Assessing exposure to cardiovascular therapy, anxiety depressive syndrome treatment and anti-infectives during pregnancy and breastfeeding

Addendum COVID19 outbreak

SIDIAP

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1. Abstract

Pharmacotherapy during pregnancy and breastfeeding implies the possible risk of congenital disorders and other diseases in the offspring, so it is necessary to assess the benefit-risk balance of all drug treatments before prescribing them in pregnant or breastfeeding women.

The drug use in pregnancy and breastfeeding has been assessed through different studies and, lately, through database studies, which offer advantages such as linked information mother-offspring, long-term follow-up periods for mothers and infants, information on maternal and birth outcomes, and information on confounding factors.

The use of drugs during pregnancy and breastfeeding has not been assessed through electronic health records in our setting and we plan to assess it through a population based study conducted with SIDIAP data in all women with pregnancy and breastfeeding registered in this database throughout 2011-2018.

We plan to analyse drug use during pregnancy and breastfeeding, focalising in cardiovascular, neurologic and psychiatric disorders; to analyse vaccines use during these periods; and to detect possible congenital disorders and other diseases during childhood which may be caused by drug exposures of the mothers during pregnancy and breastfeeding.

Due to the actual pandemic situation of COVID19 we would like to explore pregnancy and perinatal outcomes of SARS-Co-V2 infections occurring during pregnancy in Catalonia (2020). Even few publications have been made, they would probably have to be updated as there is still a lot to know regarding SARS-Co-V2 infection.

Keywords:

Pregnancy; Breastfeeding; Pharmaceuticals; Drug Utilization Review; Pregnancy exposure registries: Electronic Health records; COVID19, SARS-Co_V2, children.

2. Background and justification

The use of therapeutic drugs during pregnancy has never been deeply explored due to the ethics problems of pregnant women participating in clinical trials. Almost all information regarding the use of drug therapies during pregnancy and breastfeeding comes from case reports series. Pharmacotherapy during pregnancy and breastfeeding implies the possible risk of congenital outcomes and other diseases in the offspring, so it is necessary to assess the benefit-risk balance of drug treatment in pregnant women properly.[1]

Despite this reality, the use of drugs in pregnancy is not uncommon and different studies have shown that there is a great variability in the frequency of drug use during pregnancy between different countries. There is also the possibility of the use of drugs during the initial phases of pregnancy as women may not be aware that they are pregnant.

An international study sponsored by the World Health Organization (WHO) in 1992,[2] which surveyed 15,000 pregnant women in 22 different countries (including Spain), concluded that approximately 86% of them consumed some medication and that the average number of drugs consumed by each of them was 2,9. In 2014 an international study[3] carried out in Europe, North and South America and Australia, reported similar results obtained by the WHO in 1992.

Mitchell et al. tried to provide wide information on drug use during pregnancy interviewing over 30,000 women with children with any major structural birth defects.[4] Even the important memory bias that this kind of study could have on the recall of medications taken by these mothers; it registered an increase in time (1976- 2008) of drugs use during pregnancy, being antibiotics amongst the most prescribed drugs.

The tragedy of thalidomide[5] in the 1960s was the starting point of knowledge of the risks of drug use during pregnancy. Now, 60 years after this tragedy, thanks to the recommendations on the use of drugs in pregnant women and the monitoring systems

of congenital defects and identification of teratogens, it is difficult to imagine a new epidemic like the one that produced thalidomide. However, there is a hard and long way to elucidate which treatments are the safest and most effective during pregnancy and breastfeeding.

The Food and Drug Administration established a classification for the use of drugs during pregnancy, each drug is classified into 1 of 5 categories (A, B, C, D and X) based on the absence or presence of data on the safety of its use during pregnancy, the type of study subjects, and the study results.[6] This system, although easy to use, might oversimplify the complexity of weighing risks to the foetus against the need to adequately manage maternal medical conditions (asthma, hypertension, psychiatric conditions… among others).[7] A new model, the pregnancy and lactation labelling rule (PLLR) is being implemented by the FDA as a requirement for the pharmaceuticals.[8]

In general, most drug treatments are absolutely contraindicated during pregnancy, even more if there are therapeutic alternatives without risk or if this risk of diseases or malformations is small or does not exist.[9,10] Nevertheless, there are some chronic pharmacological treatments that are not recommended to be discontinued during pregnancy and breastfeeding due to the possible increase in risk of complications in the basal pathology of the mother and the risk in the offspring, despite the lack of exhaustive safety information in the foetus during the pregnancy period.

Pharmacotherapy used in maternal pathologies such as asthma[11,12], autoimmune disorders,[13,14] atrial fibrillation,[15,16] diabetes mellitus,[17,18] epilepsy[19] or psychiatric disorders[20, 21,22] are some of these special situations. When these cases are presented and pharmacological therapy is maintained, it is important to gather information on the evolution of pregnancy and the outcomes in foetus and new-borns.

Epidemiological studies may be important to assess the current medication prescribing pattern and identifying drug use during pregnancy or during breastfeeding and its correlation with safety issues in the offspring. In the last decades several studies in European populations based on use of database records demonstrated the need to

develop strategies to improve prescribing safety in women in the gestation and breastfeeding periods. Olesen et al.[23] in Denmark in the period 1991 to 1996 and Engeland et al.[24] in Norway in 2004-2006 are examples of this development.

Due to the COVID19 outbreak and the few studies on pregnant women and children, we aim to provide data regarding the outcomes on pregnant women with COVID disease and their offspring during the outbreak. Pregnant women are susceptible to COVID-19, drugs used against it are worthy of consideration for pregnant women with COVID-19, such as chloroquine, metformin, statins, lopinavir/ritonavir among others, with also no clear results in the general population and hypoxia must be translated into fetal grow restriction. Also, there is no evidence for intrauterine infection by vertical transmission COVID19 neither contraindication for vaginal delivery. [(a, b)] Also COVID19 symptoms among pregnant women can vary and turn out into different health outcomes for they and their offspring [(c)]

Nowadays, having huge databases would allow us to explore drug use during pregnancy or during breastfeeding and its correlation with safety issues in the offspring.[25,26] This data would allow us to establish strategies to improve the prescription profile and support pharmacotherapy decisions for the medical treatment of female patients during pregnancy or breastfeeding, helping to decide if continue or stop treatment, or switch to a less teratogenic drug.

Databases offer a number of advantages in studying medication safety in pregnancy.[25]

The strengths of using databases are linked information mother-offspring and information on long-term follow-up of infants or mother, information on maternal and birth outcomes and information on confounding factors.[25] The limitations that the databases studies could be can be partially addressed by linking it with other electronic data sources.

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4. Hypothesis

General hypothesis: The use of SIDIAP database to analyse drug use during pregnancy and breastfeeding would help as in assessing its outcomes in the offspring and would eventually allow us to establish improvements in the tools which support pharmacotherapy decisions during pregnancy and breastfeeding.

Hypothesis

- Women have increased the use of medications during pregnancy because chronic diseases in which the pharmacological treatment cannot be stopped during pregnancy or because they are taking some medication previous to become aware of their pregnancy.
- Children born from mothers who have been taking medication during pregnancy or breastfeeding have more congenital disorders as well as more health problems.
- The use of SIDIAP database to analyse the COVID19 in pregnant women, their outcomes and the outcomes in children would help to get a deeper knowledge of this new disease and its behaviour in a population like pregnant women.

5. Objectives

5.1 Main objectives

a) To analyse drug use during pregnancy

b) To analyse drug use during breastfeeding

c) To analyse diagnoses in the offspring of mothers with drug exposure during pregnancy and breastfeeding

d) To analyse SARS-Co-V2 infection in pregnant women

5.2 Secondary objectives

a) To analyse cardiovascular therapy use during pregnancy and breastfeeding

b) To analyse drug use for anxiety-depressive syndrome during pregnancy and breastfeeding

c) To analyse vaccines use in pregnancy and breastfeeding

d) To detect congenital and other diseases during childhood (0-12 years) which could be due to these drugs use during pregnancy and breastfeeding

e) To estimate the prevalence of COVID19 disease in pregnant women

f) To describe the symptoms and outcomes in pregnant women with COVID19 disease

g) To assess the risk of COVID19 in the offspring of women with a COVID19 disease during the gestation.

6. Methods

6.1 Study design

Population-based observational cohort study.

6.2 Study period

From 2011-2020.

6.3 Study population

Women with pregnancy and breastfeeding registered at SIDIAP database and their offspring linked during the study period.

Inclusion criteria:

- Women from 12-50 years
- Women identified with a pregnancy code during the study period (2011-2020)
- Women with at least one visit registered in primary care/ASSIR during the study period

6.4 Data source

SIDIAP (Information System for Research in Primary Care),[27] which contains anonymized clinical information of all 279 PHC centers managed by the ICS in Catalonia

(North-East Spain), covering a population of more than 5.8 million patients (about 80% of the total of 7.5 million population in Catalonia).

The information contained in SIDIAP is registered by PHC general practitioners (GP), nurses and administrative staff in ECAP (electronic health records in primary care in the Catalan Health Institute, ICS): comprehensive socio-demographic information, health conditions registered as ICD10 codes,[28] specialist referrals, clinical parameters, toxic habits, PHC laboratory test results, General Practitioners' (GP) prescriptions and their corresponding pharmacy invoice data registered as ATC codes,[29] date of sickness leave due to any cause, and date of death.

Several reports have shown that SIDIAP data is useful for epidemiological research.[30-34] SIDIAP is listed under the ENCePP resources database.[35]

6.5 Sample size

The sample size will be all women aged 12-50 years with pregnancy registered in SIDIAP database during the study period.

6.6 Variables

Diseases of study

We aim to analyse:

- rhythm related diseases
- depression and anxiety disorder
- bacterial infections.
- COVID disease: symptoms, fatality outcomes in the mother/offspring

Drug use

Women participating in the study will be classified as "exposed" to the study drugs if they are prescribed any of them during the pregnancy or breastfeeding period.

We consider study drugs all those used for the cardiovascular, neurologic and psychiatric conditions described above:

- Cardiac therapy: C01B, C07, C08

- Psychiatric drugs: N05B, N05C, N06A
- Antiinfeccives: J01 (Antibacterials for systemic use) and J07 (vaccines)

Socio-demographic variables

Date (period) of pregnancy, date (period) of breastfeeding, age, sex, MEDEA index (socioeconomic deprivation index)[3], smoking status, alcohol intake.

Other variables

- Congenital disorders during childhood of the offspring of the women included in the study
- Teratogenic outcomes in the offspring of the women included in the study
- Health problems related to the offspring

COVID19 variables

- Diagnosis (B34.2, B97.21, J12.81, B97.29, J12.89)
- PCR for COVID19
- Symptoms
- Hospital variables (intensive care unit, ventilatory support)
- Death

6.7 Statistical analysis

All processes of data management and statistical analysis will be carried out using statistical package R 3.3 (2016). At the exploratory level, the demographic data and baseline characteristics of the study population will be described using relative and absolute frequencies for the categorical and mean variables, standard or median deviation and interquartile range for the continuous variables.

In the bivariate analysis, we will consider the Chi-square test or the Fischer exact test for categorical variables and the Student t test or Mann-Whitney U test for continuous variables according to their distribution.

The evaluation of mothers' drugs exposures and the risk of diseases and congenital outcomes in their offspring will be carried out by means of multiple logistic regression models or proportional risk models (Cox). The adjustment for risk factors will be determined based on the characteristics of the study population.

No imputation method is foreseen for the management of lost or missing data.

7. Strenghts and limitations

The strengths of using databases and SIDIAP in particular are large number of patients included, representativeness for the general population, complete socio-demographic and health records, linked information mother-offspring and information on long-term follow-up of infants or mothers, information on maternal and birth outcomes and information on confounding factors. The limitations that the databases studies could be can be partially addressed by linking it with other electronic data sources or through Cox regression models adjusted for socio-demographic characteristics and for possible confounders and predictive factors.

8. Ethical aspects and data confidentiality

The present study follows national and international regulations: Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and Good Research Practice principles and guidelines.

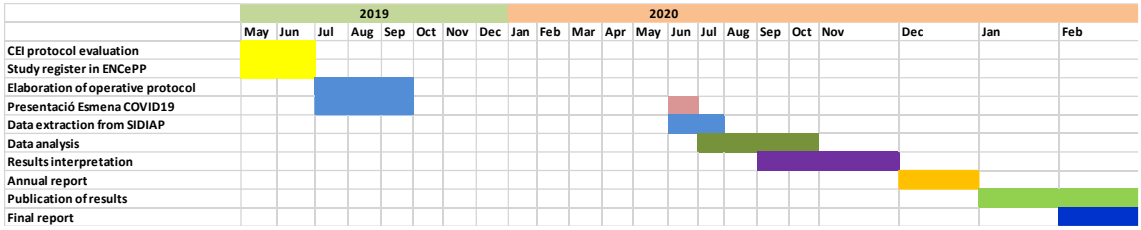
The study protocol will be evaluated for IDIAP Jordi Gol Clinical Research Ethics Committee, the reference institution for research in PHC of the ICS.

Regarding the data contained in the databases and according to Spanish legislation about confidentiality and data protection (Ley 3/2018de 5 Diciembre de Protección de datos y Garantías de Derechos Digitales) data included in SIDIAP are pseudoanonymized. Thus, it is not necessary to ask for informed consent from the participants.

9. Workplan

We plan to conduct our study within one year period.

1. Evaluation of the protocol by the CEI IDIAP Jordi Gol
2. Study register in ENCePP
3. Elaboration of the operative protocol with SIDIAP team
4. Data extraction from SIDIAP database
5. Data analysis
6. Results interpretation and discussion
7. Elaboration of study reports
8. Publication and diffusion of results



10.Scientific and technical background of the research team

10.1 Principal investigator

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Ainhoa Gomez-Lumbreras is a physician specialist in Family Medicine and in Clinical Pharmacology, with a PhD in Pharmacology. She works as a researcher in Pharmacoepidemiology and Pharmacovigilance at Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAPJGol), mainly developing Pharmacoepidemiology and Pharmacovigilance research projects with SIDIAP database, among other technical tasks in the field of Medicines Research in Primary Healthcare. She is an associate professor in the Faculty of Medicine at Universitat de Girona. All her scientific publications and collaborations in research projects can be found in her ORCID profile. GRENSSAP member.

10.2. Co-investigators

Marta Lestón Vázquez

Marta Lestón Vázquez is a Hospital Pharmacy specialist. She is currently working as Primary Healthcare pharmacist at Institut Català de la Salut, Barcelona, Spain. She is the member of the research team who will conduct her doctoral thesis with this research project. Her publications are listed next: VV.AA. Monografías de Farmacia Hospitalaria y de Atención Primaria: Trazabilidad y seguridad clínica (nº 5). Barcelona: Bayer Hispania SL, 2016. Capítulo Herramientas de trazabilidad y nuevas tecnologías. Editado por la Sociedad Española de Farmacia Hospitalaria. ISBN: 978-84-608-7393-8.

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Rosa Morros Pedrós is a Clinical Pharmacology specialist and PhD in Pharmacology. She is the coordinator of the Medicines Research Unit at IDIAPJGol, which develops independent clinical trials and observational cohort studies with SIDIAP database. She is an associate professor in the Pharmacology Department at Universitat Autònoma de Barcelona and coordinates the Pharmacoepidemiology office at the Institut Català de la Salut (ICS), Barcelona, Spain. She participates in different committees of medicines evaluation at AEMPS, CatSalut and ICS, and she is the president of the Research Ethics Committee (CEI) of IDIAPJGol. All her scientific activity can be consulted in her ORCID profile. GRENSSAP member.

Ester Amado Guirado

Ester Amado Guirado is a Pharmacist with a Master in Health and Medicines Economics and a PhD in Health Sciences. She is the Pharmacy referent in Primary Healthcare at ICS in Barcelona. She participates in different committees of medicines evaluation at CatSalut and ICS and she is an expert in strategies of improvement of drug use, and development of indicators of pharmacy prescription, and she has a wide experience in medicines research. Her scientific publications in the last five years are listed below:

- Morros R, Vedia C, Giner-Soriano M, Casellas A, Amado E, Baena JM; en representación de los investigadores del proyecto PNEUMOCORT. Neumonías adquiridas en la comunidad en pacientes con enfermedad pulmonar obstructiva crónica tratados con corticoides inhalados u otros broncodilatadores. Estudio PNEUMOCORT. Aten Primaria 2018.
https://doi.org/10.1016/j.aprim.2018.02.007
- Comin E, Catalan-Ramos A, Iglesias-Rodal M, Grau M, Del Val JL, Consola A, Amado E, Pons A, Mata-Cases M, Franzi A, Ciurana R, Frigola E, Cos X, Davins J, Verdu-Rotellar JM. Impacto de la implementación de las guías de práctica clínica electrónicas en el diagnóstico, control y tratamiento de los factores de riesgo cardiovascular: un estudio

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- Laura Diego, Ester Amado Guirado. Información de medicamentos a pacientes: necesario pero insuficiente. FMC 2015;22:90-7 - Vol. 22 Núm.2 DOI: 10.1016/j.fmc.2015.02.007
- Catalán A, Borrell F, Pons A, Amado E, Baena JM, Morales V. Seguridad de Atención Primaria: Proyecto PREFASEG. Med Clin (Barc). 2014 Jul;143 (Suppl 1): 32-5.

She is currently participating in the following research projects:

- 2017. Patrons de multimorbiditat, polimedicació i seguretat de la prescripció en persones majors de 65 anys: cohort poblacional basada en la història clínica electrònica d'atenció primària. Departament de Salut. PERIS 2017. Codi projecte: SLT002/16/00058. Investigadora Principal.
- 2016. Análisis longitudinal de los patrones de multimorbilidad y polimedicación en personas mayores de 65 años: estudio de una cohorte de personas basado en la historia clínica electrónica. Instituto de Salud Carlos III. Codi projecte: PI16/00639. Investigadora col·laboradora.
- 2015. Avaluació d'una intervenció per millorar la seguretat de la prescripció en persones grans amb multimorbiditat i polimedicació ateses a l'atenció primària. Fundació Atenció Primària CAMFyC. Investigadora col·laboradora.

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Maria Giner-Soriano is a Hospital Pharmacy specialist with a PhD in Pharmacology. She is currently working as a research pharmacoepidemiologist at IDIAPJGol and at the Pharmacoepidemiology office at ICS, Barcelona, Spain, mainly developing Pharmacoepidemiology and Pharmacovigilance research projects with SIDIAP database, among other technical tasks in the field of Medicines Research in Primary Healthcare. All her scientific publications, technical documents and participations in research projects can be found in her ORCID profile. GRENSSAP member.

11.Applicability and utility of the study

The implementation of the results from clinical trials and cohort studies is not always complete in the clinical practice. The availability of population-based studies allows a better implementation of these results through guidelines in our setting. Studies with information systems based on electronic health records as SIDIAP may accelerate the implementation of these results.

The data provided by this study will allow us to establish hypothesis of the risk of these pharmacological therapies when used during pregnancy or breastfeeding and to develop tools which can help clinicians in pharmacotherapy decisions in women who are pregnant or breastfeeding.

Data provided regarding pregnant women with COVID19 disease and their outcomes and their offspring outcomes in terms of transmission and severity would help to a better understanding of an emerging disease for which there is a lot to know.

12.Available resources for study conduction

We have enough human and material resources to conduct this study.

The research team is composed by members of the Medicines Research Unit fromIDIAPJGol, which has large experience in conducting SIDIAP Pharmacoepidemiology studies, and two Primary Healthcare pharmacists. A pre-doctoral researcher is included in the research team and she plans to conduct her PhD project with this research study.

All members of the research team have abilities to manage clinical data. We also have access to the necessary scientific and technic information for conducting the study. The Medicines Research Unit has enough material resources, such as software needed to manage the data generated in this type of studies.

13.Budget request and justification

We present this study protocol to the “8ª convocatòria d’ajuts SIDIAP” in order to obtain funding for the elaboration of the operative protocol and the data extraction.

Other expenses related to the implementation of this project are the protocol elaboration, data analysis and results dissemination through different publications.

These expenses will be assumed with the coordinated work of all the research team. In case an extra-budget is necessary, we will present the project to other competitive calls.

14.Conflict of interest

The authors declare no conflicts of interest.