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# Drug Exposure During Pregnancy: A Case-Control Study from a Primary Care Database

Ainhoa Gomez-Lumbreras,<sup>1</sup> Marta Leston Vazquez,<sup>2,3</sup> Carles Vilaplana-Carnerero,<sup>3-5</sup> Oriol Prat-Vallverdu,<sup>4,6</sup>  
Cristina Vedia,<sup>3,7</sup> Rosa Morros,<sup>3-5,8</sup> and Maria Giner-Soriano<sup>3,4,\*</sup>

## Abstract

**Objective:** Drug exposure during pregnancy is frequent, even more during first trimester as pregnant women might not be aware of their condition. We used available electronic health records (EHRs) to describe the use of medications during the first trimester in pregnant women and to compare drug exposure between those women who had an abortion (either elective or spontaneous) compared to those who had live births.

**Materials and Methods:** Case-control study of abortions, either elective or spontaneous (cases), and live birth pregnancies (controls) in Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (Catalan Primary Health electronic health records) from 2012 to 2020. Exposure to drugs during first trimester of pregnancy was considered to estimate the association with abortion by conditional logistic regression and adjusted by health conditions and other drugs exposure.

**Results:** Sixty thousand three hundred fifty episodes of abortions were matched to 118,085 live birth pregnancy episodes. Cases had higher rates of alcohol intake (9.9% vs. 7.2%,  $p < 0.001$ ), smoking (4.5% vs. 3.6%,  $p < 0.001$ ), and previous abortions (9.9% vs. 7.8%,  $p < 0.001$ ). Anxiety (30.3% and 25.1%,  $p < 0.001$ ), respiratory diseases (10.6% and 9.2%,  $p < 0.001$ ), and migraine (8.2% and 7.3%,  $p < 0.001$ ), for cases and controls, respectively, were the most frequent baseline conditions. Cases had lower rate of drug exposure, 40,148 (66.5%) versus 80,449 (68.1%),  $p < 0.001$ . Association with abortion was found for systemic antihistamines (adjusted odds ratio [OR<sub>adj</sub>] 1.23, 95% confidence interval [CI] 1.19–1.27), antidepressants (OR<sub>adj</sub> 1.11, 95% CI 1.06–1.17), anxiolytics (OR<sub>adj</sub> 1.31, 95% CI 1.26–1.73), and nonsteroidal anti-inflammatory drugs (OR<sub>adj</sub> 1.63, 95% CI 1.59–1.67).

**Conclusions:** These high rates of drug exposures during the first trimester of pregnancy highlights the relevance of informed prescription to women with childbearing potential.

<sup>1</sup>Department of Pharmacotherapy, College of Pharmacy, University of Utah, Salt Lake City, Utah, USA.

<sup>2</sup>Àrea del Medicament i Servei de Farmàcia, Gerència d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut, Barcelona, Spain.

<sup>3</sup>Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain.

<sup>4</sup>Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain.

<sup>5</sup>Plataforma SCReN, UIC IDIAPJGol, Barcelona, Spain.

<sup>6</sup>Marketing farmacèutic & Investigació clínica, Barcelona, Spain.

<sup>7</sup>Servei d'Atenció Primària Maresme, Barcelona, Spain.

<sup>8</sup>Institut Català de la Salut, Barcelona, Spain.

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\*Address correspondence to: Maria Giner-Soriano, PharmD, PhD, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Gran Via de les Corts Catalanes 587, àtic, Barcelona 08007, Spain, E-mail: [mginer@idiapjgol.info](mailto:mginer@idiapjgol.info)



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## Introduction

The study of the use of drugs during pregnancy is mainly made by observational approaches, by analyzing pregnancy registries, case series, or cohort studies due to the ethics concerns of pregnant women's participation in clinical trials.<sup>1</sup> During pregnancy, women can face chronic or acute illness, and the therapeutic approach is mainly based on clinical guidelines.<sup>2</sup>

Spontaneous abortion or miscarriage, described as the loss of pregnancy less than 20 weeks gestation, has not clearly been related to drug exposure as most of the times, a genetic factor lays as the main cause.<sup>3</sup> Abortion can also be elective, decided by the pregnant woman if legally admitted, and can be induced, by medical decision. In Europe and North America, the unintended pregnancy rate is 35 per 1,000 women (aged between 15 and 49 years), the abortion rate of 17 per 1,000 women, but this rate increases up to 49% in the case of unintended pregnancies.<sup>4</sup> Pregnant women could unintentionally be exposed to drugs and, according to the country legal basis, they may decide to have an elective abortion, which could be seen as a failure on the counseling when prescribing those drugs to women with childbearing potential.<sup>5,6</sup>

Special attention to drugs used in women with childbearing potential must be made, as exposure in the first trimester is often unintentional as they are unaware of their pregnancy. We aimed to assess the potential relationship of pregnant women's drug exposure and abortion during the first trimester of pregnancy.

## Materials and Methods

### Study design

This is a matched case-control study of pregnancy episodes to describe the first trimester of pregnancy drug exposure and assess the association with abortion.

### Study source

Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària database characteristics have been described elsewhere.<sup>7</sup> It contains electronic health records (EHRs) of the Primary Care Centers of the Catalan Health Institute (ICS), covering up to 6 million people and almost 500,000 pregnancy

episodes. SIDIAP contains data also from the sexual and reproductive health care services (ASSIR) of the ICS. In Catalonia, most of the nonrisk pregnancies are followed at the ASSIR. Pregnancy episodes occurring during 2011–2020 were identified from the SIDIAP ASSIR module and through International Classification of Diseases 10th (ICD-10) diagnosis codes for gestation, abortion, and delivery (8–42 weeks) registered in the EHR.<sup>8</sup>

### Study population and matching

Pregnancy episodes in women from 12 to 50 years old were classified as cases (abortions) and as controls (pregnancies with a live-birth delivery), please see Case Definition section and Control Definition section. Data missing for pregnancy start date (PSD) and pregnancy end date (PED) were imputed based on average duration from the ASSIR data and final outcome for delivery or abortion was made based on clinical assumptions from data registered (e.g., ICD 10th code registered for Encounter for supervision of normal pregnancy, unspecified, first trimester-Z34.91, O03 spontaneous abortion, etc.).<sup>8</sup>

**Case definition.** Pregnancy episodes with a PSD, a PED, and an outcome for the end of pregnancy registered as “Abortion” within the first 120 days since the PSD. The outcome was not an ICD code, but an internal SIDIAP code for abortion, so no differences between elective or spontaneous abortion could be done.

**Control definition.** Pregnancy episodes with a date for the PSD and PED and outcome for the end of pregnancy as labor (“vaginal” or “C-section,” both included) were live-birth pregnancies (either full term or preterm birth).

Exclusion criteria were those pregnancies with no SIDIAP code for the PED even if the PSD was registered.

Cases were matched 1:2 to controls by mother's age by episode PSD ( $\pm 3$  years).

### Variables

Demographic characteristics, body mass index, smoking status, and alcohol intake were considered from 12 months before PSD up to 120 days after. Variables on medical conditions by ICD 10th diagnoses codes (to



see those of interest please see Supplementary File S1) registered up to 120 after PSD. Previous episodes on live-birth pregnancies and abortions were considered if not occurring before the start of the study period (2011).

### Exposures

SIDIAP pharmacy invoice data were used to define drug exposure; any invoice occurring either 30 days before the PSD up to 120 days after this date or the date of abortion (whichever occurs first). Drugs were classified into the group according to the Anatomic Therapeutic Chemical classification level 3.<sup>9</sup> Those drugs with less than a 3% case exposure or a different nonsignificant exposure ( $p > 0.05$ ) were not included in the final analysis.

### Statistical analysis

Descriptive data, crude odds ratio ( $OR_{crude}$ ), and adjusted odds ratio ( $OR_{adj}$ ) with 95% confidence intervals (95% CI) were calculated using conditional logistic regression. Adjusted for these variables and for drug groups accounted for  $\geq 3\%$  of cases, for which the chi-square test showed significant differences ( $p < 0.05$ ).

A sensitivity analysis for a subset of complete data with no imputations - only of those pregnancies' records from the ASSIR with a spontaneous abortion label and deliver or C-section one for control was conducted. Clinical Trial Registration: EUPAS47450.

### Results

A total of 60,350 episodes of abortion were matched to 118,085 live-birth pregnancy episodes. Women's mean age was 33 years (interquartile range 28.9, 37.9). Higher rates of smoking and alcohol intake were registered for the cases (4.5% vs. 3.6%,  $p < 0.001$  and 9.9% vs. 7.2%, respectively,  $p < 0.001$ ). There were no differences on history of previous pregnancies with live-birth outcomes, although a higher rate of previous abortions was found for cases when compared to controls (9.9% vs. 7.8%,  $p < 0.001$ ). Pregnant women characteristics at the pregnancy episodes are shown in Table 1. Cases had overall a higher prevalence of medical conditions, being anxiety the highest [18,268 (30.3%) compared to 29,614 (25.1%) in controls], followed by respiratory diseases [(6,410 (10.6%) and 10,915 (9.2%)] and migraine [(4,919 (8.2%) and 8,573 (7.3%)]. The overall drug exposure rate was higher among the controls [40,148 (66.5%) vs. 80,449 (68.1%),  $p < 0.001$ , cases].

The drug group with the highest rates of exposure was iodine therapy followed by those supplements indicated during pregnancy (vitamin B12 and folic acid and iron preparations). See Table 2 for specific active substance for each medication group, only most frequent active substance showed. The largest difference among drug exposure between cases and controls was for the Iodine therapy group (23.9% of use in cases and 35.2% in controls) and for nonsteroidal anti-inflammatory drugs (NSAIDs) (13.8% in cases and 6.1% in controls). Pregnancy episodes were most exposed to amoxicillin and fosfomycin among the rest of antibiotics of systemic use [10,119 (56.9%) and 11,344 (98.4%) cases and controls, respectively], and to omeprazole [4,028 (59.8%)] and ranitidine [2,160 (32.1%)] in the group of drugs for peptic ulcer and gastroesophageal reflux disease. Ibuprofen was the most used NSAID (9,598, 57.3%) and levonorgestrel and ethinylestradiol (2,170, 51.7%) among the systemic contraceptives group.

The  $OR_{adj}$  for any drug exposure was 1.014 (1.010–1.019),  $p < 0.001$  when compared to nonexposure. For the drug groups that showed a statistically significant different exposure among cases and controls and a frequency of exposure higher than 3% the  $OR_{crud}$  and  $OR_{adj}$  are shown in Table 3. Association was found for antihistamines for systemic use [ $OR_{adj}$  (95% CI) 1.23 (1.19–1.27)], antidepressants [1.11 (1.06–1.17)], anxiolytics [1.31 (1.26–1.73)], NSAIDs [1.63 (1.59–1.67)] and hormonal contraceptives for systemic use [1.71 (1.65–1.78)]. The results of the sensitivity analysis did not differ from the ones using all data. Results for the sensitivity analysis conducted only with those pregnancy episodes defined by the complete data nonimputed can be seen in Supplementary File S2.

### Discussion

This case-control study shows a high rate of exposure to drugs during first trimester of pregnancy comparing those pregnancies ending in abortion to those ending in a live birth. Hormonal contraceptives for systemic use, NSAIDs, anxiolytics, systemic antihistamines, and antidepressants showed association with abortion. Among the group of drugs studied, the supplements such as iodine or folic acid showed no relationship with abortion.

The use of these supplements (iodine therapy, folic acid and derivatives, and iron preparations) is supported by most of the pregnancy guidelines.<sup>10</sup> Planned pregnancies are more likely to adhere to pregnancy recommendations and, women with chronic medical



**Table 1. Descriptive Characteristics of the Pregnancy Episodes (Characteristics Are for the Pregnancy at That Specific Episode Accounting)**

N (%)	Abortions (N=60,350)	Live-birth pregnancies (N=118,085)	
Complete data, no imputation	N=48,733 (80.7)	N=102,908 (87.1)	
Mother age at pregnancy episode (mean, IQR 25–75)	33.7 (28.9, 37.9)	33.5 (28.7, 37.5)	<0.001
Smoking (yes)	2,695 (4.5)	4,295 (3.6)	<0.001
Alcohol intake (yes)	5,993 (9.9)	8,552 (7.2)	<0.001
Obese (BMI=> 30 and/or Dx)	11,499 (19.1)	23,763 (20.1)	
MEDEA			<0.001
Rural	10,430 (17.3)	21,873 (18.5)	
Urban	6,134 (10.2)	11,101 (9.4)	
Level 1	6,630 (11.0)	12,173 (10.3)	
Level 2	8,029 (13.3)	15,821 (13.4)	
Level 3	8,523 (14.1)	16,314 (13.8)	
Level 4	9,519 (15.8)	18,388 (15.6)	
Level 5	11,040 (18.3)	22,360 (18.9)	
NA	45 (0.1)	55 (0.0)	
History of previous life births	4,721 (7.8)	9,476 (8.0)	0.138
History of abortions	5,970 (9.9)	9,220 (7.8)	<0.001
Diseases			
Mental disorders			
Anxiety	18,268 (30.3)	29,614 (25.1)	<0.001
Depression bipolar	4,590 (7.6)	7,060 (6.0)	<0.001
Eating disorders	2,926 (4.8)	4,553 (3.9)	<0.001
Personality disorder	446 (0.7)	556 (0.5)	<0.001
Psychosis	176 (0.3)	252 (0.2)	0.002
Cardiovascular			
Atrial fibrillation	17 (0.0)	22 (0.0)	0.263
Heart failure	10 (0.0)	17 (0.0)	0.881
Hypertension	958 (1.6)	1,478 (1.3)	<0.001
Ischemic heart disease	17 (0.0)	19 (0.0)	0.128
Myocarditis	1 (0.0)	6 (0.0)	0.488
Cerebrovascular disease	79 (0.1)	115 (0.1)	0.050
Diabetes mellitus	514 (0.9)	662 (0.6)	<0.001
Chronic kidney disease	55 (0.1)	54 (0.0)	<0.001
Neurologic diseases			
Epilepsy	390 (0.6)	599 (0.5)	<0.001
Migraine	4,919 (8.2)	8,573 (7.3)	<0.001
Immune mediated			
Immunodeficiencies	10 (0.0)	15 (0.0)	0.659
Lupus	26 (0.0)	43 (0.0)	0.582
Rheumatoid arthritis	163 (0.3)	293 (0.2)	0.412
Autoimmune thyroiditis	202 (0.3)	336 (0.3)	0.075
Transplant	16 (0.0)	25 (0.0)	0.590
Neoplasm	586 (1.0)	923 (0.8)	<0.001
Respiratory diseases	6,410 (10.6)	10,915 (9.2)	<0.001
HIV	37 (0.1)	34 (0.0)	0.002
Drug exposure			
No drug exposure	20,202 (33.5)	37,636 (31.9)	<0.001
Number of drugs			
1	14,740 (24.4)	30,570 (25.9)	
2–3	16,378 (27.1)	34,771 (29.4)	
4–5	6,175 (10.2)	11,138 (9.4)	
>5	2,855 (4.7)	3,970 (3.4)	

BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; MEDEA, socioeconomic index.

conditions are more likely to adhere to these, supporting the protective association of these supplements.<sup>11</sup>

Among the anti-infectives, our results agree with previous studies, beta-lactams are the most used during pregnancy, but no risk of spontaneous abortion has been shown for beta-lactams, while for quinolones, tetracyclines, sulfonamides, metronidazole, and macrolides, this potential risk has been defined.<sup>12,13</sup>

No association was found for drugs used to treat peptic ulcer and gastroesophageal reflux, histamine 2 receptor antagonist (H<sub>2</sub>RA), or proton pump inhibitors (PPI). Considering heartburn is one of the most common complaints during pregnancy and that up to now no other studies have found any risk of abortion for PPI or H<sub>2</sub>RA, we think these results can support the safe use of these during the pregnancy.<sup>14</sup>



**Table 2. Medication Groups and More Frequent Active Substances**

Medication group	Abortions exposure, N (%)	Live-birth pregnancies exposure, N (%)	Total exposure, N (%)
Active substance			
Iodine therapy	14,407 (23.9)	41,525 (35.2)	
Potassium iodide + vitamin B12 + folic acid	13,424 (92.5)	37,733 (88.9)	51,157 (89.8)
Potassium iodide	1,080 (7.3)	4,702 (11.1)	5,782 (10.1)
Vitamin B12 and folic acid	7,877 (13.1)	21,422 (18.1)	
Folic acid	4,987 (62.0)	13,061 (59.4)	18,048 (60.1)
Cyanocobalamin, combinations	2,953 (36.7)	8,781 (39.9)	11,734 (39.1)
Iron preparations	4,781 (7.9)	12,502 (10.6)	
Ferrous sulfate	3,250 (65.7)	8,141 (62.1)	11,391 (63.1)
Ferrous glycine sulfate	860 (17.4)	2,844 (21.7)	3,704 (20.5)
Ferric proteinsuccinylate	530 (10.7)	1,295 (9.9)	1,825 (10.1)
Iron mannitol (ferrimanitol)	256 (5.2)	664 (5.1)	920 (5.1)
Other antibacterials	3,035 (5.0)	8,430 (7.1)	
Fosfomycin	3,004 (98.3)	8,340 (98.4)	11,344 (98.4)
Beta-lactam antibacterials, penicillins	5,420 (9.0)	11,344 (9.6)	
Amoxicillin	3,101 (53.9)	7,018 (58.3)	10,119 (56.9)
Amoxicillin and beta-lactamase inhibitor	2,402 (41.8)	4,524 (37.6)	6,926 (38.9)
Drugs for peptic ulcer and GORD	2,464 (4.1)	3,908 (3.3)	
Omeprazole	1,906 (73.5)	2,122 (51.2)	4,028 (59.8)
Ranitidine	363 (14.0)	1,797 (43.4)	2,160 (32.1)
Antihistamines for systemic use	2,905 (4.8)	3,567 (3.0)	
Cetirizine	948 (30.1)	1,105 (28.7)	2,053 (29.4)
Loratadine	680 (21.6)	896 (23.3)	1,576 (22.5)
Ebastine	691 (22.0)	762 (19.8)	1,453 (20.8)
Dexchlorpheniramine	296 (8.6)	526 (13.7)	795 (11.4)
Antidepressants	2,195 (3.6)	2,252 (1.9)	
Citalopram	462 (18.7)	454 (18.3)	916 (18.5)
Paroxetine	442 (17.9)	452 (18.2)	894 (18.0)
Fluoxetine	311 (12.6)	344 (13.9)	655 (13.2)
Sertraline	314 (12.7)	328 (13.2)	642 (13.0)
Escitalopram	220 (8.9)	213 (8.6)	433 (8.8)
Amitriptyline	217 (8.8)	200 (8.1)	417 (8.4)
Venlafaxine	135 (5.5)	139 (5.6)	274 (5.5)
Anxiolytics	3,147 (5.2)	2,506 (2.1)	
Diazepam	1,542 (44.5)	1,112 (41.5)	2,654 (43.2)
Alprazolam	802 (23.2)	645 (24.1)	1,447 (23.6)
Lorazepam	783 (22.6)	626 (23.4)	1,409 (23.0)
Anti-inflammatory and rheumatic products, nonsteroids (NSAIDs)	8,332 (13.8)	7,234 (6.1)	
Ibuprofen	4,974 (54.5)	4,624 (60.6)	9,598 (57.3)
Naproxen	1,449 (15.9)	1,316 (17.2)	2,765 (16.5)
Dexketoprofen	1,801 (19.7)	777 (10.2)	2,578 (15.4)
Diclofenac	691 (7.6)	678 (8.9)	1,369 (8.2)
Anti-infectives and antiseptics, excl combination with corticosteroids	2,717 (4.5)	7,383 (6.3)	
Clotrimazole	1,581 (52.6)	5,195 (63.7)	6,776 (60.7)
Fenticonazole	568 (18.9)	1,407 (17.2)	1,975 (17.7)
Clindamycin	334 (11.1)	614 (7.5)	948 (8.5)
Dequalinium	248 (8.2)	452 (5.5)	700 (6.3)
Hormonal contraceptives for systemic use	2,633 (4.4)	1,496 (1.3)	2,170 (51.7)
Levonorgestrel and ethinylestradiol	1,343 (49.9)	827 (54.9)	759 (18.1)
Desogestrel	401 (14.9)	358 (23.8)	486 (11.6)
Drospirenone and ethinylestradiol	362 (13.4)	124 (8.2)	396 (9.4)
Dienogest and ethinylestradiol	284 (10.5)	112 (7.4)	231 (5.5)
Etonogestrel	208 (7.7)	23 (1.5)	

Only medication groups with over 3% (either cases or controls) frequency of exposure during the first trimester of the pregnancy episodes and statistical difference ( $p < 0.05$ ).

GORD, gastroesophageal reflux disease; NSAIDs, nonsteroidal anti-inflammatory drugs.

Our study shows association to abortion for the first trimester exposure to antihistamines for systemic use. There are controversial results on the association between early exposure to antihistamines and malformations.<sup>15,16</sup> Contrary to our results, meta-analysis of

Etwel et al. did not find any association between the first trimester exposure to H<sub>1</sub> antihistamines and abortion.<sup>15</sup> In a German study on chronic diseases in women with childbearing potential, the prevalence of allergies (either systemic or dermatological) was up to





**Table 3. Odds Ratios for Association with Abortion for Each of the Medication Groups**

Medication group (ATC code)	OR <sub>crude</sub> (95% CI)	OR <sub>adj</sub> (95% CI)
Iodine therapy (H03C)	0.69 (0.68–0.70)	0.71 (0.69–0.72)
Folic acid and derivatives (B03B)	0.76 (0.75–0.78)	0.77 (0.75–0.79)
Iron preparations (B03A)	0.80 (0.78–0.82)	0.86 (0.84–0.89)
Other antibacterials (J01X)	0.77 (0.74–0.80)	0.81 (0.78–0.84)
Beta-lactam antibacterials, penicillins (J01C)	0.95 (0.93–0.98)	0.87 (0.84–0.89)
Drugs for peptic ulcer and GORD (A02B)	1.14 (1.09–1.19)	0.98 (0.94–1.02)
Antihistamines for systemic use (R06A)	1.34 (1.29–1.39)	1.23 (1.19–1.27)
Antidepressants (N06A)	1.46 (1.40–1.52)	1.11 (1.06–1.17)
Anxiolytics (N05B)	1.67 (1.61–1.73)	1.31 (1.26–1.73)
Anti-inflammatory and rheumatic products, nonsteroids (NSAIDs) (M01A)	1.67 (1.63–1.71)	1.63 (1.59–1.67)
Anti-infectives and antiseptics, excl combination with corticosteroids (G01A)	0.79 (0.76–0.82)	0.83 (0.79–0.86)
Hormonal contraceptives for systemic use (G03A)	1.95 (1.87–2.02)	1.71 (1.65–1.78)

Adjusted by: Anxiety, bipolar depression, eating disorder, migraine, respiratory diseases, MEDEA index, obesity (BMI >= 30 and diagnosis), alcohol intake, smoking, or previous abortions, and completed pregnancies.

ATC, anatomic therapeutic chemical classification of drugs; CI, confidence interval; OR<sub>adj</sub>, adjusted odds ratio; OR<sub>crude</sub>, crude odds ratio.

11.3%, and exposure to antihistamines in pregnant women has been described up to 1%, as they are also indicated in some other medical conditions such as urticaria, dermatitis, pruritus, rhinitis, nausea, and motion sickness, making any concern about their safety during pregnancy a priority.<sup>17</sup>

Central nervous system drugs use has increased among women with childbearing potential, and no clear recommendations on their continuing use during pregnancy exist, as also negative outcomes have been described among those women with untreated depression during pregnancy.<sup>18</sup> Our results in a Catalan population are in line with the ones published by the Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria database that showed a risk for abortion for the use of antidepressants and anxiolytics during pregnancy, and the metanalysis by Xing et al. found similar risk of abortion for antidepressants.<sup>19,20</sup> Two observational studies in Danish population did not find any risk for mirtazapine or duloxetine specifically, neither one for fluoxetine with American population.<sup>21,22</sup> Women can already be on antidepressants or anxiolytics when becoming pregnant or initiate these treatments during the pregnancy, and up to now no clear conclusions to guide their use during pregnancy have been established.

We must acknowledge that elective abortion due to negative pregnancy outcomes described while on central nervous system drugs, even more if an unplanned pregnancy, can be biasing the association we found, as it is also acknowledged by the authors of the Danish population observational studies.

During pregnancy, up to 10% of women experience primary headaches such as migraine and tension headache as a cause of the hormonal fluctuation, and also women with rheumatic diseases during pregnancy may need analgesia.<sup>23</sup> NSAIDs, mainly represented by ibuprofen, naproxen, and diclofenac showed association between the first trimester exposure and abortion. The latest meta-analysis on the early exposure in pregnancy to NSAIDs and abortion confirms our results.<sup>24</sup> However, the rates of NSAIDs exposure, as these are often in use in an “as needed” basis or as over the counter (OTC) drugs make it difficult to be accurate assessing their exposure.<sup>25</sup>

Up to 40% of women with potential childbearing have reported not to be using contraception and abortion rates have increased in the last decades.<sup>4,26</sup> For women with chronic conditions, induced abortion rates have demonstrated to be similar to those without diseases, so if we focus only on drug exposure, our results raise the concern of unplanned pregnancies and elective abortion.<sup>27</sup> Because high-income countries have lower rates of unplanned pregnancies but higher rates of abortion, our findings on the association between abortion and contraceptives may be explained by women not wanting to become pregnant and contraceptive failure or fear to undesired birth outcomes once exposed.

Our results show that drug prescription in women with childbearing potential is very important and may lead to better family planning information. Thus, it may be necessary to advert women with childbearing potential on the risks of use of drugs.

As it may be necessary to advert women on the potential risks of use of drugs, more studies are needed, not only about the specific knowledge of potential teratogenic effects of some drugs but also on the effects of suspending or changing a chronic treatment during pregnancy on the women’s and on the infants’ health, or about the safety of drugs during pregnancy. This information obtained in research would directly impact on the clinical practice.



This study has two important strengths to highlight. First, it has been conducted in a database containing information on pregnancy duration and ending causes and also relied in an algorithm using obstetrics ICD-10 codes diagnoses. These codes have been used previously to identify pregnancy episodes and their duration.<sup>28-30</sup> Our results did not change for the sensitivity analysis, using only those pregnancies with complete ASSIR data. Second, we defined the population at a pregnancy episode level, although we did not make any differences between new users and prevalent ones, but we did consider previous pregnancies outcomes (abortion or stillbirth).

This study has some limitations. Those regarding the accuracy of data register in EHRs have been already defined and some specific to the topic.<sup>31</sup> Abortion in EHRs is not consistently recorded and also different models for its register protecting women's privacy may be difficult, the correct classification of abortion in spontaneous, elective, or induced, and the outcome registered in SIDIAP did not specify the abortion type, so cases could be spontaneous abortions or induced/elective ones. As an example, in the ASSIR, the emergency contraception is recorded in a module to what SIDIAP has not access to and, these are not prescribed and dispensed in community pharmacies, so there is no information on emergency contraception. We might have underregister supplements or NSAIDs as these are OTC drugs in Catalonia.

Exposure definition was at an invoice level, we did not have information on the strength, so the amount of exposure could not be quantified. We cannot rule out that a potential indication bias, as women in chronic therapies such as antidepressants, or not willing pregnancy, in contraceptives, may elect the abortion, this we cannot specify if women with unplanned pregnancy may choose intentional abortion were on these medications. However, in the case of antihistamines for systemic use, this association should be studied deeply as this group of drugs is not pregnancy or chronic disease related.

## Conclusions

Use of drugs during the first trimester of pregnancy, when women may not be aware that they are pregnant, is common making necessary to inform women in childbearing age of the risk of use of drugs during pregnancy. Association with abortion

for frequently used drugs such as NSAIDs, antihistamines, and central nervous system need to be further investigated. The potential confounding bias in our study highlights the importance of a good adherence to contraceptives and an improvement in contraception plans.

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## Authors' Contributions

A.G.-L.: conceptualization, research design, data curation, original draft, and editing. M.L.V.: research design, data curation, and review and editing. C.V.-C.: formal analysis, data curation, and review and editing. O.P.-V.: formal analysis, data curation, writing, and review and editing. C.V.: data curation and review and editing. R.M. and M.G.-S.: conceptualization, research design, data curation, and review and editing.

## Ethics Approval and Consent to Participate

The study has been conducted following the Declaration of Helsinki (Fortaleza, Brasil 2013) and the IDIAP Jordi Gol Ethics Committee has approved it (CEIm 18/451-IDIAP 4R18/188). The study is using only de-identified data. Confidentiality of patient records has been maintained at all times. All study reports will contain aggregate data only and those cells showing less than five patients will not be shown. Real Decreto 957/2020, de 3 de noviembre, por el que se regulan los estudios observacionales con medicamentos de uso humano (Royal Decree 957/2020, of November 3, regulating observational studies with medicinal products for human use) and Organic Law 3/2018, of December 5, on Protection of Personal Data and Guarantee of Digital Rights have been followed at all times.

## Consent for Publication

SIDIAP does not provide information subject to re-identification and aggregations or deletions are applied to protect pseudoanonymization.

## Registration

EUPAS37675 (<https://www.encepp.eu/encepp/viewResource.htm?id=37676>). AEMPS classification EPA-OD (IDI-BRO-2020-21, September 16, 2020).



## Author Disclosure Statement

No competing financial interests exist.

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## Supplementary Material

Supplementary File S1

Supplementary File S2

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### Abbreviations Used

95% CI = 95% confidence interval  
ASSIR = sexual and reproductive health care services  
ATC = anatomic therapeutic chemical classification of drugs  
BMI = body mass index  
EHR = electronic health records

GORD = gastroesophageal reflux disease  
H<sub>2</sub>RA = histamine 2 receptor antagonist  
ICD-10 = International Classification of Diseases 10th version  
ICS = Catalan Health Institute  
MEDEA = socioeconomic index  
NSAIDs = nonsteroidal anti-inflammatory drugs  
OR<sub>adj</sub> = adjusted odds ratio  
OR<sub>crude</sub> = crude odds ratio  
OTC = over the counter  
PED = pregnancy end date  
PPI = proton pump inhibitors  
PSD = pregnancy start date  
SIDIAPI = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

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