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ORIGINAL RESEARCH ARTICLE

Real-World Data Insights into Antidepressant Prescription and Adherence During Pregnancy in Catalonia (Spain)

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Abstract

Background Affective disorders, particularly depression, are common among women of childbearing age, and pregnancy often exacerbates symptoms. Antidepressants are often required for treatment, but adherence during pregnancy is variable. Although some studies suggest potential risks to the foetus, many cannot rule out confounding by indication. In this context, understanding real-world patterns of antidepressant prescription and adherence during pregnancy is essential to inform clinical practice and ensure adequate mental healthcare.

Objective The aim of the present study was to characterise the use of antidepressants in a cohort of pregnant women using electronic health records.

Methods This observational cohort drug-utilisation study assessed antidepressant prescription patterns, adherence and persistence among pregnant women using data from the SIDIAP (Information System for the Development of Research in Primary Care) database in Catalonia from January 2011 to June 2020.

Results Among 99,605 pregnancies, 14.9% involved antidepressant prescriptions, but only 5.8% of these were collected from pharmacies. The median pregnancy duration was 38.4 weeks, and the median maternal age was 33.5 years. Anxiety was the most common health issue associated with an antidepressant prescription. Paroxetine was the most frequently prescribed antidepressant, although sertraline usage increased over time. Antidepressant prescriptions and adherence decreased during pregnancy, with an increase in the postpartum period. About 11.6% of pregnancies involved a concurrent prescription of another antidepressant, and 29.2% of women resumed antidepressant use after pregnancy. Women who initiated antidepressants during pregnancy were more likely to persist with treatment than those with pre-existing prescriptions.

Conclusions Our study describes antidepressant use during pregnancy in Catalonia. It is remarkable that there is a notable gap between antidepressant prescriptions and dispensations. Given the risks of untreated maternal depression, strengthening primary care with adequate resources and personalised support is essential for improving perinatal mental healthcare.

1 Introduction

Affective disorders, particularly depression, significantly impact women of childbearing age, with higher prevalence rates compared with men of all ages and postmenopausal women [1, 2]. During pregnancy, around 70% of women experience depressive symptoms and a notable percentage meet criteria for major depressive disorder (10–16%) [3]. Postpartum depression also affects a significant number of women following childbirth [4–6]. Psychotherapy is recommended as the first-line approach for moderate depression during pregnancy, with antidepressant medications reserved for cases of major depressive disorder, especially those with suicidal ideation [5, 7].

According to previous studies, selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are the most prescribed type of antidepressants during pregnancy for managing depressive symptoms, followed by tricyclic antidepressants [8]. Despite that, some SSRIs and SNRIs have shown an association with an increased risk of congenital malformations, specific birth defects and pulmonary hypertension in the newborn, among others [8–10]. However, there are conflicting data on congenital malformation with antidepressants. Other studies do not support this association and there seems to be a growing consensus that the risk is minimal, particularly if factors such as confounding by indication are taken into account [11–13].

A notable limitation of the studies that reported these risks is their inability to completely rule out confounding

Extended author information available on the last page of the article

Key Points

The difference between the percentage of prescriptions issued by physicians and the actual dispensation of antidepressant medications at pharmacies is remarkable. This discrepancy underscores the role of the quality of interactions with healthcare professionals in managing decisional conflict and supporting informed decision making in the context of perinatal mental health.

Persistence in incident and prevalent subjects indicated high rates of antidepressant discontinuation during pregnancy.

The most prescribed type of antidepressants in our cohort were selective serotonin reuptake inhibitors. The most frequently prescribed antidepressant globally was paroxetine. Sertraline indicated a monthly prescription increase in the last few years of the observation span. Our research also indicates a decrease in the prevalence of prescriptions, dispensation and primary adherence to antidepressants as pregnancy progresses.

by indication. Consequently, they could not control for the potential effects of a depressive disorder when reporting these risks [10]. This limitation makes it challenging to differentiate the association with underlying mood disorders, which may act as confounding variables [5]. Additionally, the analysis is further complicated by women who are prescribed antidepressants for various uncontrolled indications, such as anxiety disorder [5, 10]. Depression during pregnancy has been associated with adverse outcomes such as poorer adherence to obstetric care, increased use of substances such as alcohol and tobacco, premature birth, low birth weight and other foetal complications [4, 14–16]. However, adherence to antidepressant treatment during pregnancy varies, impacting its effectiveness in managing maternal depression and reducing the risk of relapse [17].

Furthermore, research on adherence among pregnant women is scarce. Available studies suggest that various complex and interlinked factors influence adherence, including age, socioeconomic status and the patient–professional relationship [17]. Moreover, some women stop taking their antidepressants once pregnancy is recognised (by themselves or by their physician) [18], which entails a higher risk of depression recurrence, up to five times higher [19]. Therefore, assessing adherence to prescriptions among pregnant women is of considerable importance. In studies using different methods to measure adherence (e.g. pill counts, questionnaires or pharmacy withdrawal studies), adherence rates to antidepressants range from 60 to 80% in the general population [20, 21]. Some studies suggest that patients who were previously prescribed the medication show a lower adherence compared with incident users [20]. It has been suggested that adherence varies depending on the type of antidepressant, being higher for SNRIs and SSRIs than to other antidepressants [20, 22]. In summary, while antidepressants play an important role in managing depression during pregnancy, their use necessitates careful consideration of potential risks and benefits to both maternal and foetal health, emphasising the importance of adherence to treatment protocols [2, 4, 8]. Therefore, the aim of the present study was to characterise the use of antidepressants in a cohort of pregnant woman. Antidepressant use was estimated by calculating the prevalence of prescriptions, dispensations and persistence of antidepressant medication using an electronic health record database from Catalonia (Information System for the Development of Research in Primary Care [SIDIAP]).

2 Design and Methods

2.1 Type of Study

We conducted an observational cohort drug-utilisation study, spanning from January 2011 to June 2020.

2.2 Data Source

Our dataset originates from SIDIAP [23, 24], a comprehensive repository that captures clinical data of around 5.8 million people living in Catalonia, constituting around 80% of the regional population. This information stems from various data sources, primarily the electronic health records of the Catalan Health Institute. The electronic health record includes a wealth of information, encompassing sociodemographic characteristics, health conditions recorded using International Classification of Diseases, Tenth Revision (ICD-10) codes [25] and details on toxic habits (smoking and alcohol intake). This information is recorded by the primary care physician during women's visits. It also includes drug prescriptions issued in primary care, categorised under the Anatomical Therapeutic Chemical classification system [26]. Outpatient (primary care and hospital) prescriptions are consolidated within the same system (ECAP). Additionally, our database incorporates records from the sexual and reproductive healthcare module (ASSIR), offering a comprehensive overview of pregnancies. This module captures important data such as the date of the last menstrual period, gestational week, and

details on delivery or pregnancy termination outcomes. Data extraction was completed in November 2021.

2.3 Pregnancies and Women

The algorithm developed to detect pregnancy episodes in the SIDIAP database, fully described elsewhere [27], identified episodes based on variables like the first day of the last menstrual period, reasons for pregnancy termination and diagnoses recorded in primary healthcare records. Out of the total number of pregnancies identified by the algorithm (327,865), we considered pregnancy episodes (99,605) with both a start and end date within the observation period (January 2011–June 2020)—to ensure a more accurate calculation of medication exposure. Different pregnancy episodes could be recorded for each woman and were considered separately. For the present study, out of those 99,605 pregnancy episodes, we considered those with a prescription of an antidepressant, which were classified as exposed (see Fig. 1S of the Electronic Supplementary Material [ESM]).

2.4 Health Conditions, Smoking Habits and Socioeconomic Characteristics of Pregnancy Episodes

We analysed diverse characteristics of pregnancy episodes in which women were prescribed an antidepressant. We identified health conditions using ICD-10 codes shown in Table 1S of the ESM. Toxic habits and economic status based in the MEDEA index [28] were included if present on the year prior to the pregnancy-onset date. The MEDEA socioeconomic index U5 quintile corresponds to the group with the most extreme socioeconomic deprivation. Pregnancy duration was estimated in weeks.

2.5 Pregnancy Outcomes

We classified pregnancy outcomes of the pregnancies prescribed an antidepressant into vaginal delivery, abortion (including induced abortion and miscarriage), caesarean section, prematurity, foetal death, ectopic pregnancy or molar pregnancy.

2.6 Antidepressant Exposure

2.6.1 General Exposure

We studied antidepressant exposure amongst this cohort of women by analysing antidepressant prescription. We also calculated its associated dispensation. We analysed data from prescriptions issued in primary healthcare. We calculated overall prevalence and monthly prevalence over the study period for prescriptions (only overall prescriptions over 10% were included in the monthly calculation). We estimated the prevalence of prescriptions and dispensations (reflecting primary adherence: dispensation by prescription rate) also by trimesters (first, second and third) as well as for two observational 3-month spans before and after pregnancy, referred to as "pregnancy intervals."

2.6.2 Multiple Prescriptions

We calculated the number of pregnancies exposed to different antidepressant agents, categorised as prescription to one, two or more than two agents. To estimate multiple active substance prescriptions, we defined a minimum overlap of 1 month between prescriptions, explicitly excluding multiple refills of the same prescription.

2.6.3 Persistence Calculations

Persistence was defined as no discontinuation of treatment in women who initially filled a prescription of antidepressants. Discontinuation rates of antidepressants were defined by a lack of subsequent dispensing of the prescribed drugs within 2 months after the last supply day of the last dispensing and were analysed by calculating the cumulative percentage of the discontinuation rate.

- Treatment duration was calculated considering days from the index date until discontinuation. Right censoring (i.e. when discontinuation occurs after the follow-up, but the exact time is unknown and therefore excluded from the analysis) was applied if the pregnancy duration was less than 40 weeks or if the medication exposure period extended beyond 40 weeks (Fig. 1). Women who were initially adherent (meaning that they filled a previous prescription) but whose prescriptions had been stopped for more than 2 months were excluded, assuming that the discontinuation of their prescriptions was not an issue of persistence but rather an intentional decision to stop the medication, potentially directed by their healthcare provider.
- We calculated persistence for prevalent users (those with a prescription and concurrent claim in the year before pregnancy, where the index date was set to the beginning of pregnancy, assuming they were taking their medication) and incident users (those without a prescription in the year before pregnancy but who were dispensed an antidepressant during pregnancy). The index date was set for them to the beginning of treatment.
- Reintroduction rate: we also estimated the restart of medication in the 3 months after the end of the pregnancy period based on dispensation, identifying women who

were dispensed antidepressant medication after stopping for at least one trimester during pregnancy.

2.7 Statistical Analysis

Baseline demographics, clinical characteristics of patients and pregnancy episodes were described as mean and standard deviation or median and quartiles for continuous variables, and as percentages for categorical variables. Prevalence and incidence (for prescriptions and adherence analysis) were calculated per 100 pregnancies with 95% confidence intervals (CIs). They were computed utilising our custom software developed in R (version 4.4.0) in conjunction with the Incidence & Prevalence package [29, 30]. We assessed changes in patterns in antidepressant prescriptions over the study time calculating monthly prevalence. Persistence was assessed conducting survival analyses of the time from the index date to the discontinuation date using survival curves drawn using the Kaplan–Meier method. Differences between the curves were evaluated using the log-rank test. We used survival functions from the Survival package in R (version 4.4.0) [31]. Figures were created with the same software.

3 Results

3.1 Pregnancies and Women

The total number of pregnancies in the cohort was 99,605 (corresponding to 79,564 women), with a median pregnancy duration of 39 weeks (interquartile range 34.5, 40.1) [see Fig. 1S of the ESM].

3.2 Exposure to Antidepressants

Of the total number of pregnancies, 14.9% (95 CI 14.6, 15.1) were prescribed an antidepressant (14,815 pregnancies). Considering dispensation, at least 5805 (5.8%, 95% CI 5.2, 6.4) out of the total pregnancies collected their medication from the pharmacy. The median duration of pregnancies in which antidepressants were prescribed was 38.4 weeks (interquartile range: 25.2, 40.0).

3.3 Health Conditions, Drinking Habits and Socioeconomic Characteristics

The median age of women exposed to antidepressants during pregnancy was 33.5 years (interquartile range: 29.2, 37.1). The most frequent identified health condition was anxiety (97.2%, 95% CI 97.0, 97.5). Most women were classified as non-drinkers at 71.1% (95% CI 70.3, 71.8). There is a high

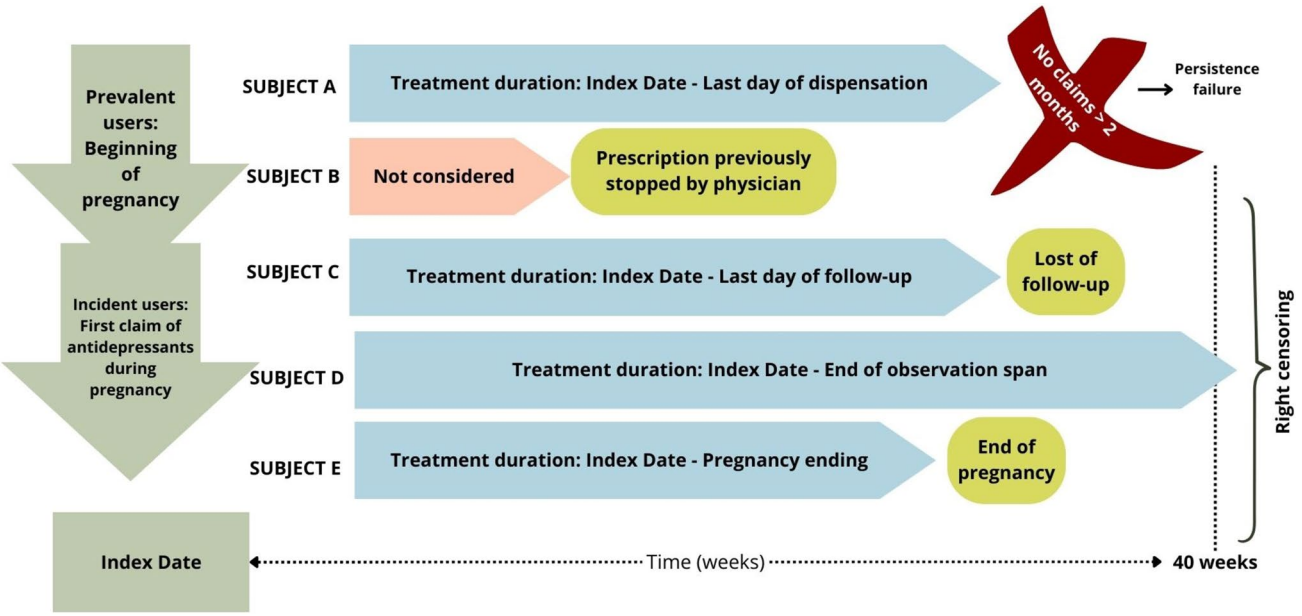


Fig. 1 Treatment duration and persistence calculation: persistence was defined as continued antidepressant use without a gap > 2 months. Discontinuation was assessed by cumulative rates, with treatment duration calculated from index date to discontinuation. Right-censoring was applied when pregnancies lasted < 40 weeks or exposure extended beyond 40 weeks. Persistence was estimated separately for prevalent users (with prior-year use) and incident users (new use during pregnancy)

number of missing data in the drinking habits, which were already detected by the algorithm [27]. Toxic habits are not normally registered in daily clinical practice. Regarding socioeconomic characteristics, most exposed episodes were from the deprived quartile in the MEDEA socioeconomic index: U5 (18.9%, 95% CI 18.2, 19.5) [Table 1]. For ICD-10 codes and associated diagnoses, as well as MEDEA index, see Tables 1S and 2S of the ESM.

3.4 Pregnancy Outcomes

Amongst women who were prescribed antidepressants during pregnancy (14,815 pregnancies), there were 8725 cases of vaginal deliveries, which represented 58.9% of the exposed cases, (95% CI 58.1, 59.7), 3662 cases of abortions, representing 24.7% (95% CI 24.0, 25.4) and 2335 cases of caesarean delivery (15.8%, 95% CI 15.2, 16.3). There were only 62 cases of prematurity, 19 of foetal death, 8 ectopic pregnancy and 4 molar pregnancies, which represent less than 0.5% each.

3.5 Antidepressant Exposure

3.5.1 General Prescriptions and Prescriptions Over Time

The most frequent type of antidepressant prescribed (among all types of antidepressants) in general and monthly over the study period were SSRIs (67.6%, 95% CI 66.9, 68.3) [see Table 3S of the ESM]. The most prescribed active substance among all was paroxetine. Global prevalence over all of the study period for citalopram, paroxetine, fluoxetine and sertraline was above 10%. Monthly prevalence for those four active substances is shown in Table 4S of the ESM. If we examine prescriptions over time of these four substances, paroxetine, citalopram and fluoxetine showed stable monthly prevalences and sertraline presented a gradual rise first, and then since January 2016 and toward the tail end of the follow-up period, rather sharply (Fig. 2).

3.5.2 Prevalence by Trimester

The prevalence of prescriptions and subsequent dispensation decrease as pregnancy progresses, dropping from 6.7% (95% CI 6.5, 6.8) in the 3 months before the pregnancy interval to 5.1% (95% CI 5.0, 5.3) in the first trimester. It continues to decline to 2.0%. (95% CI 1.9, 2.2) in the second trimester and 1.7% (95% CI 1.6, 1.8) in the third trimester. However, in the 3 months following pregnancy, we observed an increase of dispensation prevalence, as it increases again to 3.7% (95% CI 3.6, 3.8) [Fig. 3]. Primary adherence (dispensation by prescription rate) in prevalent users drops from 34.7% in the first trimester to 24.4% in the third trimester, rising again after pregnancy (38.7%). Prescriptions follow a similar trend (prescriptions and primary adherence are detailed in Fig. 3, and in Table 5S of the ESM).

Table 1 Sociodemographic characteristics of pregnancies that were prescribed antidepressants

	N, % (95% CI)
Health conditions	
Anxiety disorder	14,405, 97.2% (96.9, 97.4)
Nicotine dependence	5880, 39.6% (38.8, 40.4)
Major depressive disorder	5438, 36.7% (35.9, 37.4)
Pruritus	4024, 27.1% (26.4, 27.8)
Obesity	3770, 25.4%, (24.7, 26.1)
Mixed anxiety and depressive disorder	3116, 20.9% (20.2, 21.5)
Drinking habit	
No drinker	10,532, 71.0% (70.3, 71.8)
Low-risk drinker	2758, 18.6% (17.9, 19.2)
High-risk drinker	154, 1.0% (0.8, 1.2)
Missing values	*1371 (9.2%)*
MEDEA, quintiles	
High socioeconomic status	1228, 8.8% (7.8, 8.7)
Moderate socioeconomic status	1876, 12.6% (12.1, 13.1)
Average socioeconomic status	2124, 14.3% (13.7, 14.9)
Low socioeconomic status	2352, 15.8% (15.2, 16.4)
Extreme socioeconomic deprivation	2797, 18.8% (18.2, 19.5)
Missing values	*4438, 29.9%*
Population	
Urban areas	11,846, 79.96% (79.3, 80.6)
Rural areas	2951, 19.9% (19.2, 20.5)

CI confidence interval

3.5.3 Multiple Prescription

Regarding multiple prescriptions, most women had a prescription of one single antidepressant (86.6%, 95% CI 86.0, 87.2) and up to 11.6% (95% CI 11.0, 12.1) had two prescriptions. Only 1.8% (95% CI 1.5, 2.0) had three or more types of antidepressants prescribed.

3.5.4 Persistence

We calculated persistence amongst women who filled at least one prescription of antidepressants (5805), comparing prevalent users (4099) and incident users (1716). We found that at week 40, persistence was 13.0% and 43.9%, respectively. Median survival time for prevalent users was 26.5 weeks and 38.8 for incident users. The log-rank test, with a statistic of 421.2 and a p-value of < 0.001, confirms the significance of differences between the survival curves of the two groups (Fig. 4).

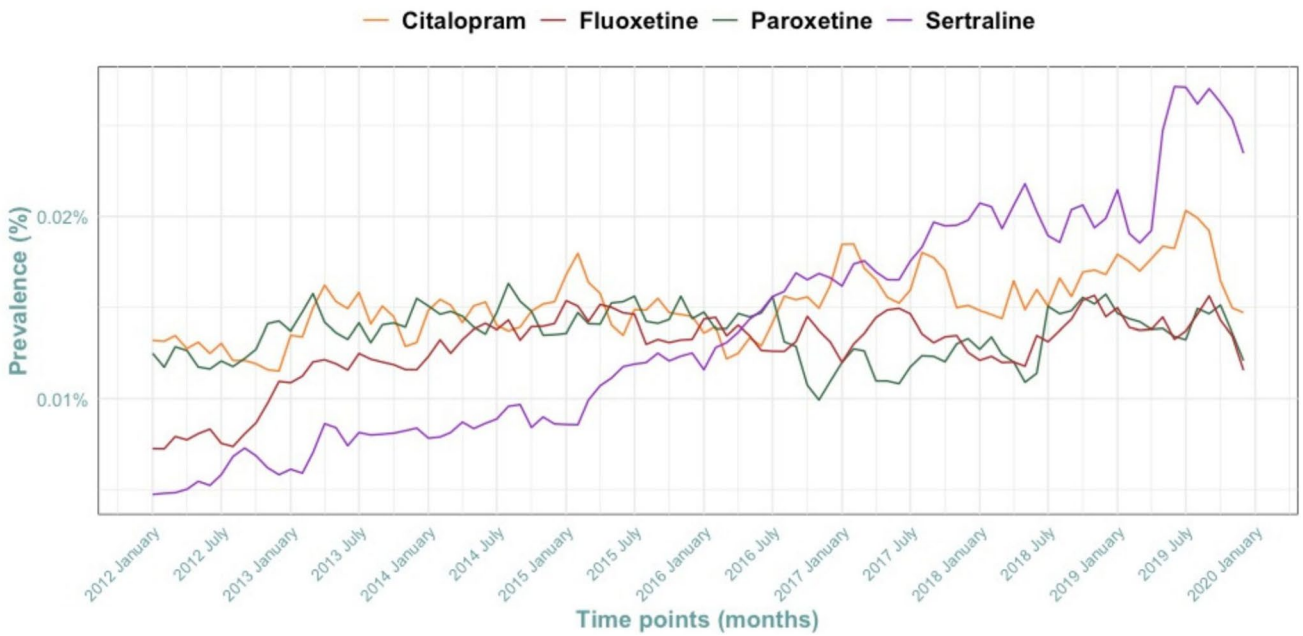


Fig. 2 Monthly prevalence of citalopram, fluoxetine, paroxetine and sertraline over the study period (January 2011–June 2020)

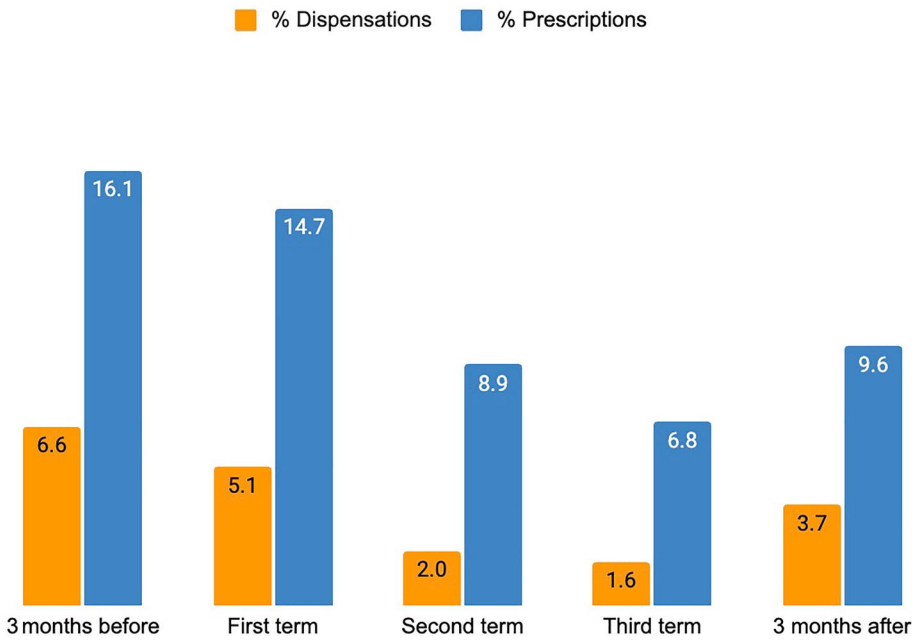
3.5.5 Reintroduction Rate

In what refers to the restart of medication in the 3 months following pregnancy, we estimated a 29.2% (95% CI 27.8, 30.6) rate in women who had discontinued their medication for at least one trimester during their pregnancy.

4 Discussion

The present study describes exposure to antidepressants during pregnancy, and the characteristics of the exposed pregnancies. We assessed the prescription and dispensation of antidepressants in a cohort of pregnant women in Catalonia. Among 99,605 pregnancies identified in 76,459 women, 14,815 pregnancies (14.9%) involved a prescription

Fig. 3 Prevalence (%) of antidepressant prescriptions and dispensation by trimesters



for antidepressants, corresponding to 13,556 women. In at least 5672 of these pregnancies (5.8% of all pregnancies and 38.2% of those who had a prescription), the medication was dispensed at the pharmacy.

Our research indicates a decrease in the prevalence of prescriptions and, by implication, adherence to antidepressants as pregnancy progresses, showing an increase after the end of pregnancy. The most prescribed type of antidepressants were SSRIs, and the most frequently prescribed active substance globally was paroxetine. However, sertraline showed a monthly prevalence prescription increase in the last few years of the observation period, first gradually, and then toward the tail end of the follow-up period, rather sharply. Most women had a prescription of one single antidepressant. The assessment of persistence in incident and prevalent users of antidepressants indicated high rates of antidepressant discontinuation during pregnancy. Specifically, incident users show more stable persistence curves over time and a higher persistence at week 40.

Comparing our results with other studies, antidepressant exposure during pregnancy seems to be much higher than in other European regions. For example, in France, dispensation of antidepressants was estimated at 1.8% during pregnancy, almost four points under the estimation of our cohort [32]. However, the use and prescription of antidepressants parallel the rates of anxiety and depression reported in previous studies in our region: both are the most common mental health conditions during pregnancy, with 12% of women reporting depression and 13% anxiety, often concurrently [33, 34]. Anxiety has also been one of the most frequently associated health conditions with antidepressant prescriptions in previous studies [35], similar to the results of our analysis. This fact aligns with indications for certain antidepressants in Spain, which also include treatment of anxiety [36, 37].

When set against other research, the sociodemographic characteristics of mothers in terms of age, toxic habits and socioeconomic context show certain similarities. The distribution of antidepressant prescription seems quite homogeneous among all socioeconomic quartiles in our cohort. Despite this, most of the exposed episodes belonged to the most deprived quartile according to the MEDEA socioeconomic index. Some research identifies low socioeconomic status as a risk factor for developing perinatal depression [38]. Women from wealthier quartiles might receive follow-up care in private settings. While prescriptions from primary care and public psychiatric services are captured in our data, those from private care are not, which may limit our ability to fully record these patients over time accurately.

Because the current database lacks a mother-child link, it was not feasible to analyse the impact of antidepressants on offspring during pregnancy, as done in prior studies [32]. Despite this limitation, we were able to analyse delivery outcomes, revealing that vaginal births were the most common (58.8%), though this percentage was lower than the 63.5% benchmark established by local perinatal health authorities [39], followed by abortions (spontaneous and induced) and 62 cases of prematurity. It should be noted that this later information is obtained either from the ICD-10 code or from the weeks of gestation, with many results imputed, based on the duration of a normal pregnancy.

The most prescribed type of antidepressants were SSRIs. According to the National Institute for Health and Care Excellence guidelines [40], which also inform Spanish

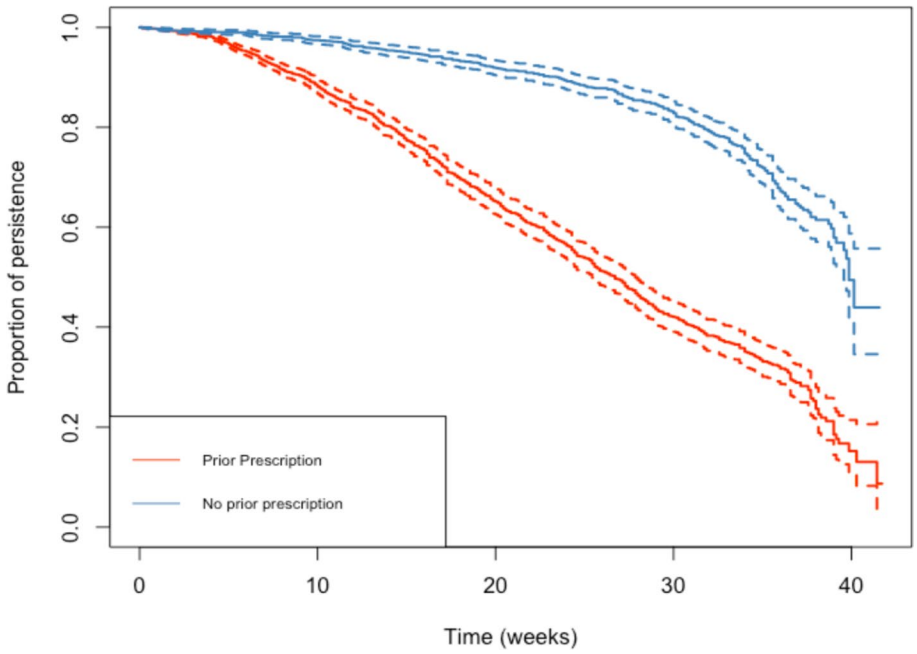


Fig. 4 Persistence with antidepressants in incident and prevalent users

recommendations [41], SSRIs are generally recommended for both mild and severe depression in the general population owing to their good safety profile and tolerability, without specifying any particular SSRI as first-line treatment. Recent studies suggest that while some antidepressants show slightly higher efficacy and adherence rates, no significant differences have been found among SSRIs in terms of effectiveness for treating major depressive disorder [42, 43]. While some SSRIs have been associated with adverse perinatal outcomes [44], it is important to interpret these findings within the broader context of maternal mental health and the methodological limitations of existing studies. In our study, paroxetine was the most frequently prescribed antidepressant, which is notable given earlier reports suggesting an increased risk of congenital malformations [15] and the warning issued by the US Food and Drug Administration in 2005 regarding the potential risk of cardiac malformations in babies when pregnant women were exposed to paroxetine during the first trimester [45]. However, these associations may be influenced by confounding by indication [10, 15], as women prescribed antidepressants may also present with more severe or poorly controlled mood disorders [5]. Our results are in line with those of a Danish study [47] where the increase in prescriptions in the period studied was mainly due to SSRIs.

In contrast, sertraline showed a monthly prevalence prescription increase in the last few years of the observation period. To our knowledge, there are no comparative safety studies demonstrating that sertraline is safer than other antidepressants during pregnancy. However, sertraline is recommended for use during pregnancy by multiple clinical guidelines, based on its overall safety profile, which includes both favourable infant outcome data and low concentrations detected in breast milk during breastfeeding [47, 48]. This fact, along with unfavourable data regarding the risk associated with paroxetine and fluoxetine [49], may have led prescribers to more frequently prescribe sertraline in recent years. Regarding multiple prescriptions, most women in our cohort were prescribed just one type of antidepressant, adhering to expert recommendations [2, 7].

Antidepressant prescription patterns by class group and by trimesters also closely resemble findings from other studies [20, 22, 32, 50]. These findings include the decrease of medication consumption as pregnancy progresses and the frequency of single antidepressant prescriptions [32]. It is noteworthy that there was a rise of prescription, dispensation, and adherence (dispensation by prescription rate) after the end of pregnancy, possibly also correlated to the diagnosis of postpartum depression [4–6]. Although most antidepressants are excreted in breast milk [51], the available evidence is reassuring because of the very low amount of antidepressant drug concentrations to which infants are exposed, and therefore, the observed increase in postpartum antidepressant use should not be considered concerning. At the time of conducting the present study, data on maternal breastfeeding were not available in our cohort and we do not have data of breastfeeding in our region. This issue should be assessed in future research.

In the case of pregnant women, primary adherence (dispensation by prescription rate) studies are scarce, but some of them indicate that many women discontinue their antidepressant once they become aware of the pregnant status [18]. Reports of the discontinuation of antidepressants during pregnancy over time is around 40% in previous studies [20, 22]. These studies suggest that the discontinuation ratio is higher in patients who were previously prescribed the medication [22]; however, it is important to consider that symptom severity may vary within this population. These observations might point toward a possible pattern: incident users could present with more acute symptoms, whereas prevalent users may have a more stable clinical profile. The discontinuation ratio also varies depending on the type of antidepressant prescribed, indicating a higher persistence for SNRIs and SSRIs compared with other antidepressants [20]. We assessed the above-mentioned hypothesis stated in previous research through persistence calculation. The difference in the Kaplan–Meier curves indicated that persistence was higher in those women defined as incident. This pattern constitutes a field to be addressed and expanded through observational studies and qualitative research.

Persistence to antidepressants throughout pregnancy seems to have been higher in other studies than in ours [22], indicating higher persistence rates in previous research. However, comparability with these studies is limited by various factors. First, the objectives of our article and other previous research differ. The factors that limit comparability also cover inclusion criteria: both studies only included women who had a prior diagnosis of depression. Additionally, definitions of discontinuation during pregnancy vary from one study to another (15 days and 1 month), and the total number of patients in the cohort is more limited than in our study. In those studies that did take 2 months as the definition for discontinuation [46], persistence was not compared between incident and prevalent patients, studying them globally. Discontinuation in our study was around 50%. Other recent investigations carried out in Europe have also reported, through modelling of longitudinal trajectories, different patterns of dispensing and dosing of antidepressants in the period around pregnancy [52].

In our cohort, during the post-partum period, 29.2% of women re-started antidepressant medication after stopping it during pregnancy, though the cause could not be identified. One recent report indicates that 17.6% of women who discontinued SSRIs during pregnancy restarted SSRIs during postpartum [50]. Other studies have reported on the risk of depression relapse in women who discontinue antidepressant

treatment during pregnancy, which ranged from a five-fold increased risk [19] to no increased risk [53]. In a recent study based on data from Denmark and Norway, the authors report a lower probability of initiating psycholeptic agents or having postpartum psychiatric emergencies in those women who discontinued their medication (early or late discontinuation) versus those who continued taking it during pregnancy. The authors state that women who discontinued antidepressants early in pregnancy or discontinued late in pregnancy after short-term use may have less severe underlying disorders and can successfully stop their medications. In contrast, those who discontinued late in pregnancy after long-term use may have had more severe episodes and may benefit from an individual assessment before discontinuation [54]. These results should be further explored in future research, particularly by investigating the underlying reasons for antidepressant discontinuation using more specific methods to better capture women's decision-making processes and clinical profiles.

Our study has several limitations. First, the impact on the offspring could not be estimated. Efforts to conduct this analysis will be made in future research. Second, estimating adherence through dispensation has the drawback of assuming that women who collected their medication took it (this may not reflect true medication usage). Third, our study did not examine concomitant medications such as anxiolytics, unlike other investigations [32]. This is itself a noteworthy point, considering that most women in our cohort had a diagnosis of anxiety. Finally, the differences between algorithms amongst databases to detect pregnancies complicate their comparability.

The strengths in our study include the following. The use of a verified database [24], ensuring the reliability of our data. The inclusion of many participants boosts the statistical power and permits more precise and generalisable results. We focused on describing precisely the sociodemographic characteristics of patients, allowing us to profile in detail our cohort. We estimated prescription, dispensation rates and primary adherence (dispensation by prescription rate) by trimesters. Furthermore, we estimated persistence and the medication reintroduction rate to understand properly the behaviour of prescribers and women in our cohort. No previous studies with similar characteristics have been conducted in this specific population, and to our knowledge, none has been performed in Spain.

Previous European studies have noted the need to identify barriers in healthcare services and prescribing behaviour to improve treatment. Risks of stopping treatment and exploring other options such as psychological interventions should be studied in rigorous trials [53]. The difference between prescriptions and dispensations found in our study is concerning, and it underscores the role of the quality of interactions with healthcare professionals in managing decisional conflict and supporting informed decision making in the context of perinatal mental health [55]. In this regard, our study highlights the use of large databases to record patient and prescriber behaviour, which could help regulatory authorities implement better prescription practices based on post-authorisation safety studies. The absence of clinical practice guidelines for peripartum depression in most European countries and the inconsistencies in recommendations can lead to disparities in managing peripartum depression [56]. Considering that untreated maternal depression during pregnancy can lead to emotional development disorders in the newborn [2], this factor is of particular interest.

5 Conclusions

We highlight the difference between the percentage of prescriptions issued by physicians and the actual dispensation of antidepressant medications at pharmacies, which is worrying because maternal depression and poor adherence may increase the risk of relapse. This difference underscores the need to advocate for a primary care system that adequately addresses the psychological needs of patients, as well as the provision of sufficient resources—both in terms of economic resources and time in consultations—for primary care physicians and psychiatrists to provide appropriate care and follow-up to patients. This emphasises the importance of healthcare providers to offer clear evidence-based information to facilitate shared decision making and to develop personalised treatment plans for women in the perinatal period who are considering the use of antidepressants during pregnancy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-025-01576-z.

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Declarations

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Conflict of interest Lucía Bellas, Lina Camacho-Arteaga, Maria Giner-Soriano, Albert-Prats-Uribe, Ainhoa Gómez-Lumbreras, Cristina Aguilera, and Antonia Agustíin have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval The study protocol was approved by the Research Ethics Committee of IDIAPJGol, ID number 22/102-P, 27 April, 2022. This is a database research study that has been conducted according to the guidelines of the Declaration of Helsinki (Fortaleza, Brazil 2013),

Good Research Practice principles and guidelines, and the Real Decreto 957/2020 (3 November, 2020) which regulates observational studies of medicines for human use.

Consent to participate The need for consent was waived by the Research Ethics Committee of IDIAPJGol as it is deemed unnecessary according to European legislation (Regulation [EU] 2016/679).

Consent for publication Not applicable.

Availability of data and material A technical Appendix is provided in the ESM.

Code availability The statistical code is available at the GitHub repository: https://github.com/luciabellas/IDIAP_AD.git.

Author contributions All authors contributed to the study design. LB and AP: data analysis. LB: creation of tables and figures. LB: wrote the draft of the manuscript. LC, MGS, AA, AG, CV, CA, AP: supervision. All authors contributed to the article and approved the submitted version. All authors read and approved the final version. Original protocol of the study [57].

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