BMJ Open

Drug exposure during pregnancy in primary care: an algorithm and observational study from SIDIAP database, Catalunya, Spain

Marta Lestón Vázquez,[1,2] Carles Vilaplana-Carnerero ,[2,3] Ainhoa Gomez-Lumbreras,[4] Oriol Prat-Vallverdu,[5,6] Josep Ramon Marsal,[6,7] Cristina Vedia Urgell,[2,8] Maria Giner-Soriano ,[2,3] Rosa Morros[2,3]

To cite: Lestón Vázquez M, Vilaplana-Carnerero C, Gomez-Lumbreras A, *et al*. Drug exposure during pregnancy in primary care: an algorithm and observational study from SIDIAP database, Catalunya, Spain. *BMJ Open* 2023;**13**:e071335. doi:10.1136/bmjopen-2022-071335

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-071335).

Received 29 December 2022
Accepted 11 July 2023

For numbered affiliations see end of article.

Correspondence to
Dr Maria Giner-Soriano; mginer@idiapjgol.info

ABSTRACT

Objectives To develop an algorithm to identify pregnancy episodes in women at childbearing age using SIDIAP (Information System for the Improvement of Research in Primary Care) data (Catalunya, Spain).
To describe drugs dispensed during gestation.

Design Construction of an algorithm to identify all pregnancy episodes occurred from January 2011 to June 2020 in women aged 12–50. The variables used to create the algorithm include first day of last menstrual period, reasons for pregnancy termination and diagnoses registered in the primary healthcare records. Population-based cohort study including the pregnancy episodes identified by the algorithm.

Setting Catalonia, Spain.

Participants All women aged 12–50 with at least one pregnancy episode occurred during January 2011–June 2020.

Interventions No interventions performed.

Primary and secondary outcome measures Identification of pregnancy episodes through an algorithm and description of drug exposure.

Results We identified 327 865 pregnancy episodes in 250 910 people with a mean age of 31.3 years. During the study period, 83.4% of the episodes were exposed to at least one drug. The most frequent groups dispensed were iron preparations (48% of pregnancy episodes), iodine therapy (40.2%), analgesics and antipyretics (28%), penicillins (19.8%), vitamin B_{12} plus folic acid (19.7%) and non-steroidal anti-inflammatory drugs (NSAIDs, 15.1%). The supplements were more frequently dispensed at least twice, and the drugs for acute conditions were mainly dispensed only once during the pregnancy episode.

Conclusions We developed an algorithm to automatically identify the pregnancy periods in SIDIAP.
We described prescription drugs used during pregnancy. The most used ones were supplements, analgesics, NSAID or antibiotics.
SIDIAP might be an efficient database to study drug safety during pregnancy and the consequences of drug use in the offspring.

Trial registration number EUPAS37675.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ One limitation of the algorithm development is the lack of information on women whose pregnancies are followed up in the hospital or in private settings.
⇒ Other limitation of the algorithm is that it has not been validated. Nevertheless, the number and distribution of pregnancies are in line with the previous algorithms published.
⇒ Despite these limitations, Information System for the Improvement of Research in Primary Care database might be a valid and efficient resource to study drug safety during pregnancy, as it captures clinical information of most of the Catalan population.

INTRODUCTION

Drug use during pregnancy and breast feeding has not been widely analysed due to the exclusion of pregnant and lactating people from the participation in clinical trials for ethical reasons and due to the generalised lack of investigation in women's health.[1–3] However, the use of drugs during gestation and breast feeding may entail risk of different health problems for these women and for the fetus and the newborns[1 4] and also the non-use of certain drugs can lead to worsening of chronical and acute conditions in the mother or to complications for the infant, such as drugs to treat asthma,[5 6] autoimmune disorders,[7 8] diabetes[9 10] or epilepsy.[11]

Deciding and planning on pharmacotherapy based on the safety profile of a drug during those periods can be challenging for prescribers. For this reason, it is necessary to assess drug safety through postapproval observational studies for drugs which cannot be discontinued during pregnancy, drugs to treat pregnancy-related conditions and drugs with preclinical evidence of risk for the offspring.[12 13]

Apart from birth cohorts established worldwide to gain knowledge on perinatal health,[14] in the last decades, database studies are offering numerous advantages to study medicines safety in pregnant and lactating women and in their offspring, such as the large number of people included, the availability of mother–child linked data, long follow-up periods, information on consequences derived from drug use or on confounders or the possibility to design algorithms through machine learning methods.[13 15–18] Algorithms are often necessary because electronic health records (EHR) lack of a unique register to unambiguously identify the gestation periods. Thus, it is usual to design algorithms to identify pregnancies with the purpose of studying drug use during gestation through database studies.[17 19 20]

We aimed to develop an algorithm to identify pregnancy episodes for all women aged from 12 to 50 between January 2011 and June 2020 using data from the EHR of primary healthcare (PHC) in Catalunya, Spain. With the pregnancies identified by the algorithm we aimed to describe the drugs dispensed during gestation.

METHODS

Study design

First, construction of an algorithm to identify all pregnancy episodes occurred from January 2011 to June 2020 in women at childbearing age (12–50 years) in Catalonia, Spain. And second, population-based cohort study including the pregnancy episodes identified by the algorithm.

Data source

The study data source is the Information System for the Improvement of Research in Primary Care (SIDIAP),[21 22] which captures clinical information of approximately 5,8 million Catalan citizens (around 80% of the Catalan population). This information is pseudonymised and it is originated from different data sources: (1) (EHR in PHC of the Catalan Health Institute); including sociodemographic characteristics, comorbidities registered as International Classification of Diseases (ICD)-10 codes,[23] specialist referrals, clinical parameters, toxic habits, sickness leave, date of death, laboratory test data and drug prescriptions issued in PHC, registered as Anatomical Therapeutic Chemical (ATC) classification system codes.[24] (2) Sexual and reproductive healthcare (ASSIR) records, which is the EHR module used by gynaecologists and midwives to register variables related with the sexual and reproductive health of women and follow-up of pregnancies, as date of last menstrual period (LMP), gestational week, date of delivery or pregnancy termination—based on ultrasound results—or termination outcomes. (3) Pharmacy invoice data corresponding to the PHC drug prescriptions, classified according to the ATC classification.[24]

We used pregnancy-related ICD-10 codes and ASSIR records to design the pregnancy algorithm.

Variables

The variables collected to describe the study population at the pregnancy start date (PSD) were: age, socioeconomic status by MEDEA (Mortalidad en áreas pequeñas Españolas y Desigualdades socioEconómicas y Ambientales) index,[25] body mass index, comorbidities, smoking status and alcohol intake; for this study the latter two correspond to records of less than 12 months before PSD.

We used the pharmacy invoice dispensing data to assess the drug exposure. Pregnancy episodes were classified as exposed to drugs when there was at least one dispensing from 30 days before PSD up to 30 days after delivery date, and per pregnancy trimester as follows; first trimester: from 30 days before PSD to 120 days after PSD; second trimester: from 120 days after PSD to 210 days after PSD and third trimester: from 210 days after PSD to 30 days after delivery date. This definition of the pregnancy trimesters was done for exposure definition purposes in order to consider the particularities of the pharmacy invoice register.

We described the most dispensed pharmacological groups (ATC) in overall pregnancies and by trimester, the frequency of groups with one or more than one dispensing during the pregnancy episode, and the most frequent active principles dispensed more than once.

Algorithm development

We created a three-step sequential algorithm to identify the pregnancy episodes occurring during the study period, define their duration and the outcome of the pregnancy.

Step 1: identification of potential pregnancies

We carried out a hierarchical and mutually exclusive search in our data source of records linked to gestation. We used the specific record of LMP to identify a potential pregnancy registered in ASSIR. If LMP was not available, the algorithm searched for the following records (figure 1): positive pregnancy test, gestational week, fetal death and PHC diagnoses indicating pregnancy or abortion (ICD-10 codes). See online supplemental table 1 for full list of codes.

Step 2: length of pregnancy

We determined the length of pregnancy using the LMP, the pregnancy episode end date (delivery or abortion), the diagnostic codes dates suggestive of pregnancy end and the weeks of gestation registries in ASSIR. If dates were unknown, they were imputed according to the criteria established (figure 1). Pregnancy episodes shorter than 4 or longer than 43 weeks were excluded.

Step 3: outcome of pregnancy

Reasons for pregnancy termination were identified by the ASSIR end label and completed by ICD-10 diagnoses related to childbirth or the puerperium. We imputed an outcome for episodes with unknown outcome and known length: abortion for length <24 weeks and live birth if ≥24 weeks (threshold for fetal viability/feasibility).

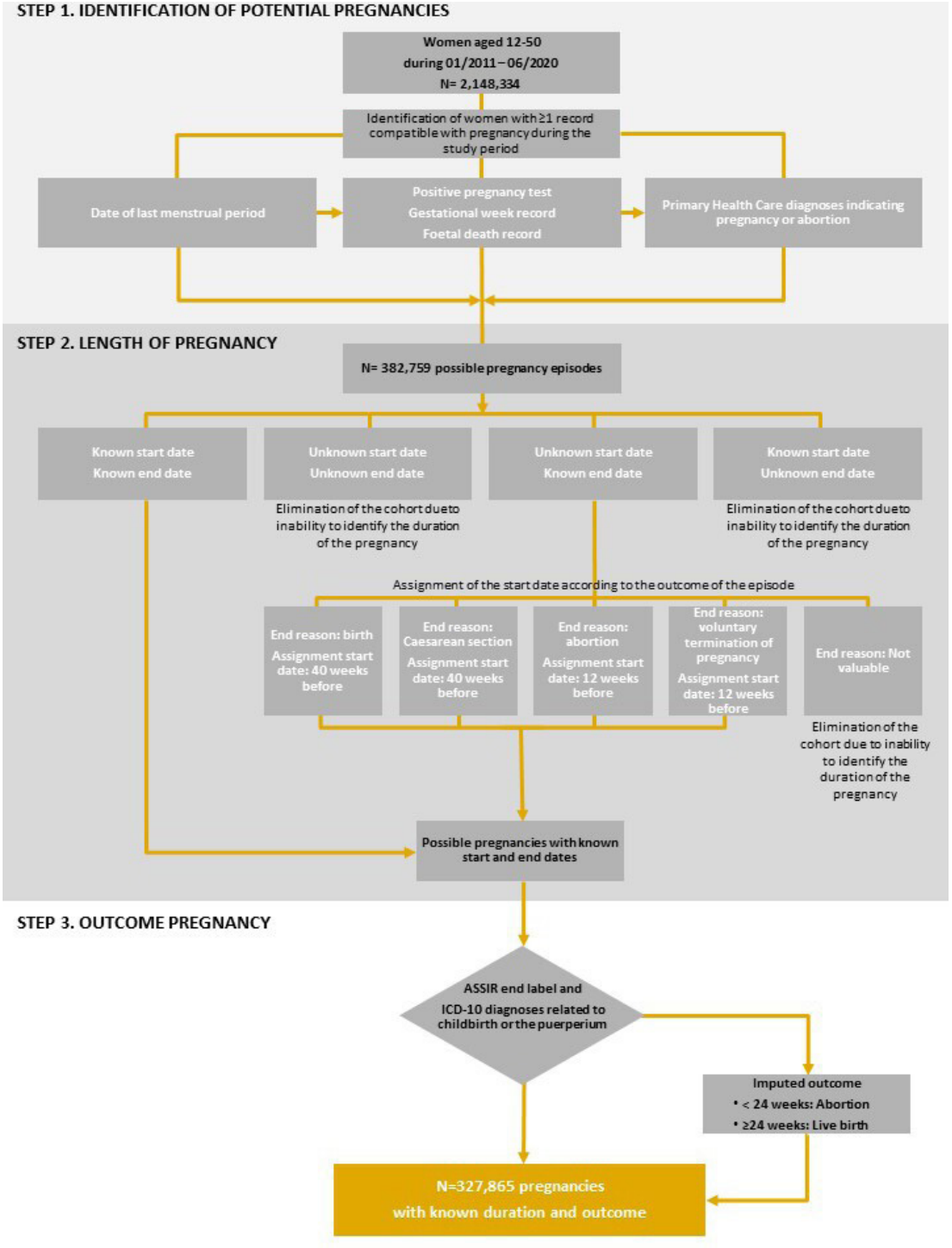

Figure 1 Algorithm flow chart with selection and validation steps. The figure shows the flow chart with the algorithm steps. ASSIR, sexual and reproductive healthcare centres; ICD-10, International Classification of Diseases 10th version.

During the development of the algorithm, pregnancy episodes were scrutinised for potential inconsistencies, such as pregnancy duration discrepancy with pregnancy outcomes, overlapping episodes, those starting or terminating out of the study period after imputation dates and finally a minimum time lapse of 4 weeks was established between the dates of the different episodes.

Study size

The study size included all pregnancy episodes identified through the algorithm in women aged 12–50 during the study period.

Statistical analysis

After identifying all women with pregnancy episodes defined by the algorithm, we described the study

population and the drug exposure, using frequencies and percentages for categorical variables and mean and SD for continuous variables.

Missing values on baseline variables are reported in table 1. Missing data for PSD, end date and labels of pregnancy termination outcomes were imputed as explained in the Algorithm development.

All analyses were conducted with R software (V.4.1 or superior).

Patient and public involvement statement

The Research Ethics Committee of IDIAPJGol has patient and public representation who participated in reviewing and approving the study protocol.

RESULTS

From January 2011 to June 2020, our algorithm identified 327 865 pregnancy episodes in 250 910 women (1.3 episodes per woman), and a total sum of follow-up of 210,463.1 years (1.6 episodes/year). These women had a mean age of 31.3 years, and 56.8% of the episodes occurred between 30 and 39 years of age. When we analysed the data from the registry of the pregnancy episodes defined by the algorithm, 76.8% of them had complete data on the start and end of the pregnancy and the results of the episode in the EHR. Out of them, 80.6% of pregnancy episodes ended with live births, 19.2% resulted in abortion, 0.15% were stillbirths and 0.08% were ectopic or molar pregnancies (online supplemental figure).

Baseline sociodemographic and clinical characteristics of pregnant women at PSD are included in table 1. Among the most frequent comorbidities at baseline, 24.5% of women had an active diagnosis of anxiety, 14.5% were obese and 9.1% had a respiratory disease. Smoking and alcohol habits had a high number of missing values at PSD.

During the period studied, 274 799 (83.4%) of the pregnancy episodes were exposed to at least one drug. The most dispensed pharmacological groups during the overall pregnancies and by trimester are shown in figure 2. Overall, the most frequent groups were iron preparations (dispensed in 48.0% of the pregnancy episodes), iodine therapy (40.2%), other analgesics and antipyretics (28.0%), penicillins (19.8%), vitamin B_{12} with folic acid (19.7%) and non-steroidal anti-inflammatory drugs (NSAID, 15.1%). In online supplemental table, we show the 15 most frequently dispensed groups and active principles during the overall pregnancies and by trimester.

Of the most used pharmacological groups, the supplements were more frequently dispensed at least twice during the pregnancy episode (69.6% for iodine, 62.5% for iron or 50.7% for vitamin B_{12} and folic acid) and the drugs used for acute conditions were mainly dispensed only once during the episode (83% of NSAID dispensing, 78.4% of penicillins and 69.3% of other analgesics and antipyretics, see table 2).

The most dispensed substances from these frequent ATC groups are shown in figure 3, being the combination of iodide, vitamin B_{12} and folic acid (42.5% of episodes), ferrous sulfate (37.6%) and paracetamol (31.1%) the most used drugs. Other frequent drugs dispensed were antibiotics (eg, fosfomycin: 14.8%).

DISCUSSION

In the absence of a unique register to identify pregnancies in our setting, we designed the algorithm in the current research context where many algorithms have been published aiming to identify pregnancies and assess drug exposure risks during pregnancy.[17 19 20 26 27] Once generated, we identified 327 865 pregnancy episodes in a cohort of women at childbearing age attended in PHC from 2011 to 2020, accounting for 1.3 episodes per woman, which matches the observed numbers in Catalonia (1.21) and Spain (1.19).[28 29] The type of pregnancy end identified with our algorithm was similar to BIFAP algorithm, which identified 21.5% pregnancy losses, 0.8% ectopic pregnancies and 0.2% stillbirths.[17] The first step of our algorithm consisted in searching for the LMP, which is a pregnancy-related specific date which is only registered in the ASSIR records at the pregnancy monitoring initiation, so we considered it as the highest quality registry to identify PSD.

Regarding the clinical characteristics of the population studied, it is remarkable the high number of missing records for tobacco and alcohol habits in pregnant women in our database (91.2% of smoking missing values the prior 12 months vs 22.1% of smoking missing values any time before PSD). It may be recommendable to reinforce the need to record these variables more accurately so health professionals attending pregnant people may initiate smoking cessation interventions when necessary.[30]

With regard to the most common comorbidities at PSD, it is noteworthy that nearly 25% of pregnant women in our study had a diagnosis of anxiety, which is frequently described in women at childbearing age with other concomitant mental disorders such as depression,[31–34] which also showed a significant prevalence in our cohort (5.7%). Respiratory diseases or migraine were frequent in our cohort, these disorders have commonly been reported during pregnancy with the challenges associated to their management.[5 6 35 36]

Dispensation of drugs was frequent in the identified pregnancy episodes. Among the most prescribed, supplements are recommended during pregnancy.[30 37] Drugs used for acute conditions, such as NSAID, analgesics or antibiotics, were also identified, as during pregnancy infectious diseases or pain conditions are also frequently reported. We need to point out that supplements or analgesics counts might be under-reported due to the availability of over the counter (OTC) medicines, not captured in our database. Other OTC drugs that can be underestimated include antacids or laxatives, which are frequently used by gestating women.[19 38 39] Among the

Table 1 Baseline sociodemographic and clinical characteristics of the women with pregnancy episodes included in the study

N (%)	Overall pregnancy episodes N=327 865
Age in years, mean (SD)	31.3 (5.8)
12–14	248 (0.1)
15–24	44 685 (13.6)
25–29	74 364 (22.7)
30–34	107 587 (32.8)
35–39	78 576 (24.0)
≥40	22 405 (6.8)
MEDEA index	
Rural	60 692 (18.5)
Urban quintiles 1–3	121 014 (36.9)
Urban quintile 4–5	114 513 (34.9)
Urban unknown	31 482 (9.6)
Missing values	166 (0.1)
BMI categorised	
Underweight (<20 kg/m^2)	12 915 (3.9)
Normal (20-25)	50 627 (15.4)
Overweight (25-29)	41 645 (12.7)
Obese (≥30)	29 561 (9.0)
Missing values	193 117 (58.9)
Smoking habit*	
Smoker	6998 (2.1)
Ex-smoker	5960 (1.8)
Non-smoker	15 883 (4.8)
Missing	299 024 (91.2)
Alcohol intake*	
High	378 (0.1)
Moderate	17 424 (5.3)
No intake	46 409 (14.1)
Missing	263 654 (80.4)
Comorbidities	
Anxiety	80 429 (24.5)
Cancer	2326 (0.7)
Depression and bipolar disorders	18 774 (5.7)
Diabetes	1724 (0.5)
Eating disorders	12 399 (3.8)
Epilepsy	1719 (0.5)
Hypertension	3402 (1.0)
Migraine	23 290 (7.1)
Obesity (ICD-10 and/or BMI≥30)	47 467 (14.5)
Respiratory diseases	29 760 (9.1)
Rheumatoid arthritis	760 (0.2)

*Women can be counted more than once, as their characteristics are counted for each pregnancy episode, Smoking and alcohol habits registered <12 months before the pregnancy start date.
BMI, body mass index; ICD-10, International Classification of Diseases 10th version; MEDEA, Mortalidad en áreas pequeñas Españolas y Desigualdades socioEconómicas y Ambientales.

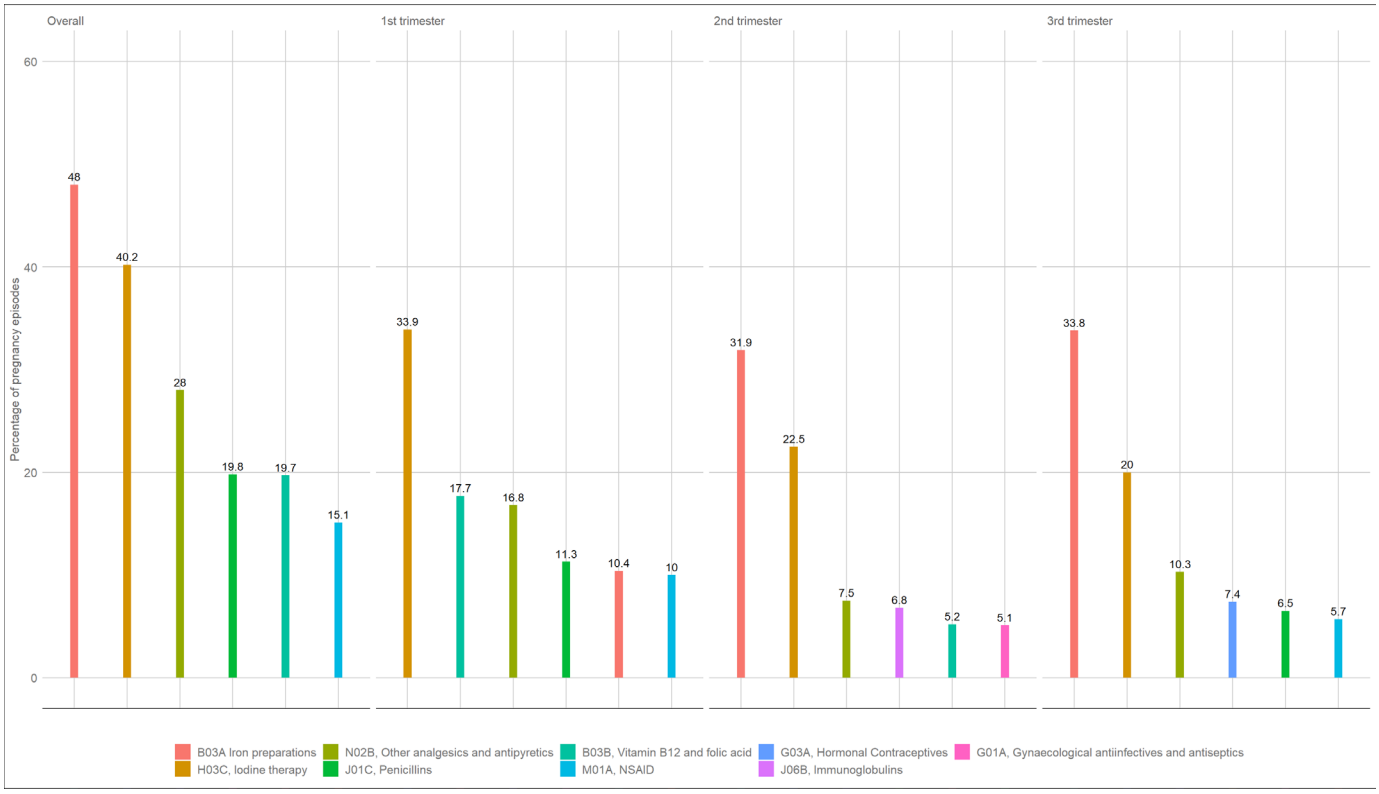

Figure 2 Frequency of drug exposure during overall pregnancy episodes and by trimester. The figure includes the six most dispensed pharmacological groups during the overall pregnancy episodes and by trimester, in percentages calculated over the number of pregnancy episodes. NSAID, non-steroidal anti-inflammatory drug.

most frequent antibiotics we found fosfomycin and amoxicillin, which might have been prescribed for common infections during pregnancy such as urinary tract infections.[30 40]

Despite the high prevalence of anxiety disorders in our cohort, anxiolytic or antidepressant drugs were not among the most used pharmacological groups. This may be related with the absence of evidence and safety concerns on the use of psychotropic medications during pregnancy.[41–43] Other studies have reported similar levels of utilisation of these drugs.[44–46]

One limitation of our study concerning the algorithm development is the lack of information on women whose pregnancies are followed up in the hospital or in private settings. The pregnancies referred to hospitals for follow-up include those women with chronic and autoimmune diseases which can increase the risk of complications during the pregnancy or at delivery. Although each ASSIR has different referral protocols, some of the conditions include: history of miscarriages, history of chromosomal anomalies, history of prematurity, morbid obesity, pre-eclampsia, gestational diabetes, severe anaemia, etc.[30]

Table 2 Exposure to the most frequent pharmacological groups during pregnancy

Pharmacological group	N (%) of pregnancy episodes exposed	N (%) episodes with one dispensing*	N (%) episodes with >1 dispensing*
B03A, iron preparations	157 467 (48.0)	59 021 (37.5)	98 446 (62.5)
H03C, iodine therapy	131 763 (40.2)	40 119 (30.4)	91 644 (69.6)
N02B, other analgesics and antipyretics	91 686 (28.0)	63 563 (69.3)	28 150 (30.7)
J01C, penicillins	65 050 (19.8)	51 019 (78.4)	14 031 (21.6)
B03B, vitamin B_{12} and folic acid	64 534 (19.7)	31 814 (49.3)	32 720 (50.7)
M01A, NSAID	49 577 (15.1)	41 130 (83.0)	8447 (17.0)

Drugs with one dispensing and drugs with more than one dispensing.
*Percentages calculated over the number of episodes exposed for each group.
NSAID, non-steroidal anti-inflammatory drug.

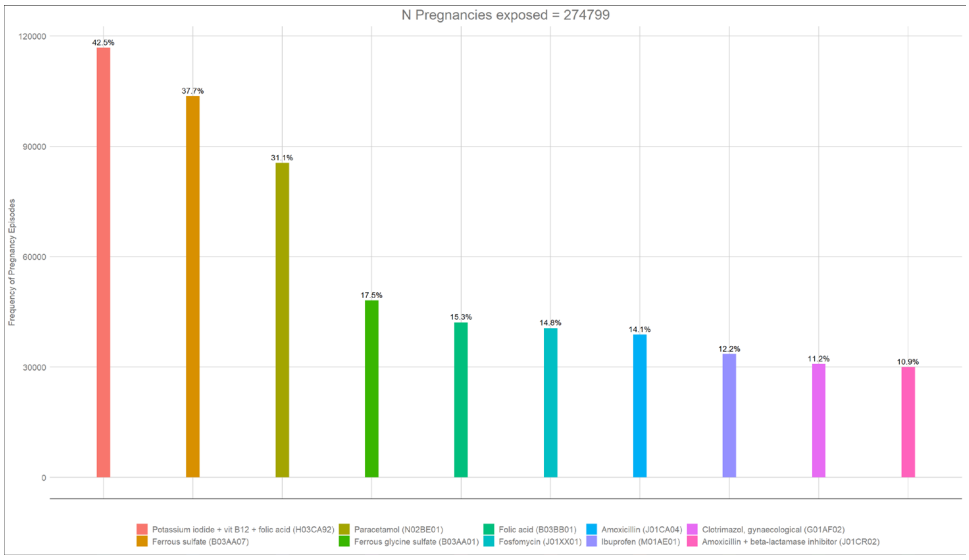

Figure 3 Most frequent drugs with more than one dispensing per pregnancy episode. The figure shows the most dispensed substances within the most frequent pharmacological groups dispensed during pregnancy, in percentages calculated over the number of pregnancy episodes.

Other limitation is the lack of a specific validation of the algorithm. Nevertheless, the number and distribution of pregnancies and the drug use during gestation are in line with previous studies,[17 19] and similar to the Catalan[28] and Spanish[29] official data.

As pointed out, some of the drug counts in our study might be underestimated, as we are not able to capture OTC drugs, which are frequently used by pregnant women and are often not registered in EHR, being one of the usual limitations of these type of studies.[18 19 47]

Despite the limitations, SIDIAP database might be a valid and efficient resource to study drug safety during pregnancy, as it captures clinical information of most of the Catalan population, we have developed an algorithm to automatically identify the pregnancy periods, and an algorithm to link mother and child pairs has also been developed and can be used to study pregnancy outcomes. It is an algorithm which establishes mother and child pairs linked through national insurance number and coinsurance status.[48] We have also mapped SIDIAP pregnancy data to the ConcePTION common data model, which has demonstrated its potential to address questions about utilisation, effectiveness and safety of medicines during pregnancy and lactation.[49] All of this might help to fill the gap in the currently available evidence, as safety concerns on drug use during pregnancy affect not only women, but also the fetus and the newborns, and it is also applicable to the lactation period, which we are also planning to assess within our database.

CONCLUSIONS

We have developed an algorithm to automatically identify the pregnancy periods, which will allow us to study not only the drug use in pregnant people, but its consequences in these women's health and in their offspring's.

We have described the use of prescription drugs in a large cohort of pregnant women. The most used drugs during pregnancy were recommended supplements and drugs used for acute conditions, such as analgesics, NSAID or antibiotics.

SIDIAP database might be an efficient resource to study drug safety during pregnancy.

Author affiliations
[1]Àrea del Medicament i Servei de Farmàcia, Gerència d'Atenció Primària Barcelona Ciutat, Institut Català de la Salut, Barcelona, Spain
[2]Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain
[3]Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain
[4]College of Pharmacy, Department of Pharmacotherapy, University of Utah, Salt Lake City, Utah, USA
[5]Marketing farmacéutico & Investigación clínica, Barcelona, Spain
[6]Former employee at IDIAPJGol, Barcelona, Spain
[7]RTI Health Solutions Barcelona, Barcelona, Spain
[8]Unitat de farmàcia, Servei d'Atenció Primària Barcelonès Nord i Maresme, Badalona, Spain

Acknowledgements The authors want to thank María Aragón and Clara Rodríguez for the data acquisition process from SIDIAP database.

Contributors MLV: conceptualisation, study design, data curation, writing (original draft), review and editing. AG-L: conceptualisation, study design, data curation, writing, review and editing. OP-V: study design, data curation, formal analysis and review. CVC: data curation, formal analysis, writing (original draft), review and editing. JRM: conceptualisation, study design, data curation and review. CVU: conceptualisation, study design, writing, review and editing. MG-S: conceptualisation, study design, data curation, writing (original draft), review and editing. RM: conceptualisation, data curation, study design, writing, review and editing. MG-S is responsible for the overall content as the guarantor.

Funding This study received funding from the 8th call for SIDIAP grants, 2018–2019, expedient number 4R18/188; and from Health Department of the Generalitat de Catalunya, in the call corresponding to 2021 for the granting of funding of the Strategic Plan for Research and Innovation in Health (PERIS) 2021–2024, modality Research Projects in Primary Care, expedient number SLT/21/000068.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study protocol was approved by the Research Ethics Committee of IDIAPJGol. Number 19/107-P, 26 June 2019. This is a database research study which has been conducted according to the guidelines of the Declaration of Helsinki (Fortaleza, Brazil 2013) and does not require consent from the people included to participate or for publication. 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).The need for consent was waived by the Research Ethics Committee of IDIAPJGol as it is deemed unnecessary according to European legislation (Regulation (EU0) 2016/679).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplemental information. The datasets generated and/or analysed during the current study are not publicly available due to patient privacy and data protection concerns, but they are available from the corresponding author on reasonable request. All data generated or analysed during this study are included in this published article and its supplementary information files.

ORCID iDs
Carles Vilaplana-Carnerero http://orcid.org/0000-0003-3780-4996
Maria Giner-Soriano http://orcid.org/0000-0003-3750-9233

REFERENCES

1 CHMP. Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data; 2005, EMEA/CHMP/313666/2005. European medicines agency 21.
2 McGregor AJ, Hasnain M, Sandberg K, *et al*. How to study the impact of sex and gender in medical research: a review of resources. *Biol Sex Differ* 2016;7(Suppl 1):46.
3 Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, *et al*. Sex and gender: modifiers of health, disease, and medicine. *The Lancet* 2020;396:565–82.
4 Briggs G, Freeman R, Yaffe S. A reference and neonatal risk. In: *Drugs in pregnancy and Lactation*. Philadelphia, USA, 2015.
5 Ali Z, Hansen AV, Ulrik CS. Exacerbations of asthma during pregnancy: impact on pregnancy complications and outcome. *J Obstet Gynaecol* 2016;36:455–61.
6 Lim A, Hussainy SY, Abramson MJ. Asthma drugs in pregnancy and Lactation. *Aust Prescr* 2013;36:150–3.
7 Marder W, Littlejohn EA, Somers EC. Pregnancy and autoimmune connective tissue diseases. *Best Pract Res Clin Rheumatol* 2016;30:63–80.
8 Østensen M, Andreoli L, Brucato A, *et al*. State of the art: reproduction and pregnancy in rheumatic diseases. *Autoimmun Rev* 2015;14:376–86.
9 American Diabetes Association. Management of diabetes in pregnancy. *Diabetes Care* 2017;40(Suppl 1):S114–9.
10 Wilmot EG, Mansell P. Diabetes and pregnancy. *Clin Med (Lond)* 2014;14:677–80.
11 Viale L, Allotey J, Cheong-See F, *et al*. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. *The Lancet* 2015;386:1845–52.
12 EMA. Good Pharmacovigilance practices. 2017 Available: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices
13 Illoh OA, Toh S, Andrade SE, *et al*. Utilization of drugs with pregnancy exposure registries during pregnancy. *Pharmacoepidemiol Drug Saf* 2018;27:604–11.
14 Birthcohorts. Birthcohorts. 2023. Available: https://www.birthcohorts.net/
15 Olesen C, Sørensen HT, Jong-van den Berg LD, *et al*. Prescribing during pregnancy and Lactation with reference to the Swedish classification system, a population-based study among Danish women. *Acta Obstet Gynecol Scand* 1999;78:686–92.
16 Engeland A, Bramness JG, Daltveit AK, *et al*. Prescription drug use among fathers and mothers before and during pregnancy. A population-based cohort study of 106 000 pregnancies in Norway 2004–2006. *Br J Clin Pharmacol* 2008;65:653–60.
17 Sanchez Ortiz S, Llorente García A, Astasio P, *et al*. An algorithm to identify pregnancies in BIFAP primary care database in Spain: results from a cohort of 155 419 pregnancies. *Pharmacoepidemiol Drug Saf* 2020;29:57–68.
18 Blotière P-O, Damase-Michel C, Weill A, *et al*. Dispensing of potentially harmful prescription drugs in 1.8 million pregnant women in France: a nationwide study based on two risk classification systems. *Drug Saf* 2021;44:1323–39.
19 Cea-Soriano L, García Rodríguez LA, Fernández Cantero O, *et al*. Challenges of using primary care electronic medical records in the UK to study medications in pregnancy. *Pharmacoepidemiol Drug Saf* 2013;22:977–85.
20 Minassian C, Williams R, Meeraus WH, *et al*. Methods to generate and validate a pregnancy register in the UK clinical practice research datalink primary care database. *Pharmacoepidemiol Drug Saf* 2019;28:923–33.
21 SIDIAP. Information system for research in primary care. 2022. Available: http://www.sidiap.org/index.php/en
22 Recalde M, Rodríguez C, Burn E, *et al*. Data resource profile: the information system for research in primary care (SIDIAP). *Int J Epidemiol* 2022;51:e324–36.
23 WHO. ICD-10 version: 2019. International statistical classification of diseases and related health problems 10th revision. 2019. Available: https://icd.who.int/browse10/2019/en
24 WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2022. 2022. Available: https://www.whocc.no/atc_ddd_index/
25 Felícitas Domínguez-Berjón M, Borrell C, Cano-Serral G, *et al*. Construcción de UN Índice de Privación a Partir de Datos Censales en Grandes Ciudades Españolas (Proyecto MEDEA). *Gaceta Sanitaria* 2008;22:179–87.
26 Sarayani A, Wang X, Thai TN, *et al*. Impact of the transition from ICD–9–CM to ICD–10–CM on the identification of pregnancy episodes in US health insurance claims data. *Clin Epidemiol* 2020;12:1129–38.
27 Charlton RA, Weil JG, Cunnington MC, *et al*. Comparing the general practice research database and the UK epilepsy and pregnancy register as tools for postmarketing teratogen surveillance. *Drug Saf* 2011;34:157–71.
28 IDESCAT I d'Estadística de C. Indicadors de Fecunditat. 2022. Available: https://www.idescat.cat/indicadors/?id=anuals&n=10343&tema=naixe
29 Instituto Nacional de Estadística. Nota de Prensa. Movimiento natural de la Población (MNP) Indicadores Demográficos Básicos (IDB) Año 2021. Datos Provisionales. 2022. Available: https://www.ine.es/prensa/mnp_2021_p.pdf
30 Departament de Salut G de C. Protocol de Seguiment de L'Embaràs a Catalunya. 2018. Available: https://salutpublica.gencat.cat/web/.content/minisite/aspcat/promocio_salut/embaras_part_puerperi/protocol_seguiment_embaras/protocol-seguiment-embaras-2018.pdf
31 Baladón L, Rubio-Valera M, Serrano-Blanco A, *et al*. Gender differences in the impact of mental disorders and chronic physical conditions on health-related quality of life among non-demented primary care elderly patients. *Qual Life Res* 2016;25:1461–74.
32 Bekker MHJ, van Mens-Verhulst J. Anxiety disorders: sex differences in prevalence, degree, and background, but gender-neutral treatment. *Gend Med* 2007;4 Suppl B:S178–93.
33 Creeley CE, Denton LK. Use of prescribed psychotropics during pregnancy: a systematic review of pregnancy, neonatal, and childhood outcomes. *Brain Sci* 2019;9:235.

34 Van de Velde S, Boyd A, Villagut G, *et al*. Gender differences in common mental disorders: a comparison of social risk factors across four European welfare regimes. *Eur J Public Health* 2019;29:481–7.
35 Nezvalová-Henriksen K, Spigset O, Nordeng H. Maternal characteristics and migraine pharmacotherapy during pregnancy: cross-sectional analysis of data from a large cohort study. *Cephalalgia* 2009;29:1267–76.
36 Chambers CD, Krishnan JA, Alba L, *et al*. The safety of asthma medications during pregnancy and lactation: clinical management and research priorities. *J Allergy Clin Immunol* 2021;147:2009–20.
37 Nutritional interventions update: multiple Micronutrient supplements during pregnancy. In: *WHO antenatal care recommendations for a positive pregnancy experience*. Geneva: World Health Organization, 2020.
38 Brown B, Wright C. Safety and efficacy of supplements in pregnancy. *Nutr Rev* 2020;78:813–26.
39 Body C, Christie JA. Gastrointestinal diseases in pregnancy. *Gastroenterology Clinics of North America* 2016;45:267–83.
40 Víquez Víquez M, Chacón González C, Rivera Fumero S. Infecciones del tracto urinario en mujeres embarazadas. *RevMédSinerg* 2020;5:e482. 10.31434/rms.v5i5.482 Available: https://revistamedicasinergia.com/index.php/rms/issue/view/63
41 Kitchin Á, Huerta C, Llorente-García A, *et al*. The role of prenatal exposure to antidepressants, anxiolytic, and hypnotics and its underlying illness on the risk of Miscarriage using BIFAP database. *Pharmacoepidemiol Drug Saf* 2022;31:901–12.
42 Bernard N, Forest J-C, Tarabulsy GM, *et al*. Use of antidepressants and anxiolytics in early pregnancy and the risk of preeclampsia and gestational hypertension: a prospective study. *BMC Pregnancy Childbirth* 2019;19:146.
43 Suarez EA, Bateman BT, Hernández-Díaz S, *et al*. Association of antidepressant use during pregnancy with risk of neurodevelopmental disorders in children. *JAMA Intern Med* 2022;182:1149–60.
44 Hanley GE, Mintzes B. Patterns of psychotropic medicine use in pregnancy in the United States from 2006 to 2011 among women with private insurance. *BMC Pregnancy Childbirth* 2014;14:242.
45 Park Y, Huybrechts KF, Cohen JM, *et al*. Antipsychotic medication use among publicly insured pregnant women in the United States. *Psychiatr Serv* 2017;68:1112–9.
46 Hanley GE, Miller T, Mintzes B. A cohort study of psychotropic prescription drug use in pregnancy in British Columbia, Canada from 1997 to 2010. *Journal of Women's Health* 2020;29:1339–49.
47 Mitchell AA, Gilboa SM, Werler MM, *et al*. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. *Am J Obstet Gynecol* 2011;205:51.
48 Duarte-Salles T, Mendez-Boo L, Diaz Y, *et al*. Abstract: linkage of mother and child pairs in the information system for research in primary care (SIDIAP) in Catalonia. *Pharmacoepidemiol Drug Saf* 2018;27:3–521.
49 Thurin NH, Pajouheshnia R, Roberto G, *et al*. From inception to conception: genesis of a network to support better monitoring and communication of medication safety during pregnancy and breastfeeding. *Clin Pharmacol Ther* 2022;111:321–31.