Eur J Clin Pharmacol (2008) 64:1125–1132
DOI 10.1007/s00228-008-0546-y

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Prescription drug use during pregnancy: a population-based study in Regione Emilia-Romagna, Italy

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Received: 16 May 2008 / Accepted: 15 July 2008 / Published online: 7 August 2008

Abstract
Purpose Drug utilization studies in pregnant women are crucial to inform pharmacovigilance efforts in human teratogenicity. The purpose of this study was to estimate the prevalence of prescription drug use among pregnant women in Regione Emilia-Romagna (RER), Italy.
Methods We conducted a retrospective prevalence study using data from the RER health care database. Outpatient prescription drug data were reconciled for RER residents who delivered a baby in a hospital between January 1, 2004 and December 31, 2004. Drug data were stratified by trimester of use, pregnancy risk categorization, and anatomical classification.
Results Among the 33,343 deliveries identified in 2004, 70% of women were exposed to at least one prescription medication during pregnancy and 48% were exposed to at least one prescription medication after excluding vitamin and mineral products. Many of the most commonly used medications were anti-infectives, such as amoxicillin, fosfomycin, and ampicillin. Nearly 1% of women were exposed to drugs contraindicated (i.e., category X) in pregnancy, including 189 women (0.6%) who received these drugs during the first trimester. Several statin medications were among the most common contraindicated drug exposures.
Conclusion A large proportion of women who gave birth in RER in 2004 were exposed to prescription medications. Approximately 1 in 100 women were exposed to contraindicated drugs. The most commonly identified drug exposures can help focus pharmacoepidemiologic efforts in drug-induced birth defects.

Keywords Pregnancy · Drug use · Utilization · Pharmacoepidemiology · Pharmacovigilance · Safety

This work was presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 13th Annual International Meeting, Toronto, Ontario, Canada, May 2008.

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Introduction

Clinical trials in drug development generally exclude pregnant women for ethical reasons but leave questions about the safety of new medications on the developing human fetus unanswered upon drug approval and marketing. Despite lingering safety questions, pregnant women may intentionally or inadvertently be exposed to various prescription drugs for pregnancy and nonpregnancy indications. Post-marketing observational studies have revealed associations between many commonly used drugs and various birth defects [1–3]. Current utilization studies that ascertain the most commonly used drugs in pregnancy are important for establishing priorities in birth-defects research with major public health implications [4].

Studies conducted among pregnant women in the U.S. and in some European countries document high rates of exposure to prescription medications, including exposure to medications with known teratogenic potential [5–17]. Engeland and colleagues found that among more than 100,000 pregnant women in Norway in 2004–2006, approximately 57% received a prescription medication [5]. Similarly, Andrade and colleagues found that among more than 150,000 deliveries in the U.S., nearly two-thirds of women received a prescription drug during the pregnancy period, including approximately 5% who received a drug with a U.S Food and Drug Administration (FDA) category X designation, which is reserved for those drugs for which risks of fetal harm outweigh any possible benefit [6].

Country-specific utilization patterns cannot be reliably extrapolated to other countries since utilization patterns differ widely by geography because of differences in drug approval policies, prescribing patterns, and pricing and reimbursement policies. Additionally, utilization patterns differ temporally within countries because drugs are continually added to or removed from markets, and safety and efficacy information and concerns change constantly [4].

Little is know about current drug use during pregnancy in Italy. In 2000, Donati and colleagues published a study based on interviews with women to record data on drugs used during pregnancy [18]. As Olesen and colleagues point out, women may not always disclose use of all drugs during pregnancy [19] so the accuracy of interview-based utilization records is questionable. Despite limitations of their own, automated databases are valuable for research on drug utilization in pregnancy because they can provide detailed prescription information collected prospectively for large numbers of pregnant women [4].

The aim of this study was to provide an updated estimate of the magnitude of prescription drug exposure during pregnancy in Italy, using the Regione Emilia-Romagna (RER) health care database and to describe the extent to which pregnant women are exposed to drugs with potential for fetal harm.

Methods

Data source

The RER database is a population-based longitudinal health care database for the entire region of approximately 4 million RER inhabitants. Since 2000, this comprehensive automated database has prospectively captured information on services rendered in various health care settings, such as hospital discharge abstract data, including diagnosis and procedure codes, admission and discharge dates, and payments based on diagnosis-related groups; and individual prescription-level outpatient pharmacy data. The pharmacy data include records for all drugs reimbursed by the Italian National Health Service (NHS). Data from each file (e.g., hospital discharge abstract data and outpatient pharmacy data) are linkable via anonymized unique patient identifiers.

Study subjects

Only individuals who were RER residents for a full year prior to delivery, and thus had data available in the RER database for this period, were eligible for inclusion in this study. Female residents of RER who delivered a baby in a hospital between January 1, 2004, and December 31, 2004 were identified using inpatient data as those individuals with a recorded International Classification of Diseases-9th revision (ICD-9) code indicating delivery. The first record of any one of these codes was taken as the date of delivery as this was the first available evidence to confirm the commencement of delivery. If a woman delivered more than once during the study period, data for only the first delivery were included in the analysis.

The Chronic Condition Drug Group (CCDG) method was used to identify the most common medical conditions afflicting the cohort of study subjects prior to pregnancy [20]. Adapted from the Chronic Disease Score classification modified by Clark and colleagues [21], CCDGs utilize pharmacy dispensing data to identify up to 31 different common chronic conditions. We tabulated CCDGs in this cohort using pharmacy dispensing data for 1 year prior to the defined date of the beginning of gestation, which is described below. CCDGs were originally developed in the same database as used in this study and have been used to identify chronic disease burden in other published studies [22, 23].

Drug exposure ascertainment

We used the delivery-date algorithm described and used by Andrade and colleagues [6, 7] and validated by Toh and colleagues [24] to define the first day of the exposure period as a proxy for the first day of gestation. In doing so, we linked the cohort of women with deliveries in 2004 from the hospital data file with outpatient pharmacy data and reconciled outpatient prescription drug use in the 360 days prior to the delivery date. We then stratified this gestational period into three 90-day intervals corresponding to trimesters of pregnancy and one 90-day period before pregnancy (i.e., the period between 360 and 271 days before delivery). Pregnancies with abortive outcomes, including both spontaneous and elective abortions, were not considered in this analysis because the pregnancy period would almost certainly be less than 270 days.

Drugs dispensed during each 90-day interval were classified by anatomical group, according to the World

Health Organization Collaborating Centre for Drug Statistics Methodology Anatomical Therapeutic Classification/ Defined Daily Dose (ACT/DDD) System 2006 [25] and by pregnancy risk category, according to the U.S. FDA pregnancy risk classification system (A, B, C, D, and X; Table 1). FDA risk categories were identified by one investigator (J.G.) by reviewing each drug's U.S. product label. If the FDA risk classification category was not specified in the product labeling, the category assigned by Briggs and colleagues [26] was used. If a product label with a corresponding FDA risk classification could not be identified and the drug was not listed in the guide by Briggs and colleagues, then the Australian risk classification system [27] was used (Table 1), as suggested by Amann and colleagues [28]. The Briggs classification system and the Australian risk classification system use A, B, C, D, and X categories similar to those of the FDA system. Drugs that could not be identified by any of these resources were considered not classified. If the product labeling indicated different FDA risk classification categories according to trimester of use (e.g., angiotensin-converting enzyme inhibitors), then the drug classification reflected the corresponding trimester of use in the analysis stratified by risk category. Prescription drugs not reimbursed by the Italian NHS (e.g., most anxiolytics), as well as nonprescription drugs (e.g., over-the-counter medications) and complementary medicines (e.g., herbal preparations), are not captured by the RER database and, thus, were not included in this analysis.

This study was approved by the Institutional Review Board of Thomas Jefferson University, Philadelphia, PA.

Results

We identified 33,343 deliveries during the 1-year study period. The mean age of these women was 32 years and the majority of women (86%) were between ages 25 and 39. The most common chronic conditions afflicting these women prior to pregnancy were thyroid disorders (4.3% of women), cardiovascular diseases (2.6%), and psychiatric conditions (2.4%). For 70% of deliveries (n=23,480), at least one prescription medication was filled during the pregnancy period (Table 2). In 48% of deliveries (n= 16,007), at least one prescription drug other than a vitamin and mineral product was dispensed during the pregnancy period. Women who received at least one medication received an average of 2.8 drug dispensings and 1.8 compounds with unique ATC codes during pregnancy. A total of 13,577 women (41% of entire cohort) received at least one drug in the first trimester, while 49% (n=16,364)

Table 1 Descriptions of pregnancy risk classification systems

Category	U.S. FDA and Briggs Risk Classification in Pregnancy[a]	Australian Categorisation of Risk of Drug Use in Pregnancy[b]
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester; possibility of fetal harm appears remote.	Drugs that have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
B	Either animal studies do not indicate a risk to the fetus, and there are no controlled studies in women; or animal studies have shown an adverse effect, but controlled studies in women failed to demonstrate a risk.	Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
C	Either animal studies indicate a fetal risk, and there are no controlled studies in women; or studies in women and animals are not available.	Drugs that, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
D	There is positive evidence of fetal risk, but the benefits may be acceptable despite the risk.	Drugs that have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
X	There is definite fetal risk based on studies in animals or humans or based on human experience, and the risk clearly outweighs any possible benefit.	Drugs that have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Note: The Briggs classification system is identical to the FDA system but classifies additional drugs not classified by FDA [26]. In the Australian categorization, the allocation of a B category does not imply greater safety than the C category. Drugs in category D are not absolutely contraindicated in pregnancy (e.g., anticonvulsants). Moreover, in some cases the 'D' category has been assigned on the basis of 'suspicion'

[a] Source: Federal Register [34] and Briggs 2005 [26]

[b] Source: Therapeutic Goods Administration [27]

Table 2 Demographics and characteristics of Regione Emilia-Romagna, Italy, residents who delivered a baby in 2004 (n=33,343)

Characteristic	Number (%)[a]
Age[b]	
<20	387 (1.2)
20–24	2,609 (7.8)
25–29	8,078 (24.2)
30–34	12,905 (38.7)
35–39	7,804 (23.4)
40–44	1,497 (4.5)
≥45	61 (0.2)
Most common chronic conditions	
Thyroid disorders	1,012 (3.0)
Cardiovascular diseases	608 (1.8)
Psychiatric diseases	553 (1.7)
Gastrointestinal diseases	529 (1.6)
Chronic respiratory illnesses	512 (1.5)
Inflammation/rheumatologic conditions	297 (0.9)
Anemia	212 (0.6)
Migraine	200 (0.6)
Diabetes	178 (0.5)
Epilepsy	132 (0.4)
At least 1 drug exposure during pregnancy (including prescription vitamins and minerals)	23,440 (70.3)
At least 1 drug exposure during pregnancy (excluding prescription vitamins and minerals)	16,007 (48.0)

[a] Percentages may not sum to 100 due to rounding
[b] Age missing for 2 subjects

received at least one drug in the second trimester, and 59% (n=19,669) received at least one drug in the third trimester.

The most commonly prescribed single chemical entity during pregnancy was iron, with more than one-third of women having been prescribed one of the various formulations of iron supplements (Table 3). Of the 25 most commonly dispensed entities, 9 were oral anti-infectives – amoxicillin, fosfomycin, ampicillin, azithromycin, clarithromycin, erythromycin, cefixime, ciprofloxacin, and spiramycin (Table 3). Female reproductive hormones, such as progesterone (7%, n=2,222), were also commonly prescribed.

Based on anatomical groupings, drugs used for conditions of the blood and blood-forming organs were observed in the highest proportion of women (41%). Other groups accounting for large numbers of dispensings included anti-infectives for systemic use (37%), drugs for conditions related to the alimentary track and metabolism (13%), and drugs for the genitourinary system and sex hormones (12%; Table 4).

Using a combination of the FDA, Briggs, and Australian classification systems, we determined that 49% of women (n=16,482) received a drug from category A; 48% (n=15,935) received a drug from category B; 19% (n=6,476) received a drug from category C; 2% (n=508) received a drug from category D; 1% (n=292) received a drug from category X, and 7% (n=2,207) received a drug that could not be classified during pregnancy (Fig. 1).

The most commonly dispensed category D drugs are listed in Table 5 and include atenolol (48 deliveries), carbamazepine (41 deliveries), and phenobarbital (33 deliveries). Three of the top six most commonly dispensed

Table 3 Most common prescription drug exposures during pregnancy in Regione Emilia-Romagna, Italy, 2004 (n=33,343)

Drug	Dispensings (n)	Deliveries, n (%)
Iron supplements (various formulations)	18,099	12,019 (36.0)
Amoxicillin (alone and with clavulanate)	6,169	5,223 (15.7)
Fosfomycin	3,088	2,620 (7.9)
Progesterone	4,983	2,222 (6.7)
Beclometasone	1,556	1,347 (4.0)
Ordinary salt combinations (i.e., antacids)	1,569	1,113 (3.3)
Levothyroxine sodium	3,093	1,047 (3.1)
Ampicillin	1,186	1,045 (3.1)
Aliginic acid	1,397	927 (2.8)
Ritodrine	1,827	876 (2.6)
Azithromycin	694	628 (1.9)
Magaldrate	798	584 (1.8)
Folic acid	1,019	532 (1.6)
Salbutamol	761	522 (1.6)
Betamethasone	451	379 (1.1)
Calcium supplements (various formulations)	495	364 (1.1)
Acetylsalicylic acid	515	310 (0.9)
Clarithromycin	342	310 (0.9)
Nifedipine	570	270 (0.8)
Erythromycin	300	241 (0.7)
Cefixime	254	232 (0.7)
Ciprofloxacin	247	215 (0.6)
Insulin (various formulations)	406	207 (0.6)
Hydroxyprogesterone	809	202 (0.6)
Spiramycin	1,106	185 (0.6)
Metoclopramide	214	179 (0.5)
Chorionic gonadotrophin	336	173 (0.5)
Fluconazole	189	173 (0.5)
Enoxaparin	1,001	172 (0.5)
Tranexamic acid	194	161 (0.5)
Itraconazole	173	159 (0.5)
Ketoprofen	165	156 (0.5)
Nimesulide	168	139 (0.4)
Flunisolide	144	133 (0.4)
Levofloxacin	138	133 (0.4)
Diclofenac	130	124 (0.4)
Prednisone	275	123 (0.4)
Methyldopa	269	116 (0.4)
Ranitidine	175	110 (0.3)
Paroxetine	199	101 (0.3)

Table 4 Prescription drug exposures during pregnancy in Regione Emilia-Romagna, Italy, by anatomical group,[a] 2004 (n=33,343)

Anatomical group	Dispensings (n)	Deliveries, n (%)
Alimentary tract and metabolism	6,430	4,460 (13.4)
Blood and blood-forming organs	21,609	13,489 (40.5)
Cardiovascular system	2,604	1,591 (4.8)
Dermatologicals	71	56 (0.2)
Genitourinary system and sex hormones	8,927	4,038 (12.1)
Systemic hormonal preparations	4,075	1,707 (5.1)
Anti-infectives for systemic use	15,299	12,387 (37.2)
Antineoplastic and immunomodulating agents	55	27 (0.1)
Musculoskeletal system	699	637 (1.9)
Nervous system	1,606	697 (2.1)
Antiparasitic products	116	81 (0.2)
Respiratory system	3,356	2,625 (7.9)
Sensory organs	197	103 (0.3)
Various	1	1 (0.0)

[a] Anatomical group based on Anatomical Therapeutic Chemical classification system used by the World Health Organization Collaborating Centre for Drug Statistics Methodology [25]

category X drugs were HMG-CoA reductase inhibitors (i.e., statins) – simvastatin (49 deliveries), atorvastatin (28 deliveries), and pravastatin (12 deliveries; Table 5). A total of 95 women (0.3%) were exposed to statins during pregnancy and 262 (0.8%) were exposed to angiotensin-converting-enzyme (ACE) inhibitors.

Discussion

In this study that included more than 30,000 deliveries in Italy in 2004, we found that a large proportion of women (70 and 48% after excluding vitamin and mineral products) were dispensed at least one drug in the 270 days before delivery, including a considerable number who were exposed to drugs with pregnancy risk designations D and X. This prevalence of exposure is of similar magnitude as those observed in other recent studies in other countries [6, 7, 9, 11]. However, the prevalence of exposure to specific drugs varies among studies. For example, some (e.g., amoxicillin, erythromycin, ampicillin) but not all (e.g., fosfomycin, azithromycin, clarithromycin) of most common exposures to anti-infectives in our study are similar to the most common anti-infectives dispensed during pregnancy in Germany [28].

Experts in the fields of teratology and drug safety agree that research priorities should target the drugs that are most commonly used in pregnancy because they have the potential for the largest public health impact [4, 29]. Although we studied drug use in a specific Italian region, we expect that the results are generalizable to the rest of Italy since the same reimbursement rules apply generally across regions and RER demographics reasonably represent the larger Italian population.

We found that nearly 1 in every 100 women had a record of a category X drug, which is contraindicated in pregnancy. This proportion is slightly smaller than that observed in other studies [6, 10] and provides some reassurance that there is no major concern in current prescribing patterns in RER as compared to other countries in this context. In particular, a small, but measurable, proportion of subjects (0.8%) were exposed to ACE inhibitors, specifically in the first trimester. According to the U.S. FDA pregnancy risk classification system, ACE inhibitors are contraindicated in the second and third trimesters of pregnancy because of an association with an increased risk of fetopathy, but they have pregnancy risk designations of C for the first trimester. A recent study, however, found that infants with only first-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations [risk ratio, 2.71; 95% confidence interval (95% CI), 1.72 to 4.27] as compared to infants who had no exposure to antihypertensive medications [1]. In addition, a meaningful proportion of women (0.3%) were exposed to statins, which are designated pregnancy risk category X because of numerous reports of adverse pregnancy outcomes after exposure to these drugs [30].

Despite evidence of potential fetal harm associated with certain medications, these drugs are still occasionally dispensed to pregnant women as documented in this study and in other studies. From clinical and public health perspectives, understanding how this problem arises is critical to reducing the potential adverse effects of drug use during pregnancy. We offer a possible explanation for why women continue to receive category X drugs during pregnancy and a therapeutic risk management solution. It is unlikely that health professionals prescribe drugs contraindicated in pregnancy to women knowing that they are pregnant, unless no treatment alternatives exist. More

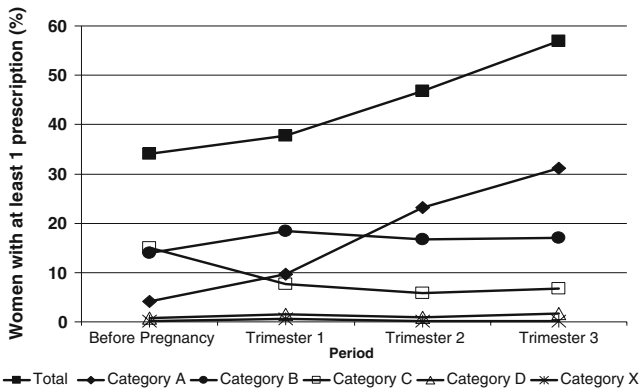

Fig. 1 Percentage of women with drug dispensings in each 90-day study interval by pregnancy risk category (n=33,343 deliveries)

Table 5 Most common pregnancy risk category D and X prescription drug exposures before and during pregnancy, excluding hormones, in Regione Emilia-Romagna, Italy, 2004 (n=33,343)

	Risk category source[a]	Before pregnancy,[b] n (%)	Pregnancy,[c] n (%)	Trimester, n (%)		
				First	Second	Third
Category D						
Atenolol	PI	21 (0.06)	48 (0.14)	23 (0.07)	22 (0.07)	18 (0.05)
Carbamazepine	PI	34 (0.10)	41 (0.12)	32 (0.10)	25 (0.07)	32 (0.10)
Phenobarbital	Briggs	18 (0.05)	33 (0.10)	23 (0.07)	20 (0.06)	25 (0.07)
Doxycycline	PI	49 (0.15)	33 (0.10)	24 (0.07)	5 (0.01)	5 (0.01)
Valproic acid	PI	18 (0.05)	17 (0.05)	15 (0.04)	9 (0.03)	10 (0.03)
Minocycline	Briggs	25 (0.07)	12 (0.04)	11 (0.03)	0 (0.00)	1 (0.00)
Clonazepam	PI	15 (0.04)	11 (0.03)	8 (0.02)	2 (0.01)	6 (0.02)
Amiodarone	PI	4 (0.01)	11 (0.03)	2 (0.01)	7 (0.02)	3 (0.01)
Phenytoin	Briggs	2 (0.01)	5 (0.01)	4 (0.01)	4 (0.01)	5 (0.01)
Azathioprine	PI	4 (0.01)	5 (0.01)	4 (0.01)	5 (0.01)	4 (0.01)
Category X						
Simvastatin	PI	18 (0.05)	49 (0.15)	19 (0.06)	17 (0.05)	19 (0.06)
Atorvastatin	PI	17 (0.05)	28 (0.08)	12 (0.04)	5 (0.01)	13 (0.04)
Warfarin	PI	6 (0.02)	18 (0.05)	6 (0.02)	8 (0.02)	6 (0.02)
Pravastatin	PI	4 (0.01)	12 (0.04)	4 (0.01)	5 (0.01)	4 (0.01)
Finasteride	PI	6 (0.02)	8 (0.02)	5 (0.01)	1 (0.00)	4 (0.01)
Dihydroergotamine	PI	5 (0.01)	7 (0.02)	3 (0.01)	4 (0.01)	2 (0.01)
Fluvastatin	PI	0 (0.00)	5 (0.01)	2 (0.01)	2 (0.01)	1 (0.00)
Isotretinoin	PI	2 (0.01)	3 (0.01)	2 (0.01)	0 (0.00)	1 (0.00)
Methotrexate	PI	0 (0.00)	2 (0.01)	1 (0.00)	0 (0.00)	1 (0.00)
Acitretin	PI	1 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

PI Prescribing information

[a] *PI* indicates U.S. FDA risk category available in the prescribing information of the product's package. *Briggs* indicates Briggs 2005 [26]. See Table 1 for descriptions of the risk categorization systems

[b] The before-pregnancy period is considered to be the period between 271 and 360 days before delivery

[c] The pregnancy period is considered to be the period between 0 and 270 days before delivery, with three 90-day trimesters: the first trimester incorporates the period between 181 and 270 days before delivery; the second trimester incorporates the period between 91 and 180 days before delivery; the third trimester incorporates the period between 0 and 90 days before delivery

likely, women who are not pregnant and who do not intend to become pregnant, but nevertheless become pregnant, consume these medications and continue to do so through at least part of their pregnancies without realizing that they are exposing their unborn babies to these potentially dangerous drugs. This rationale is supported by evidence suggesting that many pregnancies are unplanned [31].

As much as possible, the administration of high risk drugs should be avoided in all women of childbearing potential regardless of pregnancy status and intention to become pregnant. However, we acknowledge that even when evidence of fetal risk does exist for certain drugs, in some circumstances clinicians must prescribe these drugs during pregnancy if, for example, alternative treatments are not available, if other drugs have been tested and failed, or if patients cannot stop taking the drugs because withdrawing from them would have serious adverse effects. In these scenarios, a woman and her partner should be counseled about the potential risk of fetal harm associated with the medication and a thorough risk-benefit discussion should ensue with documentation to follow. Typically, the drugs involved in these scenarios are those with category D designations. For example, several anticonvulsant drugs were among the most commonly dispensed category D drugs. These drugs are associated with an increased risk of major congenital abnormalities [32], but are critical in epilepsy management. The major limitation of the current risk classifications systems is that they are "based on the degree to which available information has ruled out risk to the fetus, balanced against the drug's potential benefits to the patient" [33, 34], and for most medications adequate safety research has not yet been conducted making accurate risk classification difficult, if not impossible, for many drugs. Furthermore, pregnancy risk classification systems may have limited utility in clinical settings in which individual risk-benefit scenarios vary. Nevertheless, such systems can serve as a beacon to guide general treatment decisions and have been used in similar studies of drug use in pregnancy, thereby enhancing the comparability of this study to others from other countries [7, 10, 11, 28].

Category X drugs, however, carry a definite risk of fetal harm which outweighs any possible benefit. Generally,

these drugs should be avoided in all women of childbearing potential. In the rare circumstance that a drug that is contraindicated during pregnancy is required for a woman of childbearing potential, health care professionals should either perform a pregnancy test to confirm that the woman is not pregnant with follow-up documentation or should document that appropriate contraception is being used.

A limitation to this study is that, although using the RER database avoided the potential for maternal underreporting of drug exposures, we were not able to ascertain whether drugs that were dispensed before delivery were taken during pregnancy. One of the major limitations of administrative pharmacy data is that they serve only as a proxy for drug exposure as they cannot ensure that medications are actually consumed. It is possible that a dispensing during pregnancy might be meant for maternal use after delivery (e.g., contraceptive hormones dispensed during the third trimester of pregnancy), leading to a possible overestimation of the burden of drug use during pregnancy. On the other hand, it is possible that some of the medications not classified in our study could be potential teratogens and thus could contribute to our prevalence estimates of category D and X drugs as underestimates. Also, nonprescription drugs such as over-the-counter analgesics and herbal products were not captured in the database, further contributing to a possible underestimate of risk exposure. Furthermore, the proportion of women reportedly exposed to folic acid in this study is likely a significant underestimate since, prior to 2005, folic acid was reimbursed in Italy only for the treatment of megaloblastic anemia. Thus, women who used folic acid before or during pregnancy for prevention of congenital malformations in 2004 were not captured in the RER database.

We applied a delivery-date algorithm to ascertain drug exposures during the gestational period that has been used by other researchers [6, 7] and recently validated [24]. Toh and colleagues found that the sensitivity of this approach in identifying any drug use in pregnancy is approximately 90.0% (95% CI, 86.6–92.7) with a specificity of 99.3% (95% CI, 99.0–99.6). The sensitivity and specificity of our approach could have been slightly enhanced by only including deliveries that were not associated with ICD-9 codes indicative of conditions commonly related to preterm births [24].

A limitation of applying this algorithm to examine drug utilization during pregnancy is that it begins by identifying only those women who delivered. Pregnancies with abortive outcomes, therefore, were not included. Despite being ignored, pregnancies with abortive outcomes may be important in the larger picture of assessing drug utilization during pregnancy because it is possible that medications could have been complicit in the abortive outcome. However, in a descriptive study such as this one, it would be impossible to ascertain whether the outcome was due to the drug use or to the condition for which the drug was used, or due to some other explanation all together.

Conclusions

More than two-thirds of women who delivered a baby in RER, Italy, in 2004, were exposed to one or more prescription medications during pregnancy. Nearly 1 in every 100 pregnant women was prescribed a contraindicated medication with a pregnancy risk designation of X. As much as possible, administration of high risk medications should be avoided in women of childbearing potential to obviate subsequent use during pregnancy. In the rare occasion when this is not possible, other appropriate therapeutic risk management strategies may be warranted. Additional research is required to elucidate associations between medications and birth defects and should focus on the drugs most commonly prescribed during pregnancy.

Acknowledgements This research was conducted through a collaborative agreement between the Regional Health Care Agency, Assessorato alla Sanità, Emilia-Romagna, Italy, and Jefferson Medical College, Philadelphia, PA, USA. We thank Carol Rabinowitz from the Center for Research in Medical Education and Health Care for assistance with data management and analytical support and Roberto Grilli, MD, and Francesco Taroni, MD, from the Regional Health Care Agency, Regione Emilia-Romagna, Italy, for providing the data.

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