

ORIGINAL REPORT

Prescription drug use during pregnancy in France: a study from the national health insurance permanent sample

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Abstract

Purpose: To provide an up-to-date account of drug prescription during pregnancy in France from 2011 to 2014 using the permanent sample of the French national computerized healthcare database and with a focus on recommended supplementations, fetotoxic drugs and teratogenic drugs.

Methods: All pregnancies identified by the *International Classification of Diseases, 10th Revision* codes list in the hospitalization database, lasting more than 9 weeks of amenorrhea and whose delivery occurred between 01/01/2011 and 12/31/2014, were included. Drugs delivered between the trimester before and until the end of the pregnancy were included. Drug exposure prevalence was calculated for each year and according to pregnancy trimesters.

Results: The study included 28,491 pregnancies with a median number of 9 [5–13] (median [IQ range]) drugs delivered. The most prescribed drug class was antianemia (in 72.5% of exposed). The prescription rate of recommended vitamins (B9 and D) increased over the study period (+10%). Influenza vaccination also increased but remained at a low rate (1%). Exposure to fetotoxic drugs decreased as pregnancy advanced. Exposure to the main teratogenic antiepileptics was stable over the study period. Low-income pregnant women had a higher average drug consumption except for recommended vitamins.

Conclusion: Pregnant French women are among the largest consumers of prescription medications worldwide. Overall, the dispensation trends observed in this study are in line with the recommendations of the French National College of Gynecologists and Obstetricians. Nevertheless, while being low, exposure to fetotoxic drugs, teratogenic drugs or those under safety alerts still occurred. Supplementations and vaccines in low-income pregnant women should also be increased.

KEYWORDS

administrative healthcare database, drug recommendations, pharmacoepidemiology, pregnancy, prescription medications

1 | INTRODUCTION

Drug use during pregnancy may be necessary to ensure maternal and fetal health. While the safety or the value of some medications has been established, others have been identified as potentially or certainly toxic for pregnancy.¹

Adverse drug effects on fetal development can be classified in 2 main classes of effects according to the period of exposure, before or after the end of the first trimester of pregnancy. A teratogenic effect

is defined as an irreversible impairment affecting organs during embryological development and causing birth defects. Some drugs have been known for decades to be teratogenic such as the retinoids^{2,3} and thalidomide,^{4,5} but some of their teratogenic mechanisms still remain to be discovered and assessed, as was recently the case with valproate and autism.^{6,7} A fetotoxic effect is a harmful effect on fetal growth and organ function. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin II type 1 receptor antagonists (sartans)^{8–10} may cause persistent or even lethal fetotoxic defects when used during the late

second or third trimester as well as non-steroidal anti-inflammatory drugs (NSAID).¹¹⁻¹³ These drugs should therefore be avoided during the pregnancy unless the benefits for the mother and the fetus outweigh their potential risks.

Pregnant women are more likely to develop deficiencies, and some supplementations are recommended by learned societies. In the United States, iodine supplementation is recommended for preventing some neurological pathologies.¹⁴ In France, as household salt is already supplemented with iodine, only 2 supplementations are systematically recommended during pregnancy: cholecalciferol (vitamin D) and folic acid (vitamin B9).¹⁵ Vitamin D is recommended during the seventh month of pregnancy to prevent rachitism, and vitamin B9 is recommended before conception and until the end of the first trimester to prevent anomalies of neural tube closure such as spina bifida.

Computerized administrative healthcare databases are increasingly used worldwide for pharmacoepidemiology studies, in particular to describe patterns and trends of medication prescription.^{16,17} In France, the national health plan database (SNIIRAM, "Système National d'Information Interrégimes de l'Assurance Maladie") covers over 97% of the population. The last study concerning drug prescription during pregnancy covered the period between 2004 and 2008 in the Haute-Garonne region.¹⁸ Using the Permanent Beneficiaries Sample (EGB) of the SNIIRAM,¹⁹ we provide a nationwide up-to-date overview of drug prescription during pregnancy with a focus on recommended and contraindicated drugs.

2 | METHODS

Data used in this study were extracted from the EGB, a representative sample, in terms of gender and age, of the population covered by the national healthcare insurance system, which includes approximately 98% of the whole French population. The EGB was obtained by 1/97 random sampling, restricted to the 3 main insurance schemes (85.6% of the French population). It has been made available to research teams and public health agencies by the French national insurance system ("Caisse Nationale de l'Assurance Maladie", CNAM). Details on the EGB database have been described elsewhere.¹⁹ It contains demographic information and all the health care reimbursements of individuals linked to hospital stays with diagnoses coded according to *International Classification of Diseases, 10th Revision* (ICD-10).²⁰ Only prescription drugs delivered by pharmacists and reimbursed are recorded. Neither non-reimbursed drugs nor those delivered in hospital are available in the database.²¹

This study was conducted between 1 January 2011 and 31 December 2014. It included all pregnancies whose duration was longer than 9 weeks of amenorrhea and excluding voluntary terminations of pregnancy. Women were included in the study if at least 1 health care reimbursement (drugs, consultation, laboratory exam, hospitalization, medical transport, etc) was recorded between the prepregnancy period and the end of pregnancy. Pregnancies were identified according to a list of ICD-10 codes and Common Classification of Medical Acts codes²² related to pregnancy defined by the National Health Insurance Fund (Supplementary Table 1).

KEY POINTS

- France is known to be a large consumer of prescription drugs but no recent study has focused on pregnancy.
- Little is known about compliance to current guideline recommendations for this specific population.
- Pregnancy drug prescription did not decrease over the study period and stayed at a high level.
- Supplementations were generally in accordance with recommendations and tended to improve. Disadvantaged women were less well covered.
- The number of pregnant women exposed to fetotoxic/teratogenic drugs was stable over the study period.

In France, the gestational age is estimated from the first-trimester ultrasound. The quality of these data, which is available in hospitalization data, is considered as reliable.²³ If missing, gestational age was predicted from the last menstrual period date through a simple linear regression model built on subjects where both gestational age and last menstrual period dates were recorded.

Drugs of interest were selected according to the French reference center for teratogenic drugs list.²⁴ Drug prevalence was described according to the Anatomical Therapeutic Chemical (ATC) classification. The second ATC level was used for general analysis and the fifth level for contraindicated and recommended drug prescription. The exposure period for each woman was the duration of pregnancy plus a 13-week prepregnancy period before conception (T0). The pregnancy itself was divided into 3 trimesters: the first lasted from conception until the 13th week of gestation (T1), the second from the 14th week until the 26th week of gestation (T2) and the third from the 27th week to the delivery (T3). A woman was considered as exposed to a drug during a given trimester if at least 1 dispensation had been recorded during it.

To evaluate the trend of the number of different drugs used in each pregnancy, the median and interquartile ranges between square brackets of drug number used by pregnancy were compared using the Kruskal-Wallis test. Prevalence was calculated by year and trimester of pregnancy (T0-T3), dividing the number of exposed pregnancies by the total number of pregnancies over the period. For rare exposures, only numbers of pregnancies exposed are given. The prevalence trends were tested by the χ^2 trend test for proportions over the 4 years included in the study.

Since very few socio-demographic variables are available in the SNIIRAM, we also analyzed prescription according to economic status using Complementary Universal Health Care Coverage (CMU-C) as binary proxy. Drug prevalence was compared between the CMU-C (ie, lower socio-economic) group and the non-CMU-C group using χ^2 tests.

Statistical analyses were performed with the R software, v3.2.3.

3 | RESULTS

Over the period 2011 to 2014, we found 30570 hospital stays related to a pregnancy excluding abortions (Figure 1). A total of 2079

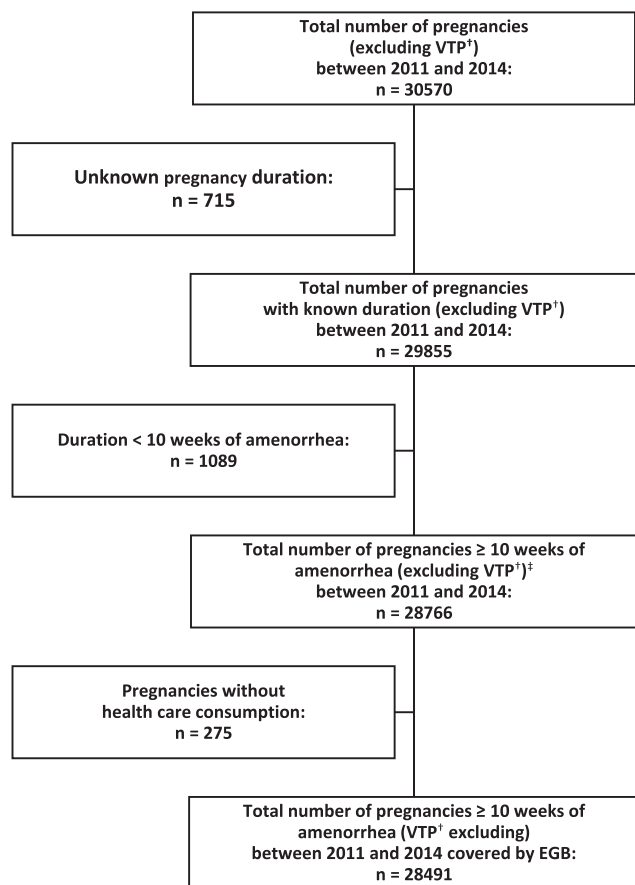


FIGURE 1 Flow chart. [†]Voluntary termination of pregnancy. [‡]Including 662 women for whom gestational age was imputed according to $y = 0.11x + 8.01$ based on 26900 women having both gestational age and a non-aberrant last menstrual period date

pregnancies were excluded owing to unknown duration of pregnancy or duration of fewer than 10 weeks of amenorrhea. The annual number of pregnancies remained stable over the period: around 7000 for a total of 28491 pregnancies included.

The median gestational age of delivery was 39 [38–40] weeks of amenorrhea. The median maternal age was 30 [27–34] years. There were 3509 women (12.3%) with 2 pregnancies over the period, 191 women (0.007%) had 3 pregnancies and 6 had 4 pregnancies.

3.1 | Trends from 2011 to 2014

The median number of drugs prescribed per pregnancy over the period, 9 [5–13], remained stable. Table 1 shows that the ranking of the most prescribed ATC classes remained the same. The most represented ATC class was ‘antianemic preparations’ (mainly iron) prescribed in 72.5% of our population. The second most prescribed drug class was ‘analgesics’ (mainly paracetamol) with a prescription in 72.0% of the patients. Third were ‘drugs for gastrointestinal disorders’ (62.2%), the most common being Phloroglucinol.

Some significant decreasing trends were noted (see Table 1 for the 20 most prescribed drugs and Supplementary Table 2 for the complete list of drugs). The third, ‘drugs for gastrointestinal disorders’, progressively decreased from 63.3% to 60.7% ($P < .001$). Drugs used to treat the common cold (nasal preparations or pills) were less prescribed in

2014 than in 2011 ($P < .001$). Antibiotic dispensations decreased from 52.6% to 48.9% ($P < .001$). Conversely, the dispensation of some drugs increased: ‘antianemic preparations’ increased from 72.7% to 76.5% (mainly by the increase in folic acid) and vitamins gained 10 percentage points to reach 52.2% in 2014. Moreover, homeopathic treatments were increasingly dispensed to pregnant women, from 9.1% to 11.5% ($P < .001$).

3.2 | Trends during pregnancy

Drug prescription per trimester of pregnancy showed some noteworthy variations (Table 2 for the 20 most prescribed drugs and Supplementary Table 3 for the complete list of drugs) such as the steady increase in antianemic preparations (27.5%–81.5%). A sharp rise was observed in the prescription of vitamins between T1 and T2 (5.7%–26.5%). Drug dispensation for gastric acidity disorders (12.0%–37.9%) and for vaginal infection (6.8%–22.6%) increased throughout pregnancy. Homeopathic treatments were prescribed throughout pregnancy with an exposure increasing from 1.5% to 7.3%.

3.3 | Recommended supplementations

The proportion of women exposed to drugs recommended during pregnancy increased over time (Figure 2). The most prescribed supplementation was iron, which remained stable between 2011 and 2014 (63.8%–64.2%, $P = .40$). Two systematic supplementations increased: cholecalciferol from 42.9% to 53.1% ($P < .001$) and folic acid from 28.2% to 37.8% ($P < .001$). Even if the changes were less pronounced, prescriptions of anti-D immunoglobulin injections (8.4%–9.2%, $P = .07$) for Rh-negative women and influenza vaccine (0.6%–1.1%, $P < .001$) for winter pregnancies increased over the period but remained at a very low rate, especially for the latter.

3.4 | Fetotoxic drugs

In the second period of gestation (T2–T3), the fetus is especially sensitive to 2 families of treatments: NSAIDs, which are commonly used as pain-killers, and the family of ACEIs and sartans, which are used as a treatment for high blood pressure. Only a few women were prescribed ACEIs or sartans during T1 (84 cases in 4 years) (Figure 3A). In most cases, the treatment was discontinued before the period of risk with only 12 women still exposed during T2 and T3. Concerning NSAIDs (Figure 3B), exposure was high before the beginning of pregnancy with 20.7% of women, a percentage that remained relatively stable over the period. Even with a rapid decrease, the exposure to NSAIDs in T1 still concerned 5.1% of pregnancies. In the risk period, the overall dispensing rate dropped to 1.2% in the second trimester and was 0.4% in the third.

3.5 | Teratogenic drugs

We focused on 4 antiepileptic drugs known to be teratogenic: the least risky drug during pregnancy, lamotrigine and 3 contraindicated ones (valproic acid, carbamazepine and topiramate). Over the 4 years, 36 women were exposed to valproic acid, 19 of whom during T1. Carbamazepine and topiramate were less prescribed with 16 and 15 women

TABLE 1 Dispensing rates of prescription medications among pregnant women in the French permanent beneficiaries sample between 2011 and 2014. Drugs are sorted by decreasing mean exposure over the 4 years

Rank	ATC code	ATC label	2011 N = 7041	2012 N = 7089	2013 N = 7219	2014 N = 7142	2011–2014 N = 28491	P [†]
1	B03	Antianemic preparations	4990 (70.9%)	5058 (71.3%)	5261 (72.9%)	5336 (74.7%)	20645 (72.5%)	<.001
2	N02	Analgesics	5076 (72.1%)	5071 (71.5%)	5246 (72.7%)	5126 (71.8%)	20519 (72%)	.91
3	A03	Drugs for functional gastrointestinal disorders	4456 (63.3%)	4456 (62.9%)	4482 (62.1%)	4335 (60.7%)	17729 (62.2%)	<.001
4	J01	Antibacterials for systemic use	3704 (52.6%)	3678 (51.9%)	3632 (50.3%)	3489 (48.9%)	14503 (50.9%)	<.001
5	A11	Vitamins	2981 (42.3%)	3235 (45.6%)	3552 (49.2%)	3729 (52.2%)	13497 (47.4%)	<.001
6	A02	Drugs for acid related disorders	2979 (42.3%)	3127 (44.1%)	3163 (43.8%)	3152 (44.1%)	12421 (43.6%)	<.001
7	G01	Gynecological anti-infectives and antiseptics	2607 (37%)	2452 (34.6%)	2414 (33.4%)	2397 (33.6%)	9870 (34.6%)	<.001
8	R01	Nasal preparations	2703 (38.4%)	2490 (35.1%)	2425 (33.6%)	2137 (29.9%)	9755 (34.2%)	<.001
9	D01	Antifungals for dermatological use	1991 (28.3%)	1983 (28%)	1991 (27.6%)	2027 (28.4%)	7992 (28.1%)	.96
10	R05	Cough and cold preparations	2146 (30.5%)	1945 (27.4%)	2017 (27.9%)	1868 (26.2%)	7976 (28%)	<.001
11	M01	Anti-inflammatory and antirheumatic products	1528 (21.7%)	1598 (22.5%)	1553 (21.5%)	1530 (21.4%)	6209 (21.8%)	.25
12	G03	Sex hormones and modulators of the genital system	1457 (20.7%)	1544 (21.8%)	1553 (21.5%)	1525 (21.4%)	6079 (21.3%)	.30
13	A06	Drugs for constipation	1084 (15.4%)	1134 (16%)	1158 (16%)	1163 (16.3%)	4539 (15.9%)	.09
14	D08	Antiseptics and disinfectants	1027 (14.6%)	1102 (15.5%)	1139 (15.8%)	1147 (16.1%)	4415 (15.5%)	.01
15	H02	Corticosteroids for systemic use	979 (13.9%)	1137 (16%)	1194 (16.5%)	1119 (15.7%)	4429 (15.5%)	<.001
16	R06	Antihistamines for systemic use	1055 (15%)	1063 (15%)	1107 (15.3%)	1123 (15.7%)	4348 (15.3%)	.11
17	A04	Antiemetics and anti-nauseants	785 (11.1%)	899 (12.7%)	1066 (14.8%)	934 (13.1%)	3684 (12.9%)	<.001
18	A01	Stomatological preparations	929 (13.2%)	895 (12.6%)	797 (11%)	829 (11.6%)	3450 (12.1%)	<.001
19	D07	Corticosteroids. Dermatological preparations	788 (11.2%)	784 (11.1%)	787 (10.9%)	775 (10.9%)	3134 (11%)	.42
20	NA [‡]	Homeopaths	638 (9.1%)	740 (10.4%)	793 (11%)	818 (11.5%)	2989 (10.5%)	<.001

[†]Trend test P values were calculated for 2011 to 2014.

[‡]There is no ATC Code corresponding to "Homeopaths" ATC label.

exposed. Lamotrigine was the most frequently used antiepileptic drug with 70 women treated. These 4 exposures were stable over the period. In most cases, French health professionals discontinued antiepileptic treatments during pregnancy and did not switch to lamotrigine. In some cases, the initial treatment was maintained throughout gestation (Figure 4). The exposure to other teratogenic drugs can be found in Supplementary Table 4.

3.6 | CMUC-C beneficiaries

Supplementary Table 5 shows that low-income pregnant women received fewer of the recommended prescriptions such as vitamins (43.5% against 49.5%, $P < .001$) and anti-D immunoglobulins (6.7% against 9.3%, $P < .001$). Conversely, for CMU-C beneficiaries, the average exposure was higher for most drugs concerning pathologies either linked with pregnancy (eg, anemia, pyrosis, mycosis and vomiting) or not (eg, flu and infection). Furthermore, the consumption of analgesics was higher (86.3% against 71.4%, $P < .001$). Fetotoxic drugs such as NSAIDs (32.8% against 20.3%, $P < .001$) and sartans (0.7% against 0.2%, $P = .03$) were more often dispensed to CMU-C beneficiaries.

Discussion

This study provides a representative national description of drug use during pregnancy. The list of the most prescribed drugs remained

stable over the study period. Iron supplementation was the most frequently dispensed drug while folic acid and cholecalciferol supplementations were increasingly prescribed, a trend corresponding to recommendations.¹⁴ Influenza vaccination remained extremely marginal. Fetotoxic drugs were avoided during the second and third trimester but less in the first. Finally, some dangerous antiepileptics are still used during pregnancy.

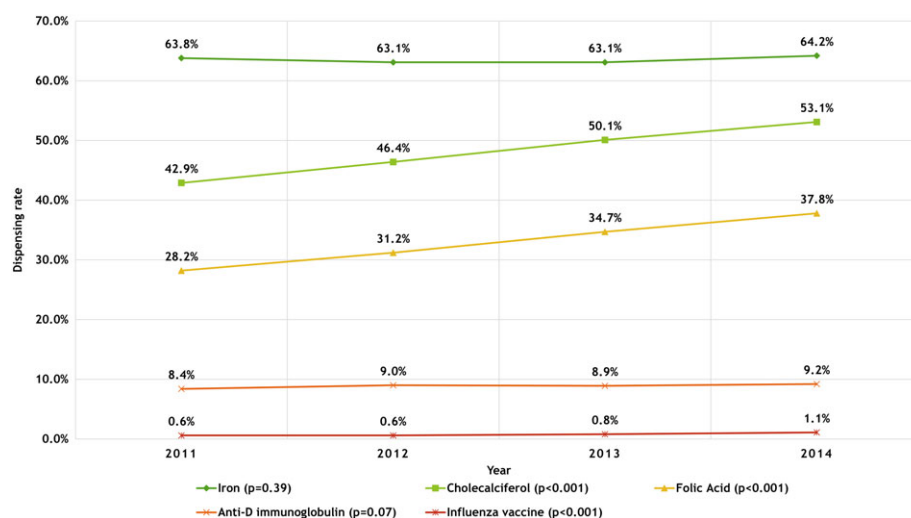
3.7 | Comparison with other countries

French women seem particularly exposed to drugs with one of the highest average number of specialties prescribed in the world, as noted in a meta-analysis in 2011 (France = 10.9–13.6, Germany = 2.0–7.0, Netherlands = 8.0, Italy = 1.8, Denmark = 2.6, United States = 1.8–2.2, Norway = 3.3, Finland = 2.1).²⁵ With a median number of 9 drugs per pregnancy, our results are consistent with those of previous French studies.^{18,26,27}

Comparisons with other countries are made difficult since differences exist in database composition, reimbursement modalities and supplementation exclusions.²⁵ Antianemic preparations were also the most prescribed in Italy²⁸ and the second most prescribed in England,²⁹ whereas they were only eighth in China.³⁰ Analgesics were the most prescribed ATC class in England,²⁹ the fifth in the United States¹⁶ and the ninth in China.³⁰ The dispensation rate

TABLE 2 Dispensing rates of prescription medications among pregnant women in the French permanent beneficiaries sample divided by trimester of dispensation over the period 2011 to 2014. Drugs are sorted by decreasing mean exposure over the 4 trimesters

Rank	ATC code	ATC label	T0 N = 28491	T1 N = 28491	T2 N = 28081	T3 N = 27242	Total N = 112305
1	B03	Antianemic preparations	7827 (27.5%)	14710 (51.6%)	15970 (56.9%)	22198 (81.5%)	60705 (54.1%)
2	N02	Analgesics	13676 (48%)	18098 (63.5%)	16930 (60.3%)	10650 (39.1%)	59354 (52.9%)
3	A03	Drugs for functional gastrointestinal disorders	4754 (16.7%)	16888 (59.3%)	11012 (39.2%)	8956 (32.9%)	41610 (37.1%)
4	J01	Antibacterials for systemic use	8550 (30%)	7536 (26.5%)	7712 (27.5%)	5521 (20.3%)	29319 (26.1%)
5	A02	Drugs for acid related disorders	3423 (12%)	5859 (20.6%)	7939 (28.3%)	10326 (37.9%)	27547 (24.5%)
6	G01	Gynecological anti-infectives and antiseptics	1931 (6.8%)	3615 (12.7%)	5691 (20.3%)	6164 (22.6%)	17401 (15.5%)
7	A11	Vitamins	1112 (3.9%)	1612 (5.7%)	7431 (26.5%)	6399 (23.5%)	16554 (14.7%)
8	R01	Nasal preparations	4312 (15.1%)	4629 (16.3%)	4434 (15.8%)	2698 (9.9%)	16073 (14.3%)
9	G03	Sex hormones and modulators of the genital system	10111 (35.5%)	5113 (18%)	532 (1.9%)	237 (0.9%)	15993 (14.2%)
10	D01	Antifungals for dermatological use	2018 (7.1%)	2961 (10.4%)	4069 (14.5%)	3698 (13.6%)	12746 (11.4%)
11	R05	Cough and cold preparations	2548 (8.9%)	3462 (12.2%)	3466 (12.3%)	2211 (8.1%)	11687 (10.4%)
12	M01	Anti-inflammatory and antirheumatic products	6441 (22.6%)	1528 (5.4%)	384 (1.4%)	127 (0.5%)	8480 (7.6%)
13	H03	Thyroid therapy	1702 (6%)	2138 (7.5%)	2228 (7.9%)	2007 (7.4%)	8075 (7.2%)
14	R03	Drugs for obstructive airway diseases	2141 (7.5%)	2084 (7.3%)	2155 (7.7%)	1510 (5.5%)	7890 (7%)
15	R06	Antihistamines for systemic use	3230 (11.3%)	1742 (6.1%)	1577 (5.6%)	1071 (3.9%)	7620 (6.8%)
16	A06	Drugs for constipation	873 (3.1%)	2247 (7.9%)	2275 (8.1%)	1847 (6.8%)	7242 (6.5%)
17	N05	Psycholeptics	2750 (9.7%)	1538 (5.4%)	1177 (4.2%)	1040 (3.8%)	6505 (5.8%)
18	H02	Corticosteroids for systemic use	2425 (8.5%)	1470 (5.2%)	1407 (5%)	1133 (4.2%)	6435 (5.7%)
19	D08	Antiseptics and disinfectants	1692 (5.9%)	1397 (4.9%)	1471 (5.2%)	1610 (5.9%)	6170 (5.5%)
20	S01	Ophthalmologicals	1883 (6.6%)	1231 (4.3%)	999 (3.6%)	740 (2.7%)	4853 (4.3%)

**FIGURE 2** Recommended drug-dispensing rate over the period 2011–2014. Trend test P values are indicated in legend. [Color figure can be viewed at wileyonlinelibrary.com]

was the highest in France (72.0% Table 1) followed by the United Kingdom²⁹ with 40% of pregnant women being prescribed an analgesic.

3.8 | Trends from 2011 to 2014

Some prescription decreases are likely due to recommendations/warnings from the French Medicine Agency (ANSM). For instance, the

decrease in the prescription of gastrointestinal drugs (Table 1) was mainly due to halving the prescription of domperidone, which was placed under surveillance by the ANSM in 2011. Furthermore, the reduction in the use of flu and cold drugs was concordant with the warning issued by the ANSM about such drugs containing vasoconstrictors. Despite an increasing trend in antibiotic consumption in the general French population³¹ between 2011 and 2013, antibiotic dispensation to the women in our study decreased.

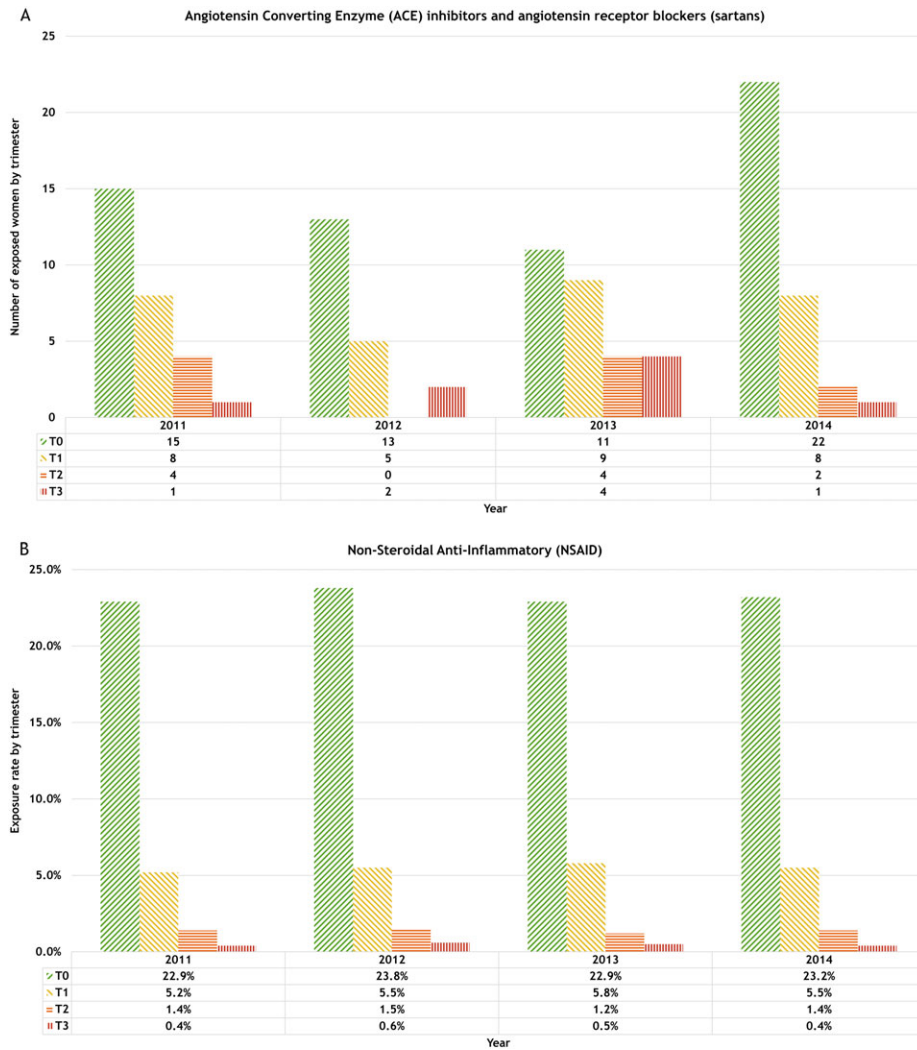


FIGURE 3 Exposure level of fetotoxic drugs per trimester from 2011 to 2014. [Color figure can be viewed at wileyonlinelibrary.com]

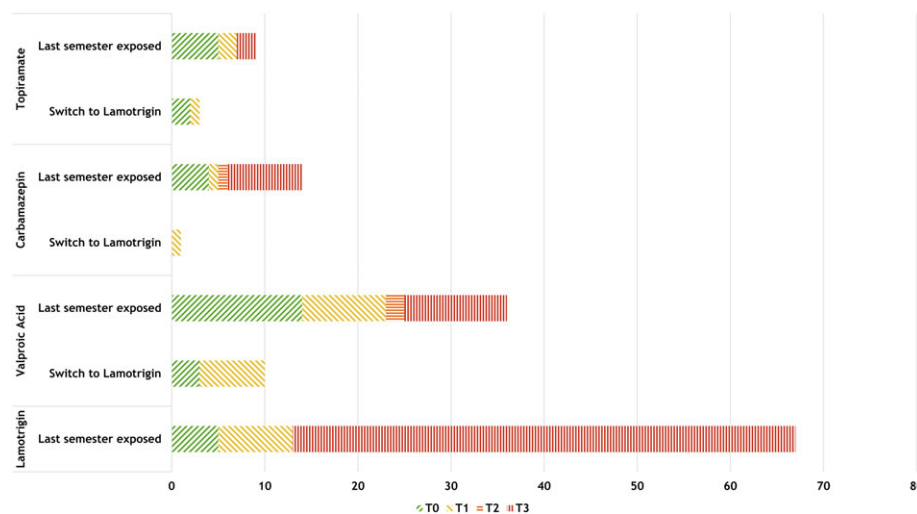


FIGURE 4 Treatment changes among epileptic pregnant women by type of treatment during prepregnancy period. [Color figure can be viewed at wileyonlinelibrary.com]

3.9 | Trends during pregnancy trimesters

The dispensation of analgesics and gastrointestinal drugs increased markedly during the first trimester, then decreased (Table 2) as shown

by Andrade et al,¹⁶ even though pain mainly due to contractions increases progressively as pregnancies advance. Since pain killers are sold in packages containing enough pills for several months when the intake is occasional, it is likely that pain killers prescribed early in

pregnancy are usually sufficient for the whole pregnancy. Screening for anemia occurs at least twice during pregnancy: first in the first trimester and a second time in the sixth month. This could explain the steady increase in the prescription of antianemics during pregnancy. Prescription of antibiotics decreased during pregnancy, a result in contradiction with the findings of Bakker et al.³² However, many pregnant women receive antibiotics in hospital during labor in the event of streptococcus B contamination or premature water breaking, neither of which can be evaluated in the EGB database. Use of acidity disorder drugs and gynecologic antiseptics increased throughout pregnancy, mimicking the increase in the prevalence of pyrosis and mycosis, a result also found in the Netherlands.³² Lastly, the increase in homeopathic prescription is likely related to the increasing discomfort experienced during pregnancy.

3.10 | Recommended supplementations

Anemia during pregnancy may be dangerous in the event of excessive bleeding after delivery. Compared to Italy (36%)²⁸ and Germany (54%),³³ iron prescription in France is high (about 64%). With an estimated prevalence of anemia during pregnancy around 25%,³⁴ iron seems to be prescribed simultaneously to treat anemia but also to prevent it, leading to a risk of overprescription that should be evaluated especially as regards the risk of oxidative stress on fetal development.¹

Cholecalciferol and folic acid supplementations increased during the period from 42.9% to 53.1% and from 28.2% to 37.8%, respectively. Our results probably underestimate the percentage of folic supplementation because of the existence of non-reimbursed vitamin and mineral supplementation containing folic acid.

Prescription of anti-D immunoglobulin increased during the study period to reach 9.2% of pregnancies in 2014, which is consistent with the rate estimated in 2008 (9.5%).¹⁸ The prevalence of negative rhesus was estimated to be 15% in women³⁵ and anti-D injection can be avoided if the paternal identity is certain and paternal rhesus is proved negative. Hence, anti-D vaccine coverage seems satisfactory.

Influenza may lead to maternal death, yet fewer than 1% of pregnant women in our study were vaccinated. Nevertheless, our results were underestimated by the fact that some pregnant women may have been vaccinated at work, for which data is not collected in the EGB.

3.11 | Fetotoxic and teratogenic drugs

Despite an increased risk of spontaneous abortion, 5.5% of pregnancies were exposed to NSAIDs during the first trimester. This percentage is high in comparison to other European countries like Sweden (1%),³⁶ a difference that remained during the second and third trimesters. Similarly, French women were more exposed to ACEIs and sartans than Swedish women.³⁶

In our study, lamotrigine was the most prescribed antiepileptic as in Denmark, Norway and the UK,³⁷ whereas carbamazepine and valproate were the most prescribed in Italy and Germany.³⁷ The average antiepileptic exposure was 0.8%, which is higher than in other European countries (from 0.4% in the Netherlands to 0.6% in Wales).³⁷ Throughout pregnancy, exposure to antiepileptics decreased from

0.8% at T0 to 0.4% in T3 in our study. In general, health professionals discontinued treatment as soon as the pregnancy was known, like other European professionals.³⁷

3.12 | CMU-C beneficiaries

The higher average exposure to drugs during pregnancy in CMUC-C beneficiaries is consistent with the results of Tuppin et al.³⁸ who found an increasing prevalence of diseases in this population. We observed a higher proportion of drug deliveries related to chronic diseases such as epilepsy, hypertension, diabetes and psychiatric disorders. The overconsumption of drugs such as antianemics, drugs for gastrointestinal disorders, antibiotics and antiseptics seemed to indicate an increase in the prevalence of pregnancy-related diseases such as anemia, pyrosis, infections and mycosis. CMU-C beneficiaries also tended less to take recommended vitamins and their dispensation of immunoglobulins for negative rhesus was also lower, while exposure to fetotoxic drugs was higher. Thus, prevention in this subgroup appeared to be less efficient.

3.13 | Strengths and limitations

Our study suffers from the limitations of administrative database use, the main one being that drug dispensation was used as a proxy for drug exposure. However, De Jonge et al.³⁹ found more than 90% compliance during pregnancy, in particular for chronic treatment. Second, the database contains only reimbursed drugs so exposure to drugs is underestimated. Notably, over-the-counter drug use was estimated to be 7.5% in France by Hurault-Delarue et al.¹⁸ In addition, the date of consumption may be long after the dispensation date, in particular for drugs used occasionally like pain killers.

The main strength of the study is that it is based on the EGB. Covering the 3 main insurance schemes, this allowed an analysis of 30,000 pregnancies over 4 years. For each woman, exhaustive information on reimbursed drug dispensation was available so the analysis was not impaired by recall bias. This period was also interesting since behavioral changes were observed and no major change occurred in reimbursement during the study. Moreover, the study provides a good overview of the importance of improving compliance with vitamin supplementation recommendations and decreasing fetotoxic drug exposure for disadvantaged pregnant women. Excluding voluntary termination of pregnancy excludes women choosing to terminate their pregnancy after the consumption of potential harmful drugs. Nevertheless, by making this choice, we did not include women with an undesired pregnancy who may not have had the same behavior toward drugs as those who did desire it, and especially toward recommended supplementations and hazardous drugs.

4 | CONCLUSION

Trends in drug prescription during pregnancy in France have developed thanks to a growing awareness by health practitioners of the importance of vitamin supplementation and to safety alerts. However,

improvements are still needed, especially regarding influenza vaccination and the avoidance of valproate during pregnancy.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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CONFLICT OF INTEREST

None.

PRIOR PRESENTATION

Some of the results of this study were presented at the ADELFI-EMOIS Congress in March 2016 in Dijon (France).

CONTRIBUTORS

RD, SE, CQ, PTB and IA planned and designed the study. RD drafted the manuscript and performed the analysis. All authors reviewed the manuscript and approved the final version.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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