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Antidepressants during pregnancy: a French drug utilisation study in EFEMERIS cohort

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Abstract

Background Previous studies have suggested that exposure to some antidepressants (AD) during pregnancy could be associated with an increased risk of congenital malformations and neurodevelopment disorders for the child. We conducted a study to describe the use of AD during pregnancy in France.

Methods We performed a drug utilisation study in EFEMERIS, a French cohort of pregnant women. At the time of the present study, 89,170 pregnant women, who were pregnant from 2005 to 2014 in Haute-Garonne were included. Prevalence and incidence of AD prescriptions during pregnancy, characteristics of AD users, and trends in AD use over the 10-year period were studied.

Results During the 10-year study period, 1620 women registered in EFEMERIS (1.8%) received at least one prescription and dispensation for AD during pregnancy: 1363 during the first (1.5%), 591 during the second (0.7%), and 412 during the third (0.5%) trimester. A total of 2874 women (3.2%) got a prescription for an AD during the 3 months before and/or during pregnancy; 2187 of them (76.1%) stopped AD before pregnancy or during the first trimester. Selective serotonin reuptake inhibitors represented the most prescribed class during pregnancy (1.3%). A very slight decrease in the prevalence of AD prescriptions in pregnant women over time (1.7% in 2014 vs 2% in 2005) and some variations within classes were observed.

Conclusions Nearly, 2% of women received antidepressant drugs during pregnancy. This assessment encourages following research on these drugs including the potential risk of neurodevelopmental disorders in children after an exposure to antidepressants during pregnancy.

Keywords Drug utilisation study · Psychotropic drugs · Antidepressant drugs · Pregnancy

Introduction

About 10% of women suffer from depressive disorders during pregnancy in economically developed countries [1, 2]. Serotonin reuptake inhibitors (SSRI) are the most prescribed antidepressant (AD) drugs during pregnancy [3]. Previous studies have suggested that exposure to some SSRI during pregnancy could be associated with an increased risk of congenital malformations; paroxetine and fluoxetine have

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been described to be associated with an increased risk of cardiac anomalies [4, 5]. Others studies did not suggest any increased risk of congenital malformations after exposure to AD [6, 7]. Persistent pulmonary hypertension [8] and neonatal behavioural syndrome [9, 10] have also been associated with SSRI exposure. Finally, controversies exist regarding SSRI use and long-term effects for the child (neurodevelopment disorders and autism spectrum disorders) [11–13].

Prevalence of SSRI use varies depending on European countries [14]. A steady increase in use of AD drugs by pregnant women, and more particularly, SSRI was observed during the past few years in Europe [3, 15]. However, to this day, information on the use of AD and trends in use during pregnancy in France is limited [16, 17].

In this context of controversies, we conducted a study to describe the use of AD during pregnancy in France over a 10-year period.

Methods

Study design

We performed a descriptive drug utilisation study among pregnant women using data from the EFEMERIS cohort (Evaluation chez la Femme Enceinte des Médicaments et de leurs RISques).

Data source

EFEMERIS is a French cohort of pregnant women in the general population developed to assess drug prescriptions and to evaluate risks associated with exposure to drugs during pregnancy. The database links individual information on mothers, especially medications prescribed to them during pregnancy and 3 months before (all reimbursed drugs prescribed and dispensed in pharmacies) and the outcome of these pregnancies with anonymous irreversible identifier (code). Women who were pregnant in Haute-Garonne, an administrative area in south-west France, and who were under general state coverage of health insurance service, are included in the database. More information about the design and features of EFEMERIS were published previously [18]. Setting up the database was approved by the Commission Nationale de l'Informatique et des Libertés (CNIL). Women were informed of the study and could refuse to participate.

Participants

The 89,170 pregnant women who delivered between 1st July 2005 and 31st December 2014 were included, except women who delivered during the second semester of 2008 and the first semester of 2009, because data are partially missing

for this period due to regulatory changes in data storage for one of the datasources. Pregnancies were included; whether it ended with birth or pregnancy loss for any cause. Women who were dispensed AD drugs on at least one date from three months prior to pregnancy or during pregnancy were identified and selected for this study.

Antidepressant drugs (AD)

The database includes the following information for each AD (prescribed, dispensed and reimbursed): name of drug, date of dispensation, and physician specialty. ADs were classified, according to the World Health Organization's Anatomical Therapeutic Chemical classification with some minor adjustments [19] (Supplementary Table 1), in five sub-classes:

- Non-selective Monoamine Reuptake Inhibitors *NSMRI* (amitriptyline, clomipramine, dosulepine, doxepine, imipramine, maprotiline, trimipramine, and amoxapine).
- "Selective" Serotonin Reuptake Inhibitors *SSRI* (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline).
- Serotonin–Norepinephrine Reuptake Inhibitor *SNRI* (duloxetine, milnacipran, and venlafaxine).
- Others (agomelatine, mianserine, mirtazapine, and tianeptine).
- MonoAmine Oxidase Inhibitors *MAOI* (iproniazide and moclobemide).

Data analysis

Prevalence and incidence of AD use

A woman was considered as an AD user if she received at least one AD dispensation during the study period. We estimated the overall prevalence and incidence of AD use and detailed these parameters estimates for each sub-class, each drug and for each period of pregnancy [the 3 months prior to the date of beginning of pregnancy (T0), and the three trimesters of pregnancy (T1, T2, and T3)]. The overall prevalence of AD use in pregnant women was defined as a proportion calculated by dividing the number of pregnant women who filled at least one dispensation for AD during pregnancy (T1, T2, or T3) by the total number of pregnant women in the study period. The incidence of AD use during pregnancy was defined as the proportion of women who started to use AD during the pregnancy (non-users in T0 period). According to the analysis, the denominator was either the total number of women in EFEMERIS database or the total number of women who received AD dispensation during the study period. Because of the small number of

users by drugs, prevalences and incidences were presented per 1000 women and the symbol ‰ was used.

Characteristics of AD users during pregnancy

The characteristics of pregnant women including maternal age at delivery, occupation, education level, presence of long-term adverse health conditions (an administrative status allowing full reimbursement of health care for a given condition; e.g., psychosis) were described. The average number of different drugs reimbursed during pregnancy after exclusion of AD and the prevalence of use of the other psychotropics prescribed during pregnancy (anxiolytics/hypnotics, neuroleptics, and antiepileptics presented in Supplementary Table 1) was also detailed. Several characteristics of children at birth such as preterm delivery (before 37 weeks of amenorrhea), APGAR score at 1 min, at 5 min, neonatal pathologies identified from the children's health certificates established on the 8th day (recorded by the physician during medical consultation) and congenital anomalies (according the ICD-10 classification) were reported. Characteristics of the general population of women included in EFEMERIS database during the same period were also shown.

Different patterns of AD use

The different patterns of AD use were presented: dispensing only before pregnancy (T0), dispensing before and during pregnancy (T0–T1, T0–T1–T2, T0–T1–T2–T3, etc.), dispensing from T1 (T1, T1–T2, etc.), dispensing from T2 (T2, T2–T3), and dispensing from T3.

Trends in AD use over a 10-year period

The prevalence of AD use over the 10 years was graphically presented by 6-month periods, except for data of the second semester of 2008 (2008–SEM2) and the first semester of 2009 (2009–SEM1) for the reason explained before (participants). Evolution of SSRI prevalence of use was more specifically studied.

Statistical analysis

Continuous variables were expressed as means (± SD), and categorical variables as percentages. Characteristics of AD users were compared statistically using student tests (for continuous variables) or Chi square tests (for categorical variables). Statistical tests were two-tailed, with $p < 0.05$ considered to represent statistical significance. The SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina) was used for statistical analysis.

Results

Prevalence and incidence of AD use

During the 10-year study period, 2874 of the women registered in EFEMERIS ($N = 89{,}170$, 32.2‰) got a prescription for an AD from the three months prior to the end of pregnancy. During the three months prior to pregnancy, 2294 women (25.7‰) received at least one dispensation for AD. During pregnancy, they were 1620 women (18.2‰): 1363 during the first (15.3‰), 591 during the second (6.9‰) and 412 during the third (4.9‰) trimester (Table 1). When prevalent AD users during pregnancy are considered, SSRI (and more particularly escitalopram, paroxetine, and fluoxetine) represented the most prescribed class during pregnancy (70.8%), followed by NSMRIs (16.3%), SNRIs (13.7%), and other ADs (5.1%). The study shows that 64.7% of ADs were prescribed by general practitioners and 31.8% by a psychiatrist or neurologist.

The incidence of AD use during pregnancy was 6.5‰ (580 women who started AD during pregnancy) (Table 2). Among them, 63.4% started their AD treatment during the first trimester; 27.2% during the second trimester and 9.3% during the third trimester. SSRIs were often chosen at AD introduction: 64.3% of women who started AD during pregnancy received an active substance of this sub-class and more particularly escitalopram as previously. Concerning prescribers, 74.8% received their first prescription of AD by a general practitioner and 19.3% by a psychiatrist or a neurologist.

Characteristics of AD users (Table 3)

Concerning AD users during pregnancy ($N = 1620$), 8.8% received at least two different AD substances. They were dispensed on average 1.1 (± 0.4) different AD with a mean of 2.7 (± 2.6) different dispensation dates during pregnancy. On average, 14.1 different medications other than AD were also dispensed during this period; more than half (52.8%) used other psychotropic drugs during pregnancy, and more particularly anxiolytics/hypnotics (49.1%) and neuroleptics (10.2%). The mean maternal age of women at delivery was 32.6 years. Long-term adverse health condition was notified for 12.8% of them; 57.9% had a higher education, and 49.3% were unemployed.

Compared to women only exposed to AD before pregnancy, pregnant AD users were older ($p = 0.0001$), more frequently reported to receive medications indicated in long-term adverse health condition ($p < 0.0001$) and other medications such as psychotropic drugs (< 0.0001);

Table 1 Prevalence of AD use before and during pregnancy by sub-classes and active substances

AD	All periods		T0		Pregnancy		T1		T2		T3	
	No.	‰	No.	‰	No.	‰	No.	‰	No.	‰	No.	‰
	$N = 89,170$		$N = 89,170$		$N = 89,170$		$N = 89,170$		$N = 85,540$		$N = 84,764$	
Overall	2874	32.2	2294	25.7	1620	18.2	1363	15.3	591	6.9	412	4.9
SSRI	**2070**	**23.2**	**1651**	**18.5**	**1147**	**12.9**	**980**	**11.0**	**392**	**4.6**	**284**	**3.4**
Escitalopram	717	8.0	568	6.4	378	4.2	334	3.7	104	1.2	74	0.9
Paroxetine	606	6.8	472	5.3	333	3.7	279	3.1	109	1.3	88	1.0
Fluoxetine	350	3.9	255	2.9	204	2.3	164	1.8	78	0.9	52	0.6
Citalopram	310	3.5	258	2.9	148	1.7	133	1.5	44	0.5	28	0.3
Sertraline	244	2.7	154	1.7	146	1.6	98	1.1	68	0.8	50	0.6
Fluvoxamine	5	0.1	5	0.1	3	0.0	3	0.0	2	0.0	2	0.0
SNRI	**422**	**4.7**	**354**	**4.0**	**222**	**2.5**	**205**	**2.3**	**73**	**0.9**	**47**	**0.6**
Venlafaxine	351	3.9	291	3.3	186	2.1	170	1.9	68	0.8	46	0.5
Duloxetine	49	0.5	45	0.5	25	0.3	25	0.3	3	0.0	1	0.0
Milnacipran	26	0.3	20	.2	13	0.1	12	0.1	2	0.0	0	0.0
NSMRI	**421**	**4.7**	**247**	**2.8**	**265**	**3.0**	**171**	**1.9**	**119**	**1.4**	**80**	0.9
Amitriptyline	308	3.5	171	1.9	188	2.1	112	1.3	79	0.9	52	0.6
Clomipramine	89	1.0	56	0.6	65	0.7	52	0.6	37	0.4	24	0.3
Dosulepine	13	0.1	11	0.1	5	0.1	4	0.0	1	0.0	1	0.0
Trimipramine	12	0.1	8	0.1	6	0.1	4	0.0	2	0.0	1	0.0
Maprotiline	6	0.1	1	0.0	5	0.1	1	0.0	1	0.0	3	0.0
Doxepine	1	0.0	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Imipramine	1	0.0	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Others	**216**	**2.4**	**169**	**1.9**	**83**	**0.9**	**69**	**0.8**	**25**	**0.3**	**14**	**0.2**
Tianeptine	104	1.2	86	1.0	35	0.4	30	0.3	9	0.1	4	0.0
Mirtazapine	61	0.7	40	0.4	31	0.3	24	0.3	10	0.1	6	0.1
Mianserine	38	0.4	32	0.4	13	0.1	11	0.1	6	0.1	3	0.0
Agomelatine	14	0.2	11	0.1	5	0.1	4	0.0	0	0.0	1	0.0

No prescription of MonoAmine Oxidase Inhibitors was found in the database

T0 3 months before pregnancy, *T1* trimester 1of pregnancy, *T2* trimester 2 of pregnancy, *T3* trimester 3 of pregnancy

their children had more often a low APGAR score at birth ($p = 0.001$ at 1 min and $p = 0.02$ at 5 min).

Patterns of AD use (before or during pregnancy) ($N = 2874$)

Among the fifteen patterns of prescriptions identifiable (Table 4), 261 (9.1%) women received AD during the three trimesters of pregnancy (± before pregnancy). Beside these women, 2187 (76.1%) stopped AD before pregnancy or during the first trimester; among them, 1267 (57.9) received at least one dispensation of anxiolytics before or during pregnancy but only 156 (7.1%) during the second trimester and 105 (4.8%) during the third trimester.

The 1254 women only exposed before pregnancy (43.6%) were younger than women who do not stop AD (31.9 vs 33.3) and less frequently with long-term adverse health conditions (6.6 vs 16.2%).

Among the 2874 AD users, 354 (12.3%) received at least two different ADs during the period. In 31.9% of the cases, the ADs belonged to the same sub-class and in 93.2%, women were in a "switch" situation (they switched between products and were not taking them in combination).

Trends in AD use over a 10-year period

We observed a very slight decrease in the prevalence of AD prescriptions during pregnancy over time (2% in the second half of the year 2005 and 1.7% in the second half of the year 2014) (Fig. 1) and some variations within SSRI class: decrease in paroxetine, fluoxetine, and citalopram prescriptions and simultaneous increase in escitalopram prescriptions.

Table 2 Incidence of AD use during pregnancy by sub-classes and active substances

AD	Pregnancy		T1		T2		T3	
	No.	‰	No.	‰	No.	‰	No.	‰
	N = 89,170		N = 89,170		N = 85,540		N = 84,764	
Overall	580	6.5	368	4.1	158	1.8	54	0.6
SSRI	**373**	**4.2**	**249**	**2.8**	**95**	**1.1**	**29**	**0.3**
Escitalopram	115	1.3	88	1.0	18	0.2	9	0.1
Paroxetine	99	1.1	70	0.8	23	0.3	6	0.1
Sertraline	60	0.7	25	0.3	27	0.3	8	0.1
Fluoxetine	57	0.6	35	0.4	18	0.2	4	0.0
Citalopram	42	0.5	31	0.3	9	0.1	2	0.0
Fluvoxamine	0	0.0	0	0.0	0	0.0	0	0.0
NSMRI	**132**	**1.5**	**60**	**0.7**	**50**	**0.6**	**22**	**0.3**
Amitriptyline	116	1.3	53	0.6	45	0.5	18	0.2
Clomipramine	8	0.1	4	0.0	3	0.0	1	0.0
Maprotiline	4	0.0	1	0.0	1	0.0	2	0.0
Trimipramine	3	0.0	1	0.0	1	0.0	1	0.0
Dosulepine	1	0.0	1	0.0	0	0.0	0	0.0
Doxepine	0	0.0	0	0.0	0	0.0	0	0.0
Imipramine	0	0.0	0	0.0	0	0.0	0	0.0
SNRI	**49**	**0.5**	**37**	**0.4**	**9**	**0.1**	**3**	**0.0**
Venlafaxine	42	0.5	31	0.3	8	0.1	3	0.0
Duloxetine	4	0.0	4	0.0	0	0.0	0	0.0
Milnacipran	3	0.0	2	0.0	1	0.0	0	0.0
Others	**31**	**0.3**	**24**	**0.3**	**7**	**0.1**	**0**	**0.0**
Mirtazapine	14	0.2	10	0.1	4	0.0	0	0.0
Tianeptine	13	0.1	10	0.1	3	0.0	0	0.0
Mianserine	3	0.0	3	0.0	0	0.0	0	0.0
Agomelatine	1	0.0	1	0.0	0	0.0	0	0.0

T1 trimester 1 of pregnancy, *T2* trimester 2 of pregnancy, *T3* trimester 3 of pregnancy

Comments

A moderate prevalence and incidence of AD use during pregnancy

In this study, conducted in France during a 10-year period, nearly, 2% of women (prevalence of 1.8%) received AD drugs during pregnancy and less than 1% of women started AD during pregnancy (incidence of 0.7%). Use of AD decreased as pregnancy progressed. These prevalence and trend are close to those noted in Denmark in 2014 (prevalence of 2.2%) [3]. In the Quebec Pregnancy Cohort, the prevalence of AD use during pregnancy was 4.5% [20] and 13% in the United States in 2003 [21].

SSRIs, considered as the first-line therapy during pregnancy,[22], represented the most prescribed AD, as in pregnant women of European countries [3, 15] and of the United States [21]. In the French cohort, 1.3% of pregnant women received an SSRI prescription during pregnancy; escitalopram, paroxetine, and fluoxetine were the most prescribed,

despite the risks associated with these last 2 ADs, especially in early pregnancy. This prevalence of SSRI use appears to be comparable to data collected in Italy, but lower than in northern European countries like The Netherlands, Denmark, UK, Iceland, or Sweden [14, 15]. The preferred prescription of SSRIs is also observed in the French general population [23] and is in agreement with the NICE 2015 guidelines for adults with depression or generalised anxiety disorder ("First-choice antidepressant use in adults with depression or generalised anxiety disorder"). Besides SSRIs, venlafaxine and amitriptyline appeared to be prescribed during pregnancy with only 0.2% of women concerned. These prevalences are close to those observed in Nordic countries and in the United States [14, 24].

A slight decrease in prevalence of use over time

Overall, between 2005 and 2014, we observed a very slight decrease over time in the proportion of women who were prescribed AD during pregnancy. However, this result must

Table 3 Characteristics of AD users

Characteristics of pregnant women during pregnancy	AD users			p value[a]	EFEMERIS[b]
	Before and/or during pregnancy	Only before pregnancy	During pregnancy		
	$N = 2874$	$N = 1254$	$N = 1620$		$N = 89{,}170$
Age at delivery (years), mean ± SD	32.3 ± 5.3	31.9 ± 5.3	32.6 ± 5.2	0.0001	30.5 ± 5.1
Long term adverse health condition, n (%)	290 (10.1)	83 (6.6)	207 (12.8)	< 0.0001	2.5%
No occupation, n (%)	($n = 920$)	($n = 385$)	($n = 535$)		
	456 (49.6)	192 (49.9)	264 (49.3)	0.9	42.4%
Higher education, n (%)	($n = 963$)	($n = 415$)	($n = 548$)		
	544 (56.5)	227 (54.7)	317 (57.9)	0.3	61.6%
Alcohol consumption, n (%)	($n = 699$)	($n = 290$)	($n = 409$)		
	8 (1.1%)	2 (0.7%)	6 (1.5%)	0.3	0.6%
Tobacco consumption, n (%)	($n = 767$)	($n = 316$)	($n = 451$)		
	200 (26.1%)	81 (25.6%)	119 (26.4%)	0.8	13.7%
Number of other different medications, mean ± SD	13.7 ± 8.2	13.2 ± 8.2	14.1 ± 8.3	0.002	9.3 ± 6.6
Other psychotropic drugs, n (%)	1090 (37.9)	235 (18.7)	855 (52.8)	< 0.0001	5.8%
Anxiolytics/hypnotics	1016 (35.4)	221 (18.7)	795 (49.1)	< 0.0001	5.2%
Neuroleptics	184 (6.4)	19 (1,5)	165 (10.2)	< 0.0001	0.7%
Antiepileptics	64 (2.2)	9 (0.7)	55 (3.4)	< 0.0001	0.2%
Characteristics of children at birth[c]	AD users			p value[a]	EFEMERIS[b]
	Before and/or during pregnancy	Only before pregnancy	During pregnancy		
	$N = 2570$	$N = 1158$	$N = 1412$		$N = 84{,}466$
Apgar score at 1 min ≤ 7, n (%)	($n = 2083$)	($n = 939$)	($n = 1144$)		
	122 (5.9)	38 (4.1)	84 (7.3)	0.001	5.1%
Apgar score at 5 min ≤ 7, n (%)	($n = 2343$)	($n = 1057$)	($n = 1286$)		
	38 (1.6)	10 (1.0)	28 (2.2)	0.02	1.0%
Neonatal pathology, n (%)	($n = 2432$)	($n = 1098$)	($n = 1334$)		
	216 (8.9)	84 (7.7)	132 (9.9)	0.05	7.2
Preterm birth (< 37SA), n (%)	209 (8.1)	88 (7.6)	121 (8.6)	0.4	6.5%
Congenital anomaly, n (%)	53 (2.1)	20 (1.7)	33 (2.3)	0.3	2.1%

[a]Comparisons between AD users "Only before pregnancy" and "During pregnancy"

[b]Reference data for complete available EFEMERIS data of pregnant woman between 2005 and 2014

[c]Other issues correspond to pregnancy losses for any cause

be considered with caution, because some data for the second semester of 2008 and the first semester of 2009 are missing. This result was not consistent with the observation performed in the United States, where an increased use of AD was noted between 1999 and 2005 [21, 24]. Other European countries, like Iceland and Denmark, showed similar trends in the prescriptions of SSRIs;[3, 14, 15]; conversely, the situation remained stable during the same period in Norway [14]. In France, the slight decrease of AD prescriptions during pregnancy, especially for paroxetine, might be in relation with the released information concerning risks associated with exposure to this drug during pregnancy by French

health authorities and pharmaceutical firms since 2005 [24, 25]. In the United States, two Food and Drug Administration public health advisories concerning treatment of depression during pregnancy were published in 2006 [27] and 2007 [28]; however, we did not find any recent studies on the impact of these recommendations.

Profiles of AD users during pregnancy

Nearly, 10% of all AD users received at least two different ADs during the period. The large majority was in a "switch" situation, respecting the recommendations not to associate

Table 4 Different patterns of AD use before and during pregnancy

Trimester of AD dispensing	No. N = 2874	%
Dispensing only before pregnancy		
T0	1254	43.6
Dispensing before and during pregnancy		
T0–T1	616	21.4
T0–T1–T2	117	4.1
T0–T1–T2–T3	238	8.3
T0–T1–T3	24	0.8
T0–T2	19	0.7
T0–T2–T3	11	0.4
T0–T3	15	0.5
Dispensing from T1		
T1	317	11.0
T1–T2	25	0.9
T1–T2–T3	23	0.8
T1–T3	3	0.1
Dispensing from T2		
T2	114	4.0
T2–T3	44	1.5
Dispensing from T3		
T3	54	1.9

T1 trimester 1 of pregnancy, *T2* trimester 2 of pregnancy, *T3* trimester 3 of pregnancy

several ADs during pregnancy. Changes for an AD with fewer side effects may be justified during pregnancy.

Depressive disorders in the perinatal period are known [29]. This could partly be explained by the parenting stress (e.g., expectations of not being able to cope with the new child) [30]. Moreover, other factors such as maternal history of child abuse have been shown to be determinants of antenatal depression [31]. Howard et al. [29] had also highlighted that young age, low socio-economic status and anxiety during pregnancy may be risk factor for this form of depression. In the present study, a high rate of unemployed women (49%) and of women exposed to anxiolytics and hypnotics (49%) was observed compared to general population of EFEMERIS for which 42.4% of pregnant women are unemployed and 5.2% are exposed to anxiolytics and/or hypnotics during pregnancy.

This last result leads us to question about the conditions for which ADs were prescribed in this population (data not available in the database). Indeed, a Canadian team has shown that 18% of AD and 66% of SSRI were prescribed for anxiety disorders in Quebec [32].

Pregnancy and persistence of AD treatment

Almost half of the women received AD only before pregnancy. For more than 30% of them, treatment interruption appeared during the first trimester. Consequently, one may wonder about the reasons of treatment interruptions. Does the re-evaluation of the relevance of AD prescription, recommended before or in early pregnancy, lead prescribers to
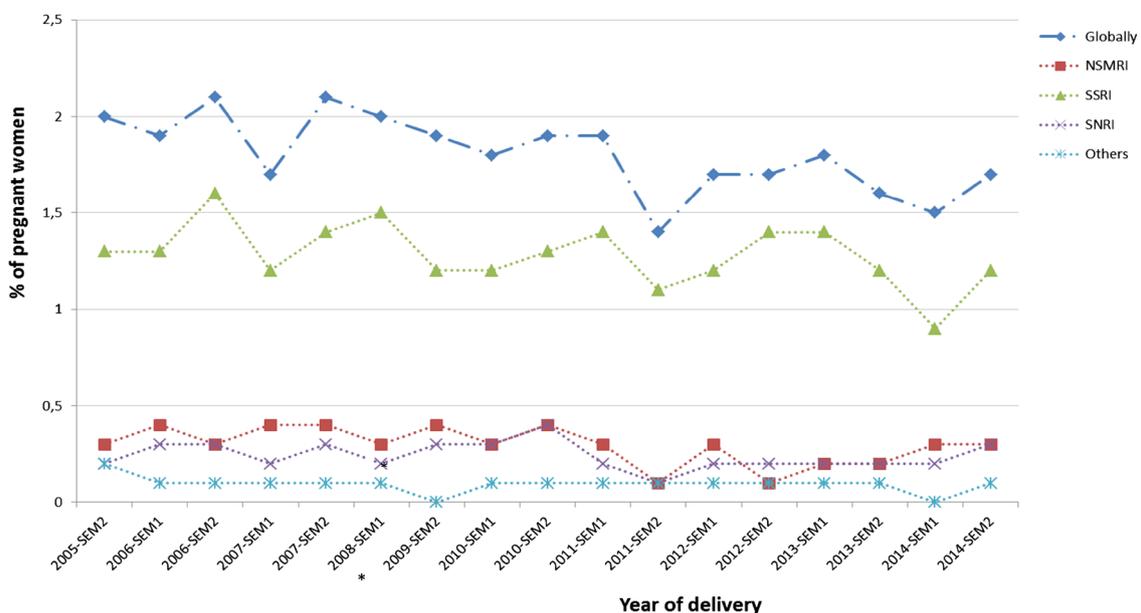

Fig. 1 Trends in AD use during pregnancy from 2005 to 2014. *SEM1* from 1 January to 30 June of the year, *SEM2* from 1 July to 31 December of the year. *Data for the second semester of 2008 (2008–SEM2) and the first semester of 2009 (2009–SEM1) are partially missing

stop treatment? Do adverse effects said to be associated with an exposure to AD drugs during pregnancy lead prescribers to stop treatment whatever the risk of exacerbation of the depression for the pregnant women?

According to Cohen et al., pregnancy represents a period at risk of major depression relapse, particularly in case of antidepressant discontinuation [33]. However, these conclusions were not confirmed by Yonkers et al., who concluded that failure to use or discontinuation of antidepressants in pregnancy did not have a strong effect on the development of a major depressive episode [34]. Despite all that, many authors agree on the fact that untreated maternal depression, anxiety or both, does present a risk to the mother and the foetus [35].

Again, one can hypothesize that the high level of AD treatment interruption could be related to several profiles of pregnant women: a first group taking AD for anxiety, switching to anxiolytic (around 10%); a second group for whom the re-evaluation of the treatment before or at the beginning of pregnancy has shown that the treatment was no longer necessary; a third group for whom the remaining safety questions on the benefit/risk ratio of AD use during pregnancy led to inappropriate interruption of the treatment.

Strengths and limitations of EFEMERIS database

This study presents some limitations inherent in the use of reimbursement databases, namely, lack of information concerning indications of prescriptions or severity of maternal disease. Information about treatment adherence is not available in EFEMERIS database. According to Wu et al. [36] and Lupatteli et al. [37], nearly, 45% of pregnant women using antidepressant medication showed low adherence in pregnancy; therefore, the results should be considered with some caution.

This study concerned only one French administrative area (around 2% of French population and deliveries in France [38]). Indeed, prescribing practices may vary according areas of residence. However, EFEMERIS database currently represents a prescription observatory on a large sample of pregnant women. Prescription data on more than 100,000 pregnancies can be studied over a period of 10 years.

Conclusion

A slight decrease of antidepressant drug use during pregnancy was observed in France. Despite the potential risks of untreated depressive disorders during pregnancy for both mother and child, treatment interruptions before pregnancy or in early pregnancy are common. Between 2005 and 2014, nearly, 2% of women received antidepressants during her pregnancy. Around 800,000 women give birth in France each year; consequently, more than 15,000 pregnant women are potentially exposed to antidepressants during their pregnancy every year in France. This assessment must encourage following research on the consequences of the use of these drugs, including long-term potential risks, such as neurodevelopmental disorders in prenatally exposed children. EFEMERIS database includes data on psychomotor development abnormalities and can also be used to study these disorders.

Compliance with ethical standards

Conflict of interest Caroline Hurault-Delarue, Isabelle Lacroix, Anne Bénard-Laribière, Jean-Louis Montastruc, Antoine Pariente and Christine Damase-Michel declare that they have no conflict of interest with the Pharmaceutical Industry.

Ethics statement The EFEMERIS database was approved by the French Data Protection Agency (Commission Nationale de l'Informatique et des Libertés, CNIL) on 7 April 2005 (authorisation number 05-1140). Women were informed of the study and could refuse to participate. In accordance with French regulations, ethics committee approval was not required for this observational study conducted on anonymous medico-administrative data.

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