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ORIGINAL RESEARCH ARTICLE

A Landscape Analysis of Post-Marketing Studies Registered in the EU PAS Register and ClinicalTrials.gov Focusing on Pregnancy Outcomes or Breastfeeding Effects: A Contribution from the ConcePTION Project

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Abstract

Introduction A large proportion of medicine product labels lack information on safety in pregnancy and breastfeeding. To address this gap, pharmaceutical companies are requested to develop post-approval studies regarding the use of drugs by pregnant and breastfeeding women.

Objective Our study aims to review key features of observational studies in pregnancy and breastfeeding and their impact on the respective medicine product labels.

Methods Observational studies focusing on the safety evaluation of medicines used during pregnancy and breastfeeding were selected from the European Union Register of Post-Authorization Studies (EU PAS register) and ClinicalTrials.gov. We extracted information on the variables of interest and performed an impact assessment on the respective label.

Results A total of 141 observational studies were eligible. Of these, 63 studies (45%) were based on primary data collection and 55 studies (39%) on secondary use of health data. A small number of studies (8%) aimed to evaluate drug safety during breastfeeding. Studies using secondary data collection lasted around 2.9 years as opposed to 7.5 years' duration for studies using primary data collection. Only two product labels were updated based on the study results.

Conclusion The duration is significantly longer for studies based on primary data collection, and these are also smaller in size (less power), whereas outcomes of interest are similar. For completed studies, the impact on the label was very low. Given the gap in adequate pregnancy information on product labels, the current process of generating evidence in pregnancy and breastfeeding seems neither efficient nor impactful. To support evidence-based decision making by prescribers, this current process might be redesigned.

Key Points

Observational studies of drug safety involving pregnant and breastfeeding women based on secondary use of health data include more study subjects and were completed faster than studies based on primary data collection.

A very low number of product labels were updated based on the respective observational studies despite the large number of completed studies.

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1 Introduction

It is well known that drug labelling documents, such as Summaries of Product Characteristics (SPCs) and Patient Information Leaflets (PILs), contain limited information about safety in pregnant and nursing women exposed to medicines [1]. While regulators such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) require that medicinal products undergo testing to determine reproductive effects in animal models, pregnant women are typically not enrolled in clinical trials to assess the safety and efficacy of new medicinal products [2, 3].

Due to this paucity of data, there is a need to identify effects on pregnant women and their children post-licensure [4]. If new evidence about safety in pregnant and breastfeeding women is found, the pharmaceutical industry usually updates the company core data sheet which serves as the global reference document to communicate the company's position to appropriate stakeholders worldwide for the inclusion of safety information on country-specific labels such as SPC and PIL [5].

In 2019, the FDA updated the guideline for pharmaceutical industries for Post-Approval Pregnancy Safety Studies (including recommendations about the pregnancy exposure registries [PERs]) [6]. In the same year, the EMA followed with the Good Pharmacovigilance Practices guide that advocates for adequate data collection and data assessment through existing PERs/databases, product-specific registries, or even a hybrid approach to enable patients and prescribers to have relevant information to make informed decisions about using medicines during pregnancy or breastfeeding [7].

Registry-based post-marketing safety studies designed only for breastfeeding women exposed to drugs and the effects on their infants are still very rare. The risk estimation for breastfed infants might come initially from the pharmacokinetic (PK) data of the product (assessed in a clinical lactation study) [8]. Nonetheless, in the case of a medicinal product frequently used by breastfeeding women, pregnancy registries in which infants are further observed could be useful to better assess the safety profile of a drug during the lactation period [7]. Despite the setup of the PER to identify potential drug effects in pregnancy and breastfeeding, there are challenges that impact the success of conducting observational studies in the pregnancy registries. PERs that include breastfeeding assessment may require long-term follow-up of children's outcomes [7]. Data quality, enrollment size/retention, selection bias, lack of appropriate comparator group (e.g., a valid unexposed comparator cohort) and missing information play a key role in the challenges of these observational studies [4, 6, 9–14].

The wide availability of electronic health records (EHR) has boosted interest in assessing whether these can be used to replace or complement existing systems given their ability to overcome the aforementioned PER design limitations [9]. Electronic databases such as the IADB.nl database, Clinical Practice Research Datalink (CPRD) in the United Kingdom, Danish National Birth/Prescription Registry, Norwegian Medical Birth Registry, Certificate of Delivery Assistance (CeDAP) in Italy, National Community Child Health Database (NCCHD) in Wales, and the Mother Child Protection Centre and Hospital Medical Information System Database in France have the potential to provide detailed data on prescription drug exposures and outcome data for mothers and children [11, 15]. The Innovative Medicines Initiative (IMI)-ConcePTION project was set up to assess whether different types of data (including EHR) may facilitate the generation of real-world evidence on medicines safety in pregnancy and breastfeeding [16]. In this study, we aim to describe a landscape analysis of clinical and observational studies focusing on pregnancy and breastfeeding registered in the European Union Register of Post-Authorization Studies (EU PAS register) and ClinicalTrials.gov. We also aim to assess whether the findings of those completed studies led to updates of the respective product label.

2 Methods

2.1 Data Sources and Selection Criteria

We identified observational studies focusing on the evaluation of medicines safety during pregnancy and breastfeeding from the EU PAS register and ClinicalTrials.gov.

EU pharmacovigilance legislation requires the EMA to make public the protocols and abstracts of results of non-interventional post-authorization safety studies (PASS) imposed as an obligation of marketing authorization by a competent authority in accordance with Article 10 or 10a of Regulation (EC) No 726/2004 or with Articles 21a or 22a of Directive 2001/83/EC. Annex III of the Commission Implementing Regulation (EU) No 520/2012 further specifies that the final report of imposed non-interventional PASS must provide the date of making it public (in the EU PAS Register) [17]. ClinicalTrials.gov is a web-based resource with easily accessed information on publicly and privately supported clinical and observational studies on a wide range of diseases and conditions (including pregnancy and breastfeeding); observational studies are not required to be listed [18]. Both databases are fully searchable and allow the identification of study design, data collection (DC) type (primary data collection vs secondary data collection), expected enrollment size, study duration, study outcomes and other relevant variables.

A list of studies in the EU PAS register were obtained from EMA from its inception to December 2018 [19]. Observational studies that tagged 'pregnant women' or 'breastfeeding mothers' in the 'Other population' field of the register were included in this study.

EU PAS register identifiers were used to retrieve the study and extract data. We created a query (see Electronic Supplementary Material [ESM] 3) using the application programming interface of ClinicalTrials.gov to retrieve the variables of interest from observational studies with 'pregnancy' or 'lactation' conditions registered up to 24 May 2020 [18, 19].

Study titles retrieved from the EU PAS register were compared with those from the ClinicalTrials.gov list to identify and remove duplicates.

After removal of duplicates, we included

(i) studies including pregnant or breastfeeding women in the study population,
(ii) observational studies (including drug utilization studies) and
(iii) studies aiming to measure medicine use or outcomes related to pregnancy or breastfeeding.

We excluded studies under the following criteria:

(i) experimental studies,
(ii) case reports and
(iii) observational studies whose exposure comprised only non-medicinal products (e.g., devices, procedures, behavioral) and studies focused on a medical abortion program.

2.2 Extraction of Information From Eligible Studies

A summary of the definitions of the variables that were collected are presented in Table 1. Full descriptions of the variables, as well as the location where they were extracted from, can be found in ESM 1. Information was extracted on a set of key parameters from high-level metadata to detailed data (Table1).

This included information regarding study classification, study design, data collection and enrollment size as provided by the respective researchers of each study from Sect. 1 of the EU PAS register and from the respective ClinicalTrials.gov field. The start date (date when contract was signed or date of first register, whichever is the earliest) and end date (date of analysis for 'ongoing studies' or date of final report entered in the forms) of each study were collected. When only month and year were available (e.g., December 2012), we considered the day to be the 15th of the month (e.g., 15 December 2012). We described the variables for each eligible observational study listed in ESM 2.

The eligible studies involved not only European countries and the US but also study sites in other continents.

2.3 Analysis

Descriptive analyses were done to describe and compare characteristics. We compared key variables between studies based on primary data collection and secondary use of health data Emphasis>from the EU PAS Register and ClinicalTrials.gov.

Kaplan-Meier plots were generated through IBM SPSS Statistics version 26.0 to compare the study period duration of primary data collection versus secondary data collection. The duration of these eligible studies was estimated using the start date and either the date of this analysis for 'ongoing' studies (they are considered as 'censored' because we did not observe their time to completion) or the end date of the study for 'completed' studies.

We performed an inter-rater reliability analysis of randomly selected studies to check consistency of data collection between two reviewers. To address potential inconsistent data extracted in ESM 1, data recorded by one reviewer was checked by another reviewer for variables in the same eligible study. All eligible studies were assessed by two independent reviewers and the adjudication of the discrepancies was documented to generate the final version of ESM 2.

2.4 Impact Assessment

We considered studies in EU PAS register/ClinicalTrials.gov to be 'completed', when the study's end date preceded the date of the extraction of this research. The study's end date is defined as the date entered by the study sponsor as either the final study report in the EU PAS register or as the study completion date in ClinicalTrials.gov. We captured the dates as shown in ESM 2.

To evaluate the impact of the results of completed studies on the respective label we first located the final reports or published papers; second, we compared the different versions of the European SPCs of corresponding drugs in the Electronic Medicines Compendium (EMC) via https://www.medicines.org.uk/emc. If the conclusion in the final report (when available) from a 'completed' observational study was similar to the respective medicine product label, we either accessed European public assessment reports or contacted the pharmaceutical companies responsible for the label (we contacted the pharmaceutical industry representatives who are part of the IMI-ConcePTION members project).

Missing data (such as confidential fields or absence of protocol/study results) were entered as Unknown (ESM 2).

Table 1 Summary of the variable definitions

	Definition
High level data variables	
Observational study [19, 25]	A study where the medicinal product(s) is (are) prescribed independent of patient inclusion in the study and as part of a therapeutic strategy which is not decided in advance by a study protocol but is applied according to the current clinical practice
Review or meta-analysis [19]	A collection or review of results from studies existing in the literature
Study design	
Descriptive study [19]	Studies that do not evaluate an outcome. Case-only types from clinical trials were also considered descriptive studies
Cohort study [19, 25]	A population of subjects presenting with an event during the follow-up of a cohort is compared, with respect to an exposure at baseline, with a control population
Cross-sectional study [19, 25]	Study in which the prevalence of a variable is measured in a population at a given moment
Case-control study [19, 25]	Epidemiological design comparing previous exposure to a risk factor of use of a drug or the presence of a characteristic in a group of subjects presenting a given event (the cases), to that in a group not presenting this event (the controls)
Cross-over study [19, 25]	Epidemiological design to evaluate a possible association between an exposure and the occurrence of an event by comparing the number of cases arising within and outside a previously defined window of exposure, in a population whose exposure status changes over time
Nested case-control [19, 25]	Case-control study carried out within the population of a cohort (from Dictionary of Pharmacoepidemiology [25])
Analytic studies—other [19]	If the analytic study design does not fit into the above categories
Data collection type	
Primary data [19]	Data of interest are collected ex novo by the researcher for a specific research or project purpose
Secondary data [19]	Data of interest are not generated ex novo for a specific research purpose but collected for administrative reasons or in the management of own clinical practice
Secondary data (MDS) [19]	Multiple database study using more than one secondary data source
Mixed [19]	Data collection method whereby the data of interest are both primary and secondary
Unknown/not applicable	Type of data collection used is either absent or unclear
Patient enrolment size	
Numerical data	Estimated number of patients enrolled. This research proposed the following arbitrary groups to transform this variable into a categorical: ≤ 100 101–500 501–5000 5001–10,000 > 10,001 Unknown
Sponsor type	
Pharmaceutical company	As per se
Academic research	As per se
Heath authority	The government authority responsible for the governance, organization, planification, and monitoring of the country's health system and healthcare provision of appropriate services, including arrangements for all levels of health care and ensuring the quality and accessibility of all health services, consistent with applicable statutes and regulations, prevailing community standards, and ethics
Other	Other entities such as European networks initiatives (e.g., ENTIS, ACRPV)
Detailed data variables	
Mechanism of exposure	
Prenatal	Fetus exposed via placenta before birth
Breastfeeding	Neonate/baby exposed via breast milk
Prenatal and breastfeeding	Fetus/baby exposed via placenta and breast milk
Enrolment gestation period	Range of time when pregnant women are exposed to study drug (e.g., from last menstrual date until delivery date)
Length of time children are followed (when applicable)	Length of time baby is observed from birth until a specific timepoint (e.g., up to 1 year)
Types of outcome categories	

Table 1 (continued)

	Definition
General maternal outcome	Outcome related to pregnancy: complications, pre-eclampsia or hypertensive disorders, gestational diabetes, induced or spontaneous abortion, elective or induced termination (including TopFA) or ectopic pregnancy
Specific maternal outcome	Outcome related to mother based on primary and secondary outcomes of the study. It includes the following outcome: specific adverse events experienced by pregnant women not stated in the general maternal category (e.g., serious Infection during pregnancy, hemorrhage, hypoglycemia, ectopic pregnancies, etc.)
General neonatal outcome	General CA—fetal anomalies/major malformation/major birth defects, or minor CA—outcomes such as live preterm delivery or stillbirths, small for gestational age, low birth weight or Apgar score measurement
Specific neonatal outcome	Specific CA or malformation/major birth defects or minor CA. Outcome related to fetus based on primary and secondary outcomes of the study. Outcome related to a specific adverse event other than general CA: neonatal infections, neonatal hypoxic ischemic encephalopathy, malignancies, autism spectrum disorder, fetal distress, blood transfusion, lab level abnormalities in neonate, etc.
Long-term/postnatal development	Postnatal developmental disorders related to children who are 1 year or older (e.g., neurocognitive/neurological disorders, psychomotor skills, psychiatric disorders, etc.)

CA congenital anomalies, *MDS* multiple data sources, *TopFA* termination of pregnancy for fetal anomaly

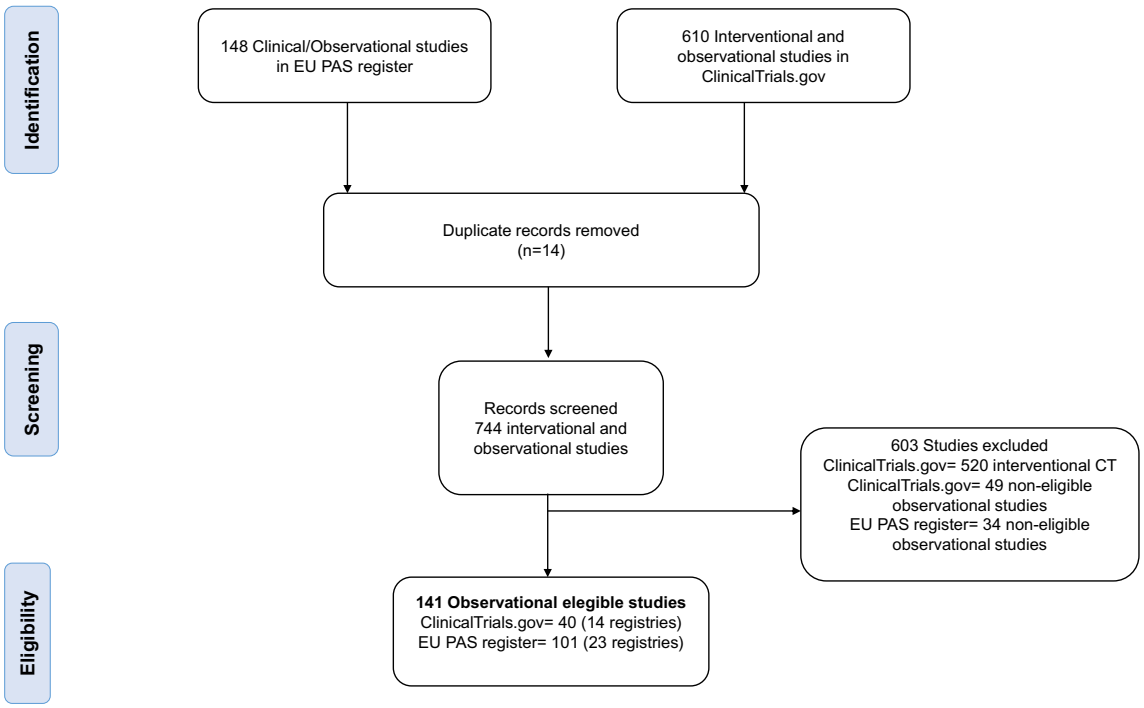

Fig. 1 Flow chart for selection of observational studies involving pregnancy and lactation. *CT* clinical trials, *EU PAS register* European Union Register of Post-Authorization Studies

3 Results

A total of 758 observational and interventional studies were identified that included a pregnant population: 610 studies in ClinicalTrials.gov and 148 studies in the EU PAS register. After the removal of 14 duplicates, 744 studies were left for further screening. A total of 603 studies were excluded Emphasis>as they were not observational, or not eligible for other reasons as shown in the flowchart (Fig. 1). The final number of studies evaluated in detail was 141 (40 from ClinicalTrials.gov and 101 from the EU PAS register).

Pharmaceutical companies were the most frequent study sponsors (76%), followed by health authorities (14%) and academic research institutions (14%) (Table 2). The cohort design was the most frequently applied (80%) followed by

Table 2 Description of the key characteristics of the studies

High-level data group variables	Levels	*N* (%)
Study classification	Observational study	135 (94)
	Review or meta-analysis	4 (3)
Study design	Cohort study	97 (69)
	Analytic studies—other	14 (10)
	Descriptive study	14 (10)
	Case-control study	9 (6)
	Cross-sectional study	5 (4)
	More than one design	3 (2)
	Unknown	1 (1)
Type of data collection	Primary data collection	63 (45)
	Secondary data (MDS)	55 (39)
	Secondary use of health data	13 (9)
	Mixed methods for data collection	7 (5)
	Not applicable	2 (1)
	Unknown	1 (1)
Study period duration	< 1 year	15 (11)
	2–4 years	46 (33)
	5–7 years	26 (18)
	8–10 years	17 (12)
	> 10 years	15 (11)
Study sponsor	Pharmaceutical company	107 (76)
	Heath authority	15 (10)
	Academia	15 (9)
	Other	7 (5)
Period of exposure	Prenatal	100 (71)
	Unknown/NA	31 (22)
	Prenatal and breastfeeding	9 (6)
	Breastfeeding	1 (1)
Gestation period patient enrolled	Unknown	58 (41)
	Anytime during pregnancy course	26 (18)
	Specific time from before LMP until birth	18 (13)
	Another specific period (including after birth)	12 (9)
	First day of LMP until birth	11 (8)
	First trimester	8 (6)
	Third trimester	6 (4)
	Second and third trimesters	1 (1)
	Second trimester	2 (1)
How long child is followed after birth	Not applicable/unknown	79 (56)
	Up to 1 year old	34 (24)
	Up to < 6 months old	10 (7)
	5 years or more	9 (6)
	From 6 months old to < 1 year old	5 (4)
	From 1 year old to < 5 years old	4 (3)
Primary study outcome	General neonatal outcome (including major and/or minor CA)	51 (36)
	Specific neonatal outcome (specific CA)	18 (13)
	General maternal outcome	44 (31)
	Specific maternal outcome	14 (10)
	Long-term/postnatal development outcome	25 (18)
	Unknown/NA	43 (30)

Table 2 (continued)

High-level data group variables	Levels	*N* (%)
Secondary study outcome	General neonatal outcome (including general/major and/or minor CA)	26 (18)
	Specific neonatal outcome (specific CA)	25 (18)
	General maternal outcome	53 (38)
	Specific maternal outcome	18 (13)
	Long-term/postnatal development outcome	12 (8)
	Unknown/NA	48 (68)
Disease specific?[a]	Not specific/unknown	37 (26)
	Influenza/H1N1	10 (7)
	Multiple sclerosis	9 (6)
	Rheumatoid arthritis/arthritis	9 (6)
	Depression	8 (6)
	Type 2 diabetes mellitus	8 (6)
	Asthma	6 (5)
	HIV	5 (4)

Each variable is defined in ESM 1

CA congenital anomaly, *HIV* human immunodeficiency virus transmission, *LMP* last menstrual period, *MDS* multiple data sources

[a]Disease reported 5% or higher

case-control (7%) and cross-sectional (4%). Regarding data collection, 63 studies (45%) were based on primary data collection, 55 studies (39%) were based on secondary use of health data across multiple databases, while single database studies utilizing secondary data made up only 9% of the total eligible studies.

The majority of the studies (71%) were designed to assess the effects of prenatal exposure on pregnancy outcomes and a few studies (around 7%) aimed to assess the effects of medicines use during breastfeeding. We noticed that the most common risk window (18%) is 'anytime during pregnancy'. When data is available, the most common period to follow a child was up to 1 year of age, as shown in Table 2.

A study may have more than one category of outcome, as defined in ESM 1 (e.g., general neonatal outcomes and specific maternal outcome as the primary study endpoint). General neonatal outcomes (including major and minor congenital anomalies [CAs]) were investigated in 36% of the selected studies as the primary study outcome, while general maternal outcome (38%) was the most frequent category in secondary study outcomes. Long-term outcomes in the child defined as any developmental outcomes (e.g., neurodevelopmental disorders) represented 18% and 8% of primary and secondary outcomes, respectively. About a quarter of the studies (26%) did not specify the disease or drug indication of the exposed pregnant women. When it was specified, influenza/H1N1, multiple sclerosis, rheumatoid arthritis/arthritis and depression were the most common disease indication areas (approximately 6%).

A descriptive comparison of studies based on primary data collection and secondary data collection (including studies with secondary use of data across multiple databases [MDS]) is presented in Table 3. Cohort studies are more common in secondary data studies (71%) compared with primary data (63%).

Studies with secondary use of health data included many patients: the most frequent were between 501 and 5000 patients (32%) followed by more than 10,000 patients (31%). In contrast, 19% of studies using primary data collection enrolled < 100 patients as opposed to 7% of the studies with secondary use of data.

Major neonatal outcomes and general maternal outcomes was the most common proposed study outcome category for studies with either primary data collection or secondary use of health data (Table 3).

Ninety-one studies were 'completed'. Survival analysis based on the time between study start and end lasted around 2.9 years as opposed to 7.5 years for duration of studies based on primary data collection (Fig. 2; completed studies with their finding [secondary data (B) × primary data (A)] over time (in days) and p-value < 0.05 long-rank test).

We could assess the impact on the pregnancy section of the product label for 46 studies with final reports or published papers. Nine labels had similar content in the pregnancy section as described in the final report/paper of the observational studies. Table 4 lists results of label updates.

Table 3 Comparison of characteristics between studies based on primary data collection and secondary use of data

Variable	Levels	Primary data collection *N* (%)	Secondary data collection *N* (%)
Study design	Cohort study	40 (63)	48 (71)
	Analytic studies—other	5 (8)	5 (7)
	Case-control study	4 (6)	3 (4)
	Descriptive study	7(11)	5 (7)
	Cross-sectional study	0	4 (6)
	Unknown	3 (5)	0
Patient target enrollment size	> 1	0	2 (3)
	≤ 100	12 (19)	5 (7)
	101–500	22 (35)	8 (12)
	501–5000	19 (30)	22 (32)
	5001–10,000	1 (2)	5 (7)
	> 10,001	2 (3)	21 (31)
	Unknown	1 (2)	6 (9)
Prospective vs retrospective	Prospective	53 (91)	31 (46)
	Retrospective	2 (3)	28 (41)
	Prospective and retrospective	1 (2)	3 (4)
	Unknown	2 (3)	2 (3)
Primary or secondary study outcomes	General/major CA (neonatal)	31 (28)	44 (27)
	Specific CA (neonatal)	15 (13)	19 (14)
	General maternal outcome	21 (19)	43 (32)
	Specific maternal outcome	12 (11)	10 (8)
	Long-term/postnatal development outcome	17 (15)	20 (15)
	Unknown	33 (29)	50 (38)

Each variable is defined in ESM 1

CA Congenital anomalies

4 Discussion

This study presents a landscape analysis of observational studies focusing on pregnancy and breastfeeding as registered in the ENCePP/EU PAS register and ClinicalTrials.gov. We also investigated whether 'completed' studies led to an update of the respective product label.

The key findings of our study are that there is about an equal number of studies that are based on primary data collection and secondary use of health data, but studies based on secondary use of health data were larger and were completed faster than studies based on primary data collection. In spite of the fact that a large number of studies were conducted, and completed, only a very low number of labels were updated based on a respective observational study. This finding is in line with an analysis conducted specifically on studies for multiple sclerosis, which concluded that "prospective, treatment-specific registries" have generally failed to deliver robust information. For this reason, other study approaches, in particular cohort studies using existing healthcare databases, should be considered for evaluating drug safety in pregnancy, including in MS [14]. Moreover, work on breastfeeding was very minimal. None of the labels assessed in this study were updated in the breastfeeding section.

More specific findings included that the period of exposure during pregnancy was not very detailed: 'anytime during pregnancy" was most frequently chosen among the study sponsors. Automated databases often lack the collection of last menstrual period (LMP) data and gestation length, which allows estimation of the due date, approximate conception date, and gestational age at birth [20]. Thus, the study protocols should clearly define the period that women who are enrolled in the observational study are exposed to the drug at the point in gestation with the highest risk of causing congenital fetal effects, which most commonly is the first trimester [3]. Long-term follow-up information with infants is very limited.

The most recent EMA guidelines suggested that long-term pregnancy outcomes might be obtained by combining data from existing registries/databases and studies with primary data collection [6].

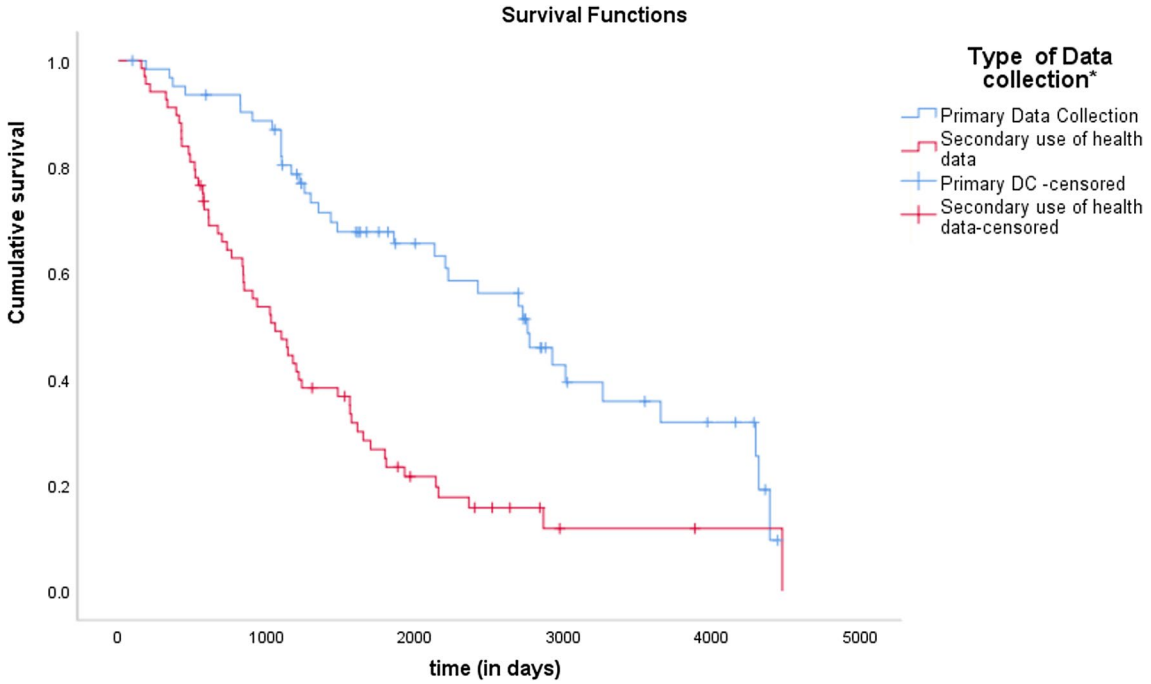

Fig. 2 Completed studies with their finding (secondary use of health data × primary data) over time (in days)

Size matters when studying rare outcomes such as CAs [13]. The desired sample size for the registry will depend on study design, frequency of that particular risk in both comparator group and exposed group as well as exposure frequency in the study population [9]. In general, pregnancy registries often fail to enroll and retain sufficient numbers of exposed pregnancies to detect rare CA [13, 21]. Tomson et al. classified registries that enroll pregnant women exposed to anti-epileptic drugs (AEDs) into categories: national registries, independent academic registries and pharmaceutical company registries [22]. The study highlights that independent academic registries enroll much larger numbers of prospective AED pregnancies compared with other studies [22]. One of the academic registries successfully recruited controls among the friends and family members of enrolled women [22].The two observational studies that impacted their respective product labels (Table 4) enrolled more than 10,000 patients through secondary use (MDS). We consider that a successful observational study should carefully project a realistic enrollment plan linked to study objective, continuous re-assessment of enrollment, and retention methods, in agreement with Sinclair et al. [23].

Another relevant finding of this study is that the studies with primary data collection lasted 5 years longer than studies with secondary data.

As health authorities and pharmaceutical companies agreed that the information from these observational studies was sub-optimal or insufficient, the question is raised whether only few studies generated meaningful evidence or whether the current product label process is ineffective in determining what constitutes adequate information to be included in the product label.

Given the tremendous lack of adequate information to guide pregnant women about the safety of medicines during pregnancy in the product labels, we would expect that study results will be included in such labels. From the 46 'completed' studies, labels were updated for only two products whose study used secondary data collection. The breastfeeding sections of product labels have not been updated as completed studies focused only on prenatal exposure. Most of the labels that were not impacted state that there is either no data or limited data on the use of drugs in pregnant women. Limited data is deemed inadequate to determine an association between a drug and the undesirable neonatal/maternal outcomes. Some of the labels state that there are no sufficiently controlled studies in pregnant women. The lack of power of the study to find a potential association was also observed by Galperin's research [13], which identified only one PER in their review as being properly designed primarily to assess the overall risk of major CA. It is acknowledged that the SPCs require several industry processes to validate their final content, which are ultimately approved by regulatory agencies, becoming an 'official' medicines information source [24]. Arguello et al. also identified that the majority of the SPCs assessed in their research stated there was no clinical experience of the use of the medicine during pregnancy

Table 4 Label impact assessment

EU PAS Register or ClinicalTrials.gov ID	Study design	Data collection type	Patient enrollment size	Medication	Date of final study report	Impact on product label	Sponsor's response or EPAR/EMA report feedback
EUPAS17505	More than one (cohort and cross-sectional study	Mixed (primary and secondary)	> 10,000	Human papillomavirus vaccine	19/12/2014	No	EMA-H-703-II-26-AR report: Section 4.6 updated based on clinical trial data
EUPAS16321	Descriptive study	Secondary data (MDS)	≤ 100	Dolutegravir	29/7/2017	No	This study is not mentioned in EPAR (EMEA/H/C/002753/X/0058/G) which shows other ongoing pregnancy registries
EUPAS13840	Analytic—other	Secondary data	≤ 100	Dolutegravir	9/10/2017	No	This study is not mentioned in EPAR (EMEA/H/C/002753/X/0058/G) which shows other ongoing pregnancy registries
EUPAS8615	Case-control study	Secondary data (MDS)	> 10,000	Lamotrigine	31/7/2007	Yes—indirect impact	Sponsor response summary: These observational EUROCAT studies among other studies were used as part of company signal assessment and then the label was updated
EUPAS8618	Case-control study	Secondary data (MDS)	> 10,000		15/3/2015		
EUPAS2566	Cohort study	Secondary data (MDS)	501–5000	Methotrexate	21/12/2012	Unclear	Label was impacted due an observational study based on the EMA report (EMEA/H/C/PSUSA/00002014/201706). It is unclear which study led to the update of the label
EUPAS12875	More than one (cohort and nested-control study)	Secondary data (MDS)	> 10,000	Oseltamivir	20/1/2017	Yes	EMA/501060/2020 report: section 4.6 of the label was updated to reflect the final study results from non-interventional safety study BV29684, which assessed the safety of oseltamivir exposure in pregnant women
EUPAS3310	Cohort study	Secondary data	501–5000	Human papillomavirus vaccine	17/3/2014	No	EMA report (EMEA/H/C/000721/II/0067) states that the pregnancy info in label was generated during clinical trial—Study HPV-040

EMA European Medicines Agency, *EPAR* European public assessment report, *EU PAS register* European Union Register of Post-Authorization Studies, *MDS* multiple data sources

and more than 60% of the SPCs indicated that excretion of the drug in human milk was unknown [24].

The sponsor should annually report on the number of pregnancies and maternal and infant outcomes from routine and additional pharmacovigilance activities (such as existing PERs and EHR) as part of the risk management plan. This approach combined with enhanced processes to obtain follow-up information on pregnancy case reports could help to overcome the challenges to generate meaningful evidence of the benefit–risk balance of medicines in pregnancy and breastfeeding. Although we used two reviewers to extract information and a structured format for such extractions, our research is limited by the fact that we use information from the EU PAS register and ClinicalTrials.gov. This information contained a significant number of 'unknown' variables, as presented in Tables 2 and 3, and they may not represent what was actually done. Another limitation is the completeness of the EU PAS register and ClinicalTrials.gov forms. Data were extracted mainly from these forms as filled out by the study investigator or sponsor and there is no policy established in the EU PAS register/ClinicalTrias.gov to check whether entry data is accurate. Alongside creating a policy, both databases should consider generating a unique identification number to avoid duplicates of the same study being entered either in the same database or in both the EU PAS register and ClinicalTrials.gov.

5 Conclusions

Our study aimed to review the observational studies involving pregnancy/breastfeeding entered in EU and US databases. It is clear that these studies are very heterogeneous and, especially when based on primary data collection, take a long time to reach the threshold of having adequate data. Despite completed studies having a limited impact on the product labels, we showed that two studies with secondary use of health data led to the respective product labels being updated. The current product label process should facilitate inclusion of new data on safety of medicines during pregnancy and breastfeeding. We also recommend making better use of existing health data across multiple databases. Ongoing consortiums such ConcePTION investigate how the power of health care sources on top of primary data collection can be best harnessed to improve the current information gap in knowledge about safety of medicines in pregnancy and breastfeeding to enhance our understanding of medication use and safety during pregnancy [16].

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Declarations

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Conflict of Interest Leonardo Roque Pereira is an employee of Roche and Deborah Layton is an employee of IQVIA. Nonetheless, this paper only reflects the personal views of the stated authors. The other authors have no conflicts of interest to declare.

Ethical approval Not applicable.

Consent to participate Not applicable.

Availability of data and material (data transparency) Datasets were retrieved from the ENCePP database (EU PAS register) and ClinicalTrials.gov. The assessment of European Summaries of Product Characteristics (SPCs) of corresponding drugs in the Electronic Medicines Compendium (EMC) were retrieved via https://www.medicines.org.uk/emc

Code availability Not applicable.

Consent to Publish Not applicable.

Author contributions The authors contributed to part of the content and/or the entire content of the manuscript, fulfilling the ICMJE authorship criteria. The Author Declaration forms from each author were uploaded to the DS platform. All authors were invited to add their input to the revised manuscript (to address DRSA comments). All authors read and approved the final version.

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