Identification of misclassified pregnancy episodes in women of childbearing potential exposed to drugs with known teratogenic potential in the CPRD GOLD Pregnancy Register

Christopher Lee[1], Silvia Rizzi[1], Ana Luiza Bierrenbach[1], Luis Antunes[1], Niina-Maria Nissinen[1], Olga Rocha[1], Jennifer Campbell[2], Caroline Minassian[3], Susan Hodgson[2], and Anne Broe[1]

[1]IQVIA Solutions UK Ltd
[2]Medicines and Healthcare Products Regulatory Agency
[3]London School of Hygiene & Tropical Medicine International Statistics and Epidemiology Group

October 2, 2023

Letter to the Editor *Pharmacoepidemiology and Drug Safety*

Authors: *Christopher Lee*[1]*, Silvia Rizzi* [1], Ana Luiza Bierrenbach[1], Luis Antunes[1], Niina-Maria Nissinen[1], Olga Rocha[1], Jennifer Campbell[2], Caroline Minassian[3], Susan Hodgson[2], Anne Broe[1]

**Shared first author.*

Affiliations:

1 IQVIA Ltd, 2 Clinical Practice Research Datalink (CPRD), 3 London school of Hygiene and Tropical medicine (LSHTM)

Title:

Identification of misclassified pregnancy episodes in women of childbearing potential exposed to drugs with known teratogenic potential in the CPRD GOLD Pregnancy Register

The Clinical Practice Research Datalink (CPRD) GOLD, based on UK primary care data, is a data source widely used in pharmacoepidemiology studies by regulators, academic researchers, and the life science industry(1). Observational research using real world data plays a crucial role in the understanding of the use of drugs in clinical practice and their impact, for example on pregnant women and their offspring. The potential to assess drug exposures before and during pregnancy as well as pregnancy and neonatal outcomes depends on the identification of pregnancy episodes from clinical events in the maternal data. For this purpose, CPRD and London School of Hygiene and Tropical Medicine (LSHTM) researchers have created a Pregnancy Register using an algorithmic approach (2) which was subsequently further developed for CPRD Aurum (3). A record in the register represents a potential pregnancy episode and includes information on pregnancy start, duration, and outcome (i.e., live birth, stillbirth, or early pregnancy loss) together with further characteristics related to the pregnancy.

Within the Pregnancy Register there are pregnancy episodes where no pregnancy outcome can be identified. Often these pregnancy episodes may be based on a single antenatal code with no information on gestational age. For these pregnancies (as for all pregnancies with unknown outcome), the date of the latest antenatal record in the episode is provided as pregnancy end date, and the pregnancy start date is imputed by

subtracting 28 days from the earliest antenatal record in the episode. The documentation accompanying the Pregnancy Register describes how the pregnancy start and end dates are estimated for each type of pregnancy including those with no outcome (4,5). Campbell et al. outlined a series of potential reasons why pregnancy episodes could have no outcome (i) pregnant women, but outcome not recorded in CPRD GOLD; (ii) pregnant women with ongoing pregnancies at the end of available follow-up; (iii) women not pregnant; (iv) pregnancy records part of other pregnancy episodes (3). Pregnancy episodes with unknown outcomes must therefore be cautiously handled by researchers in pharmacoepidemiology studies, which currently requires access to code lists and full CPRD GOLD data used for current pregnancy data build.

In the framework of the ongoing regulatory focus on the impact of Risk Minimisation Measures (RMMs) and pregnancy prevention programme (PPP) of several known teratogenic drugs, the CPRD GOLD Pregnancy Register has been used to assess the PPP impact in several post-authorisation safety studies (PASS).

A recent publication assessed the impact of the 2018 PPP implementation in five countries and reported a decline in pregnancies exposed to valproate as well as a decline in the risk of falling pregnant while exposed to valproate in all involved countries but the United Kingdom. Results from CPRD GOLD showed an increase from 1.13 to 5.07 exposed pregnancies per 1,000 valproate users in the pre- to post-PPP-implementation period, respectively. Additionally, the risk of women exposed to valproate falling pregnant increased from 1.10 per 1000 users to 6.16 per 1,000 users. All other countries showed a decline in pregnancies in the post implementation period (6).

Similar trends were observed in other ongoing studies, with an unexpectedly high number of pregnancy episodes in the post-implementation period. After careful data investigation and quality checks, it was discovered that pregnancy episodes recorded during the post-implementation period in the CPRD Pregnancy Register shared similar features: 1) unknown outcome of pregnancy and mostly of 28 days duration; and 2) identified based on codes solely used for pregnancy counselling consultations, i.e., 'advice' codes.

The inflated number of pregnancy episodes in the post implementation period were directly linked to pregnancy episodes identified by the CPRD GOLD Pregnancy Register algorithm and included records based on advice consultations with no further records providing evidence of ongoing pregnancy. In particular, records with Read code *67Iu.00 "Advice on risk harm to fetus from maternl medictn dur preg"* and to lesser extend *67It.00 "Advice on risk harm to mother from maternl medictn dur preg"* were frequently used during the post implementation period among women exposed to drugs with known teratogenic potential.

General practitioners are expected to provide advice against pregnancy while exposed to teratogenic drugs, and the use of pregnancy advice codes denotes a positive direction of clinical practice reinforced by the PPP introduced for several drugs with known teratogenic potential. The potential for pregnancy episodes without a recorded outcome to be based on a single pregnancy advice code recorded during a pre-pregnancy discussion with the GP was outlined by Campbell et al. The current CPRD Pregnancy code lists (provided on request) enable researchers to identify which codes have been used to indicate pregnancy events and how these codes are classified in the algorithm.

The current CPRD GOLD and Aurum Pregnancy Register algorithm utilises some advice codes as pregnancy markers. Utilising pregnancies episodes based solely on advice codes could lead to the inclusion of false pregnancies in a study and, subsequently, biased conclusions potentially impacting regulatory decision making. Going forward, CPRD will supply to researchers the relevant pregnancy code list and advice (i.e., Campbell et al., 2022) when releasing the CPRD Pregnancy Register to support informed decision making on inclusion and exclusion of uncertain pregnancy episodes. CPRD will also review whether these advice codes should be excluded from the antenatal code list used to identify pregnancies in the Register. However, it is important to note that similar misclassification could arise from other pregnancies based on other single antenatal codes, and pregnancies with unknown outcomes more generally.

With this letter, we wanted to highlight an example to researchers of the limitations of including all uncertain pregnancy episodes in the CPRD Pregnancy Registers. Correct identification of pregnancies requires careful examination of the codes upon which they are based, and this letter provide detailed context to

enable researchers to correctly identify pregnancies in relation to drug utilisation and drug safety studies. We urge users of the CPRD Pregnancy Registers to consider carefully how they handle pregnancies with unknown outcomes in their studies and the implications of including or excluding these pregnancies on the interpretation of their results.

References

1. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015 Jun;44(3):827–36.

2. Minassian C, Williams R, Meeraus WH, Smeeth L, Campbell OMR, Thomas SL. Methods to generate and validate a Pregnancy Register in the UK Clinical Practice Research Datalink primary care database. Pharmacoepidemiol Drug Saf. 2019 Jul;28(7):923–33.

3. Campbell J, Shepherd H, Welburn S, Barnett R, Oyinlola J, Oues N, et al. Methods to refine and extend a Pregnancy Register in the UK Clinical Practice Research Datalink primary care databases. Pharmacoepidemiology and Drug Safety. 2023;32(6):617–24.

4. CPRD algorithm derived data | CPRD [Internet]. 2023 [cited 2023 Sep 26]. Available from: https://www.cprd.com/cprd-algorithm-derived-data

5. Campbell J, Bhaskaran K, Thomas S, Williams R, McDonald HI, Minassian C. Investigating the optimal handling of uncertain pregnancy episodes in the CPRD GOLD Pregnancy Register: a methodological study using UK primary care data. BMJ Open. 2022 Feb 22;12(2):e055773.

6. Abtahi S, Pajouheshnia R, Durán CE, Riera-Arnau J, Gamba M, Alsina E, et al. Impact of 2018 EU Risk Minimisation Measures and Revised Pregnancy Prevention Programme on Utilisation and Prescribing Trends of Medicinal Products Containing Valproate: An Interrupted Time Series Study. Drug Saf. 2023;46(7):689–702.