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ORIGINAL RESEARCH ARTICLE

# Dispensing of Potentially Harmful Prescription Drugs in 1.8 Million Pregnant Women in France: A Nationwide Study Based on Two Risk Classification Systems

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## Abstract

**Introduction** Nationwide prevalence of potentially harmful drug prescribing during pregnancy is unknown in France, and several risk classification systems (RCS) exist to guide prescribers.

**Objective** The aim of this study was to estimate the nationwide prevalence of potentially harmful drug prescribing during pregnancy in France and to describe maternal characteristics associated with this prescription.

**Methods** This drug utilisation study, conducted on the French health databases (67 million beneficiaries), included all pregnancies beginning in 2016–2017, regardless of pregnancy outcome. Potentially harmful drug prescribing was defined as at least one reimbursement during pregnancy of Swedish RCS category D drugs, Australian RCS category D/X drugs, or contraindicated drugs in France for drugs not listed in these two RCSs. Maternal characteristics associated with potentially harmful drug prescribing were described using a univariate logistic regression analysis.

**Results** Among the 1,844,447 pregnant women identified, the prevalence of potentially harmful drug prescribing was higher according to the Australian RCS (3.9%) than according to the Swedish RCS (2.2%), with good agreement between the two RCSs (Kappa = 0.81 [0.74–0.87]). This prevalence increased to 9.2% and 6.9%, respectively, when considering contraindications in France. Prescribing of teratogenic drugs, including retinoids and valproate, was highest during the first trimester, whereas prescribing of foetotoxic drugs decreased after the first trimester but remained high for nonsteroidal anti-inflammatory drugs ($N = 10{,}021$). In women with no chronic diseases, polymedication (five or more drugs) was the strongest maternal characteristic associated with potentially harmful drug prescribing in both RCSs.

**Conclusions** Potentially harmful drug prescribing during pregnancy is not uncommon in France. This study supports the comparative analysis of RCS to assess potentially harmful drug prescribing in claims databases.

## 1 Introduction

The recent valproate crisis in Europe [1], and especially in France, has increased the need for studies investigating potentially harmful drug prescribing during pregnancy in order to establish priorities for pregnancy safety research; however, drug safety during pregnancy can be difficult to assess and this assessment must be updated when new data become available. To guide both health care professionals and women in the prescribing/use of drugs during pregnancy, various risk classification systems have therefore been developed to classify drugs into risk groups according to their foetal safety. Three classification systems, based on data from human and animal studies, are mainly used [2]: (1) the US FDA system, abandoned in 2015 and replaced by a narrative structure for pregnancy labelling in order to more clearly distinguish different degrees of foetal risk and to facilitate informed prescribing decisions and patient counselling [3]; (2) the Australian Therapeutic Goods Administration system [4]; and (3) the Swedish catalogue of registered pharmaceutical specialties system [5]. No such classification is available in France, where drug prescribing during pregnancy is frequent [6, 7] and is higher than in other countries [2]. However, the French Reference Centre for Teratogenic Agents (Centre de référence sur les agents

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**Key Points**

Based on data for nearly 2 million pregnancies and using two risk classification systems, this study provides the first nationwide prevalence of potentially harmful drug prescribing in France, i.e. up to 9.2%, regardless of pregnancy outcome.

A high prevalence of nonsteroidal anti-inflammatory drug (NSAID) prescribing was observed after the first trimester of pregnancy.

Several groups of pregnant women who might benefit the most from prepregnancy counselling were identified, including women with chronic diseases, polymedicated women, and women of younger age or deprived.

This study supports the comparative analysis of updated risk classification systems as a convenient tool to assess potentially harmful drug prescribing during pregnancy in studies based on health care databases.

tératogènes chez la femme enceinte [CRAT]) website provides freely available, reliable, evidence-based, and accurate information about the use of medicines in pregnancy to guide prescribers [8], as has also been developed in other countries, such as the website developed by the UK Teratology Information Service [9].

Based on these three risk classification systems, previous studies have reported large variations in the prevalence of potentially harmful drug prescribing during pregnancy, ranging from 1 to 21% [2]. These variations could be explained by not only the use of different risk groups to define a drug as potentially harmful but also by differences in terms of risk category allocation for the same drug across these three systems [10]. In France, few studies on potentially harmful drug prescribing during pregnancy have been published, most of which were based on regional surveys dating back to the 1990s [11–13], while two more recent studies, based on a sample of the French population, assessed the use of few specific potentially harmful drugs [6, 7]. The current use of potentially harmful drugs during pregnancy at a national level in France therefore remains largely unknown and has never been assessed by using risk classification systems. The maternal factors associated with potentially harmful drug prescribing have also never been reported in France and rarely in Europe [14].

We therefore investigated potentially harmful drug prescribing during pregnancy in France using both the Swedish and Australian risk classification systems, to account for potential differences between these two systems and to allow international comparisons, and described maternal characteristics associated with this prescribing. This study was based on the French healthcare databases, allowing nationwide assessment of potentially harmful drug prescribing during pregnancy.

## 2 Methods

### 2.1 Data Sources

In France, national health insurance (*Assurance Maladie*) provides mandatory health insurance cover for the entire population living in France; all individuals are affiliated from birth or immigration until death or emigration, irrespective of healthcare provider, age, socioeconomic status or retirement status. The corresponding French national health database (Système national des données de santé [SNDS]) therefore covers 99% of the 67 million people living in France [15] and consists of three nationwide datasets linked by a unique patient identifier: the French national health insurance database, the French hospital discharge database, and the national death registry. The health insurance database contains all individualised and anonymous health care claims reimbursed by French National Health Insurance, as well as demographic and socioeconomic data. In particular, it contains all prescription drugs dispensed by community or hospital pharmacies to outpatients and reimbursed by *Assurance Maladie*, which are coded according to the Anatomical Therapeutic Chemical (ATC) classification, as well as medical procedures, which are coded according to the French medical classification of clinical procedures (*Classification commune des actes médicaux* [CCAM]). The hospital discharge database provides detailed medical information on all admissions to public and private hospitals in France, including discharge diagnosis International Classification of Diseases, Tenth Revision (ICD-10) codes, medical procedures coded according to the CCAM, and expensive drugs administered in hospital, which have to be invoiced in addition to the stay.

This linkage has previously been used to conduct large-scale studies on drug use and safety during pregnancy [16–18].

### 2.2 Study Design and Population

In this drug utilisation study, all pregnancies starting between January 2016 and December 2017 were eligible for inclusion regardless of the outcome. The pregnancy outcomes considered were live birth, stillbirth, induced abortion (elective and therapeutic), spontaneous abortion, ectopic pregnancy and hydatidiform mole or other abnormal products of conception (e.g., blighted ovum, non-hydatidiform mole or early foetal death with retention of the dead foetus).

These pregnancies were identified by using a published algorithm based on discharge diagnoses and medical procedures indicative of completion of pregnancy [19] (electronic supplementary material [ESM] Table 1). The procedure date, when available, or admission date, was used as the pregnancy outcome date. The pregnancy start date was calculated from this outcome date and gestational age for all outcomes except for outpatient medical abortion, for which gestational age was not available and was considered to be 6 weeks [19], corresponding to the median gestational age for outpatient medical abortions in a French survey. When a woman had several pregnancies during the study period, all pregnancies were considered.

The mother had to have at least one health care reimbursement by any mandatory health insurance scheme during the 12-month period before the trimester preceding pregnancy to ensure comprehensive assessment of drug use from the trimester preceding pregnancy until the end of pregnancy.

### 2.3 Exposure

A drug was considered to be prescribed to a pregnant woman when she had been reimbursed for this drug at least once between the estimated first day of pregnancy to the estimated last day of pregnancy. In France, chronic medication dispensing usually cannot exceed a 30-day supply. All reimbursed prescription drugs were taken into account except for homeopathic medicines, for which no risk classification exists, misoprostol (Cytotec®, Pfizer, Paris; indicated for the healing of duodenal ulcer and gastric ulcer or for the prophylaxis of nonsteroidal anti-inflammatory drug (NSAID)-induced ulcers, withdrawn from the market on 1 March 2018) used off-label to induce abortion in France, the mifepristone/misoprostol combination specifically reimbursed to induce elective abortion (see pregnancy outcomes in ESM Table 1), and hormones, including contraceptives and drugs indicated for fertility disorders, for which available evidence suggests that the potential for foetal harm is unlikely [20–23]. Furthermore, regarding contraceptives, only first-generation (norethisterone-containing pills) or second-generation (levonorgestrel- or norgestrel-containing pills) combined oral contraceptives and certain pills containing desogestrel are reimbursed in France.

All excluded drugs and their ATC classes are indicated in ESM Table 2. The term 'drug' is used throughout the manuscript as a synonym for the 5th-level ATC class.

For pregnancies resulting in a live birth, the gestation period was divided into three 90-day intervals corresponding to the three trimesters of pregnancy: days 0–90 (first trimester), days 91–181 (second trimester) and day 182 until delivery (third trimester).

### 2.4 Outcome

The outcome was the prevalence of potentially harmful drug prescribing during pregnancy.

Each drug reimbursed during pregnancy was classified according to its foetal safety. Two risk classification systems were used—the Swedish and Australian risk classification systems. These two classification systems are similar except that, in addition to categories A, B1, B2, B3, C and D, the Australian system uses a category X for drugs with the highest risk of causing permanent damage to the foetus. The definitions of these categories are presented in ESM Table 3. Data from the French Summary of Product Characteristics (SmPCs), provided by the French Ministry of Health and available online [24], were also reviewed.

Two definitions were used to define potentially harmful drugs during pregnancy: (1) category D drugs according to the Swedish system, or category D or X drugs according to the Australian system (Table 1); and (2) drugs not listed in the Swedish or Australian systems and contraindicated in the French SmPCs, in addition to the potentially harmful drugs identified by using definition 1. A drug was considered to be contraindicated in the French SmPCs when pregnancy was mentioned in the 'Contraindication' section, or when the 'Fertility, pregnancy and lactation' section stated that the drug must not be used during pregnancy. Labelling of the contraindications in the French SmPCs is based on human and animal data rather than a lack of evidence, according to the European guidelines on risk assessment of drugs on human reproduction [25].

Details on the algorithm used to classify drugs according to their foetal safety are presented in ESM Table 4.

### 2.5 Statistical Analysis

All results are reported separately for the Swedish and Australian risk classification systems.

The prevalence of potentially harmful drug prescribing during pregnancy was defined as the number of pregnancies with a reimbursement for a potentially harmful drug divided by the number of pregnancies reported in the study population and expressed as a percentage. Prevalence rates were also stratified by pregnancy outcome and by trimester of pregnancy for live births, and detailed for each potentially harmful drug. For the calculation of prevalence rates in the second or third trimester, only pregnancies lasting beyond the first or second trimester, respectively, were considered in the denominator.

Two sensitivity analyses were conducted. To define outcome, potentially harmful drug prescribing during pregnancy was assessed by pooling categories C and D/X, and also by pooling categories B3, C and D/X (see ESM Table 3 for the definitions of these risk categories). To define

**Table 1** Definition of potentially harmful drugs according to the Swedish and Australian risk categories D and D/X for prescribing medicines in pregnancy

| | Swedish classification | Australian classification |
|---|---|---|
| D | Drugs which, in humans, have caused or may be expected to cause an increased frequency of foetal malformations or other permanent damage. This category includes drugs with primarily teratogenic effects. If the drug also has negative pharmacological effects that can directly or indirectly result in adverse effects on the foetus, this is also stated. | Drugs which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. |
| X | | Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy. |

exposure, the reimbursement window was extended to the 90-day period before pregnancy.

To assess potential differences in risk category allocation (categories D or D/X versus other categories) of the drugs prescribed in the study population, Cohen's Kappa coefficient was calculated to assess the agreement between the two risk classification systems after restriction to ATC drugs present in both systems. The specialty (hospital practitioner, general practitioner, private specialists) of physicians prescribing potentially harmful drugs were also reported.

To identify subgroups of women who were more likely to be prescribed potentially harmful prescription drugs, maternal characteristics associated with the prescribing of potentially harmful drugs during pregnancy were described according to the Swedish and Australian systems. These characteristics included sociodemographics, chronic diseases and healthcare system utilisation, and are listed in ESM Table 5. Crude odds ratios (OR) with their 95% confidence intervals were calculated using univariate logistic regression models, accounting for correlations within women with multiple pregnancies by using generalised estimating equations with a binomial distribution. The study population for this analysis was restricted to women enrolled in the French national health insurance general scheme for salaried workers, representing 82.7% of all pregnancies included in this study, for whom complete data are available to define maternal characteristics. The association between each maternal characteristic and potentially harmful drug prescribing was therefore described in this population and in women with no chronic diseases.

In addition, prevalence estimates were reported for the prescription of the most harmful drugs or drug classes during pregnancy according to the French Reference Centre for Teratogenic Agents (CRAT) [26]. All ATC codes are provided in ESM Table 6.

## 3 Results

A total of 1,844,447 pregnancies starting in 2016 or 2017 were included in the study population, of which 1,348,098 (73.1%) ended in a live birth, 374,483 (20.3%) ended in an induced abortion (elective or therapeutic), 69,127 (3.7%) ended in a spontaneous abortion, 23,134 (1.3%) ended in an ectopic pregnancy, 7049 (0.4%) ended in a stillbirth and 22,556 (1.2%) ended as a result of other outcomes (Fig. 1).

Among the study population, 1,682,156 pregnancies (91.2%) were exposed to at least one reimbursed drug, with a median of six different drugs (interquartile range [IQR] 4–9). After exclusion of reimbursements for misoprostol and hormones, a total of 1097 different drugs were prescribed in this population (Fig. 1).

### 3.1 Prevalence of Potentially Harmful Drug Prescribing During Pregnancy According to Two Classification Systems

#### 3.1.1 Differences Between the Australian and Swedish Risk Classification Systems

Of the 1097 different drugs, 699 (63.7%) were listed in the Swedish system and 692 (63.1%) were listed in the Australian system (Fig. 1).

Considering all pregnancy outcomes, the prevalence of potentially harmful drug prescribing during pregnancy was higher according to the Australian risk classification system (3.9%; 72,568 pregnancies) than according to the Swedish system (2.2%; 40,131 pregnancies), and increased to 9.2% and 6.9%, respectively, when taking into account drugs that are contraindicated during pregnancy in France. These prevalence rates were lower when the study population was restricted to live births (1.8% vs. 2.2%, and 3.8% vs. 3.9% for the Swedish and Australian systems, respectively), and higher when the study population was restricted to induced

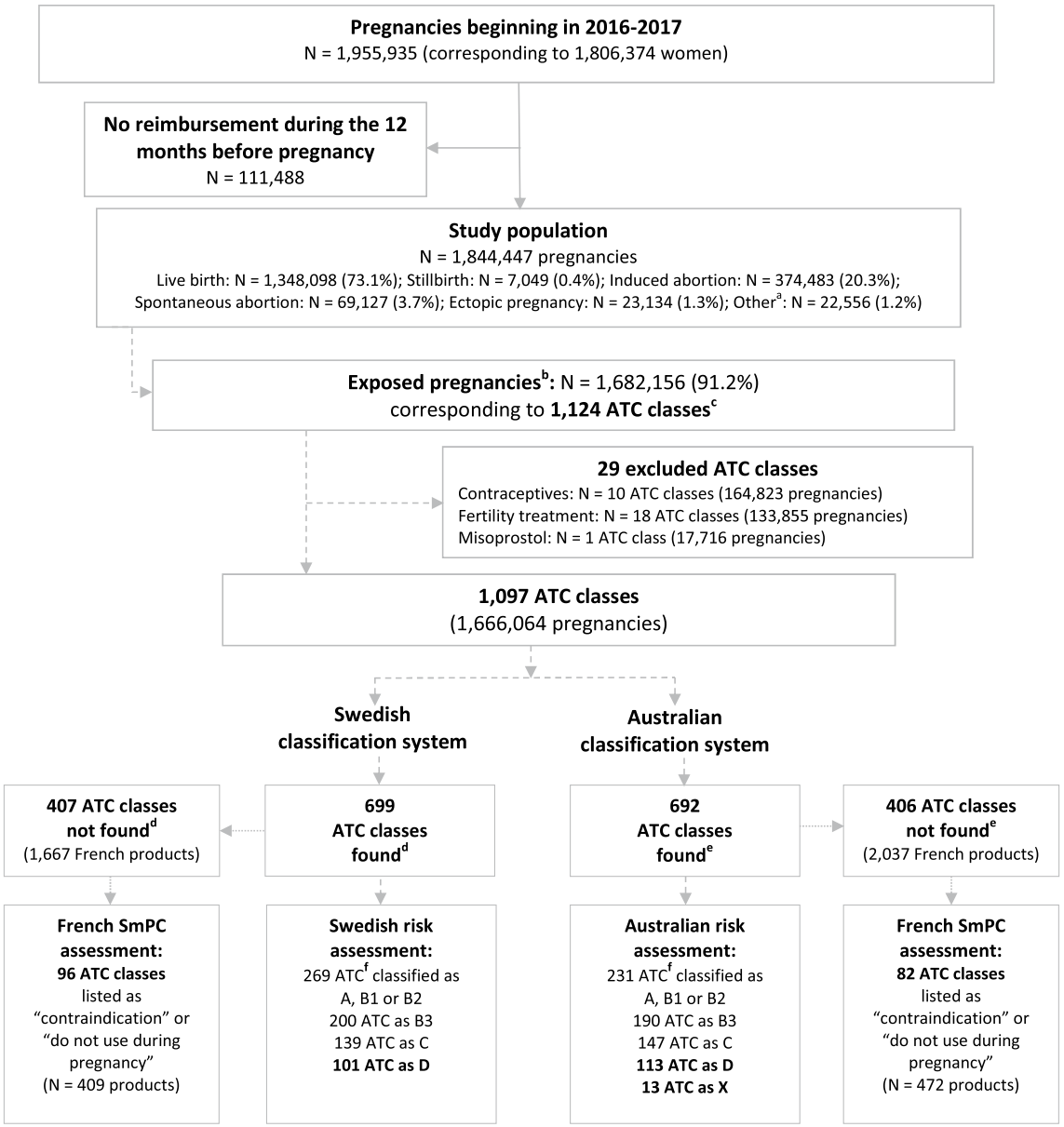


**Fig. 1** Flowchart: definition of the study population and classification of ATC codes according to the two classification systems. Solid lines correspond to the definition of the study population, while dotted lines refer to the attribution of risk categories to ATC classes prescribed to pregnant women exposed to at least one drug during pregnancy. [a]Hydatidiform mole or other abnormal products of conception. [b]Excluding homeopathic medicines. [c]Fifth-level ATC classes. [d]Nine ATC classes corresponding to drug combinations (A02AD01, A06AD10, B01AC30, B05BA10, B05XA31, C03EA01, N01BB52, S01CA01 and S01XA20) are classified in both groups: the Swedish risk category was only applied to French products composed of the same molecules. [e]ATC class B02BD02 is classified in both groups, as all types of coagulation factor VIII are listed in the Australian classification system except for turoctocog alfa and human coagulation factor VIII. [f]Numbers do not add up because some ATC classes were assigned different risk categories due, in particular, to the existence of different routes of administration for the same ATC class, corresponding to different risk categories (e.g., tobramycin for inhalation classified as B3, and tobramycin for injection classified as D; see ESM Table 4 for other reasons). *ATC* anatomical therapeutic chemical, *SmPC* summary of product characteristics

abortions. A decrease in prevalence rates was observed throughout pregnancy according to both the Australian and Swedish systems (Table 2).

Among pregnant women to whom at least one potentially harmful drug was prescribed, 2.9% and 5.3% of women had two or more different potentially harmful drugs according

to the Swedish and Australian systems, respectively (9.2% and 11.2% when also considering drugs contraindicated in France). Furthermore, 20.0% and 30.2% of women were reimbursed for a potentially harmful drug two or more times during pregnancy according to the Swedish and Australian systems, respectively (17.2% and 24.2%). In addition to the potentially harmful drug, a median of 2.0 (IQR 1–3) drugs were also dispensed on the same day, according to both systems.

Potentially harmful drugs were mainly prescribed by hospital and general practitioners regardless of the classification system used (40.8% and 34.3% according to the Swedish system, and 39.3% and 36.5% according to the Australian system). Gynaecologists accounted for 10.3% and 7.6% of all potentially harmful drug prescriptions, respectively.

#### 3.1.2 Sensitivity Analyses

When considering category C (or categories B3 and C) [see ESM Table 3], the prevalence of potentially harmful drug prescribing increased to 23.5% (46.0%) according to the Australian system and 44.3% (71.7%) according to the Swedish system (Table 2).

When the reimbursement window was extended to the 90-day period before pregnancy, the prevalence increased to 6.7% (18.7% when considering drugs contraindicated in France) according to the Australian system and 4.1% (16.2%) according to the Swedish system (Table 2).

### 3.2 Nature of Potentially Harmful Drugs Prescribed during Pregnancy

#### 3.2.1 Differences Between the Australian and Swedish Classification Systems

Table 3 reports the potentially harmful drug prescribing prevalence rates in descending order, according to the Swedish or Australian systems, for drugs with an exposure rate of at least 1 per 10,000 pregnancies, i.e. 40 different potentially harmful drugs. Twenty (50%) of these drugs were not common to both classifications. Among these 20 drugs, 13 were classified as potentially harmful in the Australian system but not in the Swedish system: four of these drugs were not found in the Swedish system (chlorpromazine, tretinoin for topical use, albendazole, retinol for systemic use [FSU]), while nine drugs were

**Table 2** Prevalence of potentially harmful drug prescribing during pregnancy according to the Swedish and Australian risk classification systems and data from French SmPCs

| | Swedish classification [*N* (%)] | | Australian classification [*N* (%)] | |
|---|---|---|---|---|
| | Category D | Category D or French contraindication | Category D or X | Category D, X or French contraindication |
| All pregnancies | 40,131 (2.2) | 127,438 (6.9) | 72,568 (3.9) | 169,020 (9.2) |
| By pregnancy outcome | | | | |
| Live births | 24,169 (1.8) | 73,363 (5.4) | 51,500 (3.8) | 114,071 (8.5) |
| Stillbirths | 164 (2.3) | 497 (7.1) | 301 (4.3) | 715 (10.1) |
| Induced abortions | 13,590 (3.6) | 44,953 (12.0) | 17,223 (4.6) | 44,808 (12.0) |
| Spontaneous abortions | 1295 (1.9) | 5317 (7.7) | 2154 (3.1) | 5817 (8.4) |
| Ectopic pregnancies | 454 (2.0) | 1553 (6.7) | 689 (3.0) | 1677 (7.2) |
| Other[a] | 459 (2.0) | 1755 (7.8) | 701 (3.1) | 1932 (8.6) |
| By trimester | | | | |
| First trimester | 16,055 (1.2) | 50,379 (3.7) | 32,585 (2.4) | 75,259 (5.6) |
| Second trimester | 7959 (0.6) | 18,203 (1.4) | 22,343 (1.7) | 39,207 (2.9) |
| Third trimester | 6,105 (0.5) | 14,116 (1.1) | 17,619 (1.3) | 27,473 (2.0) |
| *Sensitivity analysis* | | | | |
| *Exposure definition* | | | | |
| *Including T-1*[b] | *74,937 (4.1)* | *298,541 (16.2)* | *123,414 (6.7)* | *345,578 (18.7)* |
| *Outcome definition* | | | | |
| *Including category C drugs* | *816,300 (44.3)* | *851,448 (46.2)* | *432,732 (23.5)* | *490,445 (26.6)* |
| *Including category C and B3 drugs* | *1,323,143 (71.7)* | *1,344,673 (72.9)* | *847,869 (46.0)* | *882,985 (47.9)* |

*SmPCs* Summary of Product Characteristics Figures in italics refer to the results of the sensitivity analyses

[a]Hydatidiform mole or other abnormal products of conception

[b]With the dispensing window including the trimester before pregnancy (90-day period before the beginning of pregnancy)

classified in another risk category (C: nicotine, paroxetine; B3: fluconazole FSU, lamotrigine, hydroxychloroquine, adapalene, simvastatin; A/B3: interferon β-1a; B2: etanercept). Finally, the remaining seven drugs were classified as potentially harmful in the Swedish system but not in the Australian system: four of these drugs were not found in the Australian system (sulfamethoxazole/trimethoprim, lymecycline, diclofenac/misoprostol, irbesartan/diuretics), and three drugs were classified in another risk category (B3: clonazepam; B1: ondansetron; A: erythromycin FSU) (Table 3).

Overall, when restricting the drugs reimbursed to pregnant women to the 549 ATCs common to the Swedish and Australian classification systems, a kappa coefficient of 0.81 (0.74–0.87) indicated good agreement between the two classification systems. The 30 potentially harmful drugs that differed between the two systems are reported in ESM Table 7.

The five potentially harmful drugs most commonly prescribed according to the Swedish system were doxycycline FSU, erythromycin FSU, ondansetron, sulfamethoxazole/trimethoprim and azathioprine, and, according to the Australian system, doxycycline, nicotine, fluconazole FSU, paroxetine and lamotrigine (Table 3 and ESM Table 8). Of the drugs contraindicated during pregnancy in France, in addition to NSAIDs (classified as C in the Swedish and Australian systems), the most commonly prescribed were tramadol/paracetamol combination, thiocolchicoside, ofloxacin FSU, progesterone/estrogen vaginal tablet and dexamethasone/oxytetracycline for ophthalmological use (ESM Table 8).

#### 3.2.2 Potentially Harmful Drug Prescribing According to Pregnancy Outcomes and Trimesters

Induced abortion represented more than one-half of all pregnancy outcomes for cyproterone, primidone, thalidomide, teriflunomide, retinoids FSU, NSAIDs FSU and tetracyclines (Tables 3, 4). Ectopic pregnancy was the most commonly observed outcome (42.7%) following methotrexate prescribing in both indications (antineoplastic and immunosuppressant agent).

The highest prevalence of teratogenic drug prescribing was observed during the first trimester of pregnancy, i.e., the highest risk period. Prescribing of foetotoxic drugs decreased during the second and third trimesters (highest risk period), but remained high, especially for NSAIDs, from the sixth month of pregnancy onwards (Table 4 and ESM Table 9). Similar trends were observed for valproic acid/valpromide, which are both teratogenic and foetotoxic, for which the most commonly observed outcome was induced abortion (41.8%) (Table 4).

### 3.3 Maternal Characteristics Associated with Potentially Harmful Drug Prescribing During Pregnancy

Maternal characteristics associated with potentially harmful drug prescribing during pregnancy are shown in Table 5. Considering both systems, eligibility for a disability allowance, chronic diseases, polymedication (five or more drugs), alcoholism and illicit drug use were the strongest maternal characteristics (OR ≥2) associated with an increased risk of potentially harmful drug prescribing during pregnancy. In women with no chronic diseases, the only maternal characteristic remaining strongly associated in both systems was polymedication (five or more drugs).

## 4 Discussion

Based on data for nearly 2 million pregnancies beginning in 2016–2017, this study provides the first nationwide estimation of the prevalence of potentially harmful drug prescribing during pregnancy in France according to the Swedish and Australian risk classification systems (2.2% and 3.9%, respectively), with good agreement between the two systems. This prevalence increased to 9.2% when drugs contraindicated during pregnancy in France were taken into account. Most women with a prescription of potentially harmful drugs had only one prescription. The highest prevalence of teratogenic drug prescribing was observed during the first trimester and, among foetotoxic drug classes prescribed after the first trimester, the prevalence of NSAID prescribing was high.

### 4.1 Comparison with Previous Studies

Most studies evaluating the nationwide prevalence of potentially harmful drug use were based on the FDA risk classification system [2]. Although direct comparisons between studies are difficult due to differences in methodology and differences in marketed drugs across countries, the prevalence rates reported in these studies using only categories D and X were comparable with those observed in this study, ranging from 1.1 to 5.8% for pregnancies ending in a live birth [20, 27–31]. NSAIDs are category C drugs according to the Swedish and Australian systems and were therefore not considered to be potentially harmful in our main analysis. However, this study showed a high prevalence of NSAID prescribing after the first trimester, albeit lower than the rates observed in the 1990s in two different French regions [11, 13]. This observed prevalence rate was higher than in Norway [32], The Netherlands [33] or Sweden [34]. Variations in the proportion of over-the-counter (OTC) NSAID

**Table 3** Prevalence of potentially harmful drug prescribing at any time during pregnancy, according to the Swedish or Australian systems (for drugs with at least 1 per 10,000 pregnancies exposed)

| ATC code | ATC name | Source (classification system) | *N* (prevalence per 100 pregnancies) | By pregnancy outcome [row % (prevalence per 100 pregnancies)] | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Live births [*N* = 1,348,098] | Induced abortions [*N* = 374,483] | Spontaneous abortions [*N* = 69,127] | Ectopic pregnancies [*N* = 23,134] | Stillbirths [*N* = 7049] | Other[a] [*N* = 22,556] |
| N07BA01 | Nicotine | Australian | 17,567 (0.952) | 95.6 (1.246) | 2.1 (0.098) | 1.3 (0.333) | 0.2 (0.125) | 0.5 (1.135) | 0.4 (0.275) |
| J01AA02 | Doxycycline | Swedish/Australian | 14,726 (0.798) | 28.8 (0.315) | 65.3 (2.568) | 3.6 (0.765) | 0.7 (0.471) | 0.1 (0.312) | 1.4 (0.913) |
| J02AC01 | Fluconazole | Australian | 9836 (0.533) | 83.4 (0.608) | 12.8 (0.337) | 2.2 (0.314) | 0.7 (0.290) | 0.3 (0.369) | 0.6 (0.279) |
| N06AB05 | Paroxetine | Australian | 7376 (0.400) | 67.4 (0.369) | 26.0 (0.512) | 3.7 (0.392) | 1.0 (0.333) | 0.5 (0.482) | 1.4 (0.452) |
| J01FA01 | Erythromycin | Swedish | 4989 (0.270) | 94.3 (0.349) | 3.6 (0.048) | 1.2 (0.087) | 0.1 (0.030) | 0.4 (0.255) | 0.4 (0.089) |
| A04AA01 | Ondansetron | Swedish | 4533 (0.246) | 92.7 (0.312) | 5.0 (0.060) | 1.1 (0.071) | 0.0 (0.009) | 0.7 (0.454) | 0.4 (0.089) |
| N03AX09 | Lamotrigine | Australian | 4461 (0.242) | 77.4 (0.256) | 15.7 (0.187) | 4.2 (0.271) | 0.9 (0.182) | 0.5 (0.326) | 1.2 (0.239) |
| J01EE01 | Sulfamethoxazole/trimethoprim | Swedish | 3897 (0.211) | 85.4 (0.247) | 10.1 (0.105) | 2.2 (0.126) | 0.4 (0.073) | 0.4 (0.227) | 1.4 (0.248) |
| N05AA01 | Chlorpromazine | Australian | 3453 (0.187) | 91.3 (0.234) | 5.3 (0.049) | 2.2 (0.110) | 0.1 (0.017) | 0.6 (0.270) | 0.5 (0.080) |
| P01BA02 | Hydroxychloroquine | Australian | 2625 (0.142) | 80.5 (0.157) | 10.7 (0.075) | 5.1 (0.195) | 1.0 (0.112) | 0.9 (0.340) | 1.7 (0.200) |
| D10AD03 | Adapalene | Australian | 1920 (0.104) | 68.8 (0.098) | 27.1 (0.139) | 2.1 (0.059) | 0.9 (0.073) | 0.3 (0.085) | 0.8 (0.067) |
| L04AX01 | Azathioprine | Swedish/Australian | 1654 (0.090) | 83.1 (0.102) | 8.8 (0.039) | 4.5 (0.108) | 1.1 (0.078) | 1.0 (0.241) | 1.5 (0.106) |
| J01AA04 | Lymecycline | Swedish | 1508 (0.082) | 56.6 (0.063) | 36.7 (0.148) | 4.2 (0.091) | 1.3 (0.082) | 0.3 (0.071) | 0.9 (0.062) |
| D10AD01 | Tretinoin | Australian | 1095 (0.059) | 69.9 (0.057) | 25.8 (0.076) | 2.1 (0.033) | 1.3 (0.061) | 0.4 (0.057) | 0.5 (0.027) |
| P02CA03 | Albendazole | Australian | 1063 (0.058) | 78.5 (0.062) | 17.0 (0.048) | 2.3 (0.035) | 1.3 (0.061) | 0.3 (0.043) | 0.7 (0.031) |
| M04AC01 | Colchicine | Swedish/Australian | 791 (0.043) | 82.3 (0.048) | 12.6 (0.027) | 3.0 (0.035) | 0.6 (0.022) | 0.5 (0.057) | 0.9 (0.031) |
| C10AA05 | Atorvastatin | Swedish/Australian | 593 (0.032) | 66.8 (0.029) | 23.4 (0.037) | 4.9 (0.042) | 2.2 (0.056) | 0.8 (0.071) | 1.9 (0.049) |
| C09AA05 | Ramipril | Swedish/Australian | 574 (0.031) | 60.3 (0.026) | 30.3 (0.046) | 5.4 (0.045) | 1.2 (0.030) | 1.0 (0.085) | 1.7 (0.044) |
| N03AG01 | Valproic acid | Swedish/Australian | 569 (0.031) | 52.7 (0.022) | 40.1 (0.061) | 4.0 (0.033) | 1.2 (0.030) | 0.7 (0.057) | 1.2 (0.031) |
| N03AF01 | Carbamazepine | Swedish/Australian | 567 (0.031) | 58.9 (0.025) | 31.0 (0.047) | 4.8 (0.039) | 3.2 (0.078) | 0.9 (0.071) | 1.2 (0.031) |
| A11CA01 | Retinol (vit a) | Australian | 534 (0.029) | 93.6 (0.037) | 4.1 (0.006) | 1.1 (0.009) | 0.2 (0.004) | 0.6 (0.043) | 0.4 (0.009) |

**Table 3** (continued)

| ATC code | ATC name | Source (classification system) | *N* (prevalence per 100 pregnancies) | By pregnancy outcome [row % (prevalence per 100 pregnancies)] | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Live births [*N* = 1,348,098] | Induced abortions [*N* = 374,483] | Spontaneous abortions [*N* = 69,127] | Ectopic pregnancies [*N* = 23,134] | Stillbirths [*N* = 7049] | Other[a] [*N* = 22,556] |
| N03AX11 | Topiramate | Swedish/Australian | 496 (0.027) | 56.3 (0.021) | 36.5 (0.048) | 5.2 (0.038) | 1.0 (0.022) | 0.4 (0.028) | 0.6 (0.013) |
| J01GB01 | Tobramycin | Swedish/Australian | 451 (0.024) | 92.5 (0.031) | 4.9 (0.006) | 1.6 (0.010) | 0.2 (0.004) | 0.2 (0.014) | 0.7 (0.013) |
| C09AA04 | Perindopril | Swedish/Australian | 436 (0.024) | 61.9 (0.020) | 29.4 (0.034) | 5.3 (0.033) | 1.6 (0.030) | 0.7 (0.043) | 1.1 (0.022) |
| N05AN01 | Lithium | Swedish/Australian | 362 (0.020) | 57.2 (0.015) | 35.4 (0.034) | 3.6 (0.019) | 2.2 (0.035) | 0.0 (0.000) | 1.7 (0.027) |
| M01AB55 | Diclofenac/misoprostol[b] | Swedish | 357 (0.019) | 60.2 (0.016) | 30.0 (0.029) | 6.7 (0.035) | 1.1 (0.017) | 0.3 (0.014) | 1.7 (0.027) |
| C09CA04 | Irbesartan | Swedish/Australian | 322 (0.017) | 58.7 (0.014) | 32.9 (0.028) | 5.6 (0.026) | 0.9 (0.013) | 0.6 (0.028) | 1.2 (0.018) |
| L03AB07 | Interferon β-1a | Australian | 310 (0.017) | 79.7 (0.018) | 13.5 (0.011) | 2.6 (0.012) | 1.9 (0.026) | 1.0 (0.043) | 1.3 (0.018) |
| N03AE01 | Clonazepam | Swedish | 288 (0.016) | 77.1 (0.016) | 16.7 (0.013) | 4.9 (0.020) | 0.0 (0.000) | 0.3 (0.014) | 1.0 (0.013) |
| B01AA03 | Warfarin | Swedish/Australian | 251 (0.014) | 54.2 (0.010) | 30.7 (0.021) | 9.6 (0.035) | 2.4 (0.026) | 0.8 (0.028) | 2.4 (0.027) |
| G03HA01 | Cyproterone | Swedish/Australian | 251 (0.014) | 36.3 (0.007) | 58.2 (0.039) | 3.2 (0.012) | 0.0 (0.000) | 0.0 (0.000) | 2.4 (0.027) |
| L04AB01 | Etanercept | Australian | 235 (0.013) | 74.5 (0.013) | 19.1 (0.012) | 3.8 (0.013) | 1.3 (0.013) | 0.4 (0.014) | 0.9 (0.009) |
| C10AA01 | Simvastatin | Australian | 232 (0.013) | 68.1 (0.012) | 22.0 (0.014) | 6.9 (0.023) | 0.4 (0.004) | 1.3 (0.043) | 1.3 (0.013) |
| C09CA03 | Valsartan | Swedish/Australian | 222 (0.012) | 57.7 (0.009) | 32.4 (0.019) | 6.3 (0.020) | 1.8 (0.017) | 0.5 (0.014) | 1.4 (0.013) |
| C10AA07 | Rosuvastatin | Swedish/Australian | 211 (0.011) | 67.3 (0.011) | 26.1 (0.015) | 3.3 (0.010) | 1.9 (0.017) | 0.5 (0.014) | 0.9 (0.009) |
| N03AF02 | Oxcarbazepine | Swedish/Australian | 206 (0.011) | 68.9 (0.011) | 24.8 (0.014) | 3.4 (0.010) | 1.0 (0.009) | 0.0 (0.000) | 1.9 (0.018) |
| C09CA06 | Candesartan | Swedish/Australian | 196 (0.011) | 59.7 (0.009) | 28.1 (0.015) | 6.6 (0.019) | 1.5 (0.013) | 1.5 (0.043) | 2.6 (0.022) |
| C09DA04 | Irbesartan/diuretics | Swedish | 190 (0.010) | 65.3 (0.009) | 26.3 (0.013) | 4.2 (0.012) | 2.1 (0.017) | 1.1 (0.028) | 1.1 (0.009) |
| C09DB01 | Valsartan/amlodipine | Swedish/Australian | 187 (0.010) | 67.4 (0.009) | 25.7 (0.013) | 3.7 (0.010) | 1.1 (0.009) | 1.6 (0.043) | 0.5 (0.004) |
| L04AX03 | Methotrexate | Swedish/Australian | 187 (0.010) | 31.0 (0.004) | 31.6 (0.016) | 3.7 (0.010) | 30.5 (0.246) | 1.6 (0.043) | 1.6 (0.013) |

*ATC* Anatomical Therapeutic Chemical

[a]Hydatidiform mole or other abnormal products of conception

[b]In France, ATC class M01AB55 only includes the combination of diclofenac and misoprostol (ARTOTEC®, Pfizer, France)

**Table 4** Prescribing prevalence for the most harmful drugs during pregnancy according to the French Reference Centre for Teratogenic Agents (CRAT)

| Harmful drug/drug class | *N*, prevalence (per 100 pregnancies) | *N*, prevalence for high-risk period (per 100 pregnancies) | By pregnancy outcome [row % (prevalence per 100 pregnancies)] | | | | | | By trimester (considering live births only) [row % (prevalence per 100 pregnancies)] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Live births [*N* = 1,348,098] | Induced abortions [*N* = 374,483] | Spontaneous abortions [*N* = 69,127] | Ectopic pregnancies [*N* = 23,134] | Stillbirths [*N* = 7049] | Other[a] [*N* = 22,556] | First trimester [*N* = 1,348,098] | Second trimester [*N* = 1,348,098] | Third trimester [*N* = 1,343,716] |
| *Teratogenic drugs to be prohibited or only to be used in the absence of a safer therapeutic alternative (risk period: first trimester)* | | | | | | | | | | | |
| Retinoids[b] | 3162 (0.171) | 2594 (0.141) | 67.2 (0.158) | 28.6 (0.242) | 2.1 (0.095) | 1.1 (0.156) | 0.3 (0.142) | 0.6 (0.089) | 73.7 (0.116) | 17.6 (0.028) | 13.3 (0.021) |
| Systemic use | 178 (0.010) | 166 (0.009) | 30.3 (0.004) | 64.6 (0.031) | 1.7 (0.004) | 3.4 (0.026) | 0.0 (0.000) | 0.0 (0.000) | 79.6 (0.003) | 18.5 (0.001) | 7.4 (0.000) |
| Topical use | 2988 (0.162) | 2432 (0.132) | 69.3 (0.154) | 26.5 (0.211) | 2.1 (0.091) | 1.0 (0.134) | 0.3 (0.142) | 0.7 (0.089) | 73.6 (0.113) | 17.6 (0.027) | 13.4 (0.021) |
| Antiepileptic drugs[c] | 1845 (0.100) | 1686 (0.091) | 55.3 (0.076) | 36.2 (0.178) | 4.9 (0.130) | 1.7 (0.138) | 0.8 (0.199) | 1.1 (0.089) | 84.8 (0.064) | 45.2 (0.034) | 41.9 (0.032) |
| Valproic acid/valpromide[d] | 737 (0.040) | 656 (0.036) | 49.8 (0.027) | 41.8 (0.082) | 4.7 (0.051) | 1.4 (0.043) | 0.9 (0.099) | 1.4 (0.044) | 78.5 (0.021) | 29.7 (0.008) | 27.5 (0.008) |
| Carbamazepine | 567 (0.031) | 524 (0.028) | 58.9 (0.025) | 31.0 (0.047) | 4.8 (0.039) | 3.2 (0.078) | 0.9 (0.071) | 1.2 (0.031) | 87.4 (0.022) | 68.6 (0.017) | 63.5 (0.016) |
| Phenobarbital | 96 (0.005) | 86 (0.005) | 75.0 (0.005) | 18.8 (0.005) | 4.2 (0.006) | 0.0 (0.000) | 1.0 (0.014) | 1.0 (0.004) | 86.1 (0.005) | 70.8 (0.004) | 65.3 (0.003) |
| Primidone | 10 (0.001) | 9 (0.000) | 50.0 (0.000) | 50.0 (0.001) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 80.0 (0.000) | 40.0 (0.000) | 20.0 (0.000) |
| Topiramate | 496 (0.027) | 466 (0.025) | 56.3 (0.021) | 36.5 (0.048) | 5.2 (0.038) | 1.0 (0.022) | 0.4 (0.028) | 0.6 (0.013) | 89.6 (0.019) | 30.1 (0.006) | 28.7 (0.006) |
| Thalidomide and derivatives | 70 (0.004) | 59 (0.003) | 47.1 (0.002) | 51.4 (0.010) | 0.0 (0.000) | 1.4 (0.004) | 0.0 (0.000) | 0.0 (0.000) | 66.7 (0.002) | 12.1 (0.000) | 30.3 (0.001) |
| Thalidomide | 1 (0.000) | 1 (0.000) | 0.0 (0.000) | 100.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) |
| Lenalidomide | 1 (0.000) | 0 (0.000) | 100.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 100.0 (0.000) |
| Teriflunomide | 45 (0.002) | 39 (0.002) | 35.6 (0.001) | 62.2 (0.007) | 0.0 (0.000) | 2.2 (0.004) | 0.0 (0.000) | 0.0 (0.000) | 62.5 (0.001) | 0.0 (0.000) | 37.5 (0.000) |
| Leflunomide | 23 (0.001) | 19 (0.001) | 69.6 (0.001) | 30.4 (0.002) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 75.0 (0.001) | 25.0 (0.000) | 18.8 (0.000) |
| Antineoplastic drugs[e] | 484 (0.026) | 414 (0.022) | 47.3 (0.017) | 24.6 (0.032) | 4.1 (0.029) | 21.5 (0.450) | 0.2 (0.014) | 2.3 (0.049) | 72.5 (0.012) | 36.7 (0.006) | 36.7 (0.006) |
| VKA oral anticoagulants | 640 (0.035) | 612 (0.033) | 54.7 (0.026) | 33.4 (0.057) | 6.9 (0.064) | 1.4 (0.039) | 0.6 (0.057) | 3.0 (0.084) | 92.3 (0.024) | 16.9 (0.004) | 12.3 (0.003) |

**Table 4** (continued)

| Harmful drug/drug class | *N*, prevalence (per 100 pregnancies) | *N*, prevalence for high-risk period (per 100 pregnancies) | By pregnancy outcome [row % (prevalence per 100 pregnancies)] | | | | | | By trimester (considering live births only) [row % (prevalence per 100 pregnancies)] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Live births [*N* = 1,348,098] | Induced abortions [*N* = 374,483] | Spontaneous abortions [*N* = 69,127] | Ectopic pregnancies [*N* = 23,134] | Stillbirths [*N* = 7049] | Other[a] [*N* = 22,556] | First trimester [*N* = 1,348,098] | Second trimester [*N* = 1,348,098] | Third trimester [*N* = 1,343,716] |
| Mycophenolic acid | 39 (0.002) | 32 (0.002) | 51.3 (0.001) | 38.5 (0.004) | 5.1 (0.003) | 2.6 (0.004) | 0.0 (0.000) | 2.6 (0.004) | 65.0 (0.001) | 30.0 (0.000) | 20.0 (0.000) |
| Lithium | 362 (0.020) | 301 (0.016) | 57.2 (0.015) | 35.4 (0.034) | 3.6 (0.019) | 2.2 (0.035) | 0.0 (0.000) | 1.7 (0.027) | 70.5 (0.011) | 51.2 (0.008) | 64.3 (0.010) |
| Carbimazole | 800 (0.043) | 586 (0.032) | 73.5 (0.044) | 23.0 (0.049) | 2.0 (0.023) | 0.4 (0.013) | 0.0 (0.000) | 1.1 (0.040) | 64.1 (0.028) | 41.2 (0.018) | 27.9 (0.012) |
| Danazol | 15 (0.001) | 11 (0.001) | 73.3 (0.001) | 6.7 (0.000) | 13.3 (0.003) | 6.7 (0.004) | 0.0 (0.000) | 0.0 (0.000) | 63.6 (0.001) | 36.4 (0.000) | 0.0 (0.000) |
| Testosterone | 7 (0.000) | 4 (0.000) | 85.7 (0.000) | 14.3 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 0.0 (0.000) | 50.0 (0.000) | 33.3 (0.000) | 50.0 (0.000) |
| *Foetotoxic drugs to be prohibited or only to be used in the absence of a safer therapeutic alternative (risk period: second and third trimesters)* | | | | | | | | | | | |
| NSAIDs[f] | 255,499 (13.852) | 17,473 (1.287) | 41.8 (7.918) | 50.8 (34.639) | 4.5 (16.792) | 1.0 (11.148) | 0.3 (10.697) | 1.6 (18.155) | 75.8 (6.005) | 19.5 (1.547) | 11.6 (0.923) |
| Systemic use | 225,926 (12.249) | 10,021 (0.738) | 35.6 (5.970) | 56.5 (34.061) | 4.9 (15.908) | 1.1 (10.439) | 0.3 (8.370) | 1.7 (17.281) | 81.1 (4.844) | 13.9 (0.829) | 9.3 (0.559) |
| Topical use | 47,799 (2.592) | 8359 (0.616) | 82.0 (2.909) | 13.3 (1.695) | 2.5 (1.748) | 0.7 (1.452) | 0.6 (4.043) | 0.8 (1.787) | 64.6 (1.881) | 28.4 (0.827) | 13.9 (0.406) |
| ACE inhibitors | 1921 (0.104) | 317 (0.023) | 63.1 (0.090) | 27.4 (0.140) | 6.0 (0.166) | 1.2 (0.099) | 0.7 (0.184) | 1.7 (0.142) | 84.0 (0.076) | 19.0 (0.017) | 10.1 (0.009) |
| ARBs | 1732 (0.094) | 304 (0.022) | 62.1 (0.080) | 27.7 (0.128) | 6.2 (0.156) | 1.4 (0.108) | 0.9 (0.227) | 1.6 (0.124) | 83.0 (0.066) | 20.7 (0.017) | 9.3 (0.007) |
| Tetracyclines | 16,535 (0.896) | 741 (0.054) | 32.0 (0.393) | 61.9 (2.735) | 3.7 (0.884) | 0.8 (0.597) | 0.2 (0.397) | 1.3 (0.989) | 89.6 (0.352) | 8.3 (0.032) | 4.5 (0.018) |

*CRAT* Centre de référence sur les agents tératogènes chez la femme enceinte, *VKA* vitamin K antagonists, *NSAIDs* nonsteroidal anti-inflammatory drugs, *ACE* angiotensin-converting enzyme, *ARBs* angiotensin II receptor blockers, *ATC* Anatomical Therapeutic Chemical

[a]Hydatidiform mole or other abnormal products of conception

[b]Note that high-dose retinol products (A11CA01) were reimbursed for a total of 534 pregnant women (159 during the first trimester when restricting to live births only)

[c]Selection: valproic acid, valpromide, carbamazepine, phenobarbital, primidone and topiramate

[d]Valproate could also have been classified in the 'Foetotoxic drugs' section of this table as the second and third trimesters are also high-risk periods

[e]L01 ATC classes only

[f]For NSAIDs, the risk period considered was from the sixth month of pregnancy

**Table 5** Association between maternal characteristics and potentially harmful drug prescribing during pregnancy [crude OR (95% CI)]

| | Swedish system | | Australian system | |
|---|---|---|---|---|
| | All women [*N* = 1,526,044] | Women with no chronic diseases [*N* = 1,336,392] | All women [*N* = 1,526,044] | Women with no chronic diseases [*N* = 1,336,392] |
| | [*N* = 34,113][a] | [*N* = 23,908][a] | [*N* = 62,422][a] | [*N* = 41,028][a] |
| *Sociodemographic data* | | | | |
| Maternal age, years | | | | |
| < 20 | Ref. | Ref. | Ref. | Ref. |
| 20–24 | 0.7 (0.7–0.8) | 0.7 (0.6–0.7) | 0.9 (0.9–1.0) | 0.9 (0.8–0.9) |
| 25–29 | 0.5 (0.5–0.6) | 0.5 (0.5–0.5) | 0.9 (0.8–0.9) | 0.8 (0.7–0.8) |
| 30–34 | 0.5 (0.5–0.6) | 0.5 (0.4–0.5) | 0.9 (0.9–1.0) | 0.7 (0.7–0.8) |
| 35–39 | 0.7 (0.6–0.7) | 0.5 (0.5–0.5) | 1.1 (1.0–1.1) | 0.8 (0.8–0.9) |
| ≥ 40 | 0.9 (0.9–1.0) | 0.6 (0.6–0.7) | 1.3 (1.2–1.3) | 0.8 (0.8–0.9) |
| Complementary universal health insurance for very-low-income people | | | | |
| No | Ref. | Ref. | Ref. | Ref. |
| Yes | 1.5 (1.5–1.5) | 1.5 (1.5–1.6) | 1.2 (1.2–1.2) | 1.2 (1.2–1.2) |
| State health cover for people on low incomes | | | | |
| No | Ref. | Ref. | Ref. | Ref. |
| Yes | 1.3 (1.3–1.4) | 1.2 (1.2–1.3) | 1.2 (1.2–1.3) | 1.1 (1.1–1.2) |
| Disability allowance | | | | |
| No | Ref. | Ref. | Ref. | Ref. |
| Yes | 4.1 (3.8–4.4) | 1.1 (0.8–1.4) | 4.6 (4.3–4.8) | 1.3 (1.1–1.5) |
| Deprivation index | | | | |
| Quintile 1 | Ref. | Ref. | Ref. | Ref. |
| Quintile 2 | 0.9 (0.9–1.0) | 0.9 (0.9–1.0) | 1.0 (1.0–1.0) | 1.0 (1.0–1.1) |
| Quintile 3 | 0.9 (0.9–1.0) | 0.9 (0.9–1.0) | 1.1 (1.0–1.1) | 1.0 (1.0–1.1) |
| Quintile 4 | 0.9 (0.8–0.9) | 0.8 (0.8–0.9) | 1.1 (1.0–1.1) | 1.1 (1.0–1.1) |
| Quintile 5 | 1.0 (1.0–1.0) | 1.0 (0.9–1.0) | 1.0 (1.0–1.1) | 1.0 (1.0–1.1) |
| French overseas territories | 1.3 (1.3–1.4) | 1.3 (1.3–1.4) | 1.2 (1.1–1.2) | 1.3 (1.2–1.4) |
| Urban area population (inhabitants) | | | | |
| Rural | Ref. | Ref. | Ref. | Ref. |
| 2000–19,999 | 1.1 (1.0–1.1) | 1.1 (1.0–1.1) | 1.0 (1.0–1.0) | 1.0 (0.9–1.0) |
| 20,000–199,999 | 1.2 (1.2–1.3) | 1.2 (1.2–1.3) | 1.0 (1.0–1.0) | 1.0 (0.9–1.0) |
| 200,000–1,999,999 | 1.5 (1.5–1.6) | 1.6 (1.6–1.7) | 1.0 (1.0–1.1) | 1.0 (1.0–1.1) |
| Paris region | 1.6 (1.5–1.6) | 1.6 (1.6–1.7) | 1.0 (0.9–1.0) | 1.0 (0.9–1.0) |
| *History of chronic diseases* | | | | |

**Table 5** (continued)

| | Swedish system | | Australian system | |
|---|---|---|---|---|
| | All women [$N = 1{,}526{,}044$] | Women with no chronic diseases [$N = 1{,}336{,}392$] | All women [$N = 1{,}526{,}044$] | Women with no chronic diseases [$N = 1{,}336{,}392$] |
| | [$N = 34{,}113$][a] | [$N = 23{,}908$][a] | [$N = 62{,}422$][a] | [$N = 41{,}028$][a] |
| Chronic diseases | | | | |
| No | Ref. | | Ref. | |
| Yes | 3.1 (3.0–3.2) | | 4.0 (3.9–4.1) | |
| *Health care utilisation* | | | | |
| Prenatal hospitalisation | | | | |
| No | Ref. | Ref. | Ref. | Ref. |
| Yes | 1.8 (1.7–1.9) | 1.4 (1.3–1.6) | 1.7 (1.6–1.8) | 1.3 (1.2–1.4) |
| Visit to a general practitioner | | | | |
| No | Ref. | Ref. | Ref. | Ref. |
| Yes | 1.4 (1.4–1.4) | 1.3 (1.3–1.3) | 1.4 (1.4–1.4) | 1.3 (1.2–1.3) |
| Visit to a private gynaecologist | | | | |
| No | Ref. | Ref. | Ref. | Ref. |
| Yes | 1.1 (1.0–1.1) | 1.1 (1.1–1.1) | 1.1 (1.1–1.1) | 1.1 (1.1–1.1) |
| Polymedication | | | | |
| 0 | Ref. | Ref. | Ref. | Ref. |
| 1–2 | 1.3 (1.2–1.3) | 1.2 (1.1–1.2) | 1.5 (1.4–1.5) | 1.2 (1.2–1.3) |
| 3–4 | 1.6 (1.6–1.7) | 1.4 (1.3–1.4) | 1.8 (1.7–1.8) | 1.4 (1.4–1.5) |
| ≥ 5 | 2.5 (2.4–2.6) | 1.9 (1.8–1.9) | 2.7 (2.7–2.8) | 1.9 (1.8–1.9) |
| *Pregnancy-related health care utilisation* | | | | |
| Recent pregnancy | | | | |
| No | Ref. | Ref. | Ref. | Ref. |
| Yes | 0.8 (0.8–0.8) | 0.8 (0.8–0.9) | 0.7 (0.7–0.8) | 0.8 (0.7–0.8) |
| Folic acid supplementation | | | | |
| No | Ref. | Ref. | Ref. | Ref. |
| Yes | 0.9 (0.9–0.9) | 0.8 (0.8–0.9) | 1.2 (1.1–1.2) | 1.1 (1.0–1.1) |
| *Proxies for smoking, alcoholism and illicit drug use* | | | | |
| Smoking | | | | |
| No | Ref. | Ref. | Ref. | Ref. |
| Yes | 1.4 (1.3–1.5) | 1.2 (1.0–1.3) | 2.6 (2.5–2.7) | 2.7 (2.5–2.8) |
| Alcoholism | | | | |
| No | Ref. | Ref. | Ref. | Ref. |

**Table 5** (continued)

| | Swedish system | | Australian system | |
|---|---|---|---|---|
| | All women [*N* = 1,526,044] [*N* = 34,113][a] | Women with no chronic diseases [*N* = 1,336,392] [*N* = 23,908][a] | All women [*N* = 1,526,044] [*N* = 62,422][a] | Women with no chronic diseases [*N* = 1,336,392] [*N* = 41,028][a] |
| Yes | 2.1 (1.8–2.4) | 1.3 (0.9–1.9) | 3.7 (3.4–4.1) | 2.4 (1.9–2.9) |
| Illicit drug use | | | | |
| No | Ref. | Ref. | Ref. | Ref. |
| Yes | 2.2 (1.9–2.6) | 1.4 (1.0–1.9) | 3.3 (2.9–3.6) | 2.0 (1.6–2.5) |

*OR* odds ratio, *CI* confidence interval, *Ref.* reference

[a]Number of pregnancies with a reimbursement for a potentially harmful drug

use across countries may also explain the observed differences, as these studies, including the present study, did not capture OTC drugs.

As described in previous European or North American studies, maternal characteristics such as chronic diseases, polymedication and young age were found to be associated with potentially harmful prescriptions during pregnancy [14, 28, 35, 36]. However, other maternal characteristics associated with an increased risk of potentially harmful prescriptions were identified, including deprived women or those living in French overseas territories. These results may help inform the planning of subsequent causal studies to identify groups of pregnant women who could benefit the most from prepregnancy counselling.

## 4.2 Clinical Implications of the Results

Unlike most studies on harmful drug prescribing, our study population was not restricted to live births. Results regarding pregnancy outcomes must be interpreted with caution, as this descriptive study was not designed to allow any causal interpretations. On the one hand, we identified some previously reported patterns of use, such as off-label use of methotrexate in ectopic pregnancies [37], use of doxycycline for antibiotic prophylaxis in surgical abortions [38], and use of NSAIDs as analgesics in induced abortions [39, 40], which could therefore be interpreted as indication bias. On the other hand, the high abortion rates observed following exposure to valproic acid and derivatives, thalidomide and derivatives, or retinoids FSU were indicative and expected given the high teratogenicity of these drugs. In line with these considerations, the high proportion of pregnancies ending in abortion and exposed to cyproterone (50 and 100 mg), teriflunomide or antiepileptic drugs such as topiramate for which a therapeutic alternative exists, are a source of concern.

Overall, as expected and as previously reported [20, 41, 42], potentially harmful drug prescribing tended to decrease throughout pregnancy, in contrast with the trends observed for certain antiepileptic drugs, antineoplastic drugs, lithium, paroxetine or azathioprine, suggesting the difficulty of stopping vital treatments for certain chronic conditions, in which these drugs may present a higher benefit–risk balance. The declining although persistent prescription of vitamin K antagonists observed during the second and third trimesters may illustrate these clinical settings, as these drugs are the only treatment options available for women with artificial heart valves. However, this study was not designed to evaluate the appropriateness of drug prescribing in individual pregnant women.

Differences were observed between the prevalence rates estimated on the basis of the two classification systems used. This can be explained by differences in the nature of the

drugs contained in the two classification systems, as some drugs are not marketed in either Australia (e.g., lymecycline) or Sweden (e.g., chlorpromazine), and as the drugs exempted from receiving a pregnancy risk category also differ. Certain marketed drug combinations are also not explicitly listed in the Australian system (e.g., sulfamethoxazole/trimethoprim) and were therefore not assigned any risk category in our study. However, the D/X risk category allocation differed for only 30 of the 549 drugs common to both systems (e.g., lamotrigine classified as B3 in Sweden versus D in Australia) and a good agreement was found between the two systems. Keeping in mind all the shortcomings inherent to classification systems [43, 44], this study therefore supports their utilisation as a convenient tool to assess potentially harmful drug prescribing at a population level based on claims data.

### 4.3 Strengths and Limitations

This is the first study to use risk classification systems to estimate the prevalence of potentially harmful drug prescribing during pregnancy based on French nationwide data, providing details on drug classes and ATC classes and maternal characteristics associated with the prescription of these drugs. All prescribed drugs reimbursed in the ambulatory setting, irrespective of their cost, and drugs for which hospitals receive additional funding (e.g., certain treatments administered for severe chronic diseases such as cancers, multiple sclerosis, inflammatory bowel disease, etc.) were considered. More than one-third of the drugs prescribed during pregnancy in this study were not classified in either the Swedish or Australian systems. Data from French SmPCs were therefore used in addition to the two classification systems, allowing more accurate estimation of prevalence rates.

Prescribing assessment was based on claims data, which do not indicate whether or not and when the woman actually took the medication. This may apply to drugs reimbursed during late pregnancy but actually used in the early postpartum period, such as NSAIDs prescribed for perineal pain [45]. However, exposure misclassification due to inaccurate estimations of pregnancy dates should be limited, as pregnancy dates were estimated using exact pregnancy outcome dates and gestational ages [19]. Another limitation was the impossibility to include certain pregnancies: spontaneous abortions not managed in hospital could not be identified, and anonymised induced abortions (up to 8% of all elective abortions in 2014), which can be requested by minors, could not be linked to drug reimbursement [19]. As the nationwide prevalence of potentially harmful drug prescribing also included foetotoxic drug prescribing during the first trimester, it may therefore have been overestimated as the use of foetotoxic drugs during this period should not be harmful for the foetus. Conversely, OTC drugs, as well as the majority of drugs administered in hospital, are not captured in the databases used, resulting in underestimation of prevalence rates. Finally, considering the descriptive design of this study and the absence of certain maternal characteristics (e.g., access to preconception counselling, contraception and appropriate pregnancy testing) due to the nature of the data used, the results of analyses of the association between maternal characteristics and potentially harmful drug prescribing should therefore be interpreted with this limitation in mind.

## 5 Conclusion

Based on nearly 2 million pregnancies beginning in 2016–2017 and identified from French nationwide data, this study showed that potentially harmful drug prescribing to pregnant women is not uncommon. For some of these drugs, especially NSAIDs, future research to determine the reasons for their prescription during pregnancy, is needed. The results of this study support comparative analysis of updated risk classification systems as a useful tool to assess potentially harmful drug prescribing during pregnancy in studies based on health care databases.

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## Declarations

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**Conflict of interest** Pierre-Olivier Blotière, Christine Damase-Michel, Alain Weill and Géric Maura have no conflicts of interest to declare. Pierre-Olivier, Alain Weill, and Géric Maura are employees of the French National Health Insurance (CNAM). Christine Damase-Michel is Associate Professor in Pharmacology, and Hospital Practitioner, at Faculté de Médecine, Université de Toulouse UPS, Inserm CERPOP, CHU, Toulouse, France.

**Availability of data and material** No additional data are available from the author (French law to access the SNDS; https://www.snds.gouv.fr). Permanent access to the French healthcare databases is automatically granted to certain government agencies, public institutions and public service authorities; however, temporary access for studies and research is possible upon request to the national health data institute (INDS). All databases used in this study contained anonymous patient records.

**Code availability** Not applicable.

**Author contributions** All authors approved the final version of this article. Pierre-Olivier Blotière and Géric Maura designed the study and drafted the article, and Pierre-Olivier Blotière also conducted data collection and statistical analysis. All authors contributed substantially to the interpretation of the results. Christine Damase-Michel and Alain Weill provided critical revision of the manuscript for important intel-

lectual content. All authors had full access to all of the study data (including statistical reports and tables) and take full responsibility for the integrity of the data and accuracy of the data analysis.

**Ethics approval/consent to participate** This observational study, which was based on the French healthcare databases, was approved by the French Data Protection Agency (Commission Nationale de l'Informatique et des Libertés, CNIL) and did not require patient consent or Ethics Committee approval. Patients and/or the public were not involved.

**Consent for publication** Not applicable.



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