the duration and timing of prescriptions dispensed.

Methods

Data Sources and Subjects

The data resources of the Health Informatics Centre (HIC), University of Dundee, Scotland, were used in this study. HIC has developed the record-linkage of multiple, routinely collected datasets to carry out drug safety research in the population of Tayside (approximately 395 000 people). The databases are record-linked using the Community Health Index Number, a unique patient identifier that is assigned to patients when they register with a general practitioner. The Medicines Monitoring Unit (MEMO) dispensed prescribing dataset contains computerized patient-specific data on prescriptions dispensed in Tayside from January 1989.[15] For every prescription dispensed, details of drug name, dose, date of prescription and drug regimen are available.[16] The Scottish Maternity Record (SMR02) comprises data submitted by maternity hospitals to the Information and Statistics Division. It contains information on estimated gestation, outcome of pregnancy, date of delivery, previous obstetric history, parity and self-reported data on smoking status at the time of booking. A measure of social disadvantage, the Scottish Index of Multiple Deprivation (SIMD),[17] which is based on post codes, was also available for all women. In this study, SMR02 data, SIMD-derived 'deprivation scores' and prescriptions dispensed to

all women who gave birth in Tayside in 2007 were linked and analysed.

Calculation of Dates Used for the Analysis

For every woman who gave birth in Tayside in 2007, the date of the last menstrual period (LMP) was estimated using the date of delivery and estimated gestation ('number of completed weeks of pregnancy, as judged by the clinician, usually on the basis of an ultrasound measurement'),[18] as recorded on SMR02. Four time periods were then defined: a 3-month preconception period (derived LMP − 70 days to derived LMP + 14 days); first trimester (derived LMP + 14 days to derived LMP + 98 days); second trimester (derived LMP + 98 days to derived LMP + 189 days); and third trimester (derived LMP + 189 days to date of delivery).

Classification of Drugs by Risk

All drugs dispensed were classified into risk groups defined by the US FDA (table I). While the FDA has recently announced that they may cease to use this system in the future,[19] it is still often used in research.[20] *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk* by Briggs et al.[21] was used to identify the FDA category for every drug prescribed. In addition to the five categories, Briggs et al.[21] defines three further groups of drugs, indicated using an *, whose risks differ according to the duration of exposure or the trimester of use. Thus, under certain circumstances D* drugs become Category X, and B* and C* drugs become Category D.

Table I. US FDA classification of drug risk groups

Category A: Adequate, well controlled studies in pregnant women have not shown an increased risk of fetal abnormalities to the fetus in any trimester of pregnancy
Category B: Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well controlled studies in pregnant women OR animal studies have shown an adverse effect, but adequate and well controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester
Category C: Animal studies have shown an adverse effect and there are no adequate and well controlled studies in pregnant women OR no animal studies have been conducted and there are no adequate and well controlled studies in pregnant women
Category D: Adequate well controlled or observational studies in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective
Category X: Adequate well controlled or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities or risks. The use of the product is contraindicated in women who are or may become pregnant

For drugs not listed in Briggs et al.,[21] the Physician's Desk Reference[22] or the Physician's Desk Reference Nurse's Handbook[23] were consulted. The Drugs.com website[24] was used when none of these reference books contained the drug. There was a further group of prescriptions that were not mentioned in any of the sources, either because they were not licensed for use in the US or because they were non-medicinal. These were classed as 'uncoded' for drugs and 'non-pharmacological' for items such as syringes and blood testing equipment, bandages, dressings, dietary products, support stockings and homeopathic preparations. Products containing a combination of drugs were assigned to the highest risk category, irrespective of the doses of drugs in the compound. For this study, potentially harmful prescribing during pregnancy was defined as the prescribing of all Category X, D, D*, C* and B* drugs.

Specific ethical approval was not required for this study because anonymized data were used. However, permission was sought (and obtained) from the Caldicott Guardian to obtain precise dates of birth of babies born in Tayside. (The Caldicott Guardian is a senior person within the National Health Service who is responsible for protecting the confidentiality of patient information and enabling appropriate information-sharing).

Results

A total of 3937 women in Tayside gave birth in 2007 (3874 single births, 63 twin births). Almost all (97%) of the women lived in Tayside for the duration of their pregnancy. Twenty-three babies were stillborn. No woman gave birth more than once during 2007. Age at conception ranged from

Table II. Characteristics of the study population (n = 3937)

Characteristic	No. of women (%)
Age at conception (y)	
<20	438 (11.1)
20–24	875 (22.2)
25–29	1042 (26.5)
30–34	977 (24.8)
≥35	605 (15.4)
Parity	
0	1285 (32.6)
1	884 (22.5)
≥2	470 (12.0)
Not known	1298 (33.0)
Deprivation score	
1–3 (affluent)	863 (21.9)
4–8	1830 (46.4)
9–10 (deprived)	1090 (27.7)
Not known	154 (3.9)
Current smoker	
Yes	592 (15.0)
No	2895 (73.5)
Not known	450 (11.4)
Estimated gestation (wk)	
<37	290 (7.4)
37–40	2584 (65.6)
>40	1063 (27.0)

14 years to 48 years (median 28 years). Median parity was 1 (range 0–8). The characteristics of the study population are presented in table II.

Summary of Prescribing

Overall, 21 093 prescriptions were dispensed during pregnancy to 3356 of the 3937 women (85.2%). The drugs most commonly prescribed in pregnancy were antacids (13.5% of all prescriptions dispensed), antibacterials (10.6%), oral iron (8.9%), folic acid preparations (6.8%) and analgesics (5.7%). These were dispensed to 29.8%, 35.0%, 34.3%, 30.0% and 15.2% of all women, respectively. Other commonly prescribed drugs were topical preparations for vaginal and vulval infection (5.5% of prescriptions), topical anti-infective agents (2.6%), drugs for nausea (3.2%), laxatives (2.9%) and topical corticosteroids (2.6%), which were dispensed to 18.3%, 11.3%, 10.3%, 10.1% and 10.1% of women, respectively. A few women (2.4%) received folic acid preparations only. It is important to note that this does not reflect all folic acid/iron use during pregnancy as many women in Scotland obtain folic acid and/or oral iron over the counter from pharmacies.

Prescribing by US FDA Category

Category A drugs (positive evidence of safety in pregnancy) and Category B drugs (some evidence of safety in pregnancy) accounted for 19.6% and 26.9% of all prescriptions dispensed, respectively (figure 1). This includes folic acid and oral iron, both of which are Category A but are shown separately in figure 1. Category C drugs, for which there is little evidence of safety, accounted for 17.3% of all prescriptions dispensed, with 3641 Category C prescriptions dispensed to 1183 women (30%) [table III]. Few prescriptions for Category D and X drugs (evidence of risk to the fetus) were dispensed. Of the 3937 women, 68 (1.7%) received 112 prescriptions

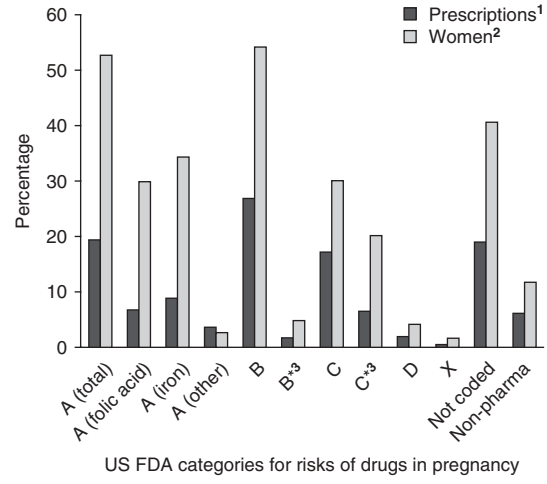

Fig. 1. Categorization of prescriptions dispensed to 3937 pregnant women (see table I and Classification of Drugs by Risk section in the text for definitions of US FDA categories for risks of drugs in pregnancy). **1** Number of prescriptions dispensed as a percentage of all prescription items. **2** Number of women receiving prescribed item as a percentage of all women. **3** * denotes that risks differ according to the duration of exposure or the trimester of use. **Folic acid** = preparations containing folic acid only and folic acid plus oral iron; **Non-pharma** = non-pharmacological items.

Table III. Prescriptions dispensed to the 3937 women who gave birth in 2007 grouped by US FDA category of risk in pregnancy[a]

FDA Category	No. of prescriptions (no. of women)				
	preconception	first trimester	second trimester	third trimester	total during pregnancy
Category X	326 (290)	97 (59)	4 (3)	11 (9)	112 (68)
Category D*[b]	2 (1)				
Category D	201 (113)	168 (100)	167 (82)	97 (51)	432 (166)
Category C*[b]	381 (278)	329 (247)	487 (366)	565 (384)	1 381 (795)
Category B*[b]	226 (147)	119 (76)	130 (71)	155 (99)	404 (194)
Category C	1440 (702)	1337 (686)	1198 (572)	1106 (550)	3 641 (1183)
Category B	1079 (703)	1504 (935)	2116 (1213)	2051 (1173)	5 671 (2128)
Category A	169 (83)	260 (93)	284 (95)	254 (96)	798 (108)
Oral iron (Category A)	18 (15)	69 (63)	272 (219)	1528 (1223)	1 869 (1351)
Folic acid/folic acid plus oral iron (Category A)	57 (51)	1065 (1011)	138 (109)	244 (206)	1 447 (1180)
Not coded (no FDA Category given)	359 (248)	538 (416)	1282 (803)	2215 (1099)	4 035 (1598)
Non-pharmacological items[c]	215 (100)	313 (150)	414 (216)	576 (252)	1 303 (459)
Total	4473 (1567)	5799 (2139)	6492 (2084)	8802 (2695)	21 093 (3356)

a See table I and Classification of Drugs by Risk section in the text for definitions of US FDA categories of risks of drugs in pregnancy.

b * denotes that risks differ according to the duration of exposure or the trimester of use.

c Syringes, blood testing equipment, bandages, dressings, support stockings, dietary products, homeopathic products.

for Category X drugs, while 166 women (4.2%) received 432 Category D prescriptions.

For 4035 prescriptions dispensed (87 different items), no category had been assigned by the FDA. 1598 women (40.6%) received such uncoded drugs, many of which were for products that are available over the counter. More than 70% of the uncoded items were antacids and other preparations for indigestion. Another 4% were for bulk forming or osmotic laxatives and 3% for anaesthetic haemorrhoidal preparations. Other products included mouthwashes, nasal decongestants, cough linctus and topical preparations such as ear drops, artificial tears and coal tar preparations for dermatological problems. Only a few preparations were for drugs not available in the US, e.g. the antibacterial flucloxacillin (122 prescriptions) and the antidepressant lofepramine (21 prescriptions).

Trends in Dispensing of Drugs by Risk Category During Pregnancy

The prescribing of categories of drugs during the different time periods is summarized in table III. The numbers of Category A and B drugs dispensed increased as the pregnancy progressed. Patterns of prescribing for folic acid and oral iron (Category A) were as might be expected: high prescribing of folic acid in early pregnancy and of iron in the third trimester.

Category C prescribing fell very modestly during pregnancy. The number of Category D drugs dispensed was lower in the third trimester than in the first two trimesters (table III). For drugs assigned Category D status under certain circumstances (Categories B* and C*), prescriptions dispensed initially fell from the preconception period then increased as pregnancy progressed. In contrast, the number of Category X drugs dispensed fell markedly from the preconception period to the third trimester. More than 86% of all Category X drugs dispensed during pregnancy were in the first trimester. Furthermore, when the timing of prescriptions dispensed was examined in relation to the date of conception, almost all were dispensed very early in the first trimester (figure 2). The prescribing of Category D drugs within the first trimester showed a much more modest decrease than Category X drugs. Prescribing of drugs that were not assigned to a category, mainly antacids, increased greatly in the second and third trimesters.

Types of Potentially Harmful Drugs Dispensed During Pregnancy

The types of Category X and D drugs dispensed and the FDA recommendations for their use during pregnancy are summarized in table IV. Contraceptives accounted for 40% of the Category X prescriptions dispensed during pregnancy. Almost all Category X drugs, with the exception of temazepam, were dispensed during the first trimester. Two women were given HMG-CoA reductase inhibitors (statins) during the first trimester and one woman whose prescription for a statin was dispensed in the preconception period was given sufficient medication to last into the first trimester if the medication was taken as directed. The remaining Category X prescriptions were for sex hormones, all of which (except one) were dispensed early in the first trimester. These included medroxyprogesterone, estradiol, norethisterone and clomifene. Although we do not know the indication for the prescriptions given to individual women, these drugs are used to treat infertility, endometriosis, dysfunctional bleeding and dysmenorrhoea, and are also used in hormone replacement therapy.

The most frequently prescribed Category D drugs were anxiolytics, particularly diazepam (which may present a risk of congenital defects in the fetus in the first trimester and neonatal withdrawal syndrome in the third trimester)[21] [table IV]. In addition to prescriptions of anxiolytic drugs dispensed during these trimesters, 25 women were given enough medication during the pre-pregnancy period or second trimester to last into the subsequent trimester, which was deemed to be 'at risk'. Nicotine replacement therapy was dispensed to 94 women during pregnancy, more often in the first and second trimesters. Prescribing of drugs for epilepsy remained stable throughout pregnancy. Two women received a prescription for a Category D drug that the FDA specified as contraindicated: one received a gonadorelin (gonadotropin-releasing hormone) analogue and one received tetracycline (contraindicated in the second and third trimesters).

Category C* and B* drugs, assigned Category D status under certain circumstances, were more commonly dispensed during pregnancy than Category D drugs (table III). Prescriptions dispensed during the 'at risk' periods are indicated in bold in table V. For drugs where there is risk if used near term, the number of women dispensed prescriptions after 36 weeks gestation are indicated in the third trimester column. Finally, the number of women who received more than one

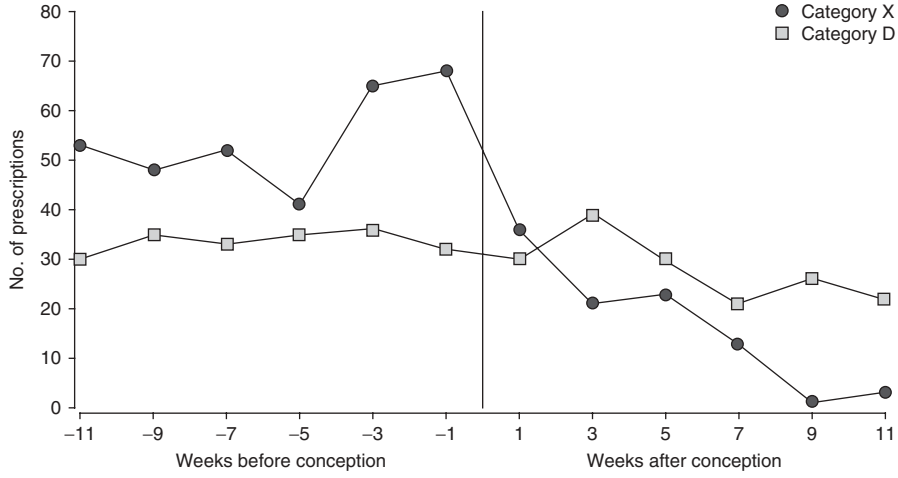

Fig. 2. Prescriptions issued during the 3 months before and after conception. Categories represent US FDA categories for risks of drugs in pregnancy (see table I for definitions).

Table IV. US FDA Category X and Category D drugs prescribed to the 3937 women who gave birth in 2007[a]

Drug category/FDA recommendation	No. of prescriptions (no. of women)				
	preconception	first trimester	second trimester	third trimester	total during pregnancy
Category X					
Contraceptives: contraindicated	269 (251)	40 (38)	1 (1)	4 (4)	45 (43)
Sex hormones: contraindicated	42 (36)	36 (15)		1 (1)	37 (15)
HMG-CoA reductase inhibitors (statins): contraindicated	1 (1) 1 cross over	3 (2)			3 (2)
Temazepam: animal data suggest risk	12 (5)	18 (4)	3 (2)	6 (4)	27 (8)
Category D					
Gonadorelin (gonadotropin-releasing hormone) analogue: contraindicated			1 (1)		1 (1)
Tetracyclines: contraindicated – second and third trimesters	40 (36)	2 (2)	1 (1)		3 (3)
Anxiolytics: risk in first and third trimesters	89 (38) 18 cross over	59 (30)	61 (20) 7 cross over	31 (12)	151 (43)
Nicotine replacement therapy	27 (21)	61 (49)	55 (40)	21 (18)	137 (94)
Antiepileptics: human data suggest risk	15 (6)	13 (7)	11 (5)	11 (5)	35 (7)
Antiproliferative immunosuppressants: human and animal data suggest risk	4 (3)	8 (3)	11 (5)	8 (3)	27 (5)
Antithyroid drugs: human data suggest risk	1 (1)	4 (3)	2 (1)	1 (1)	7 (3)
β-Adrenoceptor antagonists: risk in second and third trimesters	6 (4)	2 (2)	3 (1)	1 (1)	6 (4)
Anti-mania drugs: human data suggest risk	1 (1)	1 (1)	1 (1)	1 (1)	3 (2)
Quinine sulphate: human data suggest risk				1 (1)	1 (1)

a See table I and Classification of Drugs by Risk section for definitions of US FDA categories of risks of drugs in pregnancy.

Cross over = woman was given enough medication to last into the subsequent trimester.

prescription for a drug that presented risks with prolonged use is indicated in italics in the right hand column of table V. Topical corticosteroids, classed as C* 'at risk' during the first trimester, were the most frequently prescribed and were given to 133 women during the first trimester. Oral corticosteroids were given to 19 women in the first trimester. A further two women issued with prescriptions before conception may have taken oral corticosteroids in the first trimester if all the medication issued was taken as prescribed. Analgesics containing opioids are assigned category D if used for prolonged periods or in high doses at term. The Category C* non-opioid analgesics (containing low-dose codeine) were the most frequently prescribed, with 80 women receiving more than one prescription during pregnancy and 45 receiving prescriptions close to term.

Lack of Evidence of Safety

More than 17% of drugs dispensed to pregnant women were Category C drugs, for which there is a lack of evidence on risks to the fetus. The most commonly dispensed Category C drugs were salbutamol, prochlorperazine, beclometasone, fluticasone propionate and fluoxetine. These drugs accounted for more than half of all Category C drugs issued during pregnancy.

Prescriptions Issued to Women with Stillbirths

A total of 94 prescriptions were issued during pregnancy to 19 of the 23 women who had stillbirths. In addition, 32 prescriptions were issued during the preconception period to nine of the women who had stillbirths. No Category D or Category X drugs were issued to any of these women during pregnancy or the preconception period.

Table V. US FDA Category C* and Category B* drugs prescribed to the 3937 women who gave birth in 2007[a]

Drug category/FDA recommendation	No. of prescriptions (no. of women)				
	preconception	first trimester	second trimester	third trimester	total during pregnancy
Category C*[b]					
Topical corticosteroids: category D in first trimester	146 (123)	**162 (133)**[c]	243 (199)	282 (219)	687 (465)
Oral corticosteroids: category D in first trimester	27 (19) **2 cross over**[c]	**27 (19)**[c]	30 (20)	17 (12)	74 (38)
Non-opioid analgesics (low-dose codeine): category D if used for prolonged periods or in high doses at term	122 (94)	102 (76)	186 (141)	245 (158) **45 near term**[c]	533 (311) *80 >1 prescription*[d]
Opioid analgesics: category D if used for prolonged periods or in high doses at term	8 (8)	14 (12)	7 (7)	14 (12) **8 near term**[c]	35 (28) *2 >1 prescription*[d]
β-Adrenoceptor antagonists and ACE inhibitors: category D in second or third trimesters	29 (20)	16 (12) **2 cross over**[c]	**7 (4)**[c]	**6 (3)**[c]	29 (16)
NSAIDs: category D in third trimester or near delivery	31 (27)	2 (2)	2 (2) **1 cross over**[c]	**1 (1)**[c]	5 (4)
Category B*[b]					
Non-opioid analgesics (dihydrocodeine): category D if used for prolonged periods or in high doses at term	58 (37)	32 (20)	40 (32)	42 (28) **10 near term**[c]	114 (66) *15 >1 prescription*[d]
Opioid analgesics: category D if used for prolonged periods or in high doses at term	38 (18)	34 (15)	38 (14)	41 (37) **24 near term**[c]	113 (55) *11 >1 prescription*[d]
NSAIDs: category D in third trimester or near delivery	97 (88)	30 (29)	2 (2) **1 cross over**[c]	**5 (4)**[c]	37 (35)
Methadone: category D if used for prolonged periods or in high doses at term	22 (8)	16 (9)	41 (15)	59 (23) **10 near term**[c]	116 (26) *23 >1 prescription*[d]
Rubefacients and other topical anti-rheumatics: category D in third trimester or near delivery	5 (5)	3 (3)	7 (7)	**8 (8)**[c]	18 (18)

a See table I and Classification of Drugs by Risk section in the text for definitions of US FDA categories of risks of drugs in pregnancy.

b * denotes that risks differ according to the duration of exposure or the trimester of use.

c Bold denotes dispensed during 'at risk' periods.

d Italics denotes women given more than one prescription for a drug that presented risks with prolonged use.

Cross over = woman was given enough medication to last into the subsequent trimester.

Discussion

The majority of women included in this study (85.2%) received prescription drugs during pregnancy, although much of the prescribing was for conditions associated with pregnancy. Prescribing of drugs known to be harmful was very low, with 1.7% of women receiving Category X drugs, most of which were dispensed early in the first trimester. Category D drugs were given to 4.2% of women during pregnancy. Drugs where the risks to the fetus are unknown accounted for more than one-third of all prescriptions issued (17.3% were Category C drugs and almost 20% were for drugs not assigned to an FDA category).

These levels of dispensed prescribing are consistent with the findings of recent studies on prescribing during pregnancy. Most studies from developed countries report low levels of prescribing of potentially harmful drugs to women during pregnancy, but there is considerable variation.[2-4,8,20,25-29] Some differences may be attributable to differences in study design or methodology. However, studies using the FDA classification show levels of Category X prescribing during pregnancy ranging from 0.4% of women in one US study[28] to 3.9% in a recent Canadian study.[26] Levels of Category D prescribing are slightly higher, with the majority of studies reporting that between 2%[2] and 5%[26] of women had received Category D drugs. In contrast, a French study found that 59% of women had received a Category D drug during pregnancy.[8] Two European studies that used different classification systems also reported much higher levels of potentially harmful prescribing: a study from Finland reported that 20.4% of women received potentially harmful drugs,[30] and a Danish study found that 17.8% of women had been exposed to drugs with ''proven or anticipated harmful effects during pregnancy.''[31] Many Category D drugs are essential for the management of chronic diseases, e.g. drugs for the control of epilepsy, anti-thyroid drugs and antimania drugs. Thus, the benefits of the drug to the mother may outweigh the harm to the fetus. Clinicians should attempt to prescribe the lowest possible dose of medication, whilst also ensuring that the fetus is not threatened because the mother's disease is not adequately managed.[9]

Several studies have shown that the prescribing of potentially harmful drugs falls from the preconception period through pregnancy,[3,26,27,30,31] but we have taken the analysis further. Our study reveals that most of the Category X prescribing occurred very early in the first trimester, suggesting that prescriptions were dispensed before the women knew they were pregnant. It appears that prescribing of Category X drugs reduces rapidly after pregnancy recognition and remains extremely low thereafter. The reduction in prescribing of Category D drugs was less marked, probably because these drugs were required to manage chronic conditions.[29] Some studies may overestimate harmful prescribing if the prescriptions are written before the clinician or the mother is aware of the pregnancy.

This study has found that the total number of prescriptions increases progressively from preconception through the three pregnancy trimesters. This increase is primarily due to Category A and B drugs. These findings are consistent with those of several other European studies that show an overall increase throughout pregnancy, particularly for Category A drugs.[2,3,7,31,32] The one study from the US that presented data on trends found that total prescriptions fell across pregnancy.[27]

To our knowledge, our study is unique in investigating separately instances where Briggs et al.[21] assign drugs to different FDA categories according to the duration of exposure or the trimester of use. Drugs in these categories (B* and C*), which move to Category D, include corticosteroids, analgesics containing opioids, methadone, NSAIDs, β-adrenoceptor antagonists and ACE inhibitors. Our study found that analgesics containing codeine were often dispensed close to term and topical corticosteroids were commonly prescribed during the first trimester – the periods assigned as at risk. These conditions make the safe prescribing of these drugs more challenging, given that clinicians need to be aware of the specific trimesters at risk. Ambiguity about trimester dates could also add to the uncertainty.

There is a risk that medication dispensed during a safe period will continue to be taken during an at-risk trimester. An important strength of our study was the opportunity to investigate this. We identified a few drugs, particularly anxiolytics, that were dispensed in sufficient amounts to be taken during an at-risk trimester (although the analysis depends on accuracy of dates and assumes that women take all of the drug as directed). This indicates a need for caution when issuing prescriptions to any women of childbearing age,[2] particularly as only about 60% of pregnancies are actively planned.[10,33]

A major problem highlighted by our study is that for many drugs prescribed during pregnancy there is a lack of evidence on possible adverse effects to the fetus. We found that 30% of women received Category C drugs (17.3% of all prescriptions issued). In contrast to Category X and D prescribing, the number of Category C drugs issued declined very little during pregnancy. Many published papers focus on Category X and D drugs only, but the majority of those that present data on Category C drugs report substantial levels of prescribing.[2,3,6,8,25,26] One author has suggested that up to two-thirds of all drugs prescribed in the US are Category C.[13] It could be argued that there is a lack of evidence for safety for most Category C drugs and for some Category B drugs (where the evidence is derived from animal studies only). However, some of these drugs were given as topical preparations, which may carry a lower risk. For example, with topical corticosteroids, which were frequently dispensed to women in this study, the doses reaching the fetus will be low.

Many drugs that have not been assigned to an FDA Category are also used during pregnancy. In our study, almost one-fifth of all prescriptions dispensed could not be coded despite using multiple compendia of drug coding,[21-24] with over 40% of women being exposed to such drugs during pregnancy. Another study reported that 78.9% of women received drugs that were uncoded,[8] while a Danish study that used the Swedish classification system reported that 28.7% of prescriptions issued were not classified.[31] In the present study, many of the prescriptions for uncoded drugs were for products that are available to buy over the counter.

The frequency with which drugs with no evidence of safety are used highlights the need for drug safety studies for drugs in common usage.[6,13] Lack of evidence may encourage manufacturers to use disclaimers stating that safe use of a drug during pregnancy has not been established and therefore should be avoided in pregnancy. Such statements may not indicate that the drugs are teratogenic but just lack safety data. Thus, appropriate prescribing may be hampered and could lead to insufficient medication or important medication being denied to pregnant women and women of childbearing age.[12,13,34]

Strengths and Limitations

This study has demonstrated the value of linked administrative data that are routinely collected for other purposes to answer specific research questions. When analysed appropriately, they represent a useful resource enabling research that is less costly than the collection of primary data. A particular strength of this design is that exposure is based on medications dispensed in pharmacies rather than on patient recall. However, the lack of information on the indications for the drugs dispensed and on co-morbidity among pregnant women is a limitation of this particular study.

Data used in this study relate to drugs that were dispensed at community pharmacies. The numbers of instances of potentially harmful prescribing by clinicians may therefore be underestimated if some women did not redeem their prescriptions. However, the converse may be true and potentially harmful prescribing may be overestimated if some women who obtained the drugs did not take them.

The study population included women who had a live birth or stillbirth in Tayside in 2007. Women who had spontaneous abortions or terminations were not included. Whether such women have different patterns of dispensed prescribing is unknown. Complete data were not available for women who moved into Tayside during their pregnancy as only prescriptions

dispensed to Tayside residents were available. This will have resulted in an underestimation of prescribing, becoming less marked as duration of the pregnancy increases. However, as the number of such women was low (3%), the effect would be very small.

This study relies upon the accuracy of the MEMO dispensed prescribing database. It is possible that individual instances of seemingly inappropriate prescribing to a pregnant woman (e.g. oral contraceptives during the second or third trimester) are errors in the dataset. However, the error rate is known to be low (<1%) and is continually monitored.

This study used the FDA classification that was not specifically designed to identify teratogenic risk, although it is used to identify potential harmful prescribing in pregnancy. Another limitation is that the FDA has recently announced that they may cease to use the current classification system for drug risk in pregnancy in the near future.[19] However, the FDA categories were still being used when these drugs were being prescribed. Possibly a different classification system would produce slightly different results, although it would be based on the same scientific evidence of the harm of drugs in pregnancy. Use of the existing classification system enables us to compare our findings with previously published studies.

Conclusions

This study shows that although prescribing of drugs during pregnancy is very common, the levels of prescribing of drugs that are known to be potentially harmful (Category D and X) were very low. While there were some instances of such prescribing, detailed analysis suggests that most would be for prescriptions for chronic conditions where the benefits to the mother could outweigh the potential risk to the fetus. Such instances also declined during the first trimester, suggesting that many may have occurred before the pregnancy was recognized.

The study has also shown that safety data during pregnancy are unavailable for many of the drugs that are commonly prescribed to pregnant women. These include some Category B drugs (where the evidence is derived from animal studies only) and Category C drugs. This highlights the need for drug safety studies for medications that are commonly used in pregnancy despite the lack of safety data.

Acknowledgements

This study was funded by a research grant from the Chief Scientist Office of the Scottish Health Department (CZG/2/338). The study design was peer reviewed for the funding organization prior to funding being awarded. Neither the funding organization nor the sponsor (University of Dundee) had any role in the conduct of the study, analysis or interpretation of the data, or in the preparation, review or approval of this manuscript. We acknowledge the staff of the Health Informatics Centre, University of Dundee, for providing the data. The authors have no conflicts of interest that are directly relevant to the content of this study.

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