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Annex 2 to the Guide on Methodological Standards in Pharmacoepidemiology

Guidance on methods for the evaluation of medicines in pregnancy and breastfeeding

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1. General considerations

Planning a pregnancy may lead to discontinuation of non-essential medicines before conception (Pregnancy as a major determinant for discontinuation of antidepressants: an analysis of data from The Health Improvement Network, J Clin Psychiatry. 2011;72(7):979-85). However, many pregnancies are unplanned, and not all medicine use can be discontinued without harm to the parent and, directly or indirectly, the foetus. Increasing average reproductive age in western societies (Women in the EU are having their first child later - Eurostat) and the growing prevalence of chronic diseases in pregnant populations (Prevalence of maternal chronic diseases during pregnancy - a nationwide population based study from 1989 to 2013, Acta Obstet Gynecol Scand. 2016;95(11):1295-1304) underscore the importance of evidence generation on medicine use in pregnancy. In particular, large, well-conducted studies suggesting 'null' associations are important to ensure availability of treatment options for pregnant people.

Some medicines' bioavailability changes during pregnancy, and some medicines cross the placental barrier (Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review, PLoS Med. 2016;13(11):e1002160). Clinically, decisions regarding medicine safety in pregnancy have to balance

the benefits of treatment for the mother (and, indirectly, for the foetus) against potential risks to the unborn child. There is often uncertainty about these risks because pregnant people rarely participate in pre-authorisation trials. Evidence regarding safety of medicines in pregnancy comes primarily from post-authorisation observational studies and prior to that, from animal studies. Increasingly, post-authorisation studies are relying on routinely collected data from large healthcare or claims databases. For these databases to yield valid results, multidisciplinary expert knowledge and tailored methodological approaches are required (Use of real-world evidence from healthcare utilization data to evaluate drug safety during pregnancy, Pharmacoepidemiol Drug Saf. 2019;28(7):906-22).

Impact of medicine use in pregnancy differs from the impact of use in breastfeeding: use of many teratogenic medicines may be incompatible with motherhood. When a medicine is harmful during breastfeeding, a benefit-risk decision needs to be made regarding whether or not to breastfeed; carefully time the medication intake vis-a-vis breastfeeding the infant; or discontinue it. It is not incompatible with motherhood.

This Annex summarises methodological aspects relevant for study design and interpretation in the evaluation of medicine safety during pregnancy and breastfeeding. Pharmacoepidemiological studies in routinely collected clinical health records and claims data are discussed, as well as aspects relevant to these studies in other data sources. For considerations related to vaccine safety and effectiveness, please refer to Chapter 15.2.1.5. The safety of medicines during breastfeeding is a relatively recent topic and is discussed at the end of this Annex.

2. Study designs and populations

As with any pharmacoepidemiological studies, thoughtful, hypothesis-driven, selection of outcomes is encouraged. In pregnancy research, outcomes of interest may vary by timing of exposure in pregnancy and hence, a good understanding of embryofoetal development is crucial. The basics of reproductive epidemiology and birth outcomes as well as basics of pregnancy-specific pharmacokinetics are covered systematically in the respective textbooks and reviews, see for example the chapter on reproductive epidemiology by Weinberg & Wilcox in *Modern Epidemiology* 4th ed. (T. Lash, T.J. VanderWeele, S. Haneuse, K. Rothman. Wolters Kluwer, 2020). Pregnancy is a unit with implications for health of two or more individuals – mother and child. Reproductive epidemiology studies usually assess a set of pregnancy, maternal, embryo-foetal, birth, and/or neonatal outcomes. Units of observation therefore could be a parent, a pregnancy, an embryo/foetus, and/or a still- or liveborn child. These outcomes are on a continuum, and are dependent on each other. For example, a pregnancy that ends in an early loss typically will not be recognised when evaluating the risk of malformations, or well-controlled disease in the mother may lead to a healthier child. Teratogenic drugs generally produce a specific pattern of abnormalities, or a single malformation during a sensitive period of gestation. To detect a potential teratogen, all types of malformations may need to be assessed initially, bearing in mind not all malformations are immediately diagnosed at birth or even in the first year of life. In addition to malformations, a teratogen may manifest in multiple adverse reproductive outcomes including reduced fertility issues, pregnancy loss. This needs to be considered when choosing pregnancy outcomes to be evaluated in the study design.

To ensure a valid study design that takes adequate account of this continuum of development, ideally, the multidisciplinary study team should include (pharmaco)epidemiologists, biostatisticians, perinatologists/embryologists, reproductive toxicologists, specialists in the maternal disease studied, pharmacokinetics, and in obstetrics and, if longer term neurodevelopmental outcomes are being considered, paediatricians and /or child psychologists/psychiatrists (depending on the outcomes under investigation). The study team needs to be able to determine, for example, during which time in gestation certain birth defects arise, which birth defects occur from interference within the same

embryonic tissue and hence, potentially may be treated as 'one outcome', as well as what the impact of 2nd or 3rd trimester exposures may be on infant growth and development and when in a child's life such impact can be assessed.

Pregnancy research is unique in that, while exposure occurs in the mother and, through the mother, in the child, outcomes can occur at the maternal level (e.g., preeclampsia, urinary tract infection), at the pregnancy level (e.g., instrumental delivery), and at the infant level (e.g., small for gestational age, congenital malformations; one infant can have multiple congenital malformations). One person can contribute several pregnancies to a given study; multi-foetal pregnancies result in more than one neonate. The unit of analysis needs to be specified for each analysis (see Table 1). Strategies to handle the potential mismatch between the number of exposed people and the number of observations that can develop the outcome include conducting analyses at the most granular level (e.g., including twins as separate units), assigning the worst outcome to multi-foetal pregnancies (e.g., if at least one foetus has a malformation, the pregnancy is considered to have resulted in a malformation) and including one pregnancy per person or one foetus per pregnancy.

Family clusters share the environment and parental characteristics (including genes, demographics, lifestyles, medical conditions, etc.) and create the potential for within-family correlation. This violates the independence assumption underlying commonly used statistical models. Problems arising from ignoring the clustering can be large when clustering is substantial (Regression models for clustered binary responses: implications of ignoring the intracluster correlation in an analysis of perinatal mortality in twin gestations, Ann Epidemiol. 2005;15(4):293-301). While selecting one pregnancy or baby per person or family eliminates the correlation, it also reduces study size and excludes potentially relevant information. An alternative is to take the clustering into account in the analyses of the data e.g., by multilevel modelling. On the other hand, family clusters allow controlling for family factors using family-specific methods, such as the sibling design (Regression models for clustered binary responses: implications of ignoring the intracluster correlation in an analysis of perinatal mortality in twin gestations, Ann Epidemiol. 2005;15(4):293-301; On Sibling Designs, Epidemiology 2013;24(3):473–74; What Is the Causal Interpretation of Sibling Comparison Designs?, Epidemiology 2020;31(1):75-81; Sibling-Comparison Designs, Are They Worth the Effort?, Am J Epidemiol. 2021;190(5):738-41).

Epidemiologically and conceptually, an ideal population in a pregnancy study should include individuals at risk for the outcome of interest at the start of eligibility. Thus, ideally, each pregnancy should be followed from pre-conception to end of pregnancy and if possible, live born infants should be followed for an appropriate period after birth to evaluate postnatal outcomes potentially related to prenatal exposure. It is even worth considering a potential impact on the next generation, such as stipulated in the Barker hypothesis, and observed, for example, after exposure *in utero* to environmental endocrine disruptors (Impact of intra-uterine life on future health, Ann Endocrinol (Paris) 2022;83(1):54-58).

For postnatal outcomes from e.g., interference through breastfeeding, the population at risk for adverse events resulting from such interference after birth are liveborn infants. Furthermore, because pregnancy studies deal with parent-foetus dyad, who is at risk, terminology, and possible study designs depend on the outcome of interest but always need to take into consideration the continuum of pregnancy outcomes.

Because it is challenging to capture all conceptuses in medicine safety studies in pregnancy, in practice these studies tend to be either studies of prevalence (the outcome at birth) or, slightly more informative although still with important limitations, cohort studies with left-truncation of data because cohort members are not observed from the start of the at-risk period (The curse of the perinatal epidemiologist: inferring causation amidst selection, Curr Epidemiol Rep. 2018;5(4):379-87). This implies that, with few exceptions of e.g., studies enrolling people trying to conceive (A successful

implementation of e-epidemiology: the Danish pregnancy planning study 'Snart-Gravid', Eur J Epidemiol. 2010;25(5):297-304), studies of birth and pregnancy outcomes are cross-sectional studies, or prevalence studies (Effect measures in prevalence studies, Environ Health Perspect. 2004;112(10):1047-50), despite being commonly referred to as cohort studies in publications (Risk of adverse fetal outcomes following administration of a pandemic influenza A(H1N1) vaccine during pregnancy, JAMA 2012;308(2):165-74; Pregabalin use early in pregnancy and the risk of major congenital malformations, Neurology 2017;88(21):2020-25). As a consequence, such studies estimate prevalence as the measure of occurrence and prevalence ratios and differences as measures of effect.

Attempts have been made to study pregnancy loss using the nested case-control design with risk-set sampling by taking the case series of e.g., spontaneous abortions and sampling controls from the reconstructed set of identifiable pregnancies that are ongoing on the case occurrence (index) date (Danish group reanalyses miscarriage in NSAID users, BMJ. 2004;328(7431):109). Such design requires information on pregnancy start date for all pregnancies. In these designs, it can be challenging to ensure controls are selected from the same population as that which gave rise to the cases, if not all conceptuses are identified and, for example, only pregnancies with a recorded pregnancy outcome are available in the database. If this is not done successfully, then the control population will come from a survivors' cohort, leading to biased risk estimates of the exposure being evaluated.

Attempts have been made to examine spontaneous abortion in a cohort design with time-to-event analysis (Oseltamivir in pregnancy and birth outcomes, BMC Infect Dis. 2018;18(1):519). However, because most studies cannot identify all conceptuses at risk and must rely on clinically recognised pregnancies, this has its limitations. Only when outcomes in neonates are of interest that result from interference in the postnatal period, can a true cohort design be used, with liveborn infants as the population at risk, provided they are captured at birth. A study of postnatal outcome that captures the subjects at the follow-up end is still a prevalence study (e.g., a study of Prenatal exposure to systemic antibacterials and overweight and obesity in Danish schoolchildren: a prevalence study, Int J Obes (Lond) 2015;39(10):1450-5).

3. Measuring medicine exposure in pregnancy

Measuring exposure and defining exposure categories as applied to pregnancy studies are similar to other pharmacoepidemiological research, including challenges of identifying over-the-counter medicine use (Medication use in pregnancy: a cross-sectional, multinational web-based study, BMJ Open 2014;4(2):e004365), defining chronic vs. occasional use (Longitudinal Methods for Modeling Exposures in Pharmacoepidemiologic Studies in Pregnancy, Epidemiol Rev. 2022;43(1):130-46) and misclassification of exposure resulting from non-adherence. However, unlike in other types of pharmacoepidemiological studies, it is not always obvious whether medicines from the same pharmacological group can be aggregated in the analysis. For studying the impact of medicine use in pregnancy, accurate exposure measurement during embryo-foetal development , i.e., the respective risk window during the pregnancy is crucial, entailing accurate measures of both pregnancy start and medicine use.

4. Measuring maternal, pregnancy, and neonatal outcomes

4.1. Different frequency of outcomes over gestational age

The frequency of many adverse pregnancy events has substantial variation over the course of pregnancy (Causal inference in studies of preterm babies: a simulation study, BJOG 2018;125(6):686-92; Two denominators for one numerator: the example of neonatal mortality, Eur J Epidemiol.

2018;33(6):523-30). For example, induced and spontaneous abortions are more frequent in early pregnancy (Incidence of early loss of pregnancy, N Engl J Med. 1988;319(4):189-94; Abortion Surveillance - United States, 2019, MMWR Surveill Summ. 2021;70(9):1-29) and stillbirths have a U-shaped distribution over gestational age later in pregnancy. Fair comparisons, in this sense, are comparisons of pregnancies at the same gestational age. This might require analysing data at various points in pregnancy (e.g., assessing the risk for foetal death by gestational week or month) in cohort studies, ensuring this is done independently of, i.e., blind to, events occurring after the index date (The fetuses-at-risk approach: survival analysis from a fetal perspective, Acta Obstet Gynecol Scand. 2018;97(4):454-65).

4.2. Safety outcomes

In observational pregnancy studies, safety outcomes are most commonly of interest. There is a set of birth and pregnancy outcomes that can be assessed, with the considerations, as above, regarding study designs, unit of observations and populations at risk.

Major congenital malformations (MCM) are often of interest. Those are often defined using the EUROCAT Methodology (Guidelines for data registration | EU RD Platform (europa.eu)). With respect to congenital malformations, it is important to acknowledge that the outcome "*Any major congenital malformation*" has its limitations as a single outcome because it is a composite, heterogeneous outcome. It is of limited use when studying medicine teratogenicity, especially for uncommon malformations and may lead to a 'false sense of security', just like there is limited rationale for aggregating all types of cancer, or all types of central nervous system disorders: any risk estimate will be biased towards the null; because of the mechanism of action of teratogens, not all organs will be affected equally. Nonetheless, because prevalence of specific birth defects identified at birth is low (e.g., spina bifida occurs at around 1:2,500 live births), and prevalence of medicine use in pregnancy is also relatively low, studies often aggregate all MCMs. Multinational studies should be used to enable adequate precision and proper causal inference based on biological mechanisms and specificity, as rarely is a medicine expected to increase the risk of all MCMs. According to the EUROCAT methodology, ascertainment of congenital malformations occurs at birth and through the first year of life and beyond, as a result of delayed detection and reporting, although of course by definition all MCMs are present at birth.

Birth outcomes typically refer to short-term (close to birth date) outcomes of a given birth relevant to the child, whereby different neonates from a multi-foetal pregnancy may be discordant with respect to the birth outcome status. Maternal outcomes typically refer to outcomes during pregnancy that affect maternal health, such as preeclampsia or diabetes. In routinely collected data, a spontaneous abortion may be recorded as a maternal diagnosis, while a stillbirth as a child's event, whereas they both represent spontaneous pregnancy loss, defined, somewhat arbitrarily, by the gestational age at pregnancy end (Estimating the proportion of all observed birth defects occurring in pregnancies terminated by a second-trimester abortion, Epidemiology. 2014;25(6):866-71).

Table 1 summarises most common safety outcomes assessed in pregnancy pharmacoepidemiological studies, with relevant populations, study designs and suggested terminology. Definitions of gestational age, pregnancy trimesters, pregnancy loss and other pregnancy outcomes vary, sometimes as a result of differences in data availability. The Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations III: Pregnant and breastfeeding people includes a more comprehensive list of pregnancy-related terminologies used in pharmacoepidemiological studies of this type.

Table 1. Summary of study populations, corresponding designs, measures of occurrence, and terminology

Outcome type	Outcome	Unit of observation	Typical study design if start of pregnancy is known (unless pregnancy planners are enrolled)	Measure of occurrence	Exposure terminology
Pregnancy or maternal	Pregnancy loss: spontaneous abortion	Pregnancy	cross-sectional, case-control (see text)	Prevalence, risk, odds ratio	Exposure during pregnancy
Pregnancy, maternal, birth	Pregnancy loss: stillbirth	Pregnancy or neonate	cross-sectional	Prevalence, risk	Prenatal exposure/in-utero exposure/maternal exposure
Pregnancy or maternal	Pregnancy loss: induced abortion for any reason	Pregnancy	cross-sectional, case-control (see text)	Prevalence, risk, odds ratio	Exposure during pregnancy
Pregnancy or maternal	Pregnancy loss: Termination of Pregnancy due to Foetal Anomaly (TOPFA)	Pregnancy	cross-sectional	Prevalence, risk	Exposure during pregnancy
Birth	Preterm birth	Neonate (multiplets contribute with own outcome multiple times)	cross-sectional	Prevalence, risk	Prenatal exposure/in-utero exposure
Pregnancy or maternal	Pregnancy-associated disorders such as pre-eclampsia, gestational diabetes	Pregnancy	cross-sectional, case-control (see text)	Prevalence, risk, odds ratio	Maternal exposure / exposure during pregnancy
Pregnancy or maternal	Placenta previa	Pregnancy	cross-sectional, case-control (see text)	Prevalence, risk, odds ratio	Maternal exposure / exposure during pregnancy
Pregnancy	Ectopic/molar pregnancy	Pregnancy	cross-sectional, case-control (see text)	Prevalence	Maternal exposure / exposure during pregnancy

Outcome type	Outcome	Unit of observation	Typical study design if start of pregnancy is known (unless pregnancy planners are enrolled)	Measure of occurrence	Exposure terminology
Birth	Low birth weight	Neonate (multiplets contribute with own outcome multiple times)	cross-sectional	Prevalence	Prenatal exposure/in-utero exposure
Pregnancy	Low birth weight	Pregnancy with at least one qualifying foetus contributes once	cross-sectional	Prevalence	Prenatal exposure/in-utero exposure
Pregnancy or maternal	Vaginal bleeding	Pregnancy	cross-sectional	Prevalence, risk	Prenatal exposure/in-utero exposure/maternal exposure
Maternal	Maternal death	Parent	Cohort	Risk, rate	Exposure during pregnancy
Birth	Congenital malformations	Neonate (multiplets contribute with own outcome multiple times)	cross-sectional	Prevalence, risk	Prenatal exposure/in-utero exposure
Postnatal	Postnatal outcomes (e.g., learning disability, obesity)	Live-born child	Cohort or cross-sectional (see text)	Prevalence (if exposure studied is prenatal) and rate / rate ratio / risk ratio if the exposure studied occurred postnatally	Prenatal exposure/in-utero exposure/maternal exposure

4.3. Effectiveness outcomes

As with other pharmacoepidemiological research, demonstrating effectiveness in an observational study design when it comes to medicine use in pregnancy and breastfeeding is challenging because treatment allocation is not random and the indication for prescribing is often correlated with the pregnancy outcomes of interest. However, some observational studies in this area have led to randomised controlled clinical trials to confirm or refute whether observed associations of effect were causal. Examples include folic acid, which was confirmed to reduce the risk of spina bifida, and sildenafil, for which the suggestion of a reduced risk of intra-uterine growth restriction was refuted. Observational studies that confirmed harm for example of pregnancy loss following influenza infection or of lower viral load in the neonate following HIV treatments in the mother have led to clinical guidelines recommending vaccination (flu) or treatment (HIV) in pregnancy. Following this as well as the experience with COVID-19, increasingly there is a recognition that effectiveness studies in pregnancy may be required.

5. Common confounders and biases in pregnancy studies

5.1. Family history and confounding by indication

Family history and confounding by indication are important sources of bias in drug safety studies in pregnancy (Core concepts in pharmacoepidemiology: Confounding by indication and the role of active comparators, Pharmacoepidemiol Drug Saf. 2022;31(3):261-69; see also Chapter 5.2). Family history is often not present in electronic health records, and it tends to be recorded selectively once a child with a malformation is born.

To avoid or at least minimise confounding by indication, indication and severity of the underlying disease need to be taken into account. As an example, in studies of Antidepressant use in pregnancy and the risk of cardiac defects (N Engl J Med. 2014;370(25):2397-407), in contrast to previous studies, no substantial increase in the risk of cardiac malformations attributable to antidepressant use during the first trimester was observed, when the cohort was restricted to people with depression, and propensity-score adjustment was used to control for depression severity and other potential confounders. However, often it is difficult to account for severity of underlying diseases as this information is not available in the dataset.

Systematic differences between treated and untreated are usually more severe in pregnant than in non-pregnant populations, which might lead to an overestimation of the risk even if standard methods to address confounding by indication are used. Thus, the impact of potential confounding (by indication) can be assessed, e.g., by triangulation (Triangulation in aetiological epidemiology, Int J Epidemiol. 2016;45(6):1866-1886; Prenatal Antidepressant Exposure and the Risk of Attention-deficit/Hyperactivity Disorder in Childhood: A Cohort Study With Triangulation, Epidemiology 2022;33(4):581-92; Chapter 5.4). By comparison of the results from each approach, the researchers may be able to disentangle sources of bias due to potential confounding, use of sibling designs (Evaluation of nature-nurture impact on reproductive health using half-siblings, Epidemiology 1997;8(1):6-11) or negative controls (Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring, JAMA. 2017;317(15):1553-62). Triangulation may be especially important in perinatal pharmacoepidemiology because of increased uncertainty regarding severity and impact of confounding by indication in any given study.

5.2. Left truncation

Left-truncation refers to the situation in which data preceding the outcome of interest are not available at the time of the measurement (Conditions for bias from differential left truncation, Am J Epidemiol. 2007;165(4):444-52). Left truncation in studies that evaluate medicines in pregnancy also plays a role when early pregnancy outcomes are not captured and therefore the fact that a pregnancy existed is not known; this leads to immortal time bias as elaborated on in the next paragraph. Left truncation results in inadequate exposure assessment but because of the continuum of outcomes in pregnancy research, it can also result in the incomplete capture of study endpoints. It will result in distorted measures of association, for example when comparing people who enrol in a pregnancy registry in early pregnancy with people who enrol later (Effects of gestational age at enrollment in pregnancy exposure registries, Pharmacoepidemiol Drug Saf. 2015;24(4):343-52).

5.3. Immortal time bias

Linked to the left-truncation of data, which is so common in drug safety in pregnancy studies, immortal time bias occurs when not all eligible person-time contributes to the analysis, and only person-time of those who 'survived' an initial phase is included (see Chapter 5.1.3). As in other areas of pharmacoepidemiology, this may lead to a spurious suggestion of a protective effect of the exposure under study.

Not all pregnancies end in a delivery of a live born infant (Educational note: addressing special cases of bias that frequently occur in perinatal epidemiology, Int J Epidemiol. 2021;50(1):337-45). Pregnancies ending in early losses and terminations are often missed in routine healthcare data and they are routinely excluded from birth registries. Many studies therefore focus on live births (i.e., they condition on survival). Estimating the proportion of all observed birth defects occurring in pregnancies terminated by a second-trimester abortion (Epidemiology. 2014;25(6):866-71) shows that the proportion of terminated pregnancies carrying birth defects is considerably greater than the corresponding proportion for pregnancies that end as live- or stillbirths, where the proportion of terminations depends on the severity of the malformations. Thus, studies including only live births are likely to underestimate the risk of congenital malformations and early adverse pregnancy outcomes, as shown in Bias toward the null hypothesis in pregnancy drug studies that do not include data on medical terminations of pregnancy: the folic acid antagonists (J Clin Pharmacol. 2012;52(1):78-83). Methodologically, this selection bias represents conditioning on the common effect of the exposure and outcomes if exposure determines both the occurrence of the outcome of interest and survival until observable birth (A structural approach to selection bias, Epidemiology. 2004;15(5):615-25).

As the probability of exposure increases the longer a pregnancy lasts, shorter pregnancies will more likely be classified as unexposed. Spontaneous abortions, terminations, and outcomes associated with shorter gestational age are overrepresented in the unexposed and risk of exposure is underestimated and might even seem protective. Some have attempted to prevent such bias by defining exposure only from the time of exposure during follow-up onward using a time-varying exposure analysis (Immortal time bias in drug safety cohort studies: spontaneous abortion following nonsteroidal antiinflammatory drug exposure, Am J Obstet Gynecol. 2015;212(3):307.e1-6) but given the challenges in identifying reliably the index date, and given the matter of competing endpoints, this needs further methodological consideration. Linked to this, exposure ascertainment clearly needs to stop once the at-risk period for the outcome ends, because the remainder of the subsequent time is no longer 'at risk'. For example, if spontaneous abortions are defined as foetal losses that occur up to week 20, all later time is not considered to be time 'at risk' for this outcome and exposure ascertainment should stop at that time.

5.4. Information bias

Sensitive exposure periods are usually short, and misclassification of exposure might result in considerable information bias (see Chapter 5.1). Based on prescription data, it is not possible to assess whether people started using the medicine at the dispensing date or later, discontinued treatment early once they knew they were pregnant, or took the medicine at all. Inclusion of all people with a respective dispensing overlapping the sensitive exposure period will increase sensitivity and sample size but might dilute effects due to low specificity.

Likewise, misclassification of outcome will also result in information bias. To address this, hypothesis driven collection of data on all relevant outcomes along the continuum of potential pregnancy outcomes is required. For longer-term outcomes such as child health or neurodevelopment, adequate duration of follow-up is needed. For example, to be accurate the age of the cohort needs to have passed the average age of diagnosis for a particular condition (or appropriate statistical methodologies employed).

Sensitivity analyses should be conducted to assess the effect of potential misclassification. Such sensitivity analyses may be informed by supplementary information from surveys or interviews of a subset of the study population, for example on treatment adherence (Associations between socio-economic factors and the use of prescription medication during pregnancy: a population-based study among 19,874 Danish women, Eur J Clin Pharmacol. 2006;62(7):547-53).

6. Identification of pregnancies

6.1. Routinely collected data

A person typically learns that they are pregnant from a pharmacy-bought home pregnancy test. This sets in motion pregnancy-specific care, some elements of which (e.g., prenatal screening, antenatal visits, obstetric ultrasounds, child health visits) are routinely recorded in some databases. In western countries, delivery generally occurs at a hospital, and databases typically capture certain details of delivery, including mode of delivery, gestational age and birth weight, child's sex, or admission to neonatal intensive care unit. Birth registries (such as The Nordic medical birth registers--a potential goldmine for clinical research, Acta Obstet Gynecol Scand. 2014;93(2):132-7) usually capture all live births and stillbirths after a certain gestational age (e.g., 22 weeks).

In pharmacoepidemiological research, pregnancies are identified in databases using these elements. As birth registries are considered reliable data sources for live births, studies in data sources that can be linked with birth registries often rely on them to identify pregnancies; information on the last menstruation period (LMP) and duration of gestation is obtained from the birth registry. In other databases, records on pregnancy loss, antenatal visits, deliveries and other end-of-pregnancy events are used to identify pregnancies; earlier pregnancy-related records are used to estimate the LMP or duration of gestation (Inferring pregnancy episodes and outcomes within a network of observational databases, PLoS One. 2018;13(2):e0192033; Development of an algorithm to identify pregnancy episodes in an integrated health care delivery system, Health Serv Res. 2007;42(2):908-27; Estimating the Beginning of Pregnancy in German Claims Data: Development of an Algorithm With a Focus on the Expected Delivery Date, Front Public Health. 2020;8:350; Repository of the script of the ConcePTION Algorithm for Pregnancies, ARS Toscana; COVID-19 infection and medicines in pregnancy – a multinational registry based study. Medication use in pregnant women with COVID-19: an interim report, Hurley E. et al. 2021; Zenodo 5775644). For example, the IMI ConcepTION algorithm uses all pregnancy-related records to identify pregnancies, giving precedence to those coming from birth registries and EUROCAT data tables. Another algorithm prospectively identifies codes for gestational

age using the US-specific ICD-10-CM coding system in US health claims (Identification of pregnancies and infants within a US commercial healthcare administrative claims database, Pharmacoepidemiol Drug Saf. 2022 May 27). The algorithm used in UK CPRD's Pregnancy Registers identifies pregnancies through pregnancy outcomes, but also identifies potential pregnancy episodes with unknown outcomes (Methods to generate and validate a Pregnancy Register in the UK Clinical Practice Research Datalink primary care database, Pharmacoepidemiol Drug Saf. 2019;28(7):923-33; 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;12(2):e055773). In German claims data, it is possible to code the expected delivery date, which can be used to estimate the onset of pregnancy (Estimating the Beginning of Pregnancy in German Claims Data: Development of an Algorithm With a Focus on the Expected Delivery Date, Front Public Health. 2020;8:350) and to identify ongoing pregnancies and pregnancies with unknown outcome. In French claims data, an algorithm has been developed to identify and categorise pregnancy outcomes (live births, stillbirths, elective abortions, therapeutic abortions, spontaneous abortions, and ectopic pregnancies) as well as estimated pregnancy start dates, based on discharge diagnoses and medical procedures (Development of an algorithm to identify pregnancy episodes and related outcomes in health care claims databases: An application to antiepileptic drug use in 4.9 million pregnant women in France, Pharmacoepidemiol Drug Saf. 2018;27(7):763-70). While studies that focus on end-of-pregnancy events require pregnancies to be completed, drug utilisation studies, studies that assess the occurrence of pregnancy and studies that assess the prevalence of health conditions in pregnancy can benefit from the identification of ongoing pregnancies and pregnancies with unknown outcome (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;12(2):e055773). In German claims data, it is possible to code the expected delivery date, which can be used to estimate the onset of pregnancy (Estimating the Beginning of Pregnancy in German Claims Data: Development of an Algorithm With a Focus on the Expected Delivery Date, Front Public Health 2020;8:350) and to identify ongoing pregnancies and pregnancies with unknown outcome. In French claims data, an algorithm has been developed to identified and categorise pregnancy outcomes (live births, stillbirths, elective abortions, therapeutic abortions, spontaneous abortions, and ectopic pregnancies) as well as estimated pregnancy start dates, based on discharge diagnoses and medical procedures (Development of an algorithm to identify pregnancy episodes and related outcomes in health care claims databases: An application to antiepileptic drug use in 4.9 million pregnant women in France, Pharmacoepidemiol Drug Saf. 2018;27(7):763-70). While studies that focus on end-of-pregnancy events require pregnancies to be completed, drug utilisation studies, studies that assess the occurrence of pregnancy and studies that assess the prevalence of health conditions in pregnancy can benefit from the identification of ongoing pregnancies and pregnancies with unknown outcome.

Identification of pregnancies in a database might be facilitated by use of a common data model, such as the ConcePTION (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(1):321-31), OMOP (Inferring pregnancy episodes and outcomes within a network of observational databases, PLoS One. 2018;13(2):e0192033) and Sentinel (Surveillance of Medication Use During Pregnancy in the Mini-Sentinel Program, Matern Child Health J. 2016;20(4):895-903) common data models. Information on the availability of pregnancies to answer a pregnancy-related research question across data sources can be facilitated through the use of catalogues like those proposed or developed for ConcePTION (Technical workshop on real-world metadata for regulatory purposes, European medicines Agency, 2021; Test report for FAIR data catalogue (1st) (D7.9), 2021, Zenodo 5829453)

Measuring exposure to medicines during breastfeeding remains a challenge in studies based on routinely collected health data.

6.2. Pregnancy registries

Product-specific or multiproduct pregnancy registries are among the most common surveillance methods for evaluating the impact of medicines in pregnancy; there are also disease specific registries that enable such studies (see Chapter 7.3.6). The advantage of disease-specific pregnancy registries over product-specific registries is similar to other areas of pharmacoepidemiology: they include comparator groups and the impact of the disease itself can be evaluated as well as the impact of medicine use (always bearing in mind confounding by indication). Product-specific registries tend to take a long time before generating information regarding the pregnancy outcomes of interest, often not all conceptuses are captured, and pregnancies with exposures to more than one product tend to be excluded. Considerations regarding pregnancy registries are provided in GVP Product population specific considerations III: Pregnant and breastfeeding women, Section P.III.B.4.2.1.

6.3. Teratology Information Services (TIS)

According to the European Network of Teratology Information Services (ENTIS, https://www.entis-org.eu), the "*main task of each TIS is to recognize and to detect risk factors with the objective of preventing birth defects. To execute this task each TIS counsels individual cases with exposure to drugs and other exogenous agents during pregnancy with respect to the risk of reproductive toxicity. The information provided is based on current scientific data, which is collected and analysed by each TIS staff.*" Notably, data collected by TIS through this counselling function is not the same as formal epidemiological research on medicine safety on population level and hence, some studies based on TIS data may overestimate the drug-malformation association. For example, a TIS-based study reported a 3-fold increased risk of any major malformation associated with prenatal exposure to pregabalin (Pregnancy outcome following maternal exposure to pregabalin may call for concern, Neurology 2016;86(24):2251-7), an association that was not corroborated in a large population-based study (Pregabalin use early in pregnancy and the risk of major congenital malformations, Neurology 2017;88(21):2020-25).

6.4. Research question(s) and fit-for-purpose data sources

When studying the safety of medicines in pregnancy and/or breastfeeding, the same principles apply as in other pharmacoepidemiological studies: exposure needs to occur before the outcome, exposure and outcome must be determined with adequate precision, sample size must be such as to ensure low likelihood of Type I and Type II errors, relevant effect modifiers and confounders – including confounding by indication - must be taken into consideration, and so on. In principle, therefore, the selection of data sources is based on the same principles as in other studies. All the following aspects require special consideration over and above these principles, when it comes to pregnancy studies:

- The ability to establish which child was born to which mother (including the ability to distinguish potential mothers within the same household);
- The duration of follow-up in the child and the ability to evaluate health and (neuro)developmental outcomes in the child;
- Study size/precision considerations, given the need to evaluate single, or small groups of, birth defects rather than all MCMs aggregated (Planning Study Size Based on Precision Rather Than Power, Epidemiology 2018;29(5):599-603).

More often than in other areas of pharmacoepidemiology does this result in considerable added value of multi-database studies that combine different data sources, such as the EUROMEDICAT studies (combining EUROCAT data with dispensing data) and of meta-analyses in which data sources from more than one country are combined.

7. Multinational studies

The general themes on multinational studies are discussed in Chapter 8, Research networks for multi-database studies. Multi-database studies enable study of rare exposures and outcomes (Ability of Primary Care Health Databases to Assess Medicinal Products Discussed by the European Union Pharmacovigilance Risk Assessment Committee, Clin Pharmacol Ther. 2020;107(4):957-65) and often use common data models (CDM). When choosing a CDM, main elements to consider are (i) the adaptability to a specific question; (ii) transparency to reproduce findings, assess validity, and instil confidence in findings; and (iii) ease and speed of use (Choosing Among Common Data Models for Real-World Data Analyses Fit for Making Decisions About the Effectiveness of Medical Products, Clin Pharmacol Ther. 2020;107(4):827-33). Element (i) is crucial to consider when selecting a CDM suitable for use in pregnancy and breastfeeding studies. Some key elements are needed to enable an untruncated assessment of the benefit or the risk of a drug of interest. As in all pharmacoepidemiological studies, the CDM must allow adequate capture of drug exposure and relevant outcomes. The need to observe the potential effect of a drug taken by a mother on her child implies that the CDM must be able to adequately represent mother-child linkage. Moreover, the CDM should also allow for the storage of additional information about pregnancy, breastfeeding or birth – e.g., gestational age, delivery data or birthweight – as these can be key covariates in analyses (Metadata-driven creation of data marts from an EAV-modeled clinical research database, Int J Med Inform. 2002;65(3):225-41). The Observational and Medical Outcomes Partnerships (OMOP) CDM and the ConcePTION CDM are two 'person-centric' CDMs increasingly used in the European data landscape that fulfil the previously enumerated prerequisites. The OMOP CDM is maintained by the Observational Health Data Sciences and Informatics (OHDSI) community. The OMOP CDM implies a syntactic and a semantic harmonisation. The ConcePTION CDM (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(1):321-31) relies on relies on syntactic harmonisation and flexible study-specific semantic harmonisation.

Large well-conducted population-based multinational studies are thus important to generate meaningful evidence of medicine safety in pregnancy and breastfeeding, also given the relative low prevalence of most exposures and outcomes. When combining results from different databases in multinational studies, conventional meta-analyses may not perform adequately if the number of cases in some strata is zero, as those would be removed from meta-analyses, potentially making a safe medicine appear unsafe. Alternative methods include pooling data using Mantel-Haenszel approach or individual-level data pooling, if permissible from a data protection perspective (A Population-based Study of the Safety of Gabapentin Use During Pregnancy, EUPAS 38620; Individual-based versus aggregate meta-analysis in multi-database studies of pregnancy outcomes: the Nordic example of selective serotonin reuptake inhibitors and venlafaxine in pregnancy, Pharmacoepidemiol Drug Saf. 2016;25(10):1160-69).

8. Reporting considerations

Checklists are helpful to promote that researchers give thought to each key element or step for that activity. The ENCePP Checklist for Study Protocols has been included in the ENCePP Code of Conduct since the first version of the Code of Conduct was issued in 2010. Pharmacoepidemiological studies related to the evaluation of medicines used in pregnancy need to heed all the elements listed in the ENCePP Checklist for Study Protocols. Another checklist, similar in structure to the ENCePP Checklist, is proposed in Perinatal pharmacoepidemiology: How often are key methodological elements reported in publications? (Pharmacoepidemiol Drug Saf. 2022;31(1):61-71), which also lists the following additional specific elements to be included in study protocols and reports:

- Source of information on the beginning and end of pregnancy (to inform about the accuracy of any estimated timing of exposure relative to the outcomes critical windows);
- Whether the study population includes multi-foetal pregnancies (to inform whether one pregnancy exposure can result in outcomes in more than one baby, and on potentially increased risks for some outcomes);
- More than one pregnancy per person (to inform on potential intrafamily correlation);
- Non-live births or neonates with chromosomal abnormalities;
- Major or minor malformations (to inform on the increased risk for some outcomes and potential for recall bias in self-reported exposures and to be explicit on outcome definitions);
- Methods and success in matching mother and baby records or records for other family members (to inform on impact on study size and potential risk for selection bias);
- Whether maternal or infant records are used as sources of information (to inform on potential under-ascertainment of some outcomes, for example because of insufficient duration of follow-up in the child);
- The unit of analysis (to clarify what the denominator is and inform on potential for correlation when one maternal exposure can result in more than one offspring outcome count);
- The gestational age at start of follow-up (to inform on left truncation and immortal-time bias) and whether intrafamily correlation is considered.

Finally, given the sensitivity of the topic, when communicating study conclusions, extra care needs to be taken to consider the target user population. In the past, 'false alarms' have led to unnecessary pregnancy terminations and studies with insufficient power have provided unfounded suggestions of safety. For other considerations on reporting, see Chapter 13, Dissemination and communication of study results.

9. Breastfeeding

For most medicines commonly used in the postnatal period, the benefits of breastfeeding for the mother and child are thought to outweigh the risks to the infant from medicine exposure through breast milk. However, to provide evidence based clinical guidelines and informative drug labels especially on the less commonly used medicines, studies assessing medicine safety in breastfed infants and human lactation studies are warranted. Passage from human blood to breastmilk is generally based on principles of passive diffusion through lipid membranes and will therefore follow a gradient from a high to a low concentration of free, unbound drug. The plasma to milk transfer depends on the pharmacokinetic (PK) properties of the substance: The drugs that most easily diffuse into mother's milk have a high concentration in maternal plasma, are fat-soluble, have a relatively low molecule weight (< 500) and a relatively low degree of protein binding in the plasma. In addition to the amount in breast milk, factors like drug toxicity and dosage, duration of treatment, as well as the infant's age, amount of breastmilk ingested per day and the infant's health condition need to be considered. Newborns, and premature infants in particular, have an immature liver and kidney function and thus eliminate many drugs at a considerably slower rate than older children and adults. Thus, there will be a risk of accumulation in the infant if the amount ingested though breast milk over time is larger than the infant's capacity for metabolising and excreting the medicine. Most drugs are transferred to breast milk in amounts well below a level to exert any pharmacological effect on the infant (Drugs and Lactation Database (LactMed), Bethesda (MD): National Library of Medicine (US); 2006; Drug use and breastfeeding, Tidsskr Nor Laegeforen. 2012;132(9):1089-93). To study outcomes for exposure through breastfeeding, information on child health and neurodevelopmental outcomes in the child will need to be evaluated.

At the time of marketing authorisation, most medicines will have no data on breastfeeding, impacting the wording in the label (Guideline on Risk Assessment of Medicinal Products on Human Reproduction

and Lactation: from Data to Labelling, European Medicines Agency, 2008). A review of the labels of 213 FDA-approved medicines in 2003-2012 found that there were no data on breastfeeding in 48% of labels, animal data was available in 43% of labels, whereas human breastmilk data was available in less than 5% of the labels (Trends in pregnancy labeling and data quality for US-approved pharmaceuticals, Am J Obstet Gynecol. 2014;211(6):690.e1-11). The situation in Europe is no different.

Historically, surveillance of spontaneous reports and published case reports/case series has been the main pharmacovigilance activity to assess medicine safety during breastfeeding. Fortunately, at an overall level, adverse drug reactions (ADRs) in breastfed infants are rare and usually mild (Adverse drug reactions in breastfed infants: less than imagined, Clin Pediatr (Phila). 2003;42(4):325-40; Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication, Am J Obstet Gynecol. 1993;168(5):1393-9). Sedation, irritability, gastro-intestinal events are reported most often, with medicines acting on the central nervous system accounting for approximately half of all published suspected ADRs among breastfed infants. In approximately 80% of reported cases, the ADRs appeared in infants less than 2 months of age (Adverse drug reactions in breastfed infants: less than imagined, Clin Pediatr (Phila). 2003;42(4):325-40; Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication, Am J Obstet Gynecol. 1993;168(5):1393-9). Published case reports of possible ADRs in breastfed infants, however, often have severe methodological limitations impairing causal inference. It is often not possible to distinguish potential drug effects from the infant's normal state or from concurrent disease. Moreover, results are often confounded by *in utero* exposure. Nevertheless, case series can be valuable if performed and reported properly. When an adverse reaction is suspected in a breastfed infant, having a blood sample from the breastfed infant will improve the causality assessment.

So far, post-authorisation safety studies in breastfed children are rare. Recent EMA guidelines recommend post-authorisation studies for medicines commonly used by breastfeeding people with an unknown potential for serious adverse reactions in breastfed children. This may include a clinical lactation study and/or a prospective study following up infants exposed to a specific medicine through breast milk. Use of pregnancy registries for follow-up of breastfed infants is also possible *(*Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations III: Pregnant and breastfeeding people). The Xolair® Pregnancy Registry is an example of a study providing information for the breastfeeding section of the product label (An Observational Study of the Use and Safety of Xolair® During Pregnancy, ClinicalTrials.gov, NCT00373061).

9.1. Clinical lactation studies

In general, human lactation studies are performed as a "milk only study" or a "blood & milk study", depending on the specific medicine and study feasibility. The EMA GVP III guidelines recommend that drug concentration levels in breast milk samples should be measured and a relative infant dose calculated to enable a risk assessment (Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations III: Pregnant and breastfeeding people). Guidelines from FDA are also available (Clinical Lactation Studies: Considerations for Study Design Guidance for Industry, FDA 2019).

Drug concentration measurements in milk should be done at steady state, and preferably, repeated over a full dose interval. Moreover, a standardized assessment of the infant should be performed. Information on infant age is crucial and should be reported. If relevant, active drug metabolites and the maternal and infant CYP genotypes should also be included. Finally, data on the effect of the medicine on milk production or composition should be collected, if potentially clinically relevant.

Recent initiatives to improve the situation in Europe include the EU funded multinational IMI ConcePTION project. One of its aims is to establish a human milk biorepository to provide researchers, pharmaceutical industry and regulators with a system to perform human lactation studies and to establish the standards to do so. Several clinical lactation demonstration projects are ongoing (for example, Levocetirizine/cetirizine levels in human milk – an observational, clinical study among breastfeeding women, Zenodo 6345335, 2022), both as "milk only" and "blood & milk" human lactation studies. Infants are followed up and monitored for potential ADRs (incl. rash, sedation, irritability, weight gain, bleeding and gastrointestinal events). Traditional PK calculations and/or Population based PK (PopPK) modelling are being used.

Recent EMA guidelines (Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations III: Pregnant and breastfeeding people) and EU initiatives such as IMI ConcePTION may increase post-marketing studies among breastfed infants and thus improve knowledge about medicine and breast feeding in Europe.

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