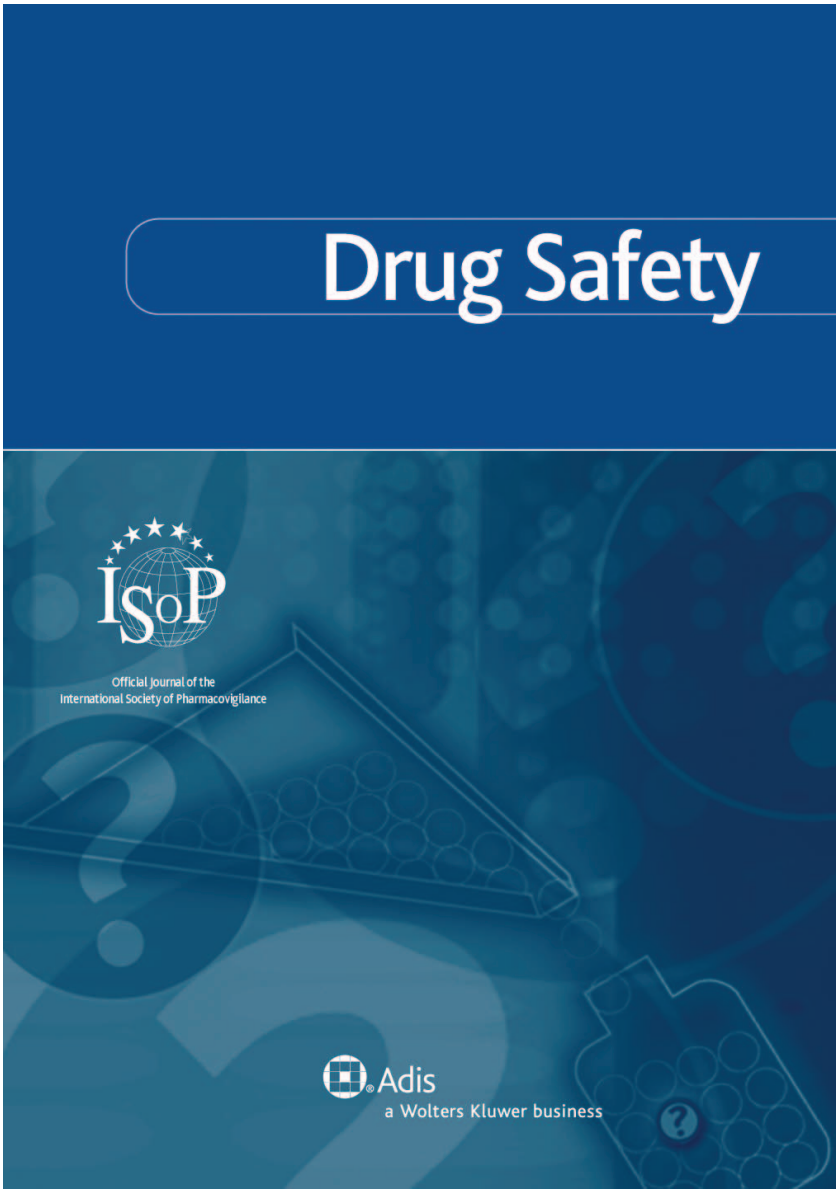

ORIGINAL RESEARCH ARTICLE

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Drug Prescribing Before and During Pregnancy in South West France

A Retrolective Study

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Abstract

Background: Several drugs that are known to exhibit teratogenic or fetotoxic risks when used during pregnancy should not be prescribed to pregnant women. However, most women of childbearing age use medications, and drug use cannot always be avoided during pregnancy, especially for women with chronic diseases for whom the benefit of treatment outweighs the potential risk of the drug for the fetus. Nevertheless, it is often possible to replace a drug with another one that has been better evaluated.

Objective: The aim of the present study was to describe the prescribing of drugs to pregnant women before and during pregnancy in order to examine whether the occurrence of pregnancy modifies drug prescribing and dispensing to women. In particular, drugs that are contraindicated or must be avoided during pregnancy, such as retinoids, ACE inhibitors, angiotensin II receptor blockers, NSAIDs and valproic acid, will be analysed.

Methods: This retrolective study used data already prospectively recorded in the database of the French Health Insurance Service. It analysed pharmacy records of women who gave birth between 1 January 2007 and 31 December 2007 in Midi-Pyrenees. Pharmacy data were analysed from 9 months before pregnancy until delivery. Drugs were classified according to the Anatomical Therapeutic Chemical code.

Results: The study included 23 898 women. Approximately 77% and 96% of the women received at least one prescription before and during pregnancy, respectively. The number of women who were prescribed contraindicated drugs significantly decreased with pregnancy ($p < 0.0001$). Most of the drugs were stopped during the 3 months before pregnancy without alternative treatment, even for chronic diseases. However, for some women, potentially dangerous prescriptions were maintained during pregnancy, and for others these drugs were dispensed for the first time during critical periods of pregnancy.

Conclusion: Despite recommendations, some teratogenic and/or fetotoxic drugs are still prescribed and dispensed to pregnant women in France. There is a need to repeat information to sensitize health professionals and women to the harmful potential of drugs. Moreover, discontinuation of a needed treatment must be avoided. Therefore, attention must be given to ensuring that younger females and women of childbearing potential who are likely to need continued treatment in adolescence and adulthood are aware of the potential risks that some drugs may pose during pregnancy.

Background

Several drugs are known to exhibit teratogenic or fetotoxic risks when they are used during pregnancy. These drugs should not be prescribed to pregnant women and several warnings have been published to inform health professionals. For example, the French Health Products Safety Agency (Agence Française de Sécurité Sanitaire des Produits de Santé [AFSSaPS]) has sent several letters to remind health professionals that the use of these drugs during pregnancy is associated with harmful effects for the embryo or fetus. In 2009, a warning was again published to reinforce the prescription requirements that had been previously published in 2002 for isotretinoin,[1] one of the most teratogenic agents inducing fetal malformations of craniofacial, cardiac, thymic and CNS structures. In 2003 and 2009, two letters regarding NSAIDs were sent to health professionals because of a risk of premature closure or constriction of the ductus arteriosus leading to persistent pulmonary hypertension, intracranial haemorrhages and renal toxicity in fetuses.[2,3] AFSSaPS have also published successive information on ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) regarding their contraindication during pregnancy.[4,5] ACEIs and ARBs are associated with numerous adverse effects (fetal hypotension, anuria, oligohydramnios, renal tubule dysplasia, hypocalvaria, death) on the fetus when taken during the second and third trimesters of pregnancy. Other warnings have been published to inform health professionals of the harmful effects of valproic acid (VPA) on child development.[6-8] For other drugs (most of them), teratogenic or fetotoxic risks are still undetermined.

However, drug use cannot always be avoided during pregnancy, especially for women with chronic diseases for whom the benefit of treatment outweighs the potential risk of the drug for the fetus. Nevertheless, it is often possible to replace a drug with one that has been better evaluated.

The aim of the present study was to describe the prescribing of drugs to pregnant women before and during pregnancy in order to examine whether the occurrence of pregnancy modifies drug prescribing and dispensing to women. In particular, drugs that are contraindicated or must be avoided during pregnancy, such as retinoids, ACEIs, ARBs, NSAIDs and VPA, will be analysed.

Methods

The present retrolective study used data already prospectively recorded in the database of the French Health Insurance Service. It analysed pharmacy records of women who gave birth between 1 January 2007 and 31 December 2007 in Midi-Pyrenees (South West France) and who were registered at the regional level of the National Health Insurance Fund for salaried employees. This fund covers 80% of the population in Midi-Pyrenees. Refunds cover the costs of care and of dispensed prescribed medications. Non-reimbursable drugs essentially concern the over-the-counter (OTC) market but also some prescription-only drugs for which the French ''Commission de transparence'' has decided that the disease they are

indicated for is not serious (e.g. venous insufficiency, cough, oropharynx disorders, etc.). For other non-reimbursed drugs, a refund has not been requested by the manufacturer (such as some recent contraceptives or smoking cessation medications); drugs dispensed during public hospitalizations are not included. For each reimbursed drug, the name of the drug, the code according to the Anatomical Therapeutic Chemical (ATC) classification, the dispensing date, the sum of repayment, the route of administration and the area of medical specialization of the practitioner were available. The indication for prescribing is not found in the database except for a list of severe diseases for which there is a full refundment. Age of women at the time of delivery, health insurance office, date of the beginning of pregnancy and delivery date were available.

A total of 23 898 women registered at the regional level of the National Health Insurance Fund gave birth in 2007 in Midi-Pyrenees, representing 81% of the total number of deliveries in this region in 2007.[9] We examined their dispensing records from 9 months before conception until delivery; thus, the time window for exposure to the drugs covered a period between 1 July 2005 and 31 December 2007.

With the date of repayment, we determined when drugs were reimbursed according to the trimesters of pregnancy. Pharmacy records for the ninth month of pregnancy (if pregnancy was >8 months) were excluded from the analysis because prescribers sometimes anticipated the date that the patient would be released from the maternity hospital, and drugs are often prescribed and dispensed for the post-partum period before delivery, e.g. NSAIDs for post-partum pain or reintroduction of a drug for chronic disease.

A woman exposed to a drug (i.e. an exposed woman) was defined as a woman who had at least one reimbursed drug within a specified period. Discontinuation was designated as the absence of dispensing of the drug of concern at least 1 month after the last dispensing until the end of study. A switch was designated as dispensing of another drug with the same indication after discontinuation of a previous drug.

The analysis was performed with SAS, using statistical tests (Student and McNemar) for paired series. The level of significance was $p < 0.05$.

Results

Drug Prescribing for the 9 Months Before and During Pregnancy

This analysis included 23 898 women registered at the regional level of the National Health Insurance Fund who gave birth between 1 January 2007 and 31 December 2007. Their mean age was 30.1 (SD ± 5.3) years (median 30; range 15–49). In the whole study period, 22 987 women (96.2%) were exposed to at least one reimbursed drug. For 18 387 women (76.9%), at least one drug had been prescribed before pregnancy, whereas 22 852 women (95.6%) received drugs during their pregnancy. They were exposed to a mean of 11 ± 8 and 9 ± 6 different active compounds during the 9 months before pregnancy and the whole pregnancy period, respectively.

The most dispensed drugs, according to the ATC classification, are shown in table I. Before pregnancy, drugs of the N group (nervous system) were the most dispensed and were taken by 54.2% of the women who gave birth in the Midi-Pyrenees in 2007. In particular, analgesics and paracetamol (acetaminophen) contributed to the large quantity of dispensing of this group of drugs. During pregnancy, women were mainly exposed to drugs from groups A (Alimentary tract and metabolism) and B (Blood and blood forming organs). A 1.7-fold increase in the number of women exposed to Group A drugs was observed during pregnancy, with a large number of these exposures being to drugs for functional gastrointestinal disorders [A03 (50% of women)] and acid-related disorders [A02 (33%)]. A 3.5-fold increase in exposure to Group B drugs was observed during pregnancy, with a large number of these exposures being to vitamins (31%) and iron (54%). Other drugs accounting for large numbers of dispensed drugs were from the M group (Musculo-skeletal system): 10 184 women (42.6%) were exposed before pregnancy, decreasing to 3150 (13.2%) during pregnancy as a con-

sequence of fewer dispensed prescriptions for NSAIDs.

Dispensing of Drugs that have Recommendations Relating to Pregnancy

Results for the period before and during pregnancy for the prescribing and dispensing of drugs that have specific recommendations relating to their use in pregnancy are summarized in table II. Except for NSAIDs, exposure to drugs of interest concerned <2% of the entire population, and the greatest number was observed with topical retinoids. Table III summarizes preconceptional prescriptions for VPA or retinoids given to women during their first trimester of pregnancy.

Retinoids

Most women prescribed and dispensed oral retinoids before pregnancy discontinued their treatment more than 3 months before conception. Three women were exposed to acitretin and isotretinoin in the last trimester before pregnancy (T-1). Their final dispensed prescription occurred 50, 46 (acitretin) and 62 (isotretinoin) days before they became pregnant. A 21-year-old woman received oral isotretinoin prescribed by a general practitioner 14 days after the onset of pregnancy. She had not had a prescription for the drug in the past.

During the first trimester of pregnancy, of the 44 women who had a prescription for a topical retinoid (tretinoin, adapalene, tazarotene), 32% (n = 14) had already been exposed before pregnancy (see table III) and the other 68% had no previous record of dispensing of these drugs. For 72% of the women, prescriptions during the first trimester were dispensed by dermatologists. Ninety-five percent of women receiving a topical retinoid during the first trimester discontinued treatment before the second trimester.

Valproic Acid

Eighty-five women received VPA before the onset of pregnancy. As pregnancy approached, many women discontinued treatment. Forty women discontinued VPA before conception, 67% of whom had no other drug therapy thereafter (table IV).

Table I. Number of women receiving a prescription for a drug according to the Anatomical Therapeutic Chemical classification main group

Group	Classification	Number of exposed women[a]		p-Value[c]
		9-month period before pregnancy (n = 18 387)	pregnancy period[b] (n = 22 083)	
A	Alimentary tract and metabolism	10 795	18 174	<0.0001
B	Blood and blood forming organs	3 644	12 449	<0.0001
C	Cardiovascular system	2 055	2 821	<0.0001
D	Dermatologicals	7 516	9 013	<0.0001
G	Genito-urinary system and sex hormones	8 547	7 016	<0.0001
H	Systemic hormonal preparations, excluding sex hormones and insulins	4 935	3 255	<0.0001
J	Antiinfectives for systemic use	10 480	10 556	NS
L	Antineoplasic and immunomodulating agents	211	17	<0.0001
M	Musculo-skeletal system	10 184	3 150	<0.0001
N	Nervous system	12 959	15 066	<0.0001
P	Antiparasitic products, insecticides and repellents	648	788	<0.0001
R	Respiratory system	10 288	11 338	<0.0001
S	Sensory agents	2 852	2 074	<0.0001
V	Various	1 397	151	<0.0001

a Defined as a woman who had at least one reimbursed drug within a specified period.

b Results without the ninth month of pregnancy.

c McNemar test.

NS = not significant.

Table II. Number of women receiving prescriptions for drugs of interest during the periods considered

Drug class	Number of exposed women[a]								
	during whole study period	before pregnancy				during pregnancy			
		(T-3 to T-1)	T-3	T-2	T-1	(T1 to T3)	T1	T2	T3
Retinoid	420	374	135	160	144	63	45	15	5
oral	21	20	14	14	3	1	1	0	0
topical	402	356	122	147	141	62	44	15	5
VPA	91	85	62	68	61	51	49	38	33
NSAID	11 745	10 641	4921	5366	5314	3219	1989	1064	562
ACEI	40	33	24	22	22	17	12	4	5
ARBs	55	77	19	19	27	19	13	8	0

a Defined as a woman who had at least one reimbursed drug within a specified period.

ACEI = ACE inhibitor; **ARBs** = angiotensin II receptor blockers; **T-1** = first pre-conception trimester; **T1** = first trimester of pregnancy; **T-2** = second pre-conception trimester; **T2** = second trimester of pregnancy; **T-3** = third pre-conception trimester; **T3** = third trimester of pregnancy; **VPA** = valproic acid.

Forty-nine women were exposed to VPA during the first trimester of pregnancy, most of whom had already received VPA prior to their pregnancy. Six percent were newly exposed and had not previously taken any other antiepileptic drug during the study period.

Among the 30 women who continued treatment until delivery, 9 had a VPA-free first trimester. For those who discontinued treatment, more than 66% had no alternative treatment thereafter, whereas the others received lamotrigine, olanzapine or a serotonin reuptake inhibitor. In addition, three women started treatment with VPA during the second trimester.

French recommendations[10] for patients with health risks, including epilepsy, a family history of neural tube defect, or patients taking an antiepileptic drug, indicate a daily supplement of folic acid 5 mg, beginning at least 4 weeks before conception and continuing until 8 weeks' post-conception. We analysed dispensing of folic acid in women who had taken VPA before and during pregnancy. Twenty-eight women received supplemental folic acid; 21% (n = 6) had the correct dose (5 mg) but did not cover the periconceptual phase with their treatment, and 79% (n = 22) respected neither the temporal period nor the dosage defined in the recommendations.

ACE Inhibitors and Angiotensin II Receptor Blockers

Four women received an ACEI during the second trimester of pregnancy; one had already been administered this drug during the first trimester and three were newly prescribed. These four women continued to fill a prescription of ACEI during the last trimester of pregnancy. A fifth woman initiated treatment with an ACEI during the last trimester.

Of the 12 women who were exposed to an ACEI during the first trimester of pregnancy, 10 of whom had already received an ACEI before the onset of pregnancy, 4 switched to a calcium channel blocker or β-blocker, 7 discontinued treatment altogether before the second trimester and the twelfth woman continued treatment. Six women started treatment with an ARB during the second trimester. All eight women treated with an ARB during their pregnancy stopped treatment before the third trimester.

Of the 33 and 77 women exposed to an ACEI and ARB, respectively, before pregnancy, 23 and 35 discontinued treatment at the onset of

Table III. Preconceptional exposure of women to teratogenic drugs during the first trimester of pregnancy (T1)

Drug name or class	Exposed women[a] at T1 [n]	Exposed women[a] at T1 who had treatment before pregnancy [n (%)]	Treatment continued until delivery [n (%)]
Valproic acid	49	46 (94)	30 (63)
Topical retinoid	44	14 (32)	2 (5)
Oral retinoid	1	0 (0)	0 (0)

a Defined as a woman who had at least one reimbursed drug within a specified period.

Table IV. Discontinuation among valproic acid (VPA)-, ACE inhibitor (ACEI)- and/or angiotensin II receptor blocker (ARB)-exposed women[a]

Drug name or class (number of exposed women[a])	Prescribing action	Stopped before pregnancy [n (%)]	During first trimester of pregnancy		During second trimester of pregnancy	
			exposed women[a] [n (%)]	[n (replacement therapy)]	exposed women[a] [n (%)]	[n (replacement therapy)]
VPA (85)	Stopped	40	13		5	
	Stopped VPA for another drug	13 (33)	5 (38)	3 (lamotrigine) 1 (olanzapine) 1 (SSRI)	1 (20)	1 (lamotrigine)
	Stopped VPA without any alternative	27 (67)	8 (62)	NA	4 (80)	NA
ACEI (33)	Stopped	23	11		2	
	Stopped for another drug	10 (43)	4 (36)	3 (calcium blockers) 1 (β-blocker)	1 (50)	1 (β-blocker)
	Stopped without any alternative	13 (57)	7 (64)	NA	1 (50)	NA
ARB (77)	Stopped	35	11		8	
	Stopped for another drug	11 (31)	4 (36)	1 (calcium blocker) 3 (β-blockers)	0 (0)	NA
	Stopped without any alternative	24 (69)	7 (64)	NA	8 (100)	NA

a Defined as a woman who had at least one reimbursed drug within a specified period.

NA = not applicable.

pregnancy. Sixty-four percent had no alternative treatment thereafter, whereas the others were dispensed alternatives such as calcium channel blockers (10%), β-blockers (12%) and methyldopa (5%). Nine percent switched from an ARB to an ACEI or from an ACEI to an ARB before pregnancy.

NSAIDs

865 women (3.6%) had an NSAID dispensed after the beginning of the sixth month (>24 weeks of amenorrhoea) despite these drugs being contraindicated. The mean number of prescriptions dispensed for each woman was one. Ibuprofen, diclofenac, ketoprofen, niflumic acid and aspirin (acetylsalicylic acid) were the most commonly dispensed drugs. Almost 47% of reimbursements for NSAIDs were for topical NSAIDs and 48% were for the oral form. Eight-six percent of NSAIDs were prescribed by general practitioners and 9% by gynaecologists.

Discussion

Many women are exposed to drugs before and during their pregnancy. Despite recommendations, drugs that are contraindicated or must be avoided in pregnant women are still dispensed during pregnancy. A large group of women of childbearing age who take harmful medicine continue to do so when they are pregnant. Treatment discontinuation mostly occurs during the first trimester of pregnancy, often without any switch.

The present study confirms the large consumption of drugs by French women, whether they are pregnant or not. A large number of women were given a prescription for drugs before and during pregnancy, with more women taking drugs during their pregnancy than before their pregnancy. We observed the same trend in other European countries.[11-14] The large number of drugs dispensed after conception could be explained by an increase in requests for drugs used for pregnancy-related symptoms.[14] An increase in prescribing

is observed for ATC group A (Alimentary tract and metabolism) and group B (Blood and blood forming organs) drugs, particularly in relation to the number of prescriptions for domperidone, iron and phloroglucinol, a French spasmolytic drug. Iron is the second most prescribed drug and is dispensed to 54% of women, although its indication is for iron-deficiency anaemia, which has a prevalence of 11.5% in pregnant women in France.[15] An excess of iron has been reported to be associated with maternal hypertension, baby hypotrophy and prematurity.[16] It is interesting to point out that some drugs are widely dispensed, although there is little information on their safety and effectiveness. Lacroix et al.[17] found that, among the 20 most frequently prescribed drugs to pregnant women in France, around half have not been evaluated during pregnancy, with some of these drugs only being marketed in some European countries.

In the present study, teratogenic or fetotoxic drugs were dispensed during early pregnancy but a large decrease in their prescription was observed after conception. One can hypothesize that unknown pregnancy could explain the dispensing of harmful drugs in early pregnancy. According to Magee,[18] 50% of pregnancies seem to be unplanned. Moreover, although almost 80% of pregnancies in the Netherlands are planned, in general a woman does not recognize her pregnancy until the third week after conception.[14]

However, because some teratogenic drugs have a long elimination half-life and remain in blood or tissues for several days or months after cessation of the drug, precautions and recommendations exist to prevent pregnant women from being exposed to such agents (e.g. isotretinoin or acitretin). In the present study, with the exception of one woman who had been prescribed isotretinoin in the early stages of the first trimester of pregnancy, all women taking isotretinoin before pregnancy stopped treatment before they became pregnant. However, discontinuation of treatment occurred too late with acitretin. Conception should normally be avoided for at least 2 months, even for 2 years, after the end of treatment because of the pharmacokinetic properties of acitretin, which particularly relates to storage of the drug in adipose tissues.[19] A 4-year survey that has been performed by the French Pharmacovigilance Center of Tours[20] showed that 16% of 147 pregnancies exposed to isotretinoin were ongoing when the drug was prescribed. Absence or failure of contraception was observed for half of these pregnancies. Forty percent of prescriptions did not correspond to the recommendations for the specific drug prescribed but were still dispensed by pharmacists, and 30% of pharmacists did not control for all the mandatory recommendations on the first prescription (negative pregnancy test within 3 days before prescribing treatment).

Women were dispensed NSAIDs and agents acting on the renin-angiotensin system after the first trimester, when pregnancy is usually known.

In the present study, NSAID dispensing corresponded to an immediate need for treatment, as previously reported by Hurault et al.[21] Nevertheless, there is a risk with NSAID treatment, even with only one intake.[22] A previous study from our group showed that more that one-third of women do not know that serious neonatal adverse effects could potentially occur after taking an NSAID during the later stages of pregnancy.[23] Moreover, according to Damase-Michel et al.,[24] 16% and 17% of health professionals think that there is no fetal or neonatal risk if aspirin or ibuprofen are administered during the later stages of pregnancy. Hurault et al.[21] found that a letter sent to healthcare professionals in 2003 contributed to a decrease in NSAID prescriptions to pregnant women. In the present study, the number of women who had at least one reimbursed NSAID (3.6%) is higher than that in the previous study (2.8%) from our group,[21] suggesting the need to reiterate information to professionals.

With regard to agents acting on the renin-angiotensin system, Bowen et al.,[25] found an increase in late exposure to ACEIs despite a US FDA black-box warning that was implemented in 1992 suggesting that women might have stopped medication use after their pregnancy was confirmed, but in many cases women continued to fill ACEI prescriptions during the second and third trimesters of pregnancy.

We established that women taking drugs for chronic diseases mostly continue to fill their prescriptions when they are pregnant. The decrease in the number of prescriptions dispensed at the beginning of pregnancy was smaller for VPA than any other studied drug. Ninety-four percent of women exposed to VPA during the first trimester of pregnancy had already initiated their treatment before the onset of pregnancy, and 63% continued VPA treatment until delivery. This illustrates that, in pregnant women, the use of medications must not only be assessed in terms of adverse fetal effects but other considerations such as the risk of recurrences and exacerbations of disease must be taken into account. Pregnancy does not seem to have any effect on seizure control in most women with epilepsy;[26] symptoms could both deteriorate or improve. Moreover, delivery and labour are associated with an increased risk of seizures, with 2–5% of women with epilepsy having seizures at these times.

Maternal folate supplementation 1 month before conception and continuing into the first 2 months of pregnancy may reduce the risk of neural tube defects. High dosages of 5 mg daily are recommended for all women taking antiepileptic drugs. In the present study, none of the women receiving VPA were given the correct dosage of concomitant folic acid or were treated with folic acid for the right duration of the periconceptional period.

Results from this study indicate that a large proportion of dispensed drugs are given as topical formulations; 68% of women receiving a topical retinoid during the first trimester are newly exposed, and 47% of dispensed NSAIDs after the beginning of the sixth month are given as topical formulations. Topical formulations seem to be considered safer than systemic formulations.[21,27] Published data on pregnancy outcomes following maternal exposure to topical retinoids are limited but several malformations similar to those observed with oral retinoids have been reported.[27,28] The *Dictionary Vidal*® contraindicates the use of retinoids in some cases, and in other cases indicates that their use should be avoided, whereas the *British National Formulary* contraindicates their use in pregnant women.[28] Moreover, information on skin absorption and interindividual variability with regard to topical drug absorption is poor. Topical NSAIDs exhibit the same harmful effects as the oral formulations;[29] therefore, it is preferable not to prescribe these during pregnancy.

Our study encountered some limitations with respect to the database we used. First, some data concerning non-reimbursable drugs were missing; therefore, drug exposure could have been underestimated. For the drugs reported and discussed in this study, this limitation only concerned NSAID prescribing as these drugs are available OTC. In 2007, a report from the French Social Protection Ministry showed that OTC drugs accounted for only approximately 10% of units sold in France.[30] Drugs prescribed during public hospitalization are also not recorded in the database but, in most cases, these drugs are continued at home. A second limitation is that the French Health Insurance Database is a reimbursement database that does not indicate which disease the drug is prescribed for and the adherence of the patient. It is not possible to ascertain from the database whether the drugs were really ingested and when they were possibly taken. In a Danish study, only 43% of all drugs dispensed to pregnant women were reported to be taken.[31] Data for the ninth month of pregnancy have been excluded from the analysis because of the possibility of those prescriptions being related to use during the post-partum period. However, because of the extent of the population covered, the French Health Insurance Database is representative of the French population.

Conclusions

This study shows that recommendations of health authorities are not fully followed. Too many women are exposed to potentially harmful drugs during their pregnancy; therefore, there is an ongoing need to repeat information to alert health professionals who prescribe, and pharmacists who dispense, as to which drugs should be avoided in the pregnant population because of their potential teratogenic or fetotoxic risks. Moreover, discontinuation of a needed treatment must be avoided. Attention must be given to

younger females and women of childbearing potential who are likely to need continued treatment during adolescence and adulthood. Because of the limited impact of official recommendations, one must consider other ways to convince health professionals and women of the possibility of preventing adverse drug events during pregnancy.

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