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Drug Exposure during the Periconceptional Period
A Study of 1793 Women

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Abstract

Background: Many studies have described the prescribing of drugs to pregnant women, but only very few have data concerning the periconceptional period specifically.

Aim: The aim of the study was to evaluate the incidence of exposure to teratogenic drugs during early pregnancy and to determine whether a safer drug exists.

Methods: In a French health insurances database, we analyzed drugs prescribed during the period starting 1 month before and ending 2 months after the beginning of pregnancy between 1 January 2006 and 31 December 2007. Based on the Summary of Product Characteristics (SPC), drugs we considered were those 'contraindicated', 'not recommended', 'to be avoided', and 'possible' for use during the first trimester of pregnancy. For drugs 'contraindicated', we established if there were alternatives with similar efficacy for the mother and lower risk for the fetus.

Results: Over a period of 2.25 years, 8754 drugs were prescribed to 1793 women starting 1 month prior to and ending 2 months after conception. Among these drugs, 20 (0.2%) were 'contraindicated', 195 (2.2%) were 'not recommended', and 1209 (13.8%) were 'to be avoided' during the first trimester of pregnancy. Twenty (1.1%) women received at least one drug that was 'contraindicated' during the first trimester, 171 (9.5%) received a drug that was 'not recommended' and 768 (42.8%) received a drug that was 'to be avoided'. At least one possible alternative was available for all except one 'contraindicated' drug.

Conclusions: During the highest teratogenic risk period, 1.1% of women received a contraindicated drug, despite existence of a safer alternative drug. This may be partly accounted for by physicians not being aware of the pregnancy at the time the drug was administered and could be reduced by adding a section entitled 'women of child-bearing potential' to the SPC.

Background

In France, the average number of drugs taken by women during pregnancy is estimated to range from 10 to 14.[1-3] The risk of fetal drug exposure is dependent on the drug itself and the exposure period. The latter, which may be significantly longer than the period during which the drug was taken, is obtained by adding the drug elimination period (five times the elimination half-life) to the drug intake period. Therefore, a drug with a 15-day elimination half-life taken 1 month prior to conception, is present in the mother's blood for 2.5 months, with the fetus being exposed to the drug for 1.5 months. The exposure period, with risks of malformation, is short but clearly defined, and corresponds to organogenesis, which occurs from day 13 to day 56 following conception. This is precisely the period when both the woman and the physician may not yet be aware of the pregnancy. To anticipate, and avoid, drug exposure in early pregnancy, when prescribing a drug to a young woman, physicians must consider that she may already be or soon become pregnant, thereby taking into account the duration

of drug exposure rather than the duration of drug intake. When prescribing a drug or renewing a prescription for long-term treatment, the prescribing physician does not always envisage the possibility of pregnancy and consult the 'pregnancy' section of the Summary of Product Characteristics (SPC). As a result, he/she may be unaware of the prescription risk for a woman who does not know that she is pregnant, does not notify the doctor, or is not yet pregnant. In fact, although information on the potential fetal risks of drugs is listed in the SPC in the 'Pregnancy' section, there is no specific section for 'women of child-bearing potential'.

The drug-exposed women often discover the risks inherent to drug therapy while reading the patient product information when they discover that they are pregnant. The wording in patient information leaflets and SPCs is rarely reassuring with regard to pregnancy, which may cause great anxiety among women[3,4] and physicians, the latter often asking for advice at specialized centers. Each year, the Clinical Pharmacology Department of the Tours Regional University Hospital (CHRU) receives approximately 500 questions pertaining to drug exposure during pregnancy, especially in the very early stages.

As only very few data on drug exposure during the periconceptional period were available,[5] our study was primarily aimed at evaluating the incidence of exposure to teratogenic drugs during early pregnancy. A secondary aim was to determine whether potential alternative drugs with similar efficacy but lower teratogenic risk could have been prescribed for pregnant women.

Methods

For our study, the prescription database of two French areas (Nord-Pas-De-Calais and Brittany) from the *Caisse d'Assurance Maladie du Régime Social des Indépendants* (RSI) was used. Like all health insurance databases, the RSI prescription database comprises all drug prescriptions that qualify for reimbursement and contains data on the prescriber (specialty), the drug (name, Anatomical Therapeutic Chemical [ATC] classification code, issue date, and number of boxes dispensed), and the patient (date of birth, place of residence); however, indication for the drug prescription is not provided. Each prescription was counted as a drug.

As the RSI also receives pregnancy notifications with the presumed date of conception as estimated by the practitioner, we selected women whose pregnancy began between 1 January 2006 and 31 December 2007. Among these women, all drugs prescribed during the period starting 1 month before and ending 2 months after the presumed beginning of pregnancy were taken into account. The inclusion of drugs prescribed 1 month prior to the presumed conception data allowed for drugs with long half-lives that might remain in the system on or after postconceptional day 13.

The SPC 'pregnancy' sections of all dispensed drugs were analyzed as this was the main information source for the prescriber. For assessment, the SPC published on the prescription date was taken into account. For defining drugs with teratogenic risks, information outlined in the SPC 'pregnancy' sections was taken into account. Label descriptions regarding the risk type and potential risk period varied. The type of risk was, at times, labeled as teratogenic (malformative), fetotoxic, or neonatal. Likewise, the period of risk was at times defined as 'beginning of pregnancy', 'last two trimesters', 'end of pregnancy', or 'during delivery'. Recommendations regarding the procedures to follow were sometimes given with respect to contraception, ultrasound, and management after the child's birth. In the best-case scenario, the entire dataset was available, enabling us to distinguish between the first and last two trimesters of pregnancy for our conclusions. However, for the majority of drugs, information in the SPC covered the overall pregnancy, whereas the conclusions only related to the fetotoxic or neonatal effects. It should be noted that many different terms are used in the 'pregnancy and lactation' sections of the SPC labeling to describe the intended use of the drug. These terms include 'contraindicated', 'not recommended', 'to be avoided', 'not to be used/administered/prescribed', 'to be preferably avoided', 'recommended not to be used/administered/prescribed', 'should not be considered', 'should be used only if the expected benefits outweigh the potential risks', or 'possible'.

For the purpose of our analysis, drugs were classified into four categories, i.e. 'contraindicated', 'not recommended', 'to be avoided', and 'possible'. We considered as 'contraindicated' and 'not recommended' those drugs for which the labeling stipulated 'contraindicated' or 'not recommended' for the first trimester of pregnancy or for pregnancy without any specification of time. Likewise, we considered as drugs 'to be avoided' to be those for which the labeling indicated 'to be avoided', 'not to be used/administered/prescribed', 'to be preferably avoided', 'recommended not to be used/administered/prescribed', 'should not be considered', or 'should be used only if the expected benefits outweigh the potential risks', either during the first trimester of pregnancy or during pregnancy without any further specification of the risk period. All the other drugs were classified into the category 'possible', including those for which the SPC provided no advice for use during pregnancy, as well as those drugs for which no section on 'pregnancy' was provided. For 'contraindicated' and 'not recommended' drugs used

during pregnancy, we examined the 'Contraindications', 'Warnings and Precautions', and 'Preclinical safety' sections to determine whether there was any explanation for not using the drug during pregnancy. Lastly, we also considered drugs to be contraindicated or not recommended when teratogenic effects had been established in humans, or if clinical data were insufficient or absent.

For drugs 'contraindicated' during pregnancy, we established if there were alternatives with similar efficacy for the mother, and lower risk for the fetus. An alternative was defined as a drug with the same clinical indications, preferably belonging to the same pharmaceutical therapeutic class, that was not 'contraindicated' or 'not recommended' for use during early pregnancy. Given that indications were not specified in the RSI database, for drugs with several clinical indications, an alternative drug was only considered available if this latter drug had the same indications as the contraindicated drug. If this was not the case, several alternatives covering the entire set of the drug indications were required. If none of these conditions were met, it was assumed that there was no alternative drug on the market. Alternatives were sought among drugs available on the market on the drug prescription date.

For drug classification, 14 classes of the ATC classification were taken into account, to which class Y (homeopathic products) and class Z (with no ATC code) were added.

Data analysis was performed using Excel® (Microsoft Corporation, Redmond, WA, USA) spreadsheet listings and SAS 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 1793 women, with a mean age of 30.7 ± 5.3 years (15–48 years), whose pregnancy began between 1 January 2006 and 31 December 2007, i.e. a period of 2.25 years, were included in the study. A total of 8754 drugs were reimbursed between 1 month prior to and 2 months after the presumed pregnancy date, resulting in a mean number of 4.88 ± 4.1 (1–41 drugs per woman). Twenty (1.1%) women received at least one drug that was contraindicated during the first trimester, 171 (9.5%) received a drug that was 'not recommended', 768 (42.8%) received a drug that was 'to be avoided', and 951 (53.0%) were administered a drug that was 'possible' during early pregnancy. The anatomical classes of drugs most frequently concerned were 'Alimentary tract and metabolism' (25.6%), 'Nervous system' (16.5%), and 'Respiratory system' (11.1%) [table I]. The therapeutic classes most frequently concerned were analgesics (14%), drugs for functional gastrointestinal disorders (12.6%), and antibacterials for systemic use (7.7%). Overall, 50 women (2.8%) re-

Table I. Drugs prescribed between 1 month prior to and 2 months after conception

Drugs (ATC classification)	No. of prescriptions (%)
Alimentary tract and metabolism (A)	2268 (25.9)
Stomatological preparations (A01)	114 (1.3)
Drugs for acid related disorders (A02)	373 (4.3)
Drugs for functional gastrointestinal disorders (A03)	1107 (12.6)
Antiemetics and antinauseants (A04)	173 (2.0)
Bile and liver therapy (A05)	1 (0.0)
Laxatives (A06)	150 (1.7)
Antidiarrheals, intestinal antiinflammatory/antiinfective agents (A07)	81 (0.9)
Drugs used in diabetes (A10)	8 (0.1)
Vitamins (A11)	46 (0.5)
Mineral supplements (A12)	213 (2.4)
Other alimentary tract and metabolism products (A16)	2 (0.0)
Blood and blood forming organs (B)	549 (6.3)
Antithrombotic agents (B01)	28 (0.3)
Antihemorrhagics (B02)	3 (0.0)
Antianemic preparations (B03)	514 (5.9)
Blood substitutes and perfusion solutions (B05)	4 (0.0)
Cardiovascular system (C)	209 (2.4)
Cardiac therapy (C01)	11 (0.1)
Antihypertensives (C02)	4 (0.0)
Diuretics (C03)	2 (0.0)
Peripheral vasodilators (C04)	4 (0.0)
Vasoprotectives (C05)	154 (1.8)
Beta blocking agents (C07)	19 (0.2)
Calcium channel blockers (C08)	8 (0.1)
Agents acting on the renin-angiotensin system (C09)	7 (0.1)
Dermatologicals (D)	607 (6.9)
Antifungals for dermatological use (D01)	228 (2.6)
Emollients and protectives (D02)	61 (0.7)
Antipsoriatics (D05)	4 (0.0)
Antibiotics and chemotherapeutics for dermatological use (D06)	52 (0.6)
Corticosteroids, dermatological preparations (D07)	90 (1.0)
Antiseptics and disinfectants (D08)	127 (1.5)
Anti-acne preparations (D10)	42 (0.5)
Other dermatological preparations (D11)	3 (0.0)
Genitourinary system and sex hormones (G)	812 (9.3)
Gynecological antiinfectives and antiseptics (G01)	252 (2.9)
Other gynecologicals (G02)	31 (0.4)

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Table I. Contd

Drugs (ATC classification)	No. of prescriptions (%)
Sex hormones and modulators of the genital system (G03)	529 (6.0)
Systemic hormonal preparations, excluding sex hormones and insulins (H)	204 (2.3)
Pituitary and hypothalamic hormones and analogues (H01)	7 (0.1)
Corticosteroids for systemic use (H02)	129 (1.5)
Thyroid therapy (H03)	68 (0.8)
Antiinfectives for systemic use (J)	756 (8.6)
Antibacterials for systemic use (J01)	677 (7.7)
Antimycotics for systemic use (J02)	4 (0.0)
Antivirals for systemic use (J05)	23 (0.3)
Immune sera and immunoglobulins (J06)	15 (0.2)
Vaccines (J07)	37 (0.4)
Antineoplastic and immunomodulating agents (L)	6 (0.1)
Antineoplastic agents (L01)	1 (0.0)
Endocrine therapy (L02)	5 (0.1)
Musculoskeletal system (M)	401 (4.6)
Antiinflammatory and antirheumatic products (M01)	264 (3.0)
Topical products for joint and muscular pain (M02)	82 (0.9)
Muscle relaxants (M03)	52 (0.6)
Antigout preparations (M04)	1 (0.0)
Drugs for treatment of bone diseases (M05)	1 (0.0)
Other drugs for disorders of the musculoskeletal system (M09)	1 (0.0)
Nervous system (N)	1444 (16.5)
Anesthetics (N01)	22 (0.3)
Analgesics (N02)	1226 (14.0)
Antiepileptics (N03)	10 (0.1)
Psycholeptics (N05)	127 (1.5)
Psychoanaleptics (N06)	47 (0.5)
Other nervous system drugs (N07)	12 (0.1)
Antiparasitic products, insecticides, and repellents (P)	16 (0.2)
Antiprotozoals (P01)	10 (0.1)
Anthelmintics (P02)	6 (0.1)
Respiratory system (R)	974 (11.1)
Nasal preparations (R01)	448 (5.1)
Throat preparations (R02)	137 (1.6)
Drugs for obstructive airway diseases (R03)	133 (1.5)
Cough and cold preparations (R05)	122 (1.4)
Antihistamines for systemic use (R06)	134 (1.5)
Sensory organs (S)	174 (2.0)
Ophthalmologicals (S01)	130 (1.5)
Otologicals (S02)	44 (0.5)
Various (V)	25 (0.3)
All other therapeutic products (V03)	11 (0.1)
Diagnostic agents (V04)	3 (0.0)
Contrast media (V08)	11 (0.1)
Homeopathic drugs	37 (0.4)
Drugs without ATC classification	272 (3.1)

ATC = Anatomical Therapeutic Chemical.

ceived at least one reimbursement for oral contraceptives administered during the periconceptional period. The most frequently prescribed chemical products were acetaminophen [paracetamol] (11.5%), phloroglucinol (5.9%), and folic acid 0.4 mg or 0.5 mg/day (3.8%).

Of the 8754 drugs prescribed to pregnant women during the first trimester of pregnancy, 20 (0.2%) were for 'contraindicated' drugs, 195 (2.2%) 'not recommended', 1209 (13.8%) 'to be avoided', and 7330 (83.7%) 'possible' (table II). Among the eight contraindicated drugs prescribed to 20 patients, labeling for four of these drugs (which were prescribed to six patients) indicated that they should not be given without efficacious contraceptive methods (misoprostol/diclofenac, misoprostol, fluconazole, and celecoxib). The reason why these drugs were contraindicated included an established teratogenic effect in women for two drugs (misoprostol/diclofenac, misoprostol) prescribed to four patients, an established teratogenic effect in animals but dubious in women for four drugs (fluconazole, celecoxib, moxifloxacin, and ganirelix) prescribed to nine patients, and insufficient or absent clinical data for two drugs (bambuterol and rabeprazole) prescribed to seven patients. Two of the four contraindicated drugs (misoprostol once and misoprostol/diclofenac three times) corresponding to eight prescriptions contained misoprostol, which is indicated for pregnancy interruption under another trade name (Gymiso®). For these eight prescriptions, designed as antacids, we checked that they were not combined with mifepristone, and thus probably not used for pregnancy interruption. The SPC of the 32 drugs 'not recommended' for use during the first trimester of pregnancy, corresponding to 195 prescriptions to 171 women, specified in two cases (mercaptopurine prescribed twice and valproate prescribed twice) that the drugs should not be used without efficacious contraception. The reason for this was an

Table II. Drugs 'contraindicated' and 'not recommended' prescribed between 1 month prior to and 2 months after conception

ATC classification	Drugs	No. of prescriptions
Drugs 'contraindicated'		
H01CC01	Ganirelix 0.25 mg/0.5 mL subcutaneous	6
A02B04	Rabeprazole tablet	6
M01AB55[a]	Diclofenac/misoprostol tablet	3
A02BB01[a]	Misoprostol tablet	1
J01MA14	Moxifloxacin tablet	1
J02AC01	Fluconazole 50 mg/5 mL oral suspension	1
M01AH01	Celecoxib capsule	1
R03CC12	Bambuterol tablet	1
Drugs 'not recommended'		
G01AA51	Neomycin/polymyxin B/nystatin vaginal tablet	34
R06AD08	Oxomemazine syrup	23
R03DX03	Fenspiride tablet, syrup	20
M03BX05	Thiocolchicoside capsule	15
R06AX22	Ebastin lyophilisat	13
D01AC08	Ketoconazole cream	12
C05AX04	Carraghenates/titane dioxide/zinc oxide cream	10
J01FA15	Telithromycin tablet	9
R05DB03	Clobutinol tablet, syrup	7
R01AD52	Prednisolone/naphazolin	5
S01CA	Bacitracin/colistin/polymyxin B intranasal drops	5
A03AX04	Pinaverium tablet	4
M03BA03	Methocarbamol tablet	4
R01AD52	Prednisolone/oxymetazoline intranasal drops	4
C09DA	Candesartan/hydrochlorothiazide tablet	3
D10AD03	Adapalene cream	3
N06BX03	Piracetam tablet, oral solution	3
C04AE51	Dihydroergocryptine/caffeine tablet, oral solution	2
C08DB01	Diltiazem capsule	2
J07BD52	Measles, mumps, rubella vaccine subcutaneous	2
N06DX02	Ginkgo biloba extract tablet	2
M04AB03	N-acetylaspartylglutamic acid intranasal solution	2
D04A	Oxatomide tablet	2
N03AG01[a]	Valproate tablet	1
A01AD11	Unsaponifiable avocado and soya capsule	1
M09AX02	Sulfate chondroitin sodium capsule	1
L01BB02	Mercaptopurine tablet	1
C03EA01	Amiloride/hydrochlorothiazide tablet	1
C04AX21	Naftidrofuryl tablet	1
C08CA05	Nifedipine tablet	1
D10AD01	Tretinoin dermatologic solution	1
R01AC01	Cromoglycate sodium intranasal solution	1

a Teratogenic effects established in humans. All other drugs are 'contraindicated' and 'not recommended' prescribed between 1 month prior to and 2 months after conception because of insufficient or absent data in humans.

ATC = Anatomical Therapeutic Chemical.

established teratogenic risk in women in one case and insufficient or absent clinical data in women in 194 cases (table II).

With the exception of ganirelix used for ovarian stimulation in medically assisted procreation, at least one possible alternative was available for all the contraindicated drugs (table III). Prescribers were general practitioners (71.8%), gynecologists (14.1%), other specialists (6.1%), and undefined (8%). For the seven contraindicated drugs prescribed by general practitioners to 13 patients, there was an alternative available. For the contraindicated drug (ganirelix) prescribed by gynecologists to six patients, no alternative existed. SPC analysis gives rise to some remarks or discrepancies likely to be responsible for inappropriate prescriptions. On the one hand, 704 SPCs did not contain any advice for use during pregnancy, and 1259 did not include a pregnancy section. On the other hand, the information about the drugs' contraindication during pregnancy was listed in the 'Pregnancy' section for eight drugs, and in the 'Contraindication' section for the six others. These six drugs contraindicated solely in the 'Contraindication' section were listed as 'to be avoided' or 'possible' in the 'Pregnancy' section (table IV).

Discussion

Our study highlights the prescription frequency during the period of highest malformation risks. To our knowledge, no other study has specifically evaluated drug consumption during this particular period of high teratogenic risk. Teratogenic risk

Table III. Drugs 'contraindicated' during pregnancy and their authorized alternatives

ATC classification	Drugs 'contraindicated'	Existence of an alternative	Which alternative(s)
A02BB01	Misoprostol	Yes	Omeprazole
M01AB55	Misoprostol/diclofenac	Yes	Omeprazole + diclofenac
J01MA14	Moxifloxacin	Yes	Other fluoroquinolones: levofloxacin, ciprofloxacin, etc.
R03CC12	Bambuterol	Yes	Terbutaline
M01AH01	Celecoxib	Yes	Other NSAIDs: ketoprofen, naproxen sodium, diclofenac, etc.
H01CC01	Ganirelix	No	None
A02BC04	Rabeprazole	Yes	Omeprazole
J02AC01	Fluconazole 50 mg/5 mL	Yes	Itraconazole 10 mg/mL

ATC = Anatomical Therapeutic Chemical.

during the periconceptional period is difficult to assess since all drug classifications used are based upon fetal risk in general and do not distinguish between teratogenic risk (at the beginning of pregnancy) and other harmful effects on the fetus and neonate (in the last two trimesters). Gagne et al.,[6] using US FDA categorizations, showed that 2% of pregnant women received a drug from category D (positive evidence of fetal risk with possible benefits outweighing the risk), and 1% received a drug from category X (definite fetal risk in animal or human studies, or based on human experience, with the risk clearly outweighing any possible benefit). Malm et al.,[7] using Swedish (Farmaceutiska Specialiteter i Sverige [FASS]), Australian (Australian Drug Evaluation Committee [ADEC]), and US (FDA) categorizations, showed that, during the first trimester, 11.2% of women purchased potentially harmful drugs, and 3.2% purchased clearly harmful drugs. These figures were lower than those collected during the 3 months prior to conception (17.9% and 5.5%, respectively).[7] Andrade et al.,[8] using US (FDA) categorizations, showed that 2.1% of pregnant women used a drug from category D, and 0.6% used a drug from category X. The mean number of drugs per women (4.88) is close to that reported in other studies that cover the entire pregnancy, ranging from 6.43[1] to 13.8.[2] Moreover, we assessed the proportion of prescriptions 'contraindicated' (0.2% of all prescriptions) and 'not recommended' (2.2% of all prescriptions) in the periconceptional period. The majority of studies conducted to date focused on drug use during overall pregnancy. The only study that evaluated prescriptions during the first trimester of pregnancy[9] revealed that 2.4% of the prescribed drugs were contraindicated. However, this figure included drugs that were both contraindicated during the first trimester because of the risk of malformations and those that were contraindicated during the last two trimesters. We also showed that the 20 prescriptions for contraindicated drugs during the first trimester of pregnancy might have been avoided in the majority of cases, as a non-contraindicated alternative was available for 70% of these drugs. This risk may be accounted for by the fact that the prescriber was not aware of the pregnancy (the most probable hypothesis, especially among the 3% of women receiving oral contraceptives during early pregnancy), failure to consult the SPC before prescribing the drug, and the necessity to prescribe a drug that was essential to the patient, such as valproate.

The only means of limiting dangerous prescriptions during early pregnancy while the pregnancy is still unknown would be to add a section entitled 'women of child-bearing potential' to the SPC to remind physicians that a woman aged 15–45 years could be or become pregnant during the next few days, and to encourage prescribers to routinely consult the 'Pregnancy' section of the SPC prior to issuing a prescription to women of this age. This is even more important because it would be difficult to justify the appropriateness of the prescription in case

Table IV. Drugs 'contraindicated' during pregnancy solely in the 'Contraindication' SPC section but listed differently under the 'Pregnancy' heading

Drug (ATC classification)	No. of prescriptions	Pregnancy heading
Racecadotril capsule (A07XA04)	10	To be avoided
Methylergometrine oral solution (G02AB01)	4	To be avoided
Acetaminophen (paracetamol)/opium/caffeine capsule (N02BE51)	3	To be avoided
Sodium p-aminosalicylate rectal solution (A07EC)	1	To be avoided
Rubella vaccine subcutaneous (J07BJ01)	1	To be avoided
Levonorgestrel intra-uterine device (G02BA03)	1	Possible

ATC = Anatomical Therapeutic Chemical.

of a compromised pregnancy. The same remarks apply to the 195 drugs 'not recommended', even if, in 194 cases, this 'non-recommendation' was due to insufficient or absent clinical data in humans. The most frequently prescribed ATC classes during the first trimester of pregnancy, i.e. alimentary tract and metabolism (25.6%), nervous system (16.5%), and respiratory system (11.1%), differ from those of a Norwegian study,[10] which revealed that during the first trimester of pregnancy, 33% of women were given at least one prescription of anti-infective agents for systemic use, respiratory system drugs, genitourinary tract system drugs or sex hormones, or alimentary tract and metabolism drugs. The significant amount of alimentary tract and metabolism drugs, found in all of the studies, is accounted for by the prescription of antiemetic drugs during the first trimester, especially domperidone, as shown in our study. The aim of our study was not to evaluate all the prescriptions made during pregnancy, as did most of the published studies,[9-14] but rather to identify risk prescriptions during the very early stages of pregnancy. A Dutch study[9] revealed that 2.4% of drugs prescribed during the first trimester belonged to the FDA category D/X (demonstrated or highly suspected malformative risk) and therefore should be considered 'contraindicated' or 'not recommended'. In a German study,[12] 1.2% of women were administered a potentially teratogenic drug during pregnancy, the exact period of prescription being unspecified. Based on the General Health Insurance database,[2] a French study showed that 1.6% of pregnant women were given an FDA category X drug (obvious fetal risk, with risks outweighing benefits), although the exposure time was not mentioned. Likewise, a recent study revealed that 2.5% and 3.2% of women received an FDA category D (obvious fetal risk, with benefits outweighing risks) drug and an FDA category X drug, respectively, during the first trimester.[5] Only 15% of the women participating in our study received reimbursement for folic acid (Spéciafoldine® 0.4 mg or 0.5 mg per day). To reduce neural tube defects, folic acid supplementation is recommended from 4 weeks before conception to 8 weeks after conception.[15] However, these figures are higher than those of a German study,[12] where only 10% of women were given folic acid preparations during the first trimester of pregnancy, the majority of whom received folic acid from the second week after conception, and only 1% of women prior to conception. Our figures are also higher than those of a Norwegian study,[10] in which 0.4% and 1.2% of women received folic acid supplementation from 3 months prior to conception and during the first trimester of pregnancy, respectively. Comparison is hazardous because in France folic acid is routinely prescribed and reimbursed, unlike in many other countries.

The most important limitation of our study is the classification into four categories of teratogenic risk, as based on the description in the SPC. Although SPC information is not standardized, the FDA or Australian risk classifications were not included despite their international use. In fact, for the French prescriber, the SPC is considered to be the main source of information for particular populations or situations such as pregnancy. Another limitation is that the study did not differentiate between drugs with short half-lives prescribed only for short-term use in the month before conception or in the first few days after conception, and drugs with longer half-lives or those prescribed for long-term use on or after postconceptional day 13; therefore, the exposure to teratogenic risk may be overestimated. The other limitations of our study are linked to the RSI database. The first of these limitations is the difficulty in extrapolating our study results to the entire French population as the RSI database represents only 3 million people insured in France. However, although physicians' prescriptions do not take into account occupation, the reimbursement levels of independent professionals have been aligned with the General Health Insurance scheme since 2001. The second limitation is that the health insurance information database was designed to facilitate and control reimbursement, rather than to evaluate medical practice. As the indications for the prescribed drugs are not known, the evaluation of the prescriptions' appropriateness without seeking alternatives, as we did, is difficult. In addition, the health insurance database contained only information on drugs that were subject to reimbursement, and not on all the drugs that were actually taken. For example, as oral contraceptives are prescribed for 1 year and reimbursed every 3 months, it is not certain that the 50 women (2.8%) who received at least one reimbursement for oral contraceptives actually took the drug during the periconceptional period. The same applies to ganirelix, indicated only in medically assisted procreation. In this case, it is difficult to know whether the drug was prescribed while the physician was unaware of the early pregnancy, or whether the drug was bought and reimbursed without actually being taken. Thirdly, our study did not differentiate between drugs used for treatment and supplements such as folic acid used for prevention. This may affect the evaluation of medicinal products used during pregnancy. The fourth limitation of our study stems from the drugs not included in the RSI database, notably those drugs that are not reimbursed or not prescribed, such as self-medication. However, although self-medication is common among pregnant women[16,17] and present in 19.5%[5] during the first trimester, no drugs with teratogenic risk may be dispensed without a prescription. Lastly, as there was no follow-up on the exposed children, we were not able to evaluate

potential consequences of contraindicated drugs based solely on a health insurance database.

Conclusions

Drug prescriptions are common among women of child-bearing potential and may occur during the period of high teratogenic risk if the pregnancy begins shortly thereafter or is unknown. Thus, during the period where teratogenic risk is at its highest, women were administered 4.88 drugs on average, and 1.1% received a contraindicated drug, whereas an alternative drug without fetal risk could have been prescribed in the majority of cases. This may be partly accounted for by physicians not being aware of the pregnancy at the moment where the risk for malformation was at its highest. Dangerous prescriptions could be reduced by adding a section entitled 'women of child-bearing potential' to the SPC, and by educating prescribers that all women aged between 15 and 45 years are potentially pregnant and therefore liable to risks.

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