

How to set up a system for monitoring
drug safety during pregnancy



Pregnancy PV Toolkit

About the Pregnancy PV Toolkit

This pregnancy pharmacovigilance (PV) toolkit is developed to support national PV centres in the practice of PV specific to the use of drugs during pregnancy. Monitoring of the safety of drug use during pregnancy is a special topic of interest in PV and requires a distinct approach.

This toolkit has been developed by the Netherlands Pharmacovigilance Centre Lareb under the guidance of the WHO.

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Contents

1	Introduction	5
1.1	Drug use during pregnancy	5
1.2	Congenital malformations	5
1.3	Other adverse pregnancy outcomes	5
1.4	Monitoring of the safety of drug use during pregnancy	6
2	How to set up a system for pregnancy PV	8
2.1	PV staff	8
2.2	Data collection	8
3	Data collection: Spontaneous reporting	10
3.1	Specific points of attention in pregnancy PV	10
3.2	Pregnancy-related information	10
3.3	Standard spontaneous reporting form	11
3.4	Pregnancy-specific reporting form	12
3.5	Pregnancy-related follow-up questions	12
3.6	Spontaneous reporting database	13
4	Data collection: Cohort event monitoring	14
4.1	Cohort event monitoring in pregnancy	14
4.2	Advantages of cohort event monitoring in pregnancy PV	14
4.3	Record linkage	15
5	Causality assessment	17
5.1	Baseline risk	17
5.2	Known risk factors	17
5.3	Timing and duration	18
5.4	Dose	18
5.5	Pharmacokinetics (including placental passage)	19
6	Signal detection	21
6.1	Signal detection: Spontaneous reporting	21
6.2	Signal detection: Cohort event monitoring	22

7	Risk communication	23
7.1	Risk communication in pregnancy PV	23
7.2	Clinical practice guidelines	23
8	Collaboration	25
8.1	National organisations	25
8.2	International organisations	25
9	Resources	27
9.1	Websites	27
9.2	Scientific articles	28
9.3	Books	29
9.4	Journals	29
9.5	Education	30
	Assessment answers	31

1 Introduction

1.1 Drug use during pregnancy

Many women will use drugs at some point during their pregnancy. They may be inadvertently exposed while they are still unaware of their pregnancy, or they are treated intentionally during pregnancy because withholding, delaying or interrupting treatment could harm the woman. Indications for using drugs during pregnancy are not only therapeutic, but also diagnostic (such as contrast media) and prophylactic (such as anti-malaria drugs and vaccines). Therapeutic use may be indicated due to chronic disease (such as epilepsy and asthma) or due to acute disease (such as infection). While some drugs are known to be safe or known to cause harm in pregnant women or their unborn child, the safety profile in pregnancy is still uncertain for most of the drugs.

1.2 Congenital malformations

The baseline risk for developing congenital malformations (when organs or tissues fail to develop normally, such as spina bifida, atrial septal defect and cleft palate) is 2 – 4%. Only a small portion of congenital malformations are directly caused by environmental exposures (including certain drugs, smoking and alcohol, workplace chemicals, maternal disease and ionising radiation). An increasing number of genetic abnormalities are being described as causes of congenital malformations. For most cases however, the cause is unknown. This may be of multifactorial origin (due to a combination of environmental exposures and a genetic predisposition), a de novo occurrence (due to chance), or due to a factor that has yet to be identified as a teratogen (harmful to the unborn child).

1.3 Other adverse pregnancy outcomes

Aside from potentially increasing the risk for congenital malformations, drugs may also adversely impact the pregnancy and (unborn) child in other ways, such as:

- Miscarriage and stillbirth
- Intrauterine growth restriction: this can result in the (unborn) child being small for gestational age and in low birth weight

- Preterm labour and preterm birth
- Functional disorders in the (unborn) child: when organs developed normally but do not function properly, such as renal failure and hypothyroidism
- Pharmacological effects in the (unborn) child: such as sedation, tachycardia and hypoglycaemia
- Withdrawal symptoms in the newborn child: such as irritability, tremors, vomiting and convulsions

Pharmacological effects and withdrawal symptoms are generally transient. However, they can still qualify as serious adverse drug reactions (ADRs), for example when the condition of the child requires admission to a neonatal intensive care unit (NICU).

Functional disorders also include neurodevelopmental disorders such as intellectual disability and autism, which are diagnosed years after the intrauterine exposure. These effects are generally permanent.

> Attention!

Aside from potentially increasing the risk for congenital malformations, drugs may also adversely impact the pregnancy and (unborn) child in other ways.

1.4 Monitoring of the safety of drug use during pregnancy

The monitoring of the safety of drug use during pregnancy is a special topic of interest in pharmacovigilance (PV). When drugs are used during pregnancy, a unique situation arises as not only the pregnant woman, but also her unborn child may develop ADRs.

Little is known about these potential risks when a drug enters the market. Pregnant women are excluded from pre-marketing trials for ethical reasons unless the drug is specifically intended to be used during pregnancy. In addition, animal studies are limited in their ability to predict whether a drug could be teratogenic in humans. Therefore, the unfortunate reality is that we learn about most teratogenic effects only after a drug has been marketed, and after it has been used by pregnant women.

A well-known historical example is the thalidomide tragedy in the late 1950s and early 1960s. The drug was marketed under many different brand names as a safe remedy for morning sickness and sleeplessness. It took 4 years before an increased incidence of specific congenital malformations (including phocomelia: shortened or absent limbs) was linked to the use of

thalidomide during pregnancy. By that time, thousands of children with congenital malformations had already been born.

Another example is the vitamin K antagonists such as warfarin. These oral anticoagulants were quickly identified as a cause for foetal loss and neonatal bleeding. However, it took 12 years after warfarin was approved for human use in the USA before the first case report was published on congenital malformations and mental retardation in a child exposed during pregnancy.

A more recent example is the anti-epileptic drug valproic acid. While an increased risk for specific congenital malformations had been well-established for decades, the safety profile of valproic acid was still far from complete. In recent years, it became apparent that prenatally (before birth) exposed children are at substantial risk for long-term neurodevelopmental disorders such as intellectual disability and autism. Since that discovery, medicines regulatory authorities have further narrowed the indications for the use of valproic acid during pregnancy.

> Attention!

PV efforts, including those of national PV centres in the post-marketing phase are critically important to obtain knowledge on potential risks during pregnancy.

Assessment

Make the right combinations for the following adverse pregnancy outcomes:

- | | |
|-----------------------------|----------------------------|
| 1. Withdrawal symptoms | A. Atrial septal defect |
| 2. Pharmacological effects | B. Intellectual disability |
| 3. Congenital malformations | C. Irritability |
| 4. Functional disorders | D. Tachycardia |

2 How to set up a system for pregnancy PV

2.1 PV staff

PV staff should have at least a basic understanding of pregnancy PV and teratology in order to adequately handle pregnancy cases. In addition to the contents of this toolkit, they could familiarise themselves with the Teratology Primer issued by the Teratology Society, which is available free of charge at <http://www.teratology.org/primer/>

If budget allows, consider taking courses in teratology or reproductive and developmental toxicology. Suggested courses are listed under Resources, Education. Alternatively, PV centres could (temporarily) acquire staff from a country with experience in pregnancy PV or with expertise in teratology to train their local PV staff.

> Attention!

PV staff should have at least a basic understanding of pregnancy PV and teratology.

2.2 Data collection

The two main methods used by PV centres to collect data are spontaneous reporting and cohort event monitoring. The same holds true for collecting data on the safety of drug use during pregnancy, but with some modifications which will be outlined in the following two chapters. As both methods come with unique advantages, they can be considered complementary to one another.

> Attention!

As in general PV, the two main methods for data collection in pregnancy are spontaneous reporting and cohort event monitoring.

Assessment

Read the following chapters of the Teratology Primer (<http://www.teratology.org/primer/>):

- What Birth Defects Are Common in Humans? How Are They Diagnosed at Birth?
- What Is the Timeline of Important Events During Pregnancy that May Be Disrupted by a Teratogenic Exposure?
- How Are New Medicines Evaluated for Developmental Toxicity?
- What is the Role of Post Marketing Surveillance in Detecting Teratogenic Exposure?
- How are Prescription Medications Labeled for Pregnancy and Lactation?

3 Data collection: Spontaneous reporting

3.1 Specific points of attention in pregnancy PV

There are specific points of attention in pregnancy PV. The timing and duration of the exposure to the suspect drug relative to the gestational age and the suspected ADR should be precisely documented, as it is crucial for causality assessment. In addition, detailed information about the case is required in order to rule out other factors that may have increased the likelihood for adverse pregnancy outcomes. These other factors include maternal diseases and genetic predispositions in the family of both parents of the (unborn) child. The collection and storage of pregnancy-related information could compel revision of the current reporting form, the follow-up questions and the spontaneous reporting database, as outlined in the following paragraphs.

3.2 Pregnancy-related information

The following items of pregnancy-related information may be relevant or applicable in addition to the standard spontaneous reporting form:

- Suspect drug
 - Use during pregnancy: continuously or during specified days or weeks of gestation
- Mother
 - Birthdate
 - Weight before pregnancy, length
 - Use of folic acid before and during pregnancy
 - Smoking status, use of alcohol and drugs of abuse
 - Obstetric medical history: previous pregnancy outcomes
 - Medical history: congenital malformations or genetic disorders (including her family)
- Father
 - Medical history: congenital malformations or genetic disorders (including his family)
- Pregnancy
 - First day of last menstrual period, estimated due date
 - Use of assisted reproductive technology
 - Abnormal findings on ultrasound, amniocentesis or other forms of prenatal tests
 - Issues or complications (such as gestational diabetes or pre-eclampsia)

- Delivery
 - Pregnancy duration at delivery
 - Use of drugs for induction of labour
 - Use of drugs for pain relief
 - Mode of delivery (vaginal with or without vacuum or forceps, caesarean section)
 - Issues or complications (such as prolonged rupture of membranes)
- Child
 - Gender
 - Birthdate
 - Weight, length
 - Apgar score
 - Issues or complications (such as meconium aspiration or infection)
 - Medical history: congenital malformations or genetic disorders
- Breastfeeding
 - Issues or complications (such as low milk supply)

There are several ways by which PV centres can obtain this information from their reporters: by revising the standard spontaneous reporting form, by developing a pregnancy-specific reporting form, and through pregnancy-related follow-up questions.

3.3 Standard spontaneous reporting form

The current reporting form may not be entirely suitable to report ADRs of drugs in pregnancy, this should be evaluated and adjusted if necessary. Not all standard questions may be applicable in this situation. For example, a question about the latency (the time between the start date of the suspect drug and the onset of the ADR) is not relevant if a woman had been taking the same drug for 10 years when the suspected ADR occurred in her unborn child. On the other hand, it may be prudent to ask additional questions regarding the pregnancy, as detailed information is required to assess these cases. Suggested items are listed above under *3.2 Pregnancy-related information*.

If the PV centres receives ADR reports through an electronic reporting form (such as a website tool or mobile phone app), it should be tested for validation errors. For example, the system may not allow reporting that the start date of the suspect drug and/or the onset of the ADR occurred prior to the birthdate of the child, which are common situations in pregnancy PV.

3.4 Pregnancy-specific reporting form

Rather than revising the standard spontaneous reporting form to make it suitable for pregnancy cases, a pregnancy-specific reporting form may be developed to be used alongside the standard form. However, it should be noted that not all items of pregnancy-related information listed above are relevant or applicable in all cases. For example, if withdrawal symptoms are reported in the child following the use of a drug in the third trimester of pregnancy, the family history for congenital malformations is irrelevant. Conversely, this information is essential when cleft palate is reported after the use of a drug in the first trimester. In addition, if an early miscarriage is reported, several items are not applicable: delivery, child and breastfeeding. Asking many questions on the report form may put a strain on the reporters, discouraging them from reporting ADRs. A possible solution is to provide open text fields instead of detailed questions, in which the reporter can clarify the case specifics.

> Attention!

Consider revision of the current spontaneous reporting form to make it suitable to report ADRs of drugs in pregnancy, or developing a pregnancy-specific reporting form.

3.5 Pregnancy-related follow-up questions

Another way to obtain this information is to draft standardised pregnancy-related follow-up questions based on the above list of items. An advantage of this method is that a selection of relevant questions can be made specifically for each case, thereby avoiding unnecessary burdening of the reporters. In addition, this method provides a second chance to obtain information when the initial report was not comprehensive enough to assess the case properly. This implies that the PV staff should have an understanding of when to ask follow-up questions and if so, which questions could be relevant.

> Attention!

Consider drafting standardised follow-up questions to obtain additional information regarding exposed pregnancies.

3.6 Spontaneous reporting database

It is possible that the current spontaneous reporting database of a PV centre was designed to store case reports concerning one individual: the patient. However, when pregnancy cases are reported, these case reports may provide data concerning two individuals: the parent and the child. For example, if the pregnancy resulted in a live-born child, there will be two birthdates to store. For analysis purposes, avoid storing this and other information in open text fields. Rather, revise the current database to facilitate the storage in data fields that can be coded and queried.

> Attention!

Consider revision of the current spontaneous reporting database to facilitate the storage of case reports concerning two individuals: parent and child.

Assessment

Why would the use of folic acid before and during pregnancy provide relevant information?

- A. Using folic acid before and during pregnancy is known to increase the risk for certain congenital malformations
- B. Using folic acid before and during pregnancy is known to decrease the risk for certain congenital malformations

4 Data collection: Cohort event monitoring

4.1 Cohort event monitoring in pregnancy

Cohort event monitoring is an active method of collecting data on the safety of drug use. When applied to pregnancy, this method is often referred to as a pregnancy (exposure) registry. A cohort may consist of pregnancies exposed to a specific drug or drug class (such as anti-epileptic or anti-retroviral drugs), a specific maternal disease (with or without drug exposures) or it may reflect the general pregnant population. Cases are enrolled as early in the pregnancy as possible and may be closely monitored until the child reaches a certain age. Depending on the duration of the monitoring period, short-term as well as long-term effects may be documented. An extensive protocol for implementing a drug exposure pregnancy registry in resource-limited settings (and pooling the data into a common WHO Pregnancy Registry) is available free of charge at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3500715/>

> Attention!

Complementary to spontaneous reporting, consider establishing or supporting cohort event monitoring such as pregnancy exposure registries.

4.2 Advantages of cohort event monitoring in pregnancy PV

Cohort event monitoring has the advantage that cases are documented prospectively before any pregnancy outcomes are known, thereby avoiding a certain selection bias. Depending on the setup, unexposed pregnancies may be included in addition to pregnancies with drug exposures. The women with unexposed pregnancies may be healthy or they may suffer from the same or a similar disease as the women with exposed pregnancies. The database may therefore contain cases of adverse pregnancy outcomes (with or without drug and/or disease exposures) as well as cases of uneventful pregnancies (with or without drug and/or disease exposures). In such circumstances, comparative cohort studies are possible. Contrary to spontaneous reporting, cohort event monitoring may allow for calculation of the prevalence of adverse pregnancy outcomes following drug and/or disease exposures, provided that the number of cases is sufficient.

> **Attention!**

Cohort event monitoring may allow for calculation of the prevalence of adverse pregnancy outcomes following drug and/or disease exposures.

4.3 Record linkage

Linkage of existing databases is another strategy for the creation of a cohorts of pregnant women and cohort studies. Relevant databases include hospital records, pharmacy records, birth records, medical insurance records, prescription databases and more. Linkage is subject to approval by local ethics committees and should occur in concordance with local privacy laws. The main advantage is the quantity of the data: a very large cohort can be constructed with relatively little additional effort, as the data are already routinely collected for other purposes. A major disadvantage is the often limited quality of the data. For example, a prescription database only reflects which drugs were prescribed to the patient, but not whether they actually took the drug. Especially in pregnancy, patients may not comply with treatment after they become wary of potential risks to the unborn child. Another disadvantage is that some adverse pregnancy outcomes (such as early miscarriages) may not be recorded in any of the linked databases.

> **Attention!**

Record linkage is another strategy for cohort studies of pregnant women, but the quality of the data is generally limited.

Assessment

Table 1 presents the results of a fictional comparative cohort study. Calculate the prevalence of children with a congenital malformation for:

1. Mothers without diabetes and without drug exposure
2. Mothers with untreated diabetes
3. Mothers with diabetes, treated with insulin
4. Mothers with diabetes, treated with metformin

		Children	
		Congenital malformation	No congenital malformation
Mothers	No diabetes, no drug exposure	120	3880
	Diabetes, no drug exposure	50	450
	Diabetes, insulin exposure	110	1890
	Diabetes, metformin exposure	84	1416

Table 1. Fictional comparative cohort study on maternal diabetes with 8000 mother-child pairs in total

5 Causality assessment

5.1 Baseline risk

Adverse pregnancy outcomes may, of course, occur in the absence of any harmful exposures or known risk factors due to the baseline risk. Also, pregnancy outcomes may be completely normal following exposure to a known teratogen, as even the most potent teratogens don't seem to affect everyone. In individual cases, it is therefore challenging to determine whether the pregnancy would have had a different outcome if the woman hadn't been exposed to the suspect drug.

5.2 Known risk factors

Many factors have been identified that will increase the likelihood that a specific adverse pregnancy outcome may occur. These include genetic predispositions in the family of both parents, maternal disorders (pre-existing as well as pregnancy-induced) and lifestyle choices. If there are known risk factors for the reported outcome, try to ascertain whether any of these were present in this case. To illustrate, some examples of known risk factors and their associated adverse pregnancy outcomes are listed below:

- Maternal smoking – Low birth weight
- Previous history of pre-eclampsia – Pre-eclampsia
- Maternal hypothyroidism – Miscarriage
- Maternal pre-existing diabetes – Congenital malformations
- Family history of autism – Autism
- Gestational hypertension – Intrauterine growth restriction
- Maternal obesity – Shoulder dystocia

5.3 Timing and duration

The timing and duration of the exposure to the suspect drug relative to the gestational age and the suspected ADR is crucial for causality assessment. A general outline of the timing and possible effects is listed below:

- Prior to conception: fertility disorders, miscarriage
- From conception until 2 weeks after conception: miscarriage
- From 2 weeks after conception until the second trimester: miscarriage, congenital malformations
- From the second trimester until the end of pregnancy: miscarriage and stillbirth, preterm labour and preterm birth, functional disorders, pharmacological effects, withdrawal symptoms

Following this outline, exposures during the first trimester are unlikely to result in withdrawal symptoms in the newborn. Likewise, if the patient started using the suspect drug during the third trimester, it is implausible that it influenced the formation of congenital malformations which generally occurs in the first trimester. Even within the first trimester timing is crucial. For example, the neural tube is completely closed after the 6th week of pregnancy, so spina bifida can only be linked to a drug if it was used prior to that.

Generally speaking, the likelihood for adverse pregnancy outcomes increases with the duration of exposure. However, even a single dose may affect the pregnancy, especially if it was ill-timed or if the drug has a long half-life, which prolongs the exposure.

5.4 Dose

A dose-response relationship has been described in many, but not all adverse pregnancy outcomes following drug exposures. In general, a higher dose may increase the likelihood that the associated adverse pregnancy outcome will occur, and/or it may result in more pronounced effects. While the opposite is true as well, often there is no known threshold level below which harmful effects will not occur.

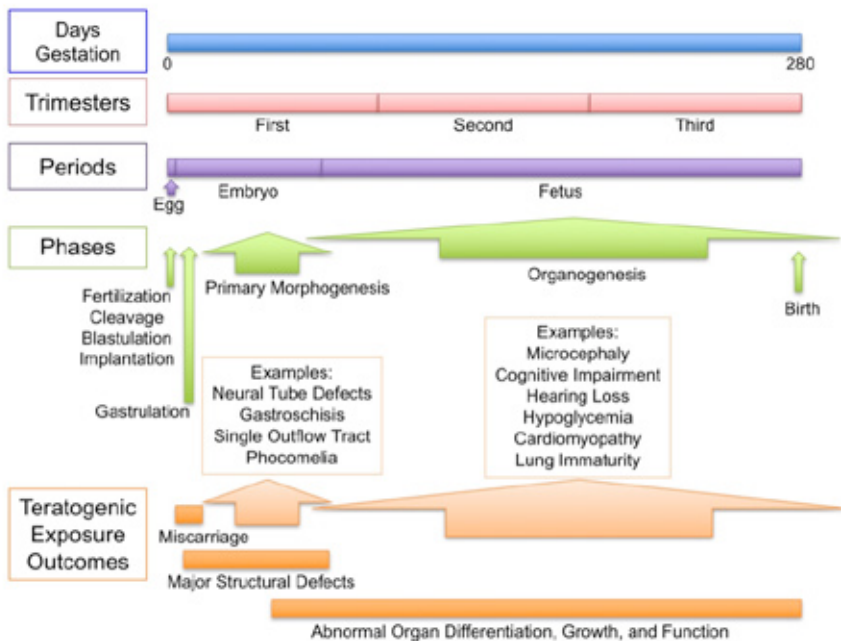
5.5 Pharmacokinetics (including placental passage)

In most cases, an approximation of the drug exposure in the foetus will provide useful information for risk and causality assessment. However, there are a few exceptions to the rule as drugs do not necessarily require placental passage to play a part in adverse pregnancy outcomes. For example, a drug that causes vasoconstriction or hypotension in the placenta would hamper the transfer of oxygen and nutrients to the foetus. In severe cases this could cause miscarriage and stillbirth, while in less severe cases this could result in intrauterine growth restriction. Another example is a drug that causes contractions of the uterus. In early pregnancy this could cause miscarriage, while it could induce preterm labour later in pregnancy.

The degree of drug exposure in the foetus depends on the biological availability and placental passage. Only the fraction of the drug (or its metabolites) that enters the systemic circulation can reach the placenta. In turn, only the fraction of the drug (or its metabolites) that passes through the placenta can reach the foetus. The placental passage is dependent on several characteristics of the drug:

- Lipophilicity (drugs with high lipophilicity can pass the placenta more easily)
- Ionisation (non-ionised drugs can pass the placenta more easily)
- Molecular weight (large molecules are unlikely to pass the placenta through diffusion)
- Plasma protein binding (the fraction bound to plasma proteins is unlikely to pass the placenta)
- Fc region (active transport is possible for monoclonal antibodies by binding to a Fc receptor)

Interestingly, enzymes in the placenta may inactivate some drugs (or its metabolites), thereby decreasing the exposure in the foetus. For example, the foetal plasma concentration of the corticosteroids prednisolone and hydrocortisone is approximately 10% of the maternal plasma concentration, while the foetal plasma concentration of another corticosteroid dexamethasone reaches almost 100% of the maternal concentration.



Source: Hales B, Scialli A, Tassinari M (editors). *Teratology Primer*, 3rd Edition. The Teratology Society. Reston, VA. 2017. Online at <http://www.teratology.org/primer/>

> Attention!

Take into account when assessing causality in pregnancy cases:

- Baseline risk for the adverse pregnancy outcome
- Known risk factors for the adverse pregnancy outcome (including genotype)
- Timing and duration of the drug exposure relative to the gestational age
- Dose of the suspect drug
- Pharmacokinetics (including placental passage) of the suspect drug

Assessment

Make the right combinations for the most likely timing of exposure:

- | | |
|------------------------|-----------------------------|
| 1. Prior to conception | A. Pharmacological effects |
| 2. Third trimester | B. Fertility disorders |
| 3. First trimester | C. Withdrawal symptoms |
| 4. During labour | D. Congenital malformations |

6 Signal detection

6.1 Signal detection: Spontaneous reporting

The main type of signals we aim to detect in pregnancy PV is whether a certain drug could be a risk factor for a certain adverse pregnancy outcome. Pregnancy-related signals may also include the compliance with pregnancy prevention programmes and with pregnancy as a labelled contraindication.

> Attention!

Examples of pregnancy-related signals:

- Drug as a potential risk factor for a certain adverse pregnancy outcome
- Compliance with pregnancy prevention programmes
- Compliance with pregnancy as a labelled contraindication

Case-by-case clinical assessment of individual reports is the main strategy for signal detection in spontaneous reporting of pregnancy cases. The method is the same as in general PV, which includes examining the official product information, checking the national and global ADR report databases for similar reports, and reviewing reference sources and medical literature for previous cases and other relevant information. Suggested sources of teratology-related information are listed in the chapter Resources.

Automated screening of the national spontaneous reporting database for potential pregnancy-related signals using statistical algorithms (such as disproportionality) is generally not feasible in national databases. Pregnancy cases represent only a small portion within such databases and the number of cases per association between a specific drug exposure and a specific adverse pregnancy outcome will be very limited.

> Attention!

In spontaneous reporting, case-by-case assessment is the main strategy for signal detection in pregnancy cases. Automated signal detection is generally not feasible in national databases.

6.2 Signal detection: Cohort event monitoring

In addition to the potential signals mentioned above, cohort event monitoring may yield a unique type of signal: the (relative) safety of using a certain drug during pregnancy. In registries where comparative cohort studies are possible, the prevalence of adverse pregnancy outcomes in the group of exposed women can be compared to those of unexposed women (with or without the same or a similar disease as the exposed women). When no statistically significant differences in adverse pregnancy outcomes are found after a substantial number of pregnant women has used a specific drug during pregnancy, these results can be reassuring.

Depending on the inclusion criteria, cohort event monitoring may also provide insight in the prevalence of using a certain drug during pregnancy. For example, if a cohort consists of pregnant women with diabetes, the percentage of insulin users can be calculated. In the course of several years, a shift towards using metformin instead of insulin may be discovered.

In cohort event monitoring, data are generally analysed at an aggregate level. As key details may be overlooked that way, case-by-case assessment within the cohort is also preferable to address this issue.

> Attention!

Cohort event monitoring may yield signals regarding the prevalence and the (relative) safety of using a certain drug during pregnancy.

Assessment

Are there any pregnancy prevention programmes in place in your country? If so, for which drugs?

7 Risk communication

7.1 Risk communication in pregnancy PV

Exposures during pregnancy can be a source of great anxiety and misunderstanding. Scientific studies may provide limited and contradictory data, and the pregnancy safety information in the official product information (Summary of Product Characteristics, drug label, patient information leaflet, patient package insert) may differ substantially from other trusted resources.

In addition, many people find it difficult to interpret relative risks. For example, a doubling of the risk for a certain congenital malformation may seem worrisome, until it becomes clear that the absolute risk was increased from 0,01% to 0,02%.

> Attention!

Exposures during pregnancy can be a source of great anxiety and misunderstanding.

When communicating with healthcare professionals and the public about pregnancy-related ADR reports or signals, it is advisable to mention absolute risks and to provide the full context: the baseline risk and known risk factors for the adverse pregnancy outcome, the risks of the (untreated) underlying disease for the pregnant woman and/or the unborn baby, and the risks of other possible treatments for that disease. All of these risks need to be carefully weighed against the benefits for each individual patient.

> Attention!

Mention absolute risks and provide the full context when communicating about pregnancy-related ADR reports or signals.

7.2 Clinical practice guidelines

PV centres with expertise in pregnancy PV and teratology should aim to actively participate in the development of national clinical practice guidelines. This ensures that healthcare professionals have access to relevant pregnancy safety information at the right time: when prescribing drugs in pregnancy or in women of reproductive age.

> Attention!

Participating in clinical practice guidelines ensures that healthcare professionals have access to relevant safety information at the right time.

Assessment

- Choose one drug that is commonly prescribed in your country
- Read the section on pregnancy in the official product information
- Then, try to find three other sources of teratology-related information in which this drug is listed. Suggested sources are listed in the chapter Resources
- Compare the texts. Are there discrepancies between them? For example: according to one source, this drug should be avoided during pregnancy, while another source considers the use acceptable
- If so, can you think of an explanation for these differences in risk communication?

8 Collaboration

8.1 National organisations

Aside from the national pharmacovigilance centre, there may be other organisations in the country operating in the same or a related field, such as Teratology Information Services, poison control centres and universities. It is important to be aware of these organisations and their activities and to reach out to them, as they may provide opportunities to work together and share knowledge.

8.2 International organisations

In addition to local initiatives, there are several international organisations that the national PV centres could reach out to:

- **Teratology Society:** <https://www.teratology.org>

Description: To understand and prevent birth defects and disorders of developmental and reproductive origin, the Teratology Society promotes multi-disciplinary research and exchange of ideas; communicates information to health professionals, decision-makers, and the public; and provides education and training.

- **European Network of Teratology Information Services (ENTIS):**

<https://www.entis-org.eu/>

Description: The general objective for ENTIS is to coordinate and collaborate the activities of the different Teratology Information Services (TIS), and to collect and evaluate data in order to contribute to the primary prevention of birth defects and developmental disorders.

- **Organization of Teratology Information Specialists (OTIS):** <https://mothertobaby.org/>

Description: MotherToBaby, a service of the non-profit Organization of Teratology Information Specialists, is dedicated to providing evidence-based information to mothers, health care professionals, and the general public about medications and other exposures during pregnancy and while breastfeeding. MotherToBaby affiliates support and contribute to worldwide initiatives for teratology education and research.

> **Attention!**

Reaching out to national and international organisations operating in the field of pharmacovigilance in pregnancy may provide opportunities for collaboration.

Assessment

Make an inventory of organisations in your country that may conduct activities concerning the safety of drug use during pregnancy.

9 Resources

9.1 Websites

- **PV Toolkit:** <http://whopvtoolkit.org>

Description: The Pharmacovigilance (PV) Toolkit is a collection of resources and information needed for the practice of pharmacovigilance. The main aim of its development is to ensure that PV practitioners in low- and middle-income countries get access to information on the processes and activities involved in PV from a trusted source. The Toolkit contents are endorsed by the WHO Advisory Committee on the Safety of Medicinal Products after the original text has been written and reviewed by global experts.

- **Teratology Primer:** <http://www.teratology.org/primer/>

Description: The first edition of the Teratology Primer was published by the Teratology Society in 2005 and a second edition was published in 2010. Thousands of paper copies were distributed to colleagues and trainees. They have now prepared a third edition, available electronically, to update and expand the discussions in the first two editions. The goal of the Primer is to give you in a few short pages, a sense of what the field of teratology means to its practitioners. What is teratology anyway? Do I want to be a teratologist? How are chemicals evaluated for reproductive risk? What exposures should concern us? This Teratology Primer is meant to answer these questions and more. Topics range from how birth defects are diagnosed, to the impact of genes or environmental exposures, to ethical considerations, to the use of systems biology and computational approaches to predict teratogenic risk, and to how information is communicated.

- **REPROTOX®:** <https://reprotox.org>

Description: REPROTOX contains more than 5,000 summaries on the effects of medications, chemicals, biologics, and physical agents on pregnancy, reproduction, lactation, and development. The REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies.

- **TERIS:** <http://depts.washington.edu/terisdb/>

Description: TERIS is a computerised database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. The database consists of a series of agent summaries, each of which is based on a thorough review of published clinical and experimental literature. Summaries may

be accessed using either generic names or domestic or foreign proprietary names. Each summary includes a risk assessment derived by consensus of an Advisory Board comprising nationally-recognised authorities in clinical teratology. An updated, automated version of Shepard's Catalog of Teratogenic Agents is distributed with TERIS. Users can access both systems simultaneously.

- **bumps:** <http://www.medicinesinpregnancy.org>
Description: the bumps (best use of medicine in pregnancy) website is provided by the Teratology Information Service of the United Kingdom (UKTIS). UKTIS is a not-for-profit organisation that has been providing scientific information to health care providers since 1983 on the effects that use of medicines, recreational drugs and chemicals during pregnancy may have on the unborn baby. On bumps, information leaflets are freely available that summarise the scientific information in a way that is understandable to everyone.

9.2 Scientific articles

- Mehta U, Clerk C, Allen E, Yore M, Sevene E, Singlovic J, Petzold M, Mangiaterra V, Elefant E, Sullivan FM, Holmes LB, Gomes M. **Protocol for a drugs exposure pregnancy registry for implementation in resource-limited settings.** BMC Pregnancy Childbirth. 2012 Sep 3;12:89.
- Allen EN, Gomes M, Yevoo L, Egesah O, Clerk C, Byamugisha J, Mbonye A, Were E, Mehta U, Atuyambe LM. **Influences on participant reporting in the World Health Organisation drugs exposure pregnancy registry; a qualitative study.** BMC Health Serv Res. 2014 Oct 31;14:525.
- Mitchell AA. **Systematic identification of drugs that cause birth defects--a new opportunity.** N Engl J Med 2003;349(26):2556-9.
- World Health Organization. **The importance of pharmacovigilance: Safety monitoring of medicinal products.** (version date: 2002, access date: 1-12-2016) <http://apps.who.int/medicinedocs/en/d/Js4893e/>.
- Conover EA, Polifka JE. **The art and science of teratogen risk communication.** Am J Med Genet C Semin Med Genet. 2011 Aug 15;157C(3):227-33.
- Margulis AV, Andrews EB. **The Safety of Medications in Pregnant Women: An Opportunity to Use Database Studies.** Pediatrics. 2017 Jul;140(1).
- Trønnes JN, Lupattelli A, Nordeng H. **Safety profile of medication used during pregnancy: results of a multinational European study.** Pharmacoepidemiol Drug Saf. 2017 Jul;26(7):802-811.

- Mosha D, Mazuguni F, Mrema S, Abdulla S, Genton B. **Medication exposure during pregnancy: a pilot pharmacovigilance system using health and demographic surveillance platform.** BMC Pregnancy Childbirth. 2014 Sep 15;14:322.

9.3 Books

- Briggs, G.G., Freeman, R.K., Towers, C.V. and Forinash, A.B. (2017). **Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 11th Edition.** Philadelphia, PA: Lippincott Williams & Wilkins.
Description: A Reference Guide to Fetal and Neonatal Risk lists more than 1,200 commonly prescribed drugs taken during pregnancy and lactation, with detailed monographs that provide the information you need on known or possible effects on the mother, embryo, fetus, and nursing infant.
- Schaefer, C., Peters, P.W.J., Miller, R.K. (2014). **Drugs During Pregnancy and Lactation: Treatment Options and Risk Assessment, 3rd Edition.** Cambridge, MA: Academic Press.
Description: A quick and reliable reference for all those working in disciplines related to fertility, pregnancy, lactation, child health and human genetics who prescribe or deliver medicinal products, and to those who evaluate health and safety risks. Each chapter contains twofold information regarding drugs that are appropriate for prescription during pregnancy and an assessment of the risk of a drug when exposure during pregnancy has already occurred. Thoroughly updated with current regulations, references to the latest pharmacological data, and new medicinal products, this edition is a comprehensive resource covering latest knowledge and findings related to drugs during lactation and pregnancy.

9.4 Journals

- **Birth Defects Research:** [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)2472-1727](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2472-1727)
- **Reproductive Toxicology:** <https://www.journals.elsevier.com/reproductive-toxicology/>
- **Neurotoxicology and Teratology:** <https://www.journals.elsevier.com/neurotoxicology-and-teratology/>

9.5 Education

- **Human Teratogens: Environmental Factors Which Cause Birth Defects**

Description: The only postgraduate course in the United States, Canada and Europe that provides new information on exposures during pregnancy which could be harmful to the fetus.

<http://cmeregistration.hms.harvard.edu/events/human-teratogens-environmental-factors-which-cause-birth-defects/event-summary-coe100ed24c6424baeb1ca37ff9c9c7c.aspx>

- **Practical Reproductive and Developmental Toxicology**

Description: This joint American College of Toxicology/Teratology Society course is designed to provide a basic understanding in reproductive and developmental biology and principles of various testing approaches for reproductive and developmental toxicology, with strong emphasis on the practical application of these principles and interpretation of nonclinical safety data as well as risk assessment.

<https://www.actox.org/meetCourses/PRDT2017.asp>

- **Building Teratovigilance Capacity in Africa**

Description: There is growing appreciation of the need to collect information on the safety of medicines and vaccines in pregnancy, particularly in sub-Saharan Africa. Maternal and neonatal pharmacovigilance (teratovigilance) in the African context requires innovation of research and surveillance approaches based on sound clinical and epidemiological principles.

Concerns about the safety of novel antiretrovirals, antituberculosis agents, antimalarials and antibiotics in pregnancy have prompted the creation of an international pregnancy exposure registry database by WHO and various initiatives aimed at building teratovigilance capacity in the Africa, and South Africa in particular.

This 3-day interactive workshop aims to provide participants with exposure to international experts who will provide up-to-date knowledge on teratovigilance.

<http://www.buildingteratovigilance.co.za/>

Assessment

Are you aware of other helpful resources concerning the safety of drug use during pregnancy? Please let us know!

Assessment answers

Chapter 1.4:

- 1 = C
- 2 = D
- 3 = A
- 4 = B

Chapter 3.6:

B. All women planning or capable of pregnancy are recommended to take a daily supplement of folic acid in order to decrease the risk for neural tube defects including spina bifida. When this type of congenital malformation is reported as an ADR, information on the use of folic acid is valuable for the causality assessment.

Chapter 4.3:

1. 3%: $120/(120+3880) = 0.03$
Notice it is not 0% for unexposed mothers, due to the baseline risk.
2. 10%: $50/(50+450) = 0.10$
Notice untreated diabetes poses a greater risk than treated diabetes.
3. 5.5%: $110/(110+1890) = 0.055$
Notice treatment reduces the risk, but not back to baseline.
4. 5.6%: $84/(84+1416) = 0.056$
Notice insulin and metformin have a similar effect on the risk.

Chapter 5.5:

- 1 = B
- 2 = C
- 3 = D
- 4 = A

As outlined in paragraph 5.3, pharmacological effects as well as withdrawal symptoms may occur following exposure during the third trimester. However, withdrawal symptoms are generally observed after prolonged use, while pharmacological effects can develop even after a single dose (including use during labour).



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