IMI2 821520 - ConcePTION

ConcePTION

WP5 Dissemination and education for HCPs, pregnant and breastfeeding women and general public

D5.7 Report on E-learning training programme and accreditation plus sustainability

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Document History

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V0.1	17-03-2023	First draft for WP review
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V1.0		Final version

Abstract

This report describes the e-learning training programme, plan for accreditation, and the sustainability. This e-learning was designed within task 5.4 for the purpose of training healthcare professionals (HCPs) about teratology and long-term outcomes of drug exposure during pregnancy, and methods of evidence generation and how they can translate this into effective messages for women and their families on drug use during pregnancy and breastfeeding.

In this task an e-learning training programme has been designed for continuous education of HCPs in English language. Topics included are: historical context, principles of embryology and teratology, principles of therapeutics in pregnancy, medications and breastfeeding, information sources, risk communication, reporting information, and patient experiences. The content has been developed by teratology experts participating in task 5.4 in close collaboration with education experts from Elevate Heath. Building and testing the technical functionalities of the e-learning was done by Elevate Health.

A request for accreditation will be submitted to the European Accreditation Council for CME (EACCME®) of the European Union of Medical Specialists (EUMS) once the e-learning building and testing is finalized. The sustainability plan has been drafted in collaboration with WP6. The general idea is to present potential funders a package of the knowledge bank (WP5), e-leaning and reporting app (WP2). The plan is for ENTIS to maintain the e-learning after the ConcePTION project. An education and knowledge bank committee will be set up and will be responsible for the content, updating, and PR around the e-learning.

Introduction

The previous deliverable about the e-learning materials (Deliverable 5.5), contained a description of the planning, learning goals, and target audience. The last year, the work package focussed on writing the content of the e-learning, building the materials into a e-learning package, exploring the process of accreditation and sustainability. These aspects are described in this report.

E-learning

Content e-learning

The overall purpose of the training programme is to train HCPs about teratology and long-term outcomes of drug exposure during pregnancy, on the methods of evidence generation and how they can effectively translate this into clear communication with women on the safe and effective use of medicines in pregnancy and breastfeeding. The expected educational outcome is that HCPs are better equipped to give advice and make decisions on the use of medicines in pregnancy and breastfeeding. The aim is twofold: on the one hand, HCPs should make better clinical decisions on the use of medicines during pregnancy or breastfeeding. On the other hand, HCPs should know how to advise their patients and communicate about possible risks in an appropriate and effective manner. The e-learning is therefore aimed at increasing clinical knowledge, as well as improving soft skills such as risk communication.

This e-learning training program consists of eleven chapters, including one advanced chapter, in English language:

Chapter 0:	General introduction
Chapter 1:	Historical context
Chapter 2:	Principles of teratology
Advanced chapter	Principles of embryology

Chapter 3:	Considerations for teratogenic exposure during pregnancy
Chapter 4a:	Principles of therapeutics in pregnancy (background)
Chapter 4b:	Principles of therapeutics in pregnancy (practice)
Chapter 5:	Medications and breastfeeding
Chapter 6:	Information sources
Chapter 7:	Risk communication
Chapter 8:	Reporting information
Chapter 9:	Course summary
Chapter 10:	Test your knowledge

The content of the e-learning (Appendix 1) has been developed by teratology experts participating in task 5.4 in close collaboration with education experts from Elevate Health. All content within this e-learning is evidence-based. References are demonstrated at the end of the course, divided per chapter, at the standard required for a publication in a scientific journal. Copyright permission has been asked for all image used in the e-learning.

Technicality aspects

Elevate Health has built the e-learning on their e-learning platform. Technical testing was done by Elevate Health. All writers checked their own chapter for inconsistencies. Each chapter of the e-learning has an approximate duration of one hour. Participants can enter the e-learning course at any time. Their course progress is automatically saved so they can exit the course and start again where they left off. Participants are also able to track their own progress within the course, as they can always see how many pages they have left within a chapter.

The e-learning is supported on the Elevate Health platform in Moodle. However, the main body of the course has been developed in Articulate Storyline and uploaded to the platform as a SCORM zip-file. The main body of the course is therefore platform independent. Administrators of the course can view participants' results on the final exam and overall progress in the form of learner analytics.

Accreditation

A request for accreditation will be submitted to the European Accreditation Council for CME (EACCME®) of the European Union of Medical Specialists (EUMS) once the e-learning building and testing is finalized (https://eaccme.uems.eu/home.aspx). As for 2022, the AECCME® has signed agreements with 25 EU countries and the UK to recognize the credits, countries include: Austria, Armenia, Belgium, Bulgaria, Croatia, Cyprus, Finland, Georgia, Greece, Hungary, Ireland, Regione Lombardia, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Tunisia, Turkey, and United Kingdom. All the other countries may recognise EACCME® credits on a voluntary basis. The coming year, the work package task group will also explore if accreditation is possible for countries that do not directly recognise EACCME® credits.

Sustainability plan

The sustainability plan has been drafted in collaboration with WP6. The general idea is to present potential funders a package of the knowledge bank (WP5), e-learning and reporting app (WP2). In principle, ENTIS is intended to maintain the e-learning after ConcePTION, assuming sufficient funding. They are planning to set up an education and knowledge bank committee which will be responsible for the content, updating, and PR around the e-learning, technical support and management positions will be set. The roadmap of sustainability

consist of the steps 1. value definition, 2. description of the needs for sustainability, and 3. the transition to sustainability.

Value of e-learning package

The novelty that the e-learning will bring is that it is a free online learning platform for HCPs in all countries covering all aspects of pregnancy and lactation. Currently, limited trainings are conducted as part of graduation and there is a lack of online trainings for graduated HCPs (general practitioners, midwives, obstetrician/gynaecologists, pharmacists) to get access to up-to-date information. Development of this e-learning within an EU initiative will furthermore avoid duplication of efforts across EU to develop materials for each country.

The e-learning can ensure that HCPs have a minimum standard of training to support the safe and effective use of medicines in pregnancy and breastfeeding. It provides access to up-to-date relevant information and/or training for key stakeholders in all EU countries to improve decision-making. Training of HCPs and key stakeholders in the field will contribute to primary prevention of birth defects and other adverse pregnancy outcomes and in saving health care costs when a disease is treated appropriately during pregnancy.

Needs for sustainability

In order for sustainable of the e-learning, it is important there is ongoing hosting for the informatics and technical infrastructure. Also, there needs to be a commission in place that takes responsibility for updating the training content en PR. This will in principle be organized by ENTIS, who will also maintain the e-learning after ConcePTION, technical support and management positions will be set. ENTIS is a voluntary network, there will be a need for dedicated paid person months for these positions. To maintain all technical and management aspects, sufficient funding must be available.

Next steps

Next steps in the process of sustainability are to identify potential operational scenario’s, including funding sources, and to meet with potential funders to discuss their funding criteria. Aside from the idea to present potentials funders a packed of the knowledge bank (WP5), e-leaning and reporting app (WP2). for the e-learning specifically, we are also considering a sustainability model in which a specific group of users (for example universities) would pay a fee to make the e-learning more tailor made for them specifically. Another option that has been brought to the table is to ask for a user fee in order to get a certificate after completing the e-learning. These ideas will to be further explored.

Appendix 1: Content of the e-learning

Note: this is still a concept document and may therefore be slightly different compared to the final content of the e-learning

Chapter 0: General Introduction

0.1 Welcome to the course

Slide #	Work form	Content
1	Text	**Welcome to the course!** The development team is delighted that you are following this course. We believe that we can prevent birth defects, optimise pregnancy outcomes and minimise the risk of maternal death by ensuring the safe and effective use of medicines in pregnancy and breastfeeding. In this course you will learn more about the safe use of medication during pregnancy and breastfeeding from a team of experts who work in this area. We strongly believe that a sound foundation course on this important topic, accessible to all healthcare professionals, will ensure that we continue to support women and families to make informed decisions on medication use during and after pregnancy.
2	Text	**There is a clear need** *Imagine you see a pregnant woman over her medication. She is taking several medicines for her asthma. Now that she is pregnant, she wonders if she can continue to use the medication. Or would that be dangerous for her unborn child?* What do you need to know regarding drug use in pregnancy? What considerations do you need to take into account? And what if the baby is born, can the mother use these drugs while breastfeeding? Of course you know that some medicines should not be used during pregnancy. On the other hand, there is no need to refrain from all medication. And chronic diseases need to be well treated, especially during pregnancy. In order to make a good decision you need to know more about the safety of the drug.

3	Text	**What will you learn?** This course will lead you through all the steps in the risk assessment for drug use during pregnancy or breastfeeding. You will learn more about the risk of congenital malformations and the contribution of a drug to this risk. You will learn what information is needed about the drug and the pregnant person to answer her question. You will learn where to find the available information, how to interpret it and how to contribute to more data. You will also learn about therapeutics during pregnancy, risk communication to- and risk perception of- patients.
4	Text	**Course structure** In this course, you will encounter reading texts, informative graphics, videos and practice questions. These questions are only meant to practice. You can also take notes during the course with the notes function at the left of your screen whenever you are in an activity. This course is divided into nine chapters. Each chapter will take you about 1 to 2 hours to read. At the end of the course you can take an exam to test your understanding. You will need to get a score of 70% or higher to pass the course and receive your certificate. Don't worry if you don't pass the first time, you can take the exam a maximum of three times.
5	Text	**Advanced chapters** The biggest part of this course is basic information, meant for all health professionals who are interested. Some, so called 'advanced' chapters will go into more detail, and are meant for those who wish to learn more about that specific subject. Please note that you do not need to know this advanced material to pass this course.
6	Text	**Glossary** On the main page, you can find the glossary. It contains all the terms used in this course and their definitions. In order to open the glossary, click on documentation on the right side of your screen on the main page. A drop down menu should appear. In this menu you can click on the glossary. The terms are also highlighted in the learning content. If you click on them, their definition becomes visible.
7	Text	**The course chapters** The chapters in this course are: 1. Historical context 2. Principles of teratology 3. Considerations for teratogenic exposure during pregnancy

		4A. Principles of therapeutics in pregnancy (background) 4B. Principles of therapeutics in pregnancy (practice) 5. Medications and breastfeeding 6. Information sources 7. Risk communication 8. Reporting information 9. Course summary 10. Test your knowledge
8	Text	**About the authors** The authors of this course are teratology information specialists from different European countries. This e-learning package is one of the products of their participation in the IMI-ConcePTION project. This project involves an EU public-private partnership, where many parties cooperate to provide evidence-based information on the safety of medications during pregnancy and breastfeeding in an efficient, systematic and ethically responsible way. All content in this course was developed and approved by ENTIS members independently of Pharmaceutical Companies involved in the IMI-ConcePTION project.
9	Text	**Good luck!** We wish you a lot of fun following this course and hope you will learn everything you always wanted to know and perhaps even more. Click [Continue] to finish this activity and get started with the course!

Chapter 1: Historical context

1.1 Introduction to the chapter

Slide #	Work form	Content
1	Text	**Welcome to the first chapter: Historical context** Pregnant women get sick and sick women get pregnant. It is inevitable that medicines will be used during pregnancy. This

		has also been the case before we had the level of teratogenic awareness we have today. In fact, historical events such as the thalidomide tragedy have led to improved teratogenic awareness and pharmacovigilance. It is important for you to know the historical context of the use of medicines in pregnancy and breastfeeding, because we are still developing our knowledge on teratology and we don't know where we're going if we don't know where we've been.
2	Text	**The thalidomide tragedy** *In short…* "Thalidomide was a widely used drug in the late 1950s and early 1960s for the treatment of nausea in pregnant women. It became apparent in the 1960s that thalidomide treatment resulted in severe birth defects in thousands of children. Though the use of thalidomide was banned in most countries at that time, thalidomide proved to be a useful treatment for leprosy and later, multiple myeloma. In rural areas of the world that lack extensive medical surveillance initiatives, thalidomide treatment of pregnant women with leprosy has continued to cause malformations." *(Kim & Scialli, 2011)* We will often refer to this event during the trajectory of this course. We can and must avoid past mistakes such as this tragedy by educating ourselves on what has happened before. In addition, past events still have consequences today.
3	Text	**What are the learning objectives?** This chapter aims to outline some of the historical aspects of medication use in pregnancy that still have consequences today for women, healthcare professionals, regulators and health systems. It will give an overview of how teratology came to public attention, among other things due to the thalidomide tragedy. In this chapter, you will learn about: ● Early experience with harmful exposures during pregnancy including viruses, medicines and vitamin deficiencies. ● Regulatory reactions to harm caused by medicines in pregnancy. ● The impact of past experiences with medicines in pregnancy on women, health professionals and regulators. ● Recent regulatory experience with medications that cause birth defects.
4	Text + afbeelding	**This chapter is written by…** The author of this chapter is Prof. Brian Cleary. Brian has worked in the maternity services since 2002 and is Chief Pharmacist in the Rotunda Hospital Dublin and Honorary Clinical Associate Professor in the School of Pharmacy at the RCSI (Royal College of Surgeons in Ireland). He has postgraduate qualifications in Clinical Pharmacy (MSc, 2006) and Pharmacoepidemiology/ Medicines in Pregnancy (PhD, 2011). [Media 1.1: Image: Prof. Brian Cleary]

		 We wish you a pleasant learning journey. Good luck!

1.2 Teratological awareness

Slide #	Work form	Content
1	Text	**The development of teratological awareness** When looking at historical events, it becomes apparent that there was teratological awareness before tragedies such as the thalidomide tragedy took place. Human studies reporting the safety of medicines in pregnancy were first published in the 1940s. Before you dive deep into teratological awareness, let us have a look at the definitions that we use in this course.
2	Text	**How do we define teratology?** **Teratology** can be defined as the scientific study of congenital abnormalities and abnormal formations. Did you know teratology comes from the Greek word root *teras*? It can be interpreted as marvel, wonder, omen or monster. To get away from this word root, some organisations have begun to minimise the use of the term teratology e.g. the Teratology Society is now known as the Society for Birth Defects Research and Prevention.
3	Text	**Which definition speaks most to you?** There are several definitions for a **teratogen.** Take a look at the following two examples. *1) A teratogen is a drug or other substance that is capable of interfering with the development of an embryo or fetus, causing birth defects.* *2) A teratogen is an agent which when administered to the pregnant mother directly or indirectly causes structural or functional abnormalities in the fetus, or in the child after birth, though these may not become apparent until later life.* Both definitions are correct. However, the first definition focuses on the short term outcomes, while the second definition takes a broader view including long term developmental outcomes.
3	Text	**Teratological awareness** Teratology began as an effort to describe the origin of birth defects stemming from a variety of mystical and pseudoscientific theories attempting to explain the causes of congenital malformations including maternal impression, the position of the stars, hybridisation and maternal injury (Ujházy et al., 2012). Let's take a look at the timeline for an overview of early teratological awareness.

4	Text + graphic + pop-ups	**Timeline** (1/2) *Early researchers and their contributions* The next slides show you an interactive timeline on animal teratology and early researchers and historical events in modern teratology. You will also learn more about human studies on the safety of medicines in pregnancy. Click on the researchers on the timeline to find out their contributions to the field. [Media 1.2 Graphic: Timeline with names of the early researchers] *(Adapted from Ujházy, Mach, Navarová, Brucknerová, & Dubovický, 2012)* **W. Harvey** W. Harvey (1578–1657) used the term “developmental arrest”. **C.F. Wolff** C.F. Wolff (1733–1794) coined the term “germ layer” in his study on the intestine. **A. von Haller** A. von Haller (1708–1777) was first to describe the development of the chicken heart. **I.G. de Saint-Hillaire** I.G. de Saint-Hillaire (1805–1861) was first to introduce the term “teratology”. **C. Dareste** C. Dareste (1822–1899) discussed the modes of artificial induction of monstrosities (particularly by mechanical impulses during incubation of hen eggs). **R. Virchow** R. Virchow (1821–1902) gathered a unique collection of rare developmental disorders of the human body in the “Museum of Pathology” in the Charité Hospital, Berlin. **CH.R. Stockard** CH.R. Stockard (1879–1936) introduced the term “critical period”.
5	Text + afbeelding + pop-ups	**Timeline** (2/2) *Animal teratology* Click on the different data to learn more about the history of animal teratology.

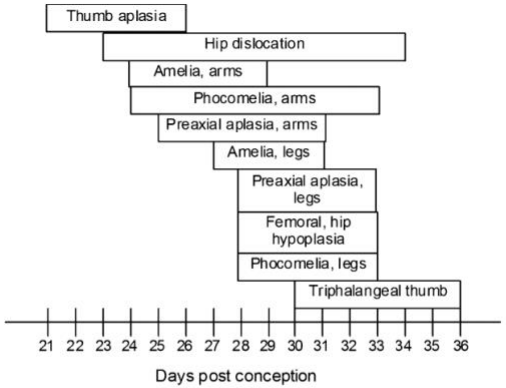
		[Media 1.3 Graphic: Visual timeline of animal teratology] *(Adapted from Ujházy, Mach, Navarová, Brucknerová, & Dubovický, 2012)* **1921** Experimentally induced teratogenicity in mammals. Lipid diet leading to disorders in limbs in pigs (Zilva et al). **1929** Harmful effects of ionizing radiation - Microcephaly due therapeutic radiation to the pelvis in pregnancy (Goldstein & Murphy). **1935** Eye disorders in pigs due to hypovitaminosis A (Hale). **1937** Masculinisation of female foetuses in mice due to the action of androgens (Raynaud). **1941** Reports of the impact of rubella infection in pregnancy on eye and cardiac disorders (McAllister Gregg). **1944** Neurodevelopmental impact of sodium bromide in rats (Hamilton & Harned). **1952** Report of multiple malformations in fetuses caused by aminopterin administered for therapeutic abortion in women with tuberculosis or cancer (Thiersch). **1959** Report of human malformations induced by environmental contamination- CNS disorders caused by methyl mercury (Kitamura).
6	Text	**Human studies of the safety of medicines in pregnancy** Around 1950, there were two important examples of large studies of the safety of medicines in pregnancy prior to the thalidomide tragedy. In 1949 Dougray noted that patients who were given antihistamines for toxaemia (pre-eclampsia) experienced relief from pre-existing nausea and vomiting. Treatment with antihistamines was not found to be associated with any adverse effects in 94 women with NVP. No adverse outcomes were reported. *(Dougray, 1949)*

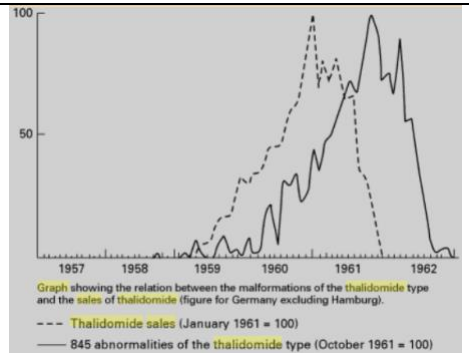
		A few years later in 1953, Lask reported on a trial of 60 women treated with antihistamines for severe NVP. Again, no adverse outcomes were reported. *(Lask, 1953)*
7	Multiple choice question	It is time for a quick practice test of your understanding. Try to answer the following question. **Which vitamin deficiency was among the first demonstrated teratogens in animal Teratology?** a. Vitamin A b. Vitamin B6 c. Vitamin C d. Vitamin D e. Folic acid Feedback correct answer: Yes, well done. Low vitamin A levels led to eye anomalies in pigs in a study reported by Hale et al in 1935. You will find a few more practice questions in the rest of this chapter. Feedback incorrect answer: No, that's incorrect. Low vitamin A levels led to eye anomalies in pigs in a study reported by Hale et al in 1935. You will find a few more practice questions in the rest of this chapter.
8	Text	**Conclusion** It is evident that there was significant teratological awareness among scientists prior to the thalidomide tragedy. It is also clear that human studies reporting the safety of medicines in pregnancy were published as far back as the 1940s. Next, we will look into the story of thalidomide. How did it come onto the market, and why? And what defects were noticed after the introduction of thalidomide on the market?

1.3 The story of thalidomide

Slide #	Work form	Content
1	Text	**The introduction of thalidomide on the market** Thalidomide was synthesised by the drug company Chemie Grunenthal in 1954, while searching for new antimicrobials. Early human studies indicated that thalidomide may aid restful sleep. This was a time when there was extensive use of sedatives and significant harm from respiratory depression with alternatives such as barbiturates. Thalidomide was licensed and marketed in up to 50 countries around the world in the late 50s and early 60s. It was marketed under a range of brand names including Softenon, Contergan and Distaval.
2	Multiple choice question	Widukind Lenz, a German Paeditrician, suspected thalidomide to be the cause of an outbreak of a certain type of malformations. **Do you know, or can you guess, what malformations we are referring to?** a. Limb and ear malformations b. Heart defects c. Head malformations d. Cleft palates Feedback correct answer: Yes, well done! Lenz suspected thalidomide to be the cause of an outbreak of limb and ear malformations. Feedback incorrect answer: No, that's incorrect. Lenz suspected thalidomide to be the cause of an outbreak of limb and ear malformations. However, thalidomide *can* be the cause of multiple malformations.
3	Text	**An outbreak of limb and ear malformations** Widukind Lenz, a German Paeditrician, suspected thalidomide as a cause of an outbreak of limb and ear malformations in Western Germany in November 1961. He advocated for the removal of thalidomide from the market as he demonstrated an association between thalidomide exposure in early pregnancy and a range of congenital anomalies. Ultimately the product was removed from markets worldwide (some countries took longer than others to do this). It is estimated that 10,000 babies were born affected by thalidomide embryopathy, of whom approximately 40-50% died before their first birthday.

4	Text + pop-up	**Thalidomide as a cause for birth defects** The use of thalidomide lead to the following birth defects: 1. Absence of the auricles with deafness. 2. Defects of the muscles of the eye and of the face. 3. Absence or hypoplasia of arms, preferentially affecting the radius and the thumb. 4. Thumbs with three joints. 5. Defects of the femur and of the tibia. 6. Malformations of the heart, the bowel, the uterus, and the gallbladder. <u>Did you know?</u> [Doctor pop-up] The first birth defects already begin to show within the sensitive period from day 21 post-conception.
5	Text + graphic	**A sequence of birth defects** There is the following sequence within the sensitive period from day 21 to day 35 post-conception. 21st – 23rd day: Absence of ears and deafness. 25th - 27th day: Absence of arms. 29th - 30th day: Phocomelia with 3 fingers. 32nd - 34th day: Thumbs with 3 joints. [Media 1.4 Graphic: Timing of exposure - day of exposure and associated anomaly]

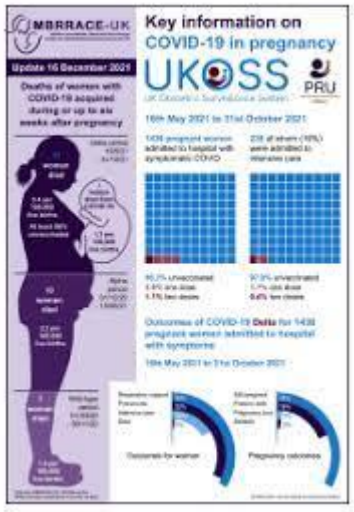
		 **FIG. 3.** Critical exposure periods for thalidomide embryopathy during human development. *(Kim & Scialli, 2011)*
6	Text + afbeelding	**No more thalidomide** Between May 1968 and December 1970 a German court case ended with a settlement between survivors and Grunenthal. The court concluded that “thalidomide was undoubtedly teratogenic and stressing it was more important to change the whole system of development, promotion and sale of drugs, of legal control and of the attitude of doctors and patients, than to find and punish a few individual scapegoats for errors by omission or commission of a sort which society almost universally had permitted or even encouraged, and which might have occurred in any pharmaceutical company.” Take a look at the following graph showing the relation between the malformations of thalidomide type and the sales of the thalodimide in Germany. [Media 1.5 Graphic: Showing the relation between the malformations of the thalidomide type and the sales of the thalodimide (figure for Germany excluding Hamburg)]

		 There was a clear temporal association between the withdrawal of thalidomide and cessation of the epidemic of birth defects. There are examples of severe effects from as little as a single dose.

1.4 Consequences for pharmacovigilance

Slide #	Work form	Content
1	Text	**Consequences for pharmacovigilance** Let's examine the impact of the thalidomide on pharmacovigilance and to place lessons learned on medicines in pregnancy in the broader historical context of pharmacovigilance. The thalidomide tragedy changed the regulation of medicines in Europe and around the world. The following five examples will give you further insight into how the tragedy made a regulatory difference.
2	Text	**#1 - The US Food, Drug and Cosmetic Act** *Proof of safety* The thalidomide tragedy accelerated the implementation of the Kefauver-Harris amendments to the Federal Food, Drug, and Cosmetic Act in the US. These amendments strengthened FDA powers to ensure that companies provided proof of efficacy as well as safety. The implementation of the original 1938 Act was precipitated by a previous pharmaceutical disaster- the case of Sulfanilimide Elixir, an oral liquid antimicrobial formulated in diethylene glycol that led to the deaths of over 100 people. Frances Kelsey, the FDA medical reviewer who prevented thalidomide being marketed in the US also played a role in investigating the sulfanilamide disaster. Her experience investigating this incident as a postgraduate student as well as experience of animal reproductive toxicology meant that she was not satisfied with the initial authorisation documents submitted to the FDA. *(Greene, 2012)* Further detail is available in the additional materials.
3	Text	**#2 - European Community directive** *Standards for approval* European Community directive 65/65 was the first European Pharmaceutical directive. It was a direct reaction to the thalidomide tragedy. It set out the standards for approval of proprietary medicinal products and the required information relating to safety and efficacy.
		#3 - US FDA Reproductive Toxicology requirements *Requirements for testing and data* Requirements for the systematic testing of pharmaceutical products for developmental toxicity prior to marketing grew from

		the thalidomide tragedy. In 1966 the US FDA outlined requirements for data on fertility and general reproduction, teratogenicity and perinatal outcomes.
4	Text	#**4 - More calls for pregnant women in clinical trials** *Inclusion of pregnant women in epidemic vaccination programmes* The thalidomide tragedy had an impact across the decades - even in the context of severe outbreaks such as Ebola, Zika or pandemics such as COVID-19, there is a strong reluctance to include pregnant women in clinical trials. Exclusion of women from clinical trials leads to exclusion from public health campaigns during outbreaks. There is potential for severe adverse outcomes as a result. During Ebola outbreaks maternal mortality ranges from 70 to 90% with near 100% fetal demise. There are calls to only exclude pregnant women from outbreak or epidemic vaccination programmes if a review of evidence by relevant experts concludes that risks to the woman and their offspring are greater than the risks of not being vaccinated. *(Krubiner, et al.)*
5	Text	**#5 - Comparison with currently marketed medicines** *An important historic example* The thalidomide tragedy was used as an example for people questioning the safety of COVID vaccines in pregnancy. Disinformation on vaccines in pregnancy significantly impaired vaccine uptake during pregnancy. Unfortunately, poor vaccine uptake led to maternal deaths in some countries. The image below shows the percentages (vaccinated and unvaccinated) of 1436 pregnant women who were admitted to the hospital with symptomatic COVID between 16th May 2021 to 31st October 2021. As you can see, over 96% of the pregnant women admitted to the hospital did not receive a single dose of the vaccine. Research also shows that during this same time period 88% of the woman who died of COVID-19 during or up to six weeks after the pregnancy were unvaccinated. [Media 1.6 Infographic MBRRACE-UK (only the squares)]

		 *(MBRRACE-UK, 2021)*
6	Text	**Conclusion** In practical terms the thalidomide tragedy altered public and professional perceptions of medication use in pregnancy. This was the start of a period of paternalism where pregnant women became therapeutic orphans due to exclusion from clinical trials and consequently the manufacturer's product information. In the next chapter, we will further examine the dangers of medication exposure in pregnancy. For example, have you already heard of Diethylstilbestrol and Valproate?

1.5 Dangers of medication exposure in pregnancy

Slide #	Work form	Content
1	Text	**Have you heard of these other historical examples?** Thalidomide is one of a number of medications that have been demonstrated to be human teratogens. Other examples include the synthetic oestrogen diethylstilboestrol and the anti-seizure medication valproate. In this chapter, we will investigate why these medications were promoted, the dangers of exposure and how their association with adverse health outcomes came to light.
2	Text + graphic	**Diethylstilbestrol** *A synthethic oestrogen* Marketed between the 1940s and 1970s, DES is a synthetic oestrogen that was promoted to “support” pregnancy. The proposed mechanism of action was to overcome oestrogen deficiencies that led to adverse pregnancy outcomes such as miscarriage, preeclampsia or preterm birth. [Media 1.7 Image: Baby ad]  *(Source: https://diethylstilbestrol.co.uk/des-adverts/)* In 1970 the association between DES exposure in utero and a rare cancer- vaginal clear cell adenoma was found in a case control study including 8 young women who developed this rare cancer. The association came to light after an observation from a mother of one of the women.
3	Text	**An ‘accidental’ discovery**

		As Ulfelder described in his paper *The stilbestrol disorders in historical perspective*, *"we were on the watch for an explanation, but none suggested itself until the mother of one of my patients reported as additional past history that she had been prescribed DES during pregnancy to minimize the chance of less of the fetus: this loss had occurred with her only previous pregnancy several years before. Somewhat to my surprise, I found on questioning that several other mothers of the group had also taken stilbestrol during pregnancy, as had been the case in two instances – one in San Francisco and one in Mexico City – cases which I learned about through visitors or medical journals." (Ulfelder, 1980).* Ulfelder was not the last to notice the association between DES exposure in utero and a rare cancer.
4	Text + afbeelding	**Further research** Follow up studies of reproductive outcomes following gestational DES exposure demonstrated that there were associations with a wide range of adverse health outcomes in the daughters of women who used DES during pregnancy: [Media 1.8 Graphic: Table Cumulative Risks] **Table 3. Cumulative Risks of Adverse Health Outcomes in Women with and Those without Diethylstilbestrol (DES) Exposure and the Excess Risk Due to Exposure.*** | Adverse Outcome	Exposed Women	Cumulative Risk†	Unexposed Women	Cumulative Risk†	Excess Risk (95% CI)‡
---	---	---	---	---	---
	no./total no.	*percent*	*no./total no.*	*percent*	
Infertility	1144/3769	33.3	252/1654	15.5	17.8 (14.5 to 20.9)
Spontaneous abortion§	916/2690	50.3	328/1291	38.6	11.7 (3.3 to 20.1)
Ectopic pregnancy§	255/2692	14.6	36/1293	2.9	11.7 (8.9 to 14.5)
Loss of second-trimester pregnancy§	201/2692	16.4	35/1293	1.7	14.7 (8.5 to 20.9)
Preterm delivery¶	590/2268	53.3	89/1140	17.8	35.4 (27.3 to 43.6)
Preeclampsia¶	209/2299	26.4	77/1072	13.7	12.7 (4.5 to 20.9)
Stillbirth¶	54/2385	8.9	16/1239	2.6	6.3 (−0.8 to 13.3)
Neonatal death¶	57/2383	7.8	7/1238	0.6	7.2 (1.9 to 12.5)
Early menopause	181/3993	5.1	49/1682	1.7	3.4 (2.1 to 4.7)
Cervical intraepithelial neoplasia, grade ≥2	208/4120	6.9	40/1785	3.4	3.5 (1.5 to 5.4)
Breast cancer at ≥40 yr	59/3693	3.9	20/1647	2.2	1.7 (−1.4 to 4.7)	 * Total numbers of women vary among outcomes, primarily reflecting whether all, gravid, or parous women were included in the analyses, but also owing to some missing responses to the questionnaires ascertaining the outcome and to missing covariates. † Cumulative risks were calculated with age as the time metric and adjustment for date of birth and cohort. ‡ Excess risk was not computed for clear-cell adenocarcinoma because there were no cases in unexposed women. The cumulative risk for exposed women was 0.1% (95% CI, 0.0 to 0.3). § The analysis was restricted to gravid women and adjusted for number of pregnancies. ¶ The analysis was restricted to parous women and adjusted for number of births. *(Hoover, Pfeiffer, Adem, Cheville, 2011)* Unfortunately, DES was widely used and continued to be used even after the findings of this study in some countries. *(Veurink, Koster, Berg, 2005)*
5	Text	**Valproate** *A synthesised valproic acid* Synthesised first in 1882, valproic acid, derived from valeric acid, a component of the valerian herb, was originally used

		as a solvent by chemists. In 1962, chance and careful observation led to the discovery of valpric acid's antiseizure activity by French researchers. While testing the antiseizure activity of other molecules, researchers discovered that valproic acid itself reduced seizures in a mouse seizure model. *(Janković & Janković, 2020).* *An effective generalized epilepsy medication* Valproic acid proved most effective in the management of generalised epilepsies with relatively good tolerability relative to other antiseizure medications. After initial marketing in France in the late 1960s, valproic acid was marketed in other European countries through the early 1970s.
6	Text + graphic + pop-ups	**Key points** Click on the timeline below to discover some key points in the timeline on valproic acid in pregnancy. [Media 1.9 Graphic: Timeline valproic acid with dates] *(IMMDS, 2020)* **1882** Valproic Acid synthesised. **1963** Discovery of antiseizure properties. **1967** Licensed in France as antiseizure medication. **1972** UK license limited to 1 year and restricted hospitals/clinics due to animal data suggesting possibility of congenital anomalies. Retrospective cohort study (Speidel & Meadow) demonstrated twice the expected frequency of major congenital malformations in 427 pregnancies in 186 women with epilepsy. *This is an adaption of the timeline included in the UK Independent Medicines & Medical Devices Safety Review (also known as the Cumberledge Review). You can download the original source from their website. The link is stated in the additional resources.* As you can see, the first data suggesting the possibility of congenital anomalies were already sourced in the early 1970s. However, it took time before restrictions and pregnancy prevention programmes were strengthened.
7	Text + afbeelding + pop-ups	**What happened next?** Click on the timeline below to discover some key points in the timeline on valproic acid in pregnancy. [Media 1.10 Graphic timeline with dates]

		(IMMDS, 2020) **1974** UK license restricts use in women of childbearing age to “severe cases or those resistant to other treatment.…This compound has been shown to be teratogenic in animals. Any benefit which may be expected from its use should be weighed against the hazard suggested by these findings.”. **1975** Irish license: “‘In view of its teratogenicity in animals it should not be used in pregnancy unless the physician considers it necessary”. **1980-87** Case reports emerged of congenital anomalies associated with valproic acid. Case series described “Fetal Valproate Syndrom”. **1997** North American AED Pregnancy Registry established. Review of 5 prospective studies- increased risk of major congenital malformations with valproic acid monotherapy. Dose response effect observed. **1999** Support groups established for families of affected children. EURAP- European Registry of Antiepileptic Drugs in Pregnancy established. A German prospective study indicated AED exposure in utero linked to long-term neurodevelopmental effects.
8	Text + graphic + pop-ups	**Research developments in the early 2000s** More and more studies demonstrated the association with serious adverse health outcomes, such as impaired mental and motor development in valproic acid exposed children. Click on the timeline below to discover the steps that were taken based on these findings. [Media 1.11 Graphic timeline steps taken with dates] *(IMMDS, 2020)* **2011** US FDA warned of the possibility of impaired cognitive development. **2013** FDA Safety announcement based on NEAD study. **2014** Australian Therapeutic Goods Administration- updated information on cognitive impairment in infants. EMA PRAC Risk benefit balance remains favourable- restrictions strengthened. Dear Healthcare Professional letter based on EMA PRAC warnings. **2017**

		EMA Public Hearings on valproic acid in pregnancy. **2018** EMA PRAC- strengthening of restrictions and pregnancy prevention programme.
8	Multiple choice question	Before we move onto the next chapter, let's see if you can answer these practice questions. **Which adverse pregnancy outcomes was diethylstilbestrol associated with among grandchildren born to women who took the drug during pregnancy?** a. Cardiac anomalies b. Cleft lip/palate c. Neonatal death d. Neural tube defects e. Virilization Feedback correct answer: Yes, well done. Exposure to diethylstilbestrol in utero led to structural malformations of the reproductive tract. This led to subsequent fertility issues and pregnancy complications for the daughters exposed to DES in utero, affecting the grandchildren of the women who took the drug originally. Are you ready for the last practice question? Feedback incorrect answer: No, that's incorrect. Exposure to diethylstilbestrol in utero led to structural malformations of the reproductive tract. This led to subsequent fertility issues and pregnancy complications for the daughters exposed to DES in utero, affecting the grandchildren of the women who took the drug originally. Are you ready for the last practice question?
9	Multiple choice question	**Which medication was found to be associated with congenital anomalies when used for termination of pregnancy in the 1950s?** **a**. Aminopterin b. 5-Mercaptopurine c. Methotrexate d. Mifepristone e. Misoprostol Feedback correct answer: Yes, well done. When used for termination of pregnancy in the context of cancer or tuberculosis, aminopterin failed to terminate the pregnancy and led to the delivery of babies with congenital anomalies including hydrocephalus, meningoencephalocoele and cleft lip/palate. Now it's time for the next chapter.

		Feedback incorrect answer: No, that's incorrect. When used for termination of pregnancy in the context of cancer or tuberculosis, aminopterin failed to terminate the pregnancy and led to the delivery of babies with congenital anomalies including hydrocephalus, meningoencephalocoele and cleft lip/palate. Now it's time for the next chapter.
9	Text	**Conclusion** Thalidomide, diethylstilboestrol and valproate have affected health professional and public perception of medicine use in pregnancy. Each example has also had a significant impact on regulators and the evolving approach to pharmacovigilance in pregnancy and breastfeeding. Lessons from history: ● Environmental exposures may affect the fetus with potential for delayed effects. ● Animal studies do not always predict human effects. ● Early warning is essential. ● Epidemiological research in this context is vital.
10	Text	**The best way to move forward** It is evident that there needs to be a co-ordinated ecosystem of clinicians, researchers and regulators to work in a responsive manner, ensuring that teratogens are promptly identified and that comprehensive regulatory responses are clearly communicated to influence HCP and patient behaviours. We must also ensure that the pendulum does not swing too far and that essential medications are not avoided during pregnancy. All healthcare professionals require a clear understanding of the benefits and risks of medication use in pregnancy and breastfeeding. They also need to be able to support patients with effective risk communication around the use of medicines in pregnancy
11	Text	**One last note** The UK Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries (MBRRACE) initiative demonstrates the long term impact of the historical context covered in this module. Repeated MBRRACE reports demonstrate the devastating outcomes of women avoiding essential medications in pregnancy. Previous reports called for pre-pregnancy counselling that addresses the safety of medicines in pregnancy and flags particular high risk groups including epilepsy, diabetes, asthma, cardiac disease, autoimmune disorders, renal or liver disease, obesity, severe pre-existing or past mental illness or HIV infection.

		Please read the recent MBRRACE reports to further study patient experiences. You can find the link to download the reports in the additional materials, as well as all other references and resources. Thank you for your participation and good luck on the next chapter!

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Veurink M, Koster M, Berg LTW de J van den. The history of DES, lessons to be learned. Pharm World Sci. 2005 Jun;27(3):139–43.
Ulfelder H. The stilbestrol disorders in historical perspective. Cancer. 1980;45(12):3008–11.

Additional resources

1. Historical context

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- Watch: Thalidomide Survivor Perspective: Video of Irish Doctor and Thalidomide Survivor. Unique perspective from personal experience and as a health professional- Spark; also sets out why the eLearning package is important
- Watch: Cartoon about Frances Oldham Kelsey (https://youtu.be/4wIBCoxuOJ0)

2. Teratological awareness

3. The story of Thalidomide

- Read: Brynner R, Stephens TD. Dark remedy: the impact of Thalidomide and its revival as a vital medicine. New York: Basic Books; 2001. 228 p.
- Read: Suffer the children: the story of thalidomide. New York: Viking Press; 1979. 309 p.
- Read: Summary of History of Thalidomide lecture given by Lenz in 1992 (https://thalidomide.ca/wp-content/uploads/2017/12/Dr-Lenz-history-of-thalidomide-1992.pdf)
- Listen: Thalidomide: An Oral History (https://wellcomecollection.org/works/dmpcsthv)
- Watch: JFK announcing new drug laws post thalidomide (https://www.britishpathe.com/video/president-kennedy-calls-for-stronger-drug-laws)
- Read: PREVENT Working Group (https://www.who.int/immunization/sage/meetings/2018/october/1_PREVENT_Recs_Excerpts_for_SAGE.PDF)
- Read: MBRRACE-UK (https://www.npeu.ox.ac.uk/assets/downloads/npeu-news/MBRRACE-UK_Rapid_COVID_19_DEC_2021_-_Infographic_v13.pdf)
- Read: Diethylstilbestrol advertisement (https://diethylstilbestrol.co.uk/des-adverts/)

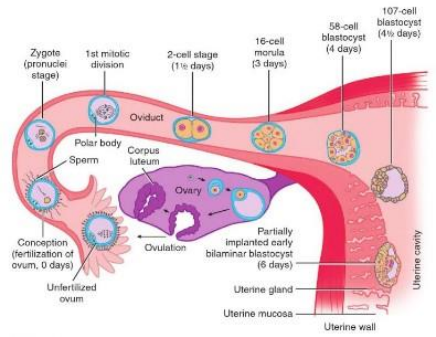
- Read: IMMDS Valproate timeline with key events (https://www.immdsreview.org.uk/downloads/Annexes/Annex-C-Valproate-timeline.pdf)
- Read: MBRRACE reports (https://www.npeu.ox.ac.uk/mbrrace-uk)

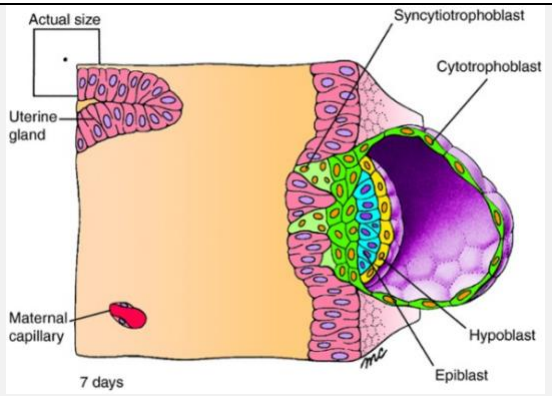
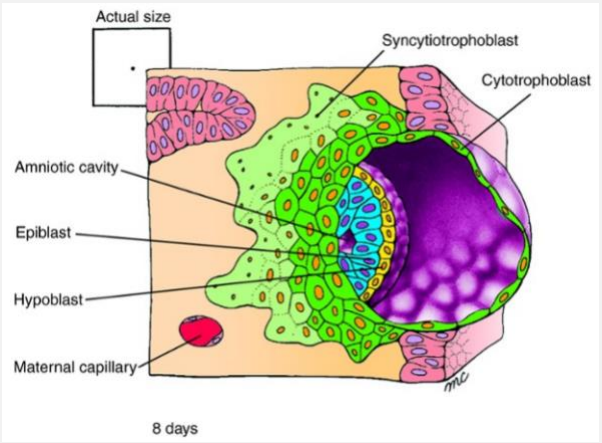
Chapter 2: Principles of teratology

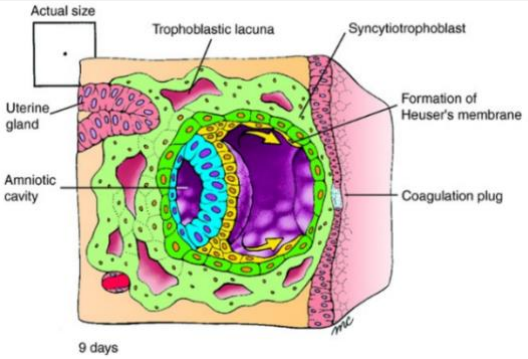
2.1 Introduction to the chapter

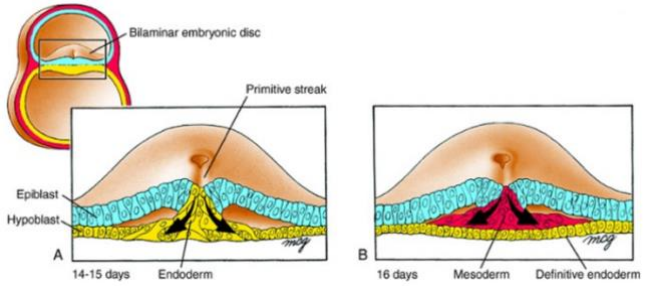
Slide #	Work form	Content
1	Text	**Welcome to chapter 2: Principles of teratology** The use of medication in pregnancy is common, more common than you might think. Research shows that around 70% of pregnant women receive a prescription and use medication at least once during their pregnancy. It is important to realize that in every pregnancy there is a chance of having a child with a malformation or a defect. However, some exposures can increase the chance of having a child with malformations. How does this work? What exactly are malformations? Who is susceptible to this increased risk? What other factors play a role?
2	Text	**What are the learning objectives?** In this chapter, we will discuss what congenital malformations are and how often they occur. You will also learn about the possible range of effects that teratogenic exposures can have. In chapter 1, you have learned about the history of teratology. In this chapter you will learn more about the starting point of teratology as a field of medicine, a concept which was described by James Wilson. Wilson's 6 basic principles of teratology will be used to explain the theoretical background in both chapter 2 and chapter 3. We assume that you have some basic knowledge in the field of embryology. If you want to have more detailed information about basic embryology, you will find it in advanced chapter 2.1.1. Good luck!
3 **ADVANCED**	Text	**Advanced knowledge on basic embryology** In this advanced chapter, we will explore the entire development of an unborn child. You will learn about human embryology from week to week and after that about the fetal period. This content will give you more background information to better understand what you will learn about the principles of teratology.
4 **ADVANCED**	Text	**Embryonic period (0 to 8 weeks after conception)** *Timeline of the embryonic period*

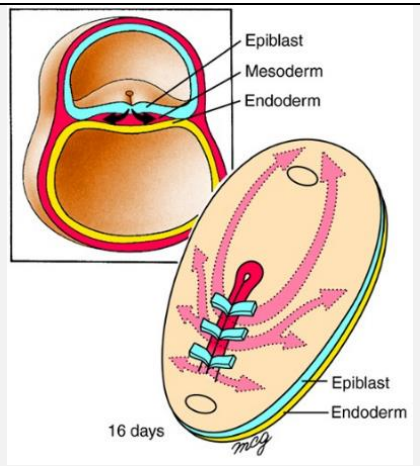
		The timeline of the embryonic period starts the second after conception up to 8 weeks after. We call this period the embryonic period. Week 1: Human embryology starts with the production of gametes, also called gametogenesis. This process occurs in the ovaries and testes and it involves meiosis. The purpose is to establish a haploid cell. In females, this process is called oogenesis and the final cells produced are eggs or oocytes. All oocytes are developed during fetal development and enter a state of dormancy. At puberty, each month one oocyte matures and is ovulated. In males, the process of spermatogenesis is a cycle of about 3 months, and the final cells produced are sperm cells or spermatozoa. Spermatozoa are produced continuously from puberty until death. When a sperm cell fertilizes an egg, the egg and sperm chromosomes are united in a new cell. In this new cell, called the *zygote*, the diploid number of chromosomes is restored. I-icon [Pop-up text Gametes] **Gametes** Gametes are reproductive cells or sex cells. Female gametes are called ova or egg cells, and male gametes are called sperm. I-icon [Pop-up text Meiosis] **Meiosis** Meiosis is a sequence of cell divisions by which the number of chromosomes in the gametes is halved. Pop-up afbeelding meiosis I-icon [Pop-up text Haploid cell] **Haploid cell** Typical body cells contain 23 pairs of chromosomes (thus 46 chromosomes in total) and are diploid. A haploid cell contains 23 chromosomes (one of each pair).
5 **ADVANCED**	Text + afbeelding	**Cleavage** *Timeline of the embryonic period* The next step is *cleavage*. The zygote divides into two cells by mitosis. Each cell then continues to divide into two more cells. This is the pre-implantation period, during which the zygote divides but does not grow larger. A solid ball of cells has formed called the *morula* and subsequently the *blastocyst*. All of the cells of the embryo are now *totipotent*, which means they can differentiate into any tissue.

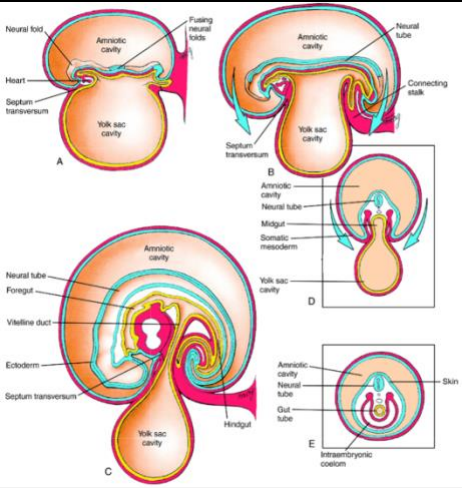
		At this stage, the embryo can obtain nutrients and eliminate waste by diffusion. [Media 2.1 Fertilization and cleavage]  *(Source?)*
6 **ADVANCED**	Text + afbeelding	**Week 2** *Timeline of the embryonic period* During the second week, the blastocyst is implanted in the uterine wall. The blastocyst consists of an inner cell mass called the embryoblast, and an outer trophoblast. The trophoblast begins to proliferate when it comes in contact with the uterine endometrium. Some of the proliferating cells lose their cell membranes and form a mass of cytoplasm called the syncytiotrophoblast. The cells on the side of the blastocyst remain their membrane and form the cytotrophoblast. These layers do not contribute to the embryo but to the extraembryonic membranes. The embryoblast splits into two layers: the epiblast and the hypoblast. These two layers are called the *bilaminar embryonic disc*. The amniotic cavity forms. [Media 2.2 Embryoblast]

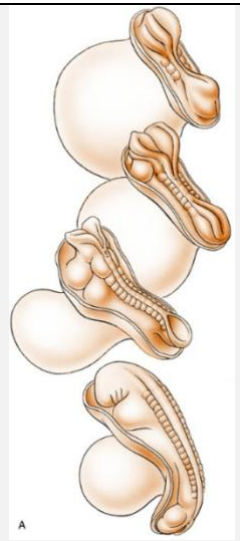
		 *(Source?)*
7 **ADVANCED**	Text + afbeelding	**After 8 days** *Timeline of the embryonic period* The syncytiotrophoblast expands and covers more of the blastocyst. The amniotic cavity is forming within the epiblast. [Media 2.3 Syncytiotrophoblast]  *(Source?)*

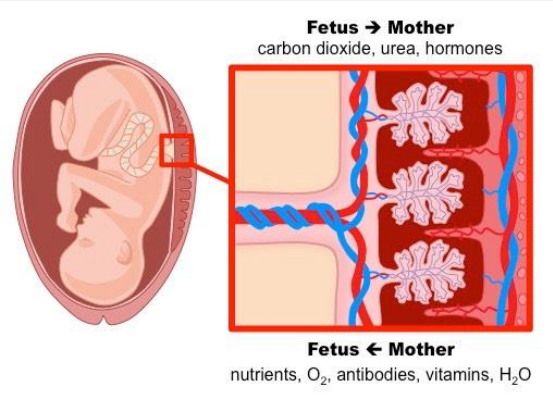
8 **ADVANCED**	Text + afbeelding	**On the 9th day** The endometrium thickens and becomes more vascularized. The uteroplacental circulation begins to form on day 9, when lacunae in the trophoblast begin to connect with maternal capillaries. [Media 2.4 Endometrium]  *(Source?)*
9 **ADVANCED**	Text + afbeelding	**Week 3** Around day 15, a thickening groove forms on the embryonic disc. This is called the primitive streak and this defines the major body axes: the cranial-caudal axis (head to tail), the dorsal-ventral axis (back to belly), and the medial-lateral axis (left to right). During *gastrulation*, the cells of the epiblast move through the primitive streak and undergo a transformation to form the mesoderm. The primitive tissue layers called *germ layers* are formed: the endoderm, mesoderm and ectoderm. Tissues and organs will rise from these germ layers during further development. The embryo now consists of a trilaminar flat disc of cells (the embryonic disc) that is positioned between two structures: the amnion and the yolk sac. [Media 2.5 Primitive streak]

		 *(Source?)*
10 **ADVANCED**	Text + afbeelding	**Around the 17th day** Around day 17 of development, the notochord begins to form as a hollow tube from the primitive streak. It is then transformed from a hollow tube to a solid rod. The notochord later plays an important role in the induction of the vertebral bodies. At this stage, the ectoderm thickens to form the neural plate. This is the rudiment of the central nervous system. The lateral edges of the neural plate give rise to the neural crest cells. These cells will later form a variety of structures. Also at this stage, the endoderm will fold to form three subdivisions of the gut: the foregut, midgut and hindgut. At the end of the third week, fetal blood vessels begin to form. [Media 2.6 Endoderm]

		 *(Source?)*
11 **ADVANCED**	Text + afbeelding	**Week 4** The next step is the formation of the body plan. This involves extensive folding of the embryo. The body folding begins near the perimeters of the embryonic disc (see figure 4). The purpose of this folding is to separate the embryo from the amnion and the yolk sac. The flat disc becomes three dimensional and is converted into the *tube-within-a-tube body plan* (see figure 4). The outer tube is formed from the ectodermal germ layer and is the primitive skin. The inner tube is formed from the endodermal germ layer and is the primitive gut. The tubes are separated by the mesoderm, which is the primitive skeletal support. <u>Did you know?</u> [Pop-up text] Note that the neural tube is not considered to be one of the tubes in the tube-within-tube body plan. [Media 2.7 Formation body plan]

		 *(Source?)*
12 **ADVANCED**	Text + afbeelding	**Around the 28th day** *Timeline of the embryonic period* The germ layers further change to establish organ rudiments. The neural plate folds to form the hollow neural tube. The neural tube first closes near the hindbrain, and then it further closes in cranial and caudal directions like a zipper. The neural tube completes closure at 28 days after conception. The neural tube differentiates into the brain and the spinal cord. [Media 2.8 Organ rudiments]

		 *(Source?)* Neural crest cells migrate to other locations where they differentiate into a wide range of structures and cell types. Other organ rudiments such as the aorta can also be seen. After this, the phase of organogenesis begins. The organ rudiments begin to grow and differentiate to form the organs. These further develop and organ systems start to function.
13 **ADVANCED**	Text	**Week 5-8** *Timeline of the embryonic period* In the next weeks of the embryonic period, the embryo will form during *morphogenesis*. The beginnings of the rudiments will develop into the organs and organ systems. Cells will change in shape, position, size and number. Cells can communicate through cell-cell interactions and signaling pathways. These signals determine the fate of each cell. Regulatory genes induce the expression of other genes, which activates the encoding of the specific cells and tissues. All organ systems are present by 8 weeks, but few of them are functional. Exceptions are the heart and blood vessels: the blood circulation begins 4 weeks after conception. During this period, genetic mutations and/or environmental exposures can disturb embryogenesis, resulting in *dysmorphogenesis*.

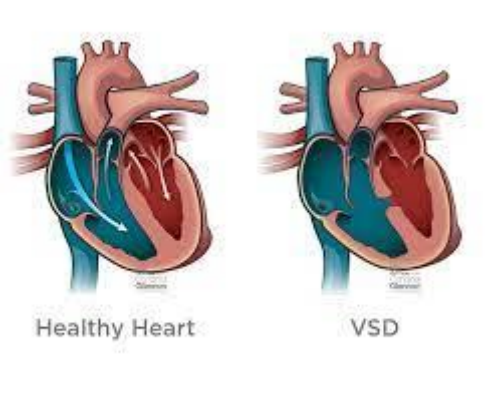
14 **ADVANCED**	Text + afbeelding	**Fetal period (9 to ± 38 weeks after conception)** *Timeline of the Fetal period* The fetal period is devoted to the maturation and growth of the organ systems. In the embryonic period, the endometrium has thickened and will begin to form the placenta. The umbilical cord forms due to the body folding that is described earlier. The placental villi continue growing during the fetal period and eventually form the placental villous tree. Maternal blood enters the placenta. Oxygen and nutrients pass from the maternal blood across the cells of the villi into the fetal blood. Likewise, waste products pass from the fetal blood to the maternal blood. Maternal antibodies can cross the placenta, giving passive immunity to the fetus, which lasts during the first months after birth. The fetus grows from about 14 grams at the beginning of the fetal period, to about 3500 grams at birth. Some organs, such as the brain, are still immature at birth and finish maturing after birth. [Media 2.9 Fetal period]  *(Image from BioNinja)*

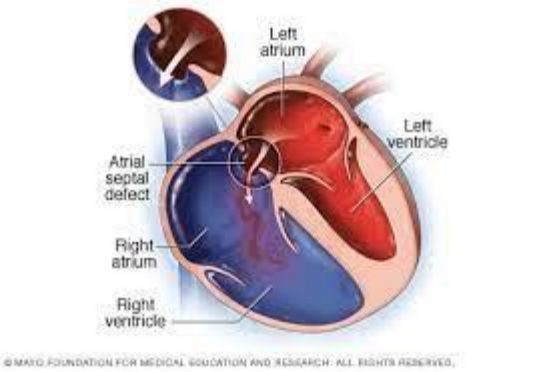
2.2 Causes of malformations at birth

Slide #	Work form	Content
1	Text	**Causes of malformation at birth**

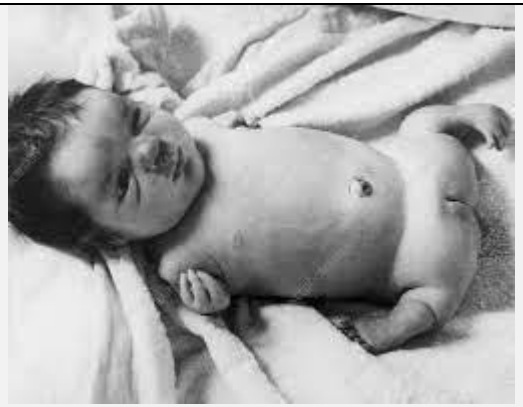
		The majority of women take some form of medication during their pregnancy. In this chapter you will be introduced to the connection between medication and causes of malformation. This chapter focuses on the different causes of malformations that can occur at birth. First, you will learn about what is considered to be a malformation. After that, it is placed in a wider context. What do we know about the causes of malformations at birth? What is the background rate of congenital anomalies in the population and what proportion of malformations are caused by exposure to medication during pregnancy? At the end of this chapter, you will be able to answer these questions.
2	Multiple choice question	Malformations can be divided into major and minor malformations. **Which one of these malformations would you classify as major?** a. Pigmented spots b. Small ears c. Cleft lip d. Heterochromia *Feedback correct answer:* Yes, correct! Major malformations can be life-threatening and can cause lifelong disability. They have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention. Cleft lip is therefore the right answer. *Feedback incorrect answer:* No, that's incorrect. Major malformations can be life-threatening and can cause lifelong disability. They have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention. Cleft lip is therefore the right answer.
2	Text	**What are malformations?** A congenital malformation or birth defect is an abnormality that is present at birth which affects a body structure or function (long term development of the child). Malformations can be divided into major and minor malformations. **Major malformations** can be life-threatening and can cause lifelong disability. They have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention. Examples of major birth defects are cleft lip, cleft palate, spina bifida and gastroschisis. **A minor malformation** poses no significant health problem in the neonatal period and tends to have limited social or cosmetic consequences for the affected individual. Examples of minor malformations are small ears and pigmented spots. Minor malformations can sometimes be associated with major malformations.

3	Text	**Causes of major malformations** For most birth defects (50%), the cause is unknown. Most birth defects are likely caused by a complex mix of factors. These factors include our genes, chromosomes, disorders and an exposure of the pregnant women to a teratogen. It's not clear how these factors might work together to cause birth defects. Many birth defects fall under the category of **multifactorial disorders** (20-30%). These are birth defects due to complex genetic and environmental interaction. There can also be **chromosome abnormalities** (6%): a chromosome or part of a chromosome is missing. Other birth defects result from having an extra chromosome. A similar percentage is related to abnormalities in the genes. In **single-gene abnormalities** (7.5%), one or more genes are changed or have a mutation that results in them not working properly. Similarly, a gene or part of the gene might be missing. A small proportion (5-10%) of major malformations are caused by exposure to a teratogen during pregnancy.
4	Text	**Causes of malformations at birth** Teratogenic agents include: ● Medication e.g. thalidomide, valproic acid, isotretinoin, misoprostol. ● Alcohol, smoking, recreational drug use. ● Chemicals e.g. methylmercury, lead, xylene. ● Maternal medical condition like diabetes, obesity, phenylketonuria. ● Maternal infections e.g. rubella, zika, cytomegalovirus. ● Radiation. ● Other agents e.g. exposure to carbon monoxide, electric shock. This course will focus mainly on the possible teratogenic effects of maternal medication. As you have just learned however, only a very small percentage of malformations can be attributed to the effects of maternal medication.
5 **ADVANCED**	Text	**Specific major malformations** *An overview* As you just learned, a malformation is classified as major if it is life-threatening or if it has medical or social implications. A major malformation often needs surgical repair. In this section you will learn about some important and/or frequently occurring major malformations.

		Many different major malformations have been described, at the end of the chapter you can find a resource for an overview of all major malformations (*UpToDate*). Research in Europe (Eurocat, 2010) showed that congenital heart defects were the most common non-chromosomal subgroup of congenital anomalies, at 6.5 per 1,000 births. Second most common were limb defects (3.8 per 1,000), followed by anomalies of the urinary system (3.1 per 1,000) and nervous system defects (2.3 per 1,000).
6 **ADVANCED**	Text + afbeelding	**Heart defect examples** *Ventricular septal defect (VSD)* VSD is one of the most common congenital heart lesions. There is a hole in the wall between the lower ventricles (heart chambers), which allows blood to flow from the left to the right ventricle. This means that oxygen-rich blood is pumped via the right ventricle to the lungs. The heart is less efficient and has to work harder. Very small VSDs will close on their own, larger defects may require surgical or medical treatment. [Media 2.9 Healthy heart + VSD]  *(Image from SSM health)*
7 **ADVANCED**	Text	**Heart defect examples** *Atrial septal defect (ASD)* ASD is a congenital heart lesion. There is a hole in the wall between the upper ventricles (atria), which normally closes before or shortly after birth. It means that more blood enters the right atrium and the lung circulation. The

		increased pressure can damage the blood vessels in the lung. Small ASDs do not cause harm and may close during childhood. Larger ASDs may require surgical or medical treatment. [Media 2.10 ASD]  *(Image from CDC)*
8 **ADVANCED**	Text + afbeelding	**Limb defect examples** *Clubfoot* Clubfoot (also known as talipes) occurs when the achilles tendon is too short. As a result the foot of the affected limb will be turned inward. It may occur in one or both feet. A child with clubfoot needs early treatment and sometimes minor surgery to correct the position of the foot. [Media 2.11 Clubfoot]

		 *(Image from Shutterstock)*
9 **ADVANCED**	Text	**Limb defect examples** *Polydactyly* Polydactyly means having more than the normal number of fingers or toes. It may range from a small bump to a complete and functioning digit. It will not cause damage or major problems but may require surgery for correction.
10 **ADVANCED**	Text + afbeelding	**Limb defect examples** *Phocomelia* Phocomelia refers to congenital malformations to the limbs. The bones in arms and/or legs are underdeveloped or absent. This condition can be inherited as part of a genetic syndrome but is also known to be part of the thalidomide syndrome (as discussed in Chapter one). [Media 2.12 Phocomelia]

		 *(Image from Sciencephoto.com)*
11 **ADVANCED**	Text + afbeelding	**Nervous system defect examples** *Spina bifida* Spina bifida is a neural tube defect. The neural tube is the structure in the developing embryo from which the brain and spinal cord will arise. A spina bifida patient has an opening in the vertebral column, exposing part of the spinal cord. The opening is caused by the failure of the neural tube to close properly during embryonic development. This can lead to significant neurological impairment and disability in life. A child with spina bifida needs surgery soon after birth. Sometimes the defect can even be repaired in utero. [Media 2.13 Spina Bifida]

		 *(Image from Commons.wikimedia.org)*
12 **ADVANCED**	Text + afbeelding	**Other commonly known defects** *Cleft lip / cleft palate* Cleft lip and cleft palate are birth defects that occur when a baby's lip or mouth do not form properly during pregnancy. Cleft lip and cleft palate are openings or splits in the upper lip, the roof of the mouth (palate) or both. Children with clefts usually need surgery, and often also dental care and speech therapy. [Media 2.14 Cleft lip]  *(Image from Alamy stock vector)*
13	Text +	**Other commonly known defects**

ADVANCED	afbeelding	*Gastroschisis* Gastroschisis is a birth defect of the abdominal wall. The baby's intestines are found outside of the baby's body, exiting through a hole beside the belly button. It occurs when the abdominal wall is not formed correctly. The baby will need surgery to replace the organs inside the body. In case of a large gastroschisis defect, the repair surgery may have to be performed in several stages. [Media 2.15 Gastroschisis]  *(Image from Commons.wikimedia.org)*
14 **ADVANCED**	Text + afbeelding	**Other commonly known defects** *Embryopathy* The malformations described so far refer to isolated defects. Some teratogenic agents can cause a combination of birth defects, called an embryopathy. An embryopathy consists of a fixed combination of major and minor malformations. However, not all abnormalities occur in each affected newborn. The thalidomide embryopathy is a well-known example, but for instance retinoic acid (such as isotretinoin used for treatment of acne), warfarin and alcohol are also known for their ability to cause their own unique pattern of congenital abnormalities.

2.3 Introducing teratology

Slide #	Work form	Content
1	Text + afbeelding	**Introducing teratology** As mentioned in the first chapter on historical context, the thalidomide tragedy changed the perception of the safety of the unborn child within the womb. It showed that maternal medication during pregnancy is capable of seriously harming the embryo or fetus. Just before this tragedy, James Wilson had published the article "Experimental Studies on Congenital Malformations" in the Journal of Chronic Diseases in 1959. He tried to provide general principles and guidelines of birth defects and teratogens. It is seen as the starting point of teratology as a field in medicine. [Media 2.16 James Wilson]  *An image of James Wilson retrieved from Wiley Online Library (see additional resources).*
2	Text + afbeelding + pop-ups	**A timeline** The timeline below shows the publications of Wilson as well as the important events in the thalidomide drama. Click on the different events for more information. [Media 2.17 Graph timeline Wilson] **1959** [Pop-up text] **1959** In this article Wilson presents five basic principles of teratology to understand the development of birth defects. It describes the susceptibility of the embryo / fetus to teratogens and tries to provide biologic plausibility for a teratogenic effect. Wilson states that he derived those principles from a number of experiments and existing literature.

		In the article he states: ‘‘After careful deliberation, and no little vacillation, as many as five generalities emerge which seem to be applicable to most teratologic situations. It is certainly premature to formulate these as universal laws of teratology. They are presented here only as points of reference for thinking and planning and as hypotheses yet to be put to the final test’’ (Wilson, 1959). **1973** [Pop-up text] **1973** Wilson later developed and articulated those teratogenic principles in 1973 in his book “Environment and Birth Defects”. He had revised the five principles and added a sixth generalization about dosage effects. **1977** [Pop-up text] **1977** By 1977, when these Principles were presented in a more definitive form in Wilson and Fraser’s “Handbook of Teratology”, they had become a standard formulation of the basic tenets of the field.
3	Text	**Wilson’s Six Principles of Teratology** Wilson’s Six Principles of Teratology as presented in the Wilson and Fraser Handbook of Teratology are: 1. Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with environmental factors. 2. Susceptibility to teratogenic agents varies with the developmental stage at the time of exposure. 3. Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis). 4. The final manifestations of abnormal development are death, malformation, growth retardation, and functional disorder. 5. The access of adverse environmental influences to developing tissues depends on the nature of the influences (agent). 6. Manifestations of deviant development increase in degree as dosage increases from the no-effect to the totally lethal level. In this chapter we will elaborate on these principles in more detail. The principles will be discussed further throughout the e-learning, but not in this specific order.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2.4 Potential range of effects and genetic susceptibility

Slide #	Work form	Content
1	Text	**Potential range of effects and genetic susceptibility** In the previous activity, you read about congenital malformations. You learned that five to ten percent of malformations are caused by a teratogenic agent, such as medication. Research often emphasizes the development of birth defects, but other effects can also occur after exposure during pregnancy (Wilson Principle 4). Did you know? [Doctor pop-up] The final manifestations of abnormal development are death, malformation, growth retardation, and functional disorder.
2	Text	**Teratogenic effects** What are the possible effects a drug may have? ● **Malformations** Physical abnormalities which are present at birth. ● **Death (spontaneous abortion or stillbirth)** Death up to 20 weeks' gestation is classified as miscarriage or spontaneous abortion. After that it is called intrauterine fetal demise or stillbirth. ● **Growth retardation** The fetus does not grow as expected. The baby is not as big as would be expected for the stage of the mother's pregnancy. ● **Functional disorders** Problem with body systems which lead to disabilities. Examples include autism spectrum disorders, sensory disorders such as blindness and deafness, immune disorders, renal impairment or metabolic disorders. ● **Pharmacological effects** A broad spectrum of effects that can affect both the pregnancy and the fetus or newborn. Examples include prematurity, lower fetal heart rate, oligohydramnios (too little amniotic fluid), growth retardation, low birth weight, withdrawal symptoms, neonatal hypoglycemia.
3	Text	**Combination of effects**

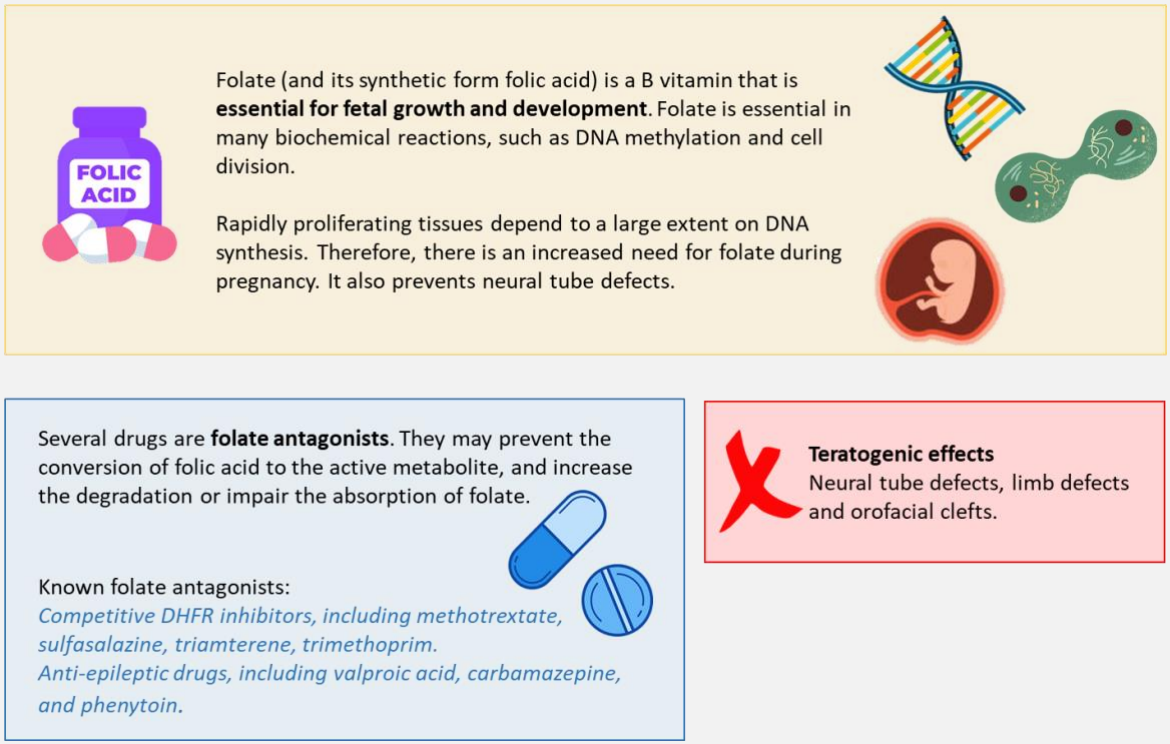
		The mentioned effects may occur separately, but a combination of effects may also occur. Teratogenic agents usually cause a so-called embryopathy: a recognizable and distinct pattern of human malformations (with or without associated growth disorders or fetal death) and functional defects. An example of such a teratogen is isotretinoin, a drug used for the treatment of acne. This drug can cause malformations of the ear, central nervous system, heart and skeleton, miscarriage and developmental defects. Drugs can also cause isolated, solitary defects. For example, topiramate can cause cleft palate.
4	Multiple choice question	Exposure to a teratogen causes abnormalities in only a (small) proportion of children and not in all that were exposed. Also, if abnormalities are seen in animal studies, they cannot automatically be expected in humans. **Why do you think that is?** a. The answer lies in inter-species and intra-species variability that causes differences in susceptibility to teratogenesis (Wilsons first principle). b. It is because of the way teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis). *Feedback correct answer:* Yes, correct! Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with environmental factors. *Feedback incorrect answer:* No, that's incorrect. Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with environmental factors.
5	Text	**Inter-species variability** High *inter-species variability* (variability between species) causes differences in susceptibility to teratogenesis. Some drugs are shown to be teratogenic in animals but not in humans, and vice versa. Animals differ from humans in metabolism, distribution, and pharmacokinetics. This makes it difficult to extrapolate data from animal studies to humans. Besides, the animal species most suitable for teratogenicity studies is not the same for every drug. Examples: ● Thalidomide: no teratogenicity was shown in animal studies during the clinical trials, but in humans there is a high risk of major malformations. ● Corticosteroids: in animals there is an increased risk of cleft lip or palate, but this is not seen in humans.

6	Text + pop-up	**Intra-species differences** In addition, *intra-species differences* (variability within species) play a role. Teratogenic drugs do not cause congenital anomalies in all embryos or fetuses that were exposed to them. Genetic differences between mothers or their fetuses can explain why one exposed fetus has congenital malformations and the other has not. Both genetic and environmental factors are important factors in the teratogenic mechanisms. <u>Did you know?</u> [Doctor pop-up] Genetic factors can influence the drug response. The study on this subject is called *pharmacogenetics or pharmacogenomics*.

2.5 Mechanisms of teratogenicity

Slide #	Work form	Content
1	Text	**Mechanisms of teratogenicity** "Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis." This is Wilson's third principle. The mechanism of action of a teratogen determines what kind of abnormalities can occur. This explains why a teratogen always shows a certain pattern of abnormalities (embryopathy) and will not be able to cause all types of abnormalities. I-icon [Pop-up text Wilson's third principle] **Wilson third principle** Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis).
2	Text	**Mysterious mechanism** Unfortunately, the specific mechanism for most teratogens is unknown. It is often a multifactorial process and effects can result from interactions between environmental and genetic factors. However, for some medications the teratogenic mechanism has been identified. In this chapter we will discuss six mechanisms of teratogenicity. Most of these are still not completely understood. You will find a short description of the mechanisms on the next slide. A more detailed explanation for each mechanism is provided in the advanced material.
3	Text	**Six known mechanisms of teratogenicity (1/2)** The following mechanisms have been identified. ● **Folate antagonism**: Folic acid is essential for fetal growth and development. Several drugs inhibit the folate methylation cycle (folate antagonists) and can therefore be teratogenic. ● **Neural crest cell disruption**: During embryogenesis, the neural crest cells migrate into the embryo and give rise to numerous structures. Some drugs can interfere with the molecular pathways that are implicated in neural crest cell development. This might induce neural crest-related malformations. ● **Endocrine disruption**: Various drugs inhibit or mimic the actions of hormones, for instance, oral contraceptives, diethylstilbestrol (DES) and hormonal fertility treatments. These medications are endocrine

		disrupting chemicals (EDCs) as they might interfere with the functions of endogenous hormones. In utero, EDCs can possibly impact the developing reproductive systems.
4	Text	**Six known mechanisms of teratogenicity (2/2)** Below you find the other three known mechanisms. ● **Vascular disruption**: Vasoactive drugs are substances that affect the blood vessels. In a pregnancy they may affect the development of blood vessels in the unborn child or decrease the blood flow in the placenta or fetus. Exposure to these agents can cause structural defects not only in the first 3 months of pregnancy, but also later in pregnancy by reducing the blood flow and thereby damaging structures that were initially formed normally. ● **Oxidative stress**: Several drugs that are used for treatment of, among others, cancer, epilepsy and cardiac arrhythmias can generate reactive oxygen species (ROS). A developing embryo has a weak antioxidant defense and therefore is susceptible to high levels of ROS. ● **Specific receptor- and enzyme mediated disruption**: Many medical drugs have their effect by acting on a specific enzyme or receptor in the human body. The inhibition or stimulation of some of these enzymes or receptors can have an effect on fetal development.
5 ADVANCED	Text + afbeelding	**Folate antagonism** The exact mechanism by which folate antagonists increase the risk of birth defects is unclear. However, we do know the following. Take a look at the infographic below to learn more about folate antagonism. [Media 2.18 Infographic Folate antagonism]

		Folate antagonism 
6 ADVANCED	Text + afbeelding	**Neural crest cells give rise to numerous embryonic structures** Take a look at the infographic below to learn more about neural crest cell disruption. [Media 2.19 Infographic Neural crest cell disruption]

		Neural crest cell disruption  **Neural crest cells give rise to numerous embryonic structures.** The neural crest is a pluripotent cell population, which can be divided into the cranial and truncal neural crest. During embryogenesis, the neural crest cells migrate into the embryo and give rise to numerous structures. The cranial neural crest produces various cell types and structures in the craniofacial region. The truncal neural crest produces components of the peripheral nervous system. The cardiac neural crest cells are a subpopulation of the cranial neural crest. **Several drugs disrupt neural crest cell development**. Various molecular pathways are implicated in the development of the neural crest cells. Some drugs can interfere with these molecular pathways and might therefore induce neural crest-related malformations. Known neural crest cell disruptors: *Bosental, excesses or shortages of retinoic acid (active form of vitamin A).*  **Teratogenic effects** Cardiovascular malformations including aortic arch anomalies, conotruncal defects and membranous ventricular septal defects. Craniofacial malformations, such as esophageal atresia and pharyngeal glands abnormalities.
7 ADVANCED	Text + afbeelding	**Endocrine disruption** Take a look at the infographic below to learn more about endocrine disruption. [Media 2.20 Infographic Endocrine disruption] *Several drugs influence the endocrine system* Various drugs are developed to inhibit or mimic the actions of hormones, for example, hormonal fertility treatments. These medications are endocrine disrupting chemicals (EDCs) as they might interfere with the function of endogenous hormones. Other examples of EDCs are bisphenol A and phthalates. Use of EDCs by a pregnant woman can possibly impact the developing reproductive systems of the unborn child. *DES* It is well known that the use of the synthetic estrogen DES by pregnant women (in the period 1947-1975) led to anomalies in their children. As described in Chapter 1 DES-daughters had an increased risk of vaginal adenocarcinoma, abnormalities of the genital organs and fertility problems. DES-sons also had an increased risk of (benign) abnormalities of the genital organs. Consequences were also seen in DES-grandchildren as outlined in Chapter 1.

		DES may be more capable of crossing the placenta than the endogenous estradiol. The placenta can reduce the transfer, plasma binding and metabolism of endogenous estradiol to less active estrogens. This is an important defense mechanism for the fetus to reduce the actions of this natural hormone. However, this defense mechanism is not effective for the synthetic estrogen DES. Examples of drugs with this teratogenic mechanism: diethylstillbestrol (DES), hormonal fertility treatments, bisphenol, phthalates.
8 ADVANCED	Text + afbeelding	**Vascular disruption** Take a look at the infographic below to learn more about vascular disruption. [Media 2.21 Infographic Endocrine disruption] It is hypothesized that prenatal exposure to vasoactive drugs, especially vasoconstrictive drugs, can cause vascular disruption defects. Vascular disruptions include hyper- or hypoperfusion, hypoxia and obstruction in the blood circulation of the uterine-placental unit, the placental-fetal unit or the fetus itself. Vasoactive substances can affect the development of blood vessels in the unborn child or decrease the blood flow in the placenta or fetus. Exposure to these agents can cause structural defects not only in the first 3 months of pregnancy, but also later in pregnancy by reducing the blood flow and thereby damaging structures that were initially formed normally. Vascular disruptions reduce the nutrient supply to the tissues, which can affect embryonic growth or cause tissue loss. The structural anomalies resulting from vascular disruptions are determined by the timing, the location and severity of tissue damage. During embryogenesis, they can result in loss of tissue or incomplete development of structures. During the fetal period, the anomalies are usually limited to functional damage to structures in the area with the disturbed blood supply. *Teratogenic effects of vascular disruptors:* Terminal limb reductions, hydranencephaly/porencephaly, gastroschisis, small intestinal atresia, Poland anomaly. *Examples of drugs with this teratogenic mechanism:* Misoprostol, high dose aspirin, ergotamine, pseudoephedrine, and potentially other drugs with **Oxidative stress** *ROS are natural metabolic by-products* In biological systems, reactive oxygen species (ROS) are natural by-products of cellular oxidative metabolism.

		Endogenous ROS have multiple functions, including cellular signaling and apoptosis of unwanted cells. However, when the production increases, ROS can be harmful by binding to cellular macromolecules. Oxidative stress occurs when there is an imbalance between the production of ROS and the antioxidant defense mechanisms. *Drugs can generate ROS, leading to oxidative stress* Several drugs that are used for treatment of, among others, cancer, epilepsy and cardiac arrhythmias can generate reactive oxygen species (ROS). This increase in ROS production can lead to oxidative stress, which causes irreversible oxidation of proteins, lipids and DNA, leading to inactivation of enzymes and cell death. It may also affect gene expression. *The embryo is susceptible to oxidative stress* ROS are generally too unstable to be maternally transferred from the pregnant woman to her unborn child. However, maternal drugs can cause changes in embryonic metabolism which result in increased ROS generation. A developing embryo has a weak antioxidant defense and therefore is susceptible to high levels of ROS. *Teratogenic effects of oxidative stress:* Wide spectrum of birth defects including skeletal malformations, limb defects, neural tube defects, cleft lip/palate and cardiovascular defects. *Examples of drugs with this teratogenic mechanism:* thalidomide, phenytoin, valproic acid, class III antiarrhythmic drugs, iron supplements, various chemotherapeutic drugs. Vasoconstrictive or vasodilating effects.
9 ADVANCED	Text + afbeelding	**Specific receptor- and enzyme mediated disruption** Take a look at the infographic below to learn more about specific receptor- and enzyme mediated disruption. [Media 2.22 Infographic Specific receptor- and enzyme mediated disruption] Many medical drugs have their effect by acting on a specific enzyme or receptor in the human body. The inhibition or stimulation of some of these enzymes or receptors can have an effect on fetal development. Examples are the angiotensin-converting enzyme and the angiotensin II receptors. The renin-angiotensin system plays an important role in the regulation of blood pressure. The components of this system are also present in the fetus. Two groups of antihypertensive drugs, the angiotensin-converting enzyme (ACE) inhibitors and the AT II receptor antagonists, may influence the angiotensin converting enzyme and the angiotensin II receptors. This causes a disruption in the renin-angiotensin system. This way, these drugs have an impact on the renal function.

		Teratogenic effects of receptor- and enzyme mediated disruption: Use of ACE-inhibitors and AT II receptor antagonists during the second and third trimester of pregnancy can impair the fetal kidney development. This can cause oligohydramnios and a specific human malformation syndrome, characterized by limb contractures, pulmonary hypoplasia, and hypocalvaria. *Examples of drugs with this teratogenic mechanism:* ACE-inhibitors like captopril, enalapril and lisinopril. AT II receptor antagonists like candesartan, losartan and valsartan. *(van Gelder, M.M.H.J., van Rooij, I.A.L.M., Miller, R.K., Zielhuis, G.A., de Jong-van den Berg, L.T.W., Roeleveld, N, 2010).*
10	Text	**Conclusion** In this chapter you have become familiar with the principles of teratology. You now know what the basic background risks of malformations are and are able to summarize different teratogens. You have been introduced to the six basic principles of teratology by Wilson. You have already learned more about his first, third and fourth principle. In the next chapter you will learn more about the rest of Wilson's principles as well as considerations on teratogenic exposure during pregnancy. We hope you enjoyed this chapter and wish you good luck with the next!

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Additional resources

- Read: UpToDate website (https://www.uptodate.com/)
- Read: https://onlinelibrary.wiley.com/doi/10.1002/tera.1420390402

Chapter 3: Considerations for teratogenic exposure during pregnancy

3.1 Introduction to the chapter

Slide #	Work form	Content
1	Text	**Welcome to the chapter 3: Consideration for teratogenic exposure during pregnancy** In this chapter, we will use a case example of a woman who has used medication during her pregnancy. She is concerned about the effects this might have on her unborn child and asks a healthcare professional for advice. Watch the video below to see this conversation taking place. Pay special attention to the kind of questions the healthcare professional asks. What kind of information do you need from the patient?
2	Text + video	**An interesting conversation with a healthcare professional** Watch the video to learn more. [Media 3.1 Video Woman asking advice + Healthcare professional] Woman: Good morning! Can I ask you some questions about the medication I am taking? Healthcare professional: Good morning, of course you can! Woman: I have just discovered that I am pregnant, but I was taking medication for a urinary tract infection until yesterday. Could this be a risk to my pregnancy? Healthcare professional: Congratulations on your pregnancy. How far along are you? Woman: Thank you. My last period was 6 weeks ago. Healthcare professional: Do you know the name of the medication you were taking? Woman: I believe it's called ciprofloxacin. Healthcare professional: What was the dose that you were prescribed? Woman: I took the medication for three days in a row, twice a day. I don't know the exact dose. Healthcare professional: * Question marks appear above the healthcare professional * "Ïs this a problem? What data do I need? Where shall I look for this information?" Healthcare professional: I'm going to find out for you.
3	Multiple answer	In such a case… **What are important considerations for you to decide whether or not this is safe?** Multiple answers are correct. a. Severity of illness.

		b. Gestational age. c. Degree of systemic exposure. d. Transfer across the placenta. e. Dose and duration. f. Experience with the medication. Feedback correct answer: Yes, correct! All these considerations are important for you to decide on whether or not it is okay for a pregnant woman to take certain medication during her pregnancy. Do not worry if you do not fully grasp all of these terms yet. Using our case example, we will discuss these considerations in the upcoming learning activities. Feedback incorrect answer (every combination of answers is correct): Yes, correct! All these considerations are important for you to decide on whether or not it is okay for a pregnant woman to take certain medication during her pregnancy. Do not worry if you do not fully grasp all of these terms yet. Using our case example, we will discuss these considerations in the upcoming learning activities.
4		**For example, what is gestational age?** Gestational age is a term used to describe the age of the embryo or fetus and refers to the number of weeks after the first day of the last menstrual period. Degree of systemic exposure refers to the route of administration which relates to pharmacokinetics, a branch of pharmacology dedicated to determining the fate of substances administered to a living organism. In the next part we will further dive into these considerations.

3.2 Gestational age

Slide #	Work form	Content
1	Text + pop-up	**The gestation period** When prescribing medicines in pregnancy or answering questions about medication that was already used, it is very important to know the gestational age. During what week or trimester of the pregnancy did (or will) the exposure occur? The answer to that question is essential, since it is an important factor in risk assessment. You will now explore why this is. A pregnancy can be divided into different developmental periods. Depending on the gestation period, the effect of a teratogen will be different. Wilson describes this in his second principle. I-icon [Pop-up text second principle] **Wilson's second principle** Susceptibility to teratogenic agents varies with the developmental stage at the time of exposure.
2	Multiple answers	The gestational age can be displayed in three different ways. **Do you know which two of these three ways are most commonly used?** a. Number of weeks pregnant counted from the conception. b. Number of weeks pregnant counted from the first day of the last menstrual period. c. Trimester number: 1 (1 – 12 weeks), 2 (13 – 27 weeks) or 3 (28 – 40 weeks). *Feedback correct answer:* Yes, correct! Number of weeks pregnant counted from the first day of the last menstrual period and trimester number are the most common ways of indicating the duration of pregnancy. Nevertheless it is wise to take into account that sometimes the duration of pregnancy is counted from conception. *Feedback incorrect answer:* No, that's incorrect. Number of weeks pregnant counted from the first day of the last menstrual period and trimester number are the most common ways of indicating the duration of pregnancy. Nevertheless it is wise to take into account that sometimes the duration of pregnancy is counted from conception.
3	Text + afbeelding	**The embryonic period** The gestation periods can be divided into two phases: the embryonic and the fetal period. The most vulnerable period is the embryonic period, which is the first 8-10 weeks after conception (the first trimester). In this period all organs and tissues are developed. A disturbance in their development can lead to structural malformations in organs or tissues.

		Click on the image below to learn about examples of drugs with an increased risk of structural birth defects when used in the first trimester. [Media 3.2 Image medicine] **Drugs leading to increased risk of structural birth defects** Isotretinoin Valproic acid Methotrexate Mycophenolate mofetil Misoprostol Acenocoumarol Carbimazole, methimazole Lithium
4	Text	**Organ development** As can be seen nicely in the figure, the development of the various organs takes place in time windows. For example, the heart develops in weeks 3-5 after conception. Once the development of an organ is completed, the chances of a drug causing a structural abnormality is very small. However, an effect on the function of the organ may occur depending on the drug. On the next slide, you will learn more about the time window of the first 2 weeks after conception.
5	Text	**The "all or none" phenomenon** *The first two weeks* The first two weeks after conception are important. It is also referred to as the all or none period. After fertilization but before implantation, the zygote divides without growing in size. At this stage, the cells of the embryo are stem cells that can differentiate into any tissue. Loss or damage to these cells will mostly not result in a specific defect. A teratogenic exposure in this period will result in the "all or none" phenomenon. ● Either the exposure has resulted in so much damage and loss of cells that it will result in embryonic death and an undetected abortion… ● …or the damage is limited, after which the remaining stem cells can replace the damaged cells and the embryo develops normally.
6	Text + pop-up	**The fetal period** *The second and third semester* After the first trimester, all tissues and organs are developed. From now on, growth, differentiation and maturation will take

<table>
<tr><td></td><td></td><td>place. Exceptions are the neuronal tissues and sense organs, which continue to develop during the fetal period or even until birth. Disruptions during the fetal period will not lead to structural abnormalities, but to functional abnormalities to organs.

Furthermore, pharmacological effects may occur during this period.

I-icon
[Pop-up text functional abnormalities]
Functional abnormalities
The function of an organ is disturbed or damaged. Examples are: low IQ, autism spectrum disorder, ADHD, impaired motor development.

I-icon

[Pop-up text pharmacological effects]
Pharmacological effects
A drug can have a direct effect on the organs of a fetus. Examples are; effect on the heart rhythm, inhibition of uterine contractions, withdrawal symptoms, oligohydramnios.</td></tr>
<tr><td>7</td><td>Text + tabel</td><td>The effects of different medication exposures

In the table you can see a number of examples of functional abnormalities or pharmacological effects caused by medication exposures during pregnancy..

<table>
<tr><th>Drug</th><th>Period</th><th>Possible effect</th></tr>
<tr><td>Beta-blockers</td><td>Around time of delivery</td><td>Bradycardia and hypotension in the neonate.</td></tr>
<tr><td>Beta-blockers</td><td>Second and 3rd trimester</td><td>Intrauterine growth restriction.</td></tr>
<tr><td>Antidepressants and opioïds</td><td>End of 3rd trimester</td><td>Withdrawal symptoms in the neonate.</td></tr>
<tr><td>NSAIDs</td><td>> 20 weeks</td><td>Closure of the ductus arteriosus, reduced kidney function, and oligohydramnios.</td></tr>
</table>
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</table>

		ACE-inhibitors | Second and 3rd trimester | Kidney damage, oligohydramnios, anuria, joint contractures (clubfoot), hypoplasia of the skull.
8	Text + tabel	**Processes in the embryonic and fetal period** This table shows the duration of the embryonic and the fetal period and the processes that take place in these periods. In the next learning activity you will learn more about the effects of systemic exposure on unborn children.
9	Text	**Conclusion** When prescribing medicines in pregnancy or answering questions about medication that was already used, it is very important to know the gestational age. The effect of a teratogen will be different, depending on the gestation period. Health professionals should be aware of the difference in effects in order to be able to help a patient correctly.

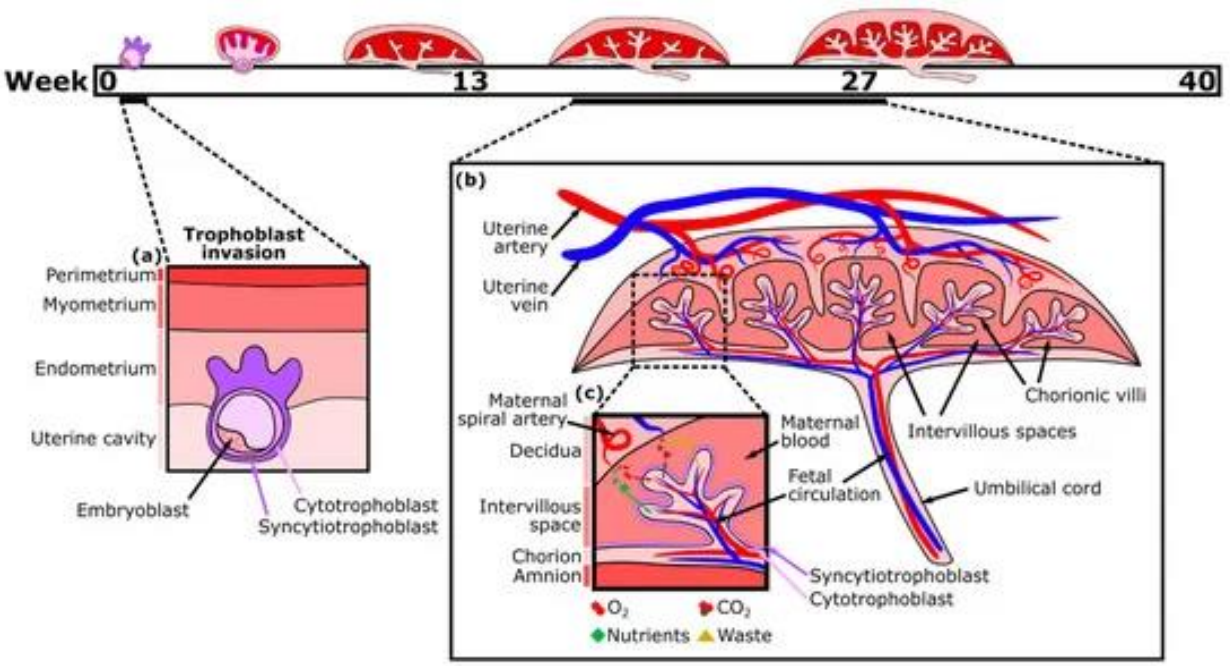
Embryonic period	**Fetal period**
0-12 weeks (gestational age)	13-40 weeks
First trimester	Second and third trimester
Organogenesis	Growth and differentiation
Structural malformations visible before/at birth	Functional disorders visible after birth

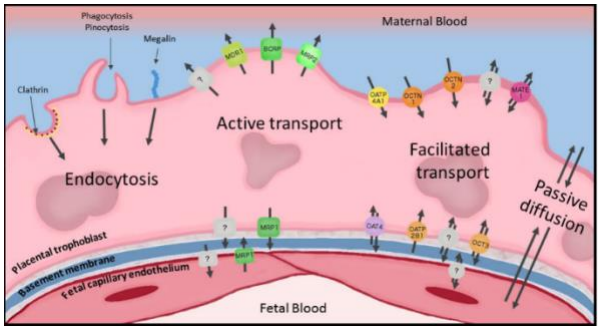
3.3 Degree of systemic exposure

Slide #	Work form	Content
1	Text	**Degree of systemic exposure** In order to affect the development of the embryo or fetus, an agent (influence) must be able to reach the unborn child. The following information will teach you how this works. There are two possible routes for an external agent to reach the unborn child: 1. By directly traversing the maternal body. 2. By indirect transmission via the maternal blood. There are only a few exposures that use route 1, the main ones being ionizing radiation and electromagnetic radiation. Route 1 does not apply to medications.
2	Text + pop-up	**That leaves route 2** Most agents are transmitted through the body. Option 2 refers to all chemical agents that can reach the bloodstream of the pregnant woman. This also includes medicines. Agents that enter the maternal bloodstream (systemic exposure) can only reach the fetus if they are able to cross the placenta. If a substance does not reach or barely reaches the bloodstream, it is unlikely that the fetus will be exposed to this substance. The route of administration of a drug plays a major role in the extent of systemic exposure. There is a big difference in absorption, thus in systemic exposure, between the different routes of administration. Wilson described this in his fifth principle. I-icon [Pop-up text fifth principle] **Wilson's fifth principle** The access of adverse environmental influences to developing tissues depends on the nature of the influences (agent).
3	Text	**Different roads of administration** ● An infusion leads to 100% absorption into the blood. ● The absorption of eye- and ear drops is low. ● The absorption after administration of a drug on the skin is limited, but usually not zero. The size of the treated area plays a role. The larger the exposed skin area, the more is systemically absorbed.

		• After oral administration of a drug there is a large variation in systemic exposure. It largely depends on the absorption from the gastrointestinal tract. This can range from 100% absorption (as with lithium) to almost no absorption (as with macrogols). Therefore, local administration of medication (if possible) is preferred over systemic exposure during pregnancy. This principle can be applied in the treatment of several diseases. • Allergy is preferably treated by eye or nose drops. • Dermal disease is preferably treated by topical administration. • Respiratory disease is preferably treated by inhaled medication.
4	Multiple choice question	Let's see if you can answer the following question. You know tablets can lead to systemic exposure. Is this also the case in the example below? Read the details of absorption from the Drug Bank and answer the question. **Drugbank:** A 250mg oral dose of ciprofloxacin reaches an average maximum concentration of 0.94mg/L in 0.81 hours with an average area under the curve of 1.013L/h*kg. The FDA reports an oral bioavailability of 70-80%Label,1 while other studies report it to be approximately 60%.8 An early review of ciprofloxacin reported an oral bioavailability of 64-85% but recommends 70% for all practical uses. **Is ciprofloxacin easily absorbed?** a. Yes b. No *Feedback correct answer:* Yes, well done! Ciprofloxacin has an oral bioavailability between 60-80%. This means it is easily absorbed. *Feedback incorrect answer:* No, that's incorrect. Ciprofloxacin has an oral bioavailability between 60-80%. This means it is easily absorbed.
5	Text	**Conclusion** What is the route of administration and how easily is the drug absorbed? Always try to find information on absorption or bioavailability of the drug(s).

3.4 Transfer across the placenta

Slide #	Work form	Content
1	Text + image	**Transfer across the placenta** After reaching the bloodstream, a drug has to cross the placenta to have a direct effect on the embryo or fetus. Drugs transferred from maternal to fetal blood must be carried into the intervillous space and pass through the syncytiotrophoblast. This layer of cells is the rate-limiting step of drug transfer. Interestingly, placental thickness and cell layers decrease as the pregnancy advances, therefore potentially increasing permeability to medications. [Media 3.3 Image placenta]  *(Image from MPDI)*
2	Text	**Routes of placental transfer**

		There are different routes of placental transfer and each has a different contribution. ● **Passive diffusion:** Predominant route of placental transfer for small molecules. ● **Facilitated diffusion**: Diffusion through special channels and carrier proteins. ● **Active transport:** Through placental transporters. Against the concentration gradient. ● **Phagocytosis/ endocytosis:** No significant distribution. [Media 3.4 Image routes]  *(Image from Sciencedirect)* We will take a look at each of these different routes.
3	Text + pop-up	**Route 1: Passive diffusion** The major route of placental transfer is passive diffusion down the concentration gradient of the drug. The rate of passive transfusion is determined by the concentration of the drug in maternal circulation and the physical and chemical properties (Wilsons <u>fifth principle</u>) of the drug. <u>I-icon</u> [Pop-up text fifth principle] **Wilson's fifth principle** The access of adverse environmental influences to developing tissues depends on the nature of the influences (agent).
4	Multiple choice question	As stated in the previous slide, the rate of passive transfusion is determined by the concentration of the drug in maternal circulation and the physical and chemical properties (Wilsons principle 5) of the drug.

		Can you guess which of these drug properties make a drug efficient in placental transfer? a. Drugs that are low in molecular weight. b. Drugs that are high in molecular weight. c. Drugs that easily bind to protein. d. Drugs that virtually do not bind to protein. Feedback correct answer: Yes, correct! In the next slide we will explain the properties of the drug that are important for passive diffusion. Feedback incorrect answer: No, that's incorrect. The correct answer was drugs that are low in molecular weight and virtually do not bind to protein. In the next slide we will further explain the properties of the drug that are important for passive diffusion.
4	Text	**Passive diffusion** The following properties of the drug are important for passive diffusion: ● **The molecular weight**. Low molecular weight (<600Da) molecules can cross the placenta via passive diffusion. Many drugs have a low molecular weight. High molecular weight drugs such as insulins and heparins are not transported to the fetus in significant amounts. ● **Plasma protein binding** Only the free, unbound fraction of a drug can cross the placenta. The bigger the unbound fraction of a drug is, the more efficiently it can transfer the placenta. For example, lithium is virtually not bound to plasma proteins, which makes it easier to cross the placenta than for omeprazole, with 95% protein binding. ● **Ionization** Drugs which are predominantly unionized at physiological pH, can easily diffuse across the placenta. Ionized molecules are less likely to cross the placenta. For example, benzodiazepines are mainly unionized and can therefore rapidly diffuse across the placenta. ● **Lipid solubility**. Lipophilic chemicals can cross the placenta more readily than other compounds. For instance central nerve system medication, known for its ability to cross the lipophilic blood brain barrier, will cross the placenta more easily than hydrophilic agents.

		In short, drugs with a low molecular weight (<600 Da), with low protein binding, which are lipophilic and predominantly unionized at physiological pH, can easily diffuse across the placenta.
5	Text	**Route 2: Facilitated diffusion** Some drugs that cannot pass through passive diffusion (i.e. charged or polar), can cross the placenta through special channels and carrier proteins. Like with passive diffusion, facilitated diffusion also takes place by a concentration gradient, so they have the potential to diffuse into (or out of) the fetal compartment. Facilitated transport proteins shield these molecules from the hydrophobic core of the membrane, providing a route by which they can cross. So far, little is known about the possible drugs that can cross the placenta this way. An example of a drug that may pass via a carrier protein is metformin, a cationic and highly hydrophilic drug.
6	Text	**Test yourself** Many drugs can pass through the placenta via passive diffusion. So it is important to find information on the properties of the drug that has been or is to be used. What can you find out about the physical and chemical properties, like molecular weight and plasma protein binding?
7	Multiple choice question	Go to https://go.drugbank.com/. What can you find about the molecular weight and plasma protein binding of ciprofloxacin? **Can ciprofloxacin pass the placenta via passive diffusion?** a. Yes b. No *Feedback correct answer:* Correct, well done! Information Drugbank: Canada reports the following: Ciprofloxacin is a small molecule (molecular weight 331 Da), with a protein binding of 20-40%. It can probably cross the placenta because of its low molecular weight and low protein binding. *Feedback incorrect answer:* No, that was incorrect. Information Drugbank: Canada reports the following: Ciprofloxacin is a small molecule (molecular weight 331 Da), with a protein binding of 20-40%. It can probably cross the placenta because of its low molecular weight and low protein binding.

<table>
<tr>
<td>8</td>
<td>Text + pop-up</td>
<td>
Route 3: Active transport

As mentioned before, many "small" molecules can pass the placenta via passive diffusion. There are also mechanisms for large or charged molecules to cross the placenta.

The placenta is a unique organ that provides nutrients and oxygen from the mother to the developing fetus and also assists in the removal of waste products from the fetus to the mother. Numerous transporters are expressed in the placenta that transport nutrients such as amino acids, vitamins and glucose, and xenobiotics such as drugs and environmental pollutants across the blood-placental barrier. These active transporter pumps can transport nutrients and drugs against a concentration gradient through the placenta. This is in contrast to passive diffusion, which follows a concentration gradient.

<u>Did you know?</u>
[Doctor pop-up]
Facts on transporters
There are numerous transporters on the placenta. The expression pattern of a transporter can change during the course of pregnancy, it can increase or decrease.
</td>
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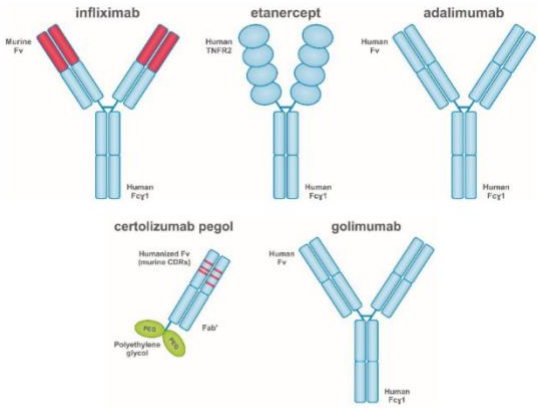
<tr>
<td>9</td>
<td>Text</td>
<td>
Important transporters

Much research is taking place on the complex transport mechanisms on the placenta and the possible substrates that can be transported with it. The table on the next slide gives an example of some important transporters, their expression in pregnancy and which drugs they can transport.

<table>
<tr><th>Transporter name</th><th>Change in expression during pregnancy</th><th>Direction</th><th>Substrates</th></tr>
<tr><td>Breast Cancer Resistance Protein (BCRP)</td><td>↓</td><td>Efflux</td><td>Antipsychotics: Risperidone, paliperidone Erythromycin, Bile Acids, Nitrofurantoin, Bupropion, Cimetidine, Fluoroquinolones</td></tr>
<tr><td>Multidrug Resistance Protein 2</td><td>↑</td><td>Efflux</td><td>atenolol, carvedilol, pravastatin, methotrexate</td></tr>
</table>
</td>
</tr>
</table>

		MATE2 ↓ Efflux atenolol, metformin, acyclovir, ganciclovir, cimetidine Organic-anion-transporting polypeptide-1B1 ↓ Influx bile acid, enalapril, cefazolin, atorvastatin, pravastatin, rosuvastatin, methotrexate, glyburide, fexofenadine P-glyco-protein ↓ Efflux Antidepressants: citalopram, amitriptyline, paroxetine, venlafaxine Anti-psychotics: aripiprazole (aripiprazole, quetiapine, olanzapine, paliperidone, chlorpromazine, Risperidone, Clozapine) Opioids: Methadone, Morphine Other: Glucocorticoids, Glyburide, Phenytoin, protease Inhibitors, Ondansetron, Cimetidine/ranitidine nFc receptor ↑ Influx TNF-alpha blockers, immunoglobulines Serotonin Transporter ↑, ↔ Influx Serotonin, Amphetamine, Methylphenidate, MDMA, Fenfluramine, Norfenfluramine *(Goetzl 2022, Dallmann 2019)*
10	Text	**Let's take a look at a case** A pregnant woman uses adalimumab for her rheumatoid arthritis during pregnancy. Adalimumab is a large molecule, so it cannot cross the placenta via passive diffusion. Therefore, there is no risk to the child or the pregnancy. Or is this not true? To learn the answer, you must first know more about TNF-alpha blockers…

11	Text + pop-up	**TNF-alpha blockers** TNF-alpha blockers refer to a group of drugs used to treat rheumatoid arthritis, among other things. Adalimumab belongs to this group. Other TNF-alpha blockers are infliximab, certolizumab, golimumab and etanercept. TNF-alpha blockers are large molecules (>600 Da) that cannot cross the placenta via passive diffusion. <u>Did you know?</u> [Doctor pop-up] **A different route** TNF-alpha blockers cannot cross the placenta via passive diffusion. However there are active transport mechanisms.
12	Text + pop-up	**Active transport of TNF-alpha blockers** There is an active transport mechanism on the placenta for the transport of maternal antibodies from the mother to the fetus. These antibodies provide the defenses of the fetus and newborn baby. Passage occurs via the neonatal Fc receptor. To act on this receptor, the drug must possess the Fc domain of an antibody. Almost all TNF-alpha blockers have this Fc domain and can cross the placenta via this transporter. ● Infliximab, adalimumab and golimumab are monoclonal antibodies (IgG). ● Etanercept is an Fc fusion protein; it contains the human IgG Fc domain of a monoclonal antibody. ● Certolizumab is an exception: it is not a complete monoclonal antibody. It contains only the Fab fragment of a monoclonal antibody and not the Fc domain. As a result it can not cross the placenta. <u>Did you know?</u> [Doctor pop-up] **Timeline over the course of pregnancy** In the first trimester, TNF-alpha blockers barely cross the placenta. From the second trimester on, they can pass the placenta by active transport through the neonatal Fc receptor. Passage increases over the course of pregnancy and is highest just before delivery. *(Suzuki et al 2010, Porter et al 2016)*
13	Text + afbeelding	**Active transport of TNF-alpha inhibitors** Take a look at the figure below to learn more about the structure of the different TNF-alpha blockers. [Media 3.4 Image structure different TNF-alpha blockers]

		
14	Text	**Degree of placental passage** There is a big difference in affinity of the TNF-alpha blockers for the neonatal Fc receptor. The IgG antibodies infliximab, adalimumab and golimumab have a higher affinity than etanercept (an Fc fusion protein). As a result, significantly more of these agents reach the fetus compared to etanercept. Infliximab induces the highest fetal exposure, followed by adalimumab. The placental transfer of etanercept is very low. Certolizumab does not contain an Fc component and therefore cannot cross the placenta via active transport.
15	Multiple choice question	Let's do a little test. Some TNF-alpha blockers are less likely to reach the fetus than others. **If a TNF-alpha blocker must be given in pregnancy, which ones are preferred?** .Adalimumab and certolizumab. a. Infliximab and etanercept. b. Etanercept and golimumab. c. Etanercept and certolizumab. *Feedback correct answer:* Yes, well done! Etanercept is an Fc fusion protein and has lower affinity for the Fc receptor. Certolizumab does not contain the Fc component and cannot pass the placenta via active transport. Of the TNF-alpha blockers, these two drugs are the least likely to reach the fetus. *Feedback incorrect answer:* No, that's incorrect. Etanercept is an Fc fusion protein and has lower affinity for the Fc receptor. Certolizumab does

		not contain the Fc component and cannot pass the placenta via active transport. Of the TNF-alpha blockers, these two drugs are the least likely to reach the fetus.
16	Text	**Conversion of active drugs** As discussed in the previous sections, many drugs can cross the placenta. However, in addition to transport across the placenta, the placenta is also capable of converting active drugs into an inactive metabolite and vice versa. These enzymes can also have an effect on the amount of drug that can reach the fetus. However, for most drugs, it is not clear whether this plays a significant role in the transfer to the fetus. The placenta contains metabolizing enzymes capable of oxidation, reduction, hydrolysis and conjugation (Koren). Examples of enzymes found in the placenta are cytochrome P450 proteins, alcohol dehydrogenases and uridine diphosphate glucoronosyltransferases (UGTs).
17	Text	**Metabolism** An important placental enzyme is *11b-HSD2 (11b-hydroxysteroid dehydrogenase type 2).* This enzyme protects the fetus from the harmful effects of endogenous glucocorticoids derived from the mother. Glucocorticoids are known to cause adrenal suppression and fetal growth retardation. The enzyme converts maternal cortisol to the inactive cortisone. (Murphy 2007) As a result of high 11b-HSD2 activity in the placenta, cortisol levels in the fetus are 5- to 10-fold lower than in the maternal circulation.
18	Text	**Glucocorticoids and metabolism** Research shows that some synthetic glucocorticoids are also metabolized by 11b-HSD2. ● Prednisone and hydrocortisone are extensively metabolized. The estimated fetal level of prednisone is only 10% of the maternal level. However, when taken in high doses and over a longer period of time, prednisolone can saturate the placental enzymes, so larger amounts of corticosteroids will be able to cross the placental barrier. ● Dexamethasone and betamethasone, on the other hand, are hardly metabolized by 11b-HSD2.
19	Text	**Difference in degradation** This difference in degradation is important for the choice of glucocorticoid when treating mother or fetus. Steroids freely crossing the placenta should be given if the fetus needs to be treated, while those being extensively metabolized should be used if maternal disorders need to be treated;

		● If a corticosteroid is needed to treat maternal rheumatoid arthritis or an asthma exacerbation, then predni(sol)one is the drug of choice. ● Betamethasone and its isomer, dexamethasone, are the preferred glucocorticoids used to accelerate fetal lung maturity. <u>Did you know?</u> [Doctor pop-up] **Other drugs that have been shown to be metabolized in the placenta are:** ● Zidovudine, which is conjugated to N-glucuronide. ● Oxcarbazepine is metabolized to some extent. ● Glyburide, buprenorphine, and methadone are metabolized through placental CYP19. ● Olanzapine.
20	Text	**Conclusion** Monoclonal antibodies with an Fc domain can cross the placenta. Passage starts from the second trimester and is highest just around delivery. When prescribing a monoclonal antibody, it is important to know if it has an Fc domain. Of the TNF-alpha blockers, infliximab, adalimumab and (probably) golimumab can easily cross the placenta. Etanercept and certolizumab have very little placental transfer. If possible, these agents are preferred in pregnancy. Some corticosteroids are metabolized in the placenta, others hardly or not. Steroids being extensively metabolized should be used if maternal disorders need to be treated, while those freely crossing the placenta should be given if the fetus needs to be treated.

3.5 Dose and duration of treatment

Slide #	Work form	Content
1	Text + pop-up	**Dose and duration of treatment** Wilson's sixth principle assumes that a substance may not pose a risk to the embryo or fetus if the dose is low enough. On the other side, any exposure can be harmful if the dose is high enough. The idea that low doses will not pose a risk is based on the concept of the "threshold dose": the lowest dose of a drug that causes a harmful effect (i.e., birth defect). Exposures that are below this threshold dose will not cause an increased risk of adverse effects. In other words, there is no risk of irreversible effects or death at doses below the threshold concentration. At exposures greater than the threshold dose, however, there is a risk of adverse effects. I-icon [Pop-up text sixth principle] **Wilson's sixth principle** Manifestations of deviant development increase in degree as dosage increases from the no-effect to the totally lethal level.
2	Text	**The concept of treshold dose** The theory behind the threshold dose is that minor damage from teratogenic exposures below the threshold dose could be overcome. Since there are repair mechanisms during embryonic development, this theory seems reasonable. Excessive cellular injury, however, cannot be repaired and instead results in widespread cell death, producing malformations. The dose dependency has not been investigated for the majority of drugs, mostly because of relatively small numbers in studies and the resultant weak statistical power to discern dose effects.
3	Text	**Examples of threshold doses** There are some agents that we know have a threshold dose, here some examples: ● **Valproic acid**: Various pregnancy register studies have shown the dose- dependent teratogenic risk of valproic acid with rates of major congenital malformations (MCMs). Daily doses of valproic acid greater than 1000 mg or 1100 mg of sodium valproate increased the prevalence of congenital malformations compared to lower doses. ● **Methotrexate:** A critical dose of ≥ 10 mg/week has been described, although not universally accepted. ● **Lithium:** There was a clear dose-dependent fetal risk with lithium in a study (Patorno E, N Engl J Med. 2017): the risk ratio was 1.11 (95% CI 0.46–2.64) for a daily dose of up to 600 mg, 1.60 (95% CI 0.67–3.80) for daily doses of 601–900 mg, and 3.22 (95% CI 1.47–7.02) for 900 mg.

		• **Aspirin:** Low-dose (60-100 mg/day) aspirin is not associated with adverse effects. High doses should be avoided. They may be related to increased perinatal mortality, intrauterine growth restriction (IUGR), and teratogenic effects. It can also affect maternal and newborn hemostasis mechanisms, leading to an increased risk of hemorrhage. • **Vitamin A:** Vitamin A intake up to 10,000 IU/day was not associated with an increased risk of congenital anomalies. The malformation risk increased at doses above 10,000 IU/day.
4	Text	**Does this concept apply to all drugs?** The concept of a threshold dose is widely recognized, but it is uncertain whether it applies to all drugs. It is also possible that no safe level of exposure exists, no matter how small the exposure. Because the dose can be important, the recommendation is that pregnant women should be treated with "the lowest effective dose" of any drug. It is important to emphasize that the dose should be effective, not just low. If the dose is not effective, the treatment is pointless. The child is then exposed to the possible harmful effects of the drug and to the possible harmful effects of the mother's disease. It is also worth noting that some drugs actually require the dose to be increased in pregnancy due to changing kinetics, e.g. some antiepileptics. Furthermore, the duration of exposure to a teratogen can have a major impact on its effect. Chronic exposure can lead to increased fetal risk. When possible, the duration of the treatment should be as short as possible.
5	Multiple choice question	In our case the dose of ciprofloxacin is 500 mg for three days twice a day. **What can we say about the dose of ciprofloxacin in terms of the height of the dose?** .This dose is standard. a. This dose is quite high. b. This dose is low. *Feedback correct answer:* Yes, well done. The dose used is normal and not extremely high. The duration is short, which is positive. *Feedback incorrect answer:* No, that's incorrect. The dose used is actually normal and not extremely high. Consider also that the duration is short, which is positive.
6	Text	**Conclusion**

		Our take away message this time is simple: use the lowest effective dose of the drug and treat for the shortest duration possible. Do not treat when not necessary.

3.6 Experience with the medication

Slide #	Work form	Content
1	Text	**The challenge of limited information** We have seen that when considering drug use in pregnancy, the period of pregnancy and the physicochemical properties of the drug are very important. However, to be able to estimate the safety of a drug, information about its use in pregnancy is needed. Finding this information can be challenging and it is not always available. There is a good reason for this. When a new drug enters the market, there is often limited information about the safety of this drug during pregnancy and lactation. Pregnant women are often excluded from clinical trials due to ethical reasons. For the same reason, the safety of the medication during pregnancy cannot be studied in randomized controlled trials. Oftentimes, animal studies have been performed to assess the safety of the drug. However, the results of animal studies cannot be extrapolated to humans. If a study shows that a drug has no adverse effects in pregnant mice, this is no guarantee that the drug is also safe in pregnant women.
2	Text	**Observational studies** For more information on the safety of drug use during pregnancy, we must often rely on observational studies. These include case reports and case series, cohort studies, case control studies, database and register studies. It can take years to perform such a study, and you will need results of multiple studies to draw any conclusions on the risks of the medicine. Therefore, for a new drug it takes an average of 27 years to estimate the safety and risks during pregnancy. In chapter 6 you will learn more about the study designs in teratology. Still, finding information about the safety of a drug is essential for making a risk assessment.
3	Text + pop-up	**Five categories of drugs** Roughly speaking, drugs can be classified in the following five categories based on the experience and outcomes during pregnancy: 1. There is ample experience with the drug in pregnancy, no evidence of adverse effects. 2. There is reasonable experience in pregnancy and no evidence of adverse effects or mostly reassuring outcomes. 3. There is little or no experience with the drug in pregnancy. 4. Use of the drug in pregnancy confers a higher risk of abnormalities. 5. No increased risk of abnormalities is described, but other adverse effects are described, such as miscarriages, IUGR, increased preterm birth or withdrawal symptoms, for example. Did you know?

<table>
<tr>
<td></td>
<td></td>
<td>[Doctor pop-up]
The need for experience
This is unlikely a surprise, but drugs that can be classified in the first two categories are preferred. Agents that give a higher risk of birth defects should not be used unless there is no alternative. However, chances are that there is little experience with a drug in pregnancy. If this is the case, see if there is an alternative medicine with which there is more experience during pregnancy. Drugs from the last category do not necessarily have to be avoided, it may be sufficient to carry out extra checks, take certain measures or not to use the drug in a certain period.</td>
</tr>
<tr>
<td>4</td>
<td>Text + tabel</td>
<td>Best practices for ‘group 5’ drugs
When no abnormalities are described, but other adverse effects may occur

Take a look at the table below to discover how to manage these types of drugs.

<table>
<tr><th>Drug</th><th>Effect</th><th>Management</th></tr>
<tr><td>NSAID</td><td>From 20-26 weeks on: premature closure of ductus arteriosus and inhibition of renal function</td><td>Avoid use in the second half of pregnancy. If used, make an ultrasound and check ductus arteriosus and amount of amniotic fluid.</td></tr>
<tr><td>Antidepressants</td><td>Withdrawal symptoms</td><td>Observation neonate</td></tr>
<tr><td>Beta-blocker</td><td>Neonatal bradycardia and hypoglycemia</td><td>Monitoring of neonatal heart rhythm and blood sugar</td></tr>
<tr><td>Corticosteroid: chronic use</td><td>Intrauterine growth retardation</td><td>Control growth during pregnancy</td></tr>
<tr><td>PTU (propylthiouracil)</td><td>Neonatal hypothyroidism and goiter</td><td>Monitoring of maternal and neonatal thyroid function</td></tr>
</table>
</td>
</tr>
</table>

		Infliximab Neonatal immunosuppression Consider stopping medication mid-pregnancy. If this is not possible, advise parents to reduce risk of infection infant.
5	Multiple choice question	Remember our case? Ciprofloxacine is used in the first trimester. Read the information about ciprofloxacine on the following websites to answer the question: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Ciprofloxacin/ https://mothertobaby.org/fact-sheets/ciprofloxacin-pregnancy/ **Which statement is correct?** a. Studies found no convincing evidence for an increased occurrence of birth defects in the offspring. b. There is a higher risk for birth defects with ciprofloxacin. c. There is no higher risk for birth defects but there is a higher risk for stillbirth. d. There is no information about the use of ciprofloxacin in pregnancy. A is correct. *Feedback correct answer:* Yes, well done. Ciprofloxacin is the best studied quinolone with approximately 2000 pregnancies followed. In the vast majority of pregnancies followed, exposure was in the first trimester. There is no evidence that the use of ciprofloxacin in the first trimester increases the risk of congenital anomalies. *Feedback incorrect answer.* No, that's incorrect. Consider going back to the websites to check out the information again. Ciprofloxacin is the best studied quinolone with approximately 2000 pregnancies followed. In the vast majority of pregnancies followed, exposure was in the first trimester. There is no evidence that the use of ciprofloxacin in the first trimester increases the risk of congenital anomalies.
6	Text	**Conclusion** Try to find information about the safety of the drug during pregnancy. Drugs with ample experience in pregnancy and no evidence of adverse effects are preferred.

3.7 Conclusion on the case example

Slide #	Work form	Content
1	Text	**Our conclusion** We will now summarize our case example and decide how to treat our patient. We base our conclusion on the answers we found to these questions: ● What is the timing of exposure? ● What is the degree of systemic exposure? ● Does the medication transfer across the placenta? ● What is the dose and duration of the medication given? ● What is the experience with this medication?
2	Text	**The answers to the key questions** Refresh your memory and check the answers once more and then give us your conclusion to the case. ● **Timing of exposure** The exposure took place in week 5-6 of the pregnancy. This is the most vulnerable period of the pregnancy, in which exposures can lead to structural malformations. ● **Degree of systemic exposure** The patient has taken oral ciprofloxacin tablets. Ciprofloxacin has an oral bioavailability of 60 - 80%, meaning that the systemic burden is relatively high. ● **Transfer across the placenta:** Ciprofloxacin is a small molecule with low protein binding. This indicates that it can pass the placenta via passive diffusion. It can also pass the placenta via active transport through the BCRP transporter. This is an efflux transporter, indicating that the drug can be transported from the fetus to the mother. ● **Dose and duration:** The drug was taken in a normal dose. This does not raise specific concerns. The duration of the exposure is short, only 3 days. This is beneficial. The shorter the exposure, the better. ● **Experience with the medication:** There is ample experience with using ciprofloxacin in the first trimester of pregnancy. Studies have not seen an

		increased risk of major malformations after use in the first trimester.
3	Multiple choice question	Considering the information at hand, what conclusion do you draw? **The right conclusion to draw is…** a. It was necessary that the disease was treated with ciprofloxacion. b. Another form of medication should have been chosen due to the expected teratogenic effects. c. More research is needed to draw a conclusion. d. It was not necessary the disease was treated at all. *Feedback correct answer:* Yes, well done! In this case, it was necessary that the disease was treated. The drug was taken in the period during which organs are developed. The drug enters the maternal bloodstream and crosses the placenta. Fortunately, there is sufficient evidence that ciprofloxacin in the first trimester is not associated with an increased risk of congenital malformations or other adverse pregnancy outcomes. Therefore we do not expect a teratogenic effect. No further actions are necessary. *Feedback incorrect answer:* No, that's incorrect. In this case, it was necessary that the disease was treated. The drug was taken in the period during which organs are developed. The drug enters the maternal bloodstream and crosses the placenta. Fortunately, there is sufficient evidence that ciprofloxacin in the first trimester is not associated with an increased risk of congenital malformations or other adverse pregnancy outcomes. Therefore we do not expect a teratogenic effect. No further actions are necessary.
4	Text	**Conclusion** You have almost reached the end of this chapter, well done. Now we will summarize the most important elements that were discussed in the chapter.
5	Text	**The main considerations when prescribing drugs in pregnancy are:** ● **Gestational age** Because the development of all tissues and organs takes place in the first trimester, a disturbance in the development during this period can lead to *structural malformations*. These malformations can be seen from birth. In the second and third trimester of pregnancy, growth, differentiation and maturation will take place. Disruption of this development will not lead to structural malformations, but may influence the *function of organs*. This is not immediately visible from birth.

		• **Degree of systemic exposure** Drugs can reach the unborn child by indirect transmission via the maternal blood. Drugs which are easily absorbed into the mothers circulation have a high systemic burden and are more likely to reach the fetus. The administration route of a drug plays a large role in determining the rate of absorption. • **Transfer across the placenta** Many drugs can pass through the placenta via passive diffusion. Passive transport across the placenta is most likely for drugs with a low molecular weight (<600 Da), with low protein binding, which are lipophilic and predominantly unionized at physiological pH. Some medicines can reach the fetus via active transport. This also includes large molecules, such as monoclonal antibodies. • **Dose and duration** The recommendation is that pregnant women should be treated with "the lowest effective dose" of any drug. It is important to emphasize that the dose should be effective, not just low. • **Experience with the drug in pregnancy** Agents that are known to give a higher risk of birth defects should not be used unless there are no alternatives. However, chances are that there is little documented experience with a drug in pregnancy. If this is the case, see if there is an alternative medicine with which there is more experience during pregnancy.
6	Text	**What is next?** Congratulations, you have reached the end of chapter 3. In chapter 4 you will learn more about the principles of therapeutics in pregnancy. On the next slides you can find all of the references for this chapter. We wish you good luck in the next chapter and hope you enjoyed this one!

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Additional resources

- Read: https://www.mdpi.com/2072-666X/12/8/884/htm

- Read: https://www.sciencedirect.com/science/article/abs/pii/S0169409X16302344

Chapter 4A: Principles of therapeutics in pregnancy (background)

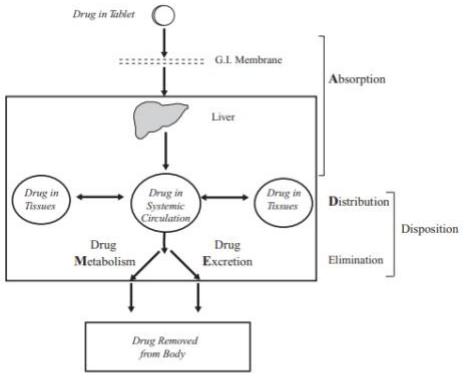
4A.1 Introduction to the chapter

Slide #	Work form	Content
1	Text	**Welcome to the chapter 4A: Principles of therapeutics in pregnancy** In this chapter you will learn more about the principles of therapeutics in pregnancy. You will learn the basics of pharmacokinetics and pharmacodynamics in pregnancy. But before we dive into the content, we would like to show you this exemplary case.
2	Video	**What do you think of the following scenario?** Please watch the video below – and click here to read a few provocative questions. Did you know? [Doctor pop-up] ● What do you think should be the recommendation/counselling? ● Do you think there is a need for some sort of active monitoring? ● Do you think the conversation would be different if she was planning pregnancy? ● Do you think the conversation was different if she told us that she still experiences seizures and her neurologist recommended treatment with Valproic acid? [Media 4.1 Video scenario 1 Principles of therapeutics in pregnancy] Woman calls TIS / enters doctor's office – just find out that she is pregnant, about week 5 of pregnancy, and she is treated with Lamotrigine for epilepsy…..
3	Text	**What are the learning objectives?** During this chapter we will try to understand: ● How the woman’s body is changing during the pregnancy and how that affects the metabolism of medications.

		● What are the medications that need close monitoring. ● How can we prevent the exposure to teratogenic medications. ● Why and when it is important to report the exposures. ● What are the ethical questions regarding the medication exposure during pregnancy. Good luck!

4A.2 The physiological effect of pregnancy on Pharmacokinetics (PK)/Pharmacodynamics (PD)

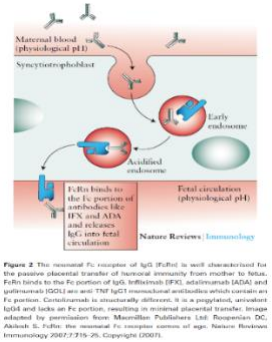
Slide #	Work form	Content
1	Text + afbeelding	**Pharmacokinetics and pharmacodynamics** Clinical pharmacology is defined as the study of drugs in humans. In pharmacology, pharmacokinetics (PK) 1 and pharmacodynamics (PD) 2 constitute two major subdivisions. During pregnancy, there are physiological changes that may affect drug absorption, distribution, metabolism and elimination. This chapter will focus on the major physiological changes during pregnancy, which might influence the pharmacokinetics and pharmacodynamics of some drugs and their effects. I-icon [Pop-up Pharmacokinetics] **Definition of Pharmacokinetics** The quantitative analysis of the process of drug absorption, distribution, metabolism and elimination that determine the time course of drug action. I-icon [Pop-up Pharmacodynamics] **Definition of Pharmacodynamics** The mechanism of drug action in the body. The figure below shows the basic process of pharmacokinetics and pharmacodynamics. [Media 4.2 Figure 1 Drug process]

		 **FIGURE 1.8** Processes of drug absorption, distribution and elimination (metabolism and excretion) (ADME). Drug contained within the tablet must undergo absorption. It must penetrate the gastrointestinal membrane and pass through the liver before reaching the systemic circulation. Once in the blood it has the opportunity to distribute to the tissues, including the site of action. As soon as drug is present in the systemic circulation, it is subject to elimination. This occurs primarily in the liver and kidney, where drugs undergo metabolism and/or excretion, respectively. The fate of a drug in the systemic circulation (distribution and elimination) is referred to as drug disposition.
2	Multiple choice question	As noted, this chapter will focus on the major physiological changes during pregnancy. One of these physiological changes during pregnancy is related to blood composition. Can you already answer the following question? **Does plasma albumin concentration increase or decrease or stay stable during pregnancy?** a. Plasma albumin concentration increases during pregnancy. b. Plasma albumin concentration decreases during pregnancy. *Feedback correct answer:* Yes, well done. Plasma albumin concentration decreases during pregnancy. This fall in albumin concentration is related to a reduction in albumin synthesis or an increase in albumin clearance. Albumin reduction can alter the binding of drug to albumin in the plasma, which leads to higher free drug concentration in the plasma. Free drugs are easily eliminated by the kidney and the liver. And just like plasma albumin concentration, there are many other physiological changes that happen during pregnancy. *Feedback incorrect answer:* No, that's incorrect. Plasma albumin concentration decreases during pregnancy. This fall in albumin concentration is related to a reduction in albumin synthesis or an increase in albumin clearance. Albumin reduction can alter the binding of drug to albumin in the plasma, which leads to higher free drug concentration in the plasma. Free drugs are easily eliminated by the kidney and the liver. And just like plasma albumin concentration, there are many other physiological changes that happen during pregnancy.

3	Text + pop-up	**Gastrointestinal changes** Let's start off with the gastrointestinal changes that happen during pregnancy. The effect of progesterone on smooth muscle activity may prolong gastric emptying and the transition time through the gastrointestinal tract. In theory, the net effect of these changes may cause prolongation in time of absorption with greater amount of drug that is absorbed, but on the other hand, prolonging the time necessary for the drug to reach the maximal concentration in blood (with maximal drug effect). In addition, there is a decrease in gastric acid secretion which may also affect drug dissolution and absorption. <u>Did you know?</u> [Doctor pop-up] Although there are many gastrointestinal changes during pregnancy, studies showed no major differences in drug absorption during all trimesters.
4	Text	**Cardiovascular effects** During pregnancy there is a plasma volume expansion, an increase in cardiac output, and changes in regional blood flow. By 6-8 weeks of pregnancy plasma volume has expanded, and continues to increase until 32-34 weeks by 40% compared to the plasma volume of non-pregnant women. The expansion is even greater for multiple gestations. Extracellular fluid space and total body water are also increased. These changes increase the cardiac output by the end of the third trimester. Regional blood flow increases in the kidney and the skin. These affect drug distribution and renal elimination. The volume of distribution increases and the glomerular filtration rate increases, hence drug elimination from the body increases. *But there is more…* <u>Did you know?</u> [Doctor pop-up] The cardiac output is increased by 30-50% by the end of the third trimester.
5	Text + afbeelding	**A summary of cardiovascular effects** Take a look at the table below for a summary of cardiovascular changes during pregnancy. Did you for example know the stroke volume increases to a maximum of 85 mL at 20 weeks of gestation?

		[Media 4.3 Table 1 Summary of cardiovascular changes during pregnancy] **Table 1 | Summary of cardiovascular changes during pregnancy.** **Variable** / **Change** Cardiac output — Increased by 30–50% Stroke volume — Increases to a maximum of 85 mL at 20 weeks of gestation Heart rate — Increased (approaches 90–100 beats/minute at rest during the third trimester) Systemic vascular resistances — Decrease 21% (nadir at 20–24 weeks) Pulmonary vascular resistances — Decrease by 34% Pulmonary capillary wedge pressure — No significant change Colloid osmotic pressure — Decreased by 14% Hemoglobin concentration — Decreased *(Costantine MM, 2014)*
6	Multiple choice question	The next changes you should know about are renal changes. Before we dive in, try to answer the following question first. **As mentioned previously, the increased blood flow to the kidneys increases the glomerular filtration rate (GFR). What process reflects this increase in GFR during pregnancy?** a. Creatine clearance b. Tubular reabsorption *Feedback correct answer:* Yes, well done. This increase in GFR is reflected in the creatinine clearance during pregnancy. This process is explained further on the next slide. *Feedback incorrect answer:* No, that's incorrect. This increase in GFR is reflected in the creatinine clearance during pregnancy. This process is explained further on the next slide.
6	Text + pop-up	**Renal changes** As you now know, the increased blood flow to the kidneys increases the glomerular filtration rate (GFR). This increase begins by the sixth week of gestation and gradually rises during the third trimester, and then plateaus until delivery. This increase in GFR is reflected in the creatinine clearance during pregnancy. For drugs cleared mostly by the kidney,

		the increase in GFR will increase drug clearance during pregnancy. For example, a cephalosporin like Cefuroxime, which is pronominally eliminated by the kidney, the clearance is significantly greater during mid trimester. This change in GFR and clearance reflects the lower blood concentration of some drugs during pregnancy, especially for antiepileptic drugs, in which, dose escalations and therapeutic drug monitoring are required to ensure therapeutic levels during pregnancy. For example, renal elimination of ampicillin increases by 50% during pregnancy with corresponding lower plasma concentration. *(Philipson, 1977)* Did you know? [Doctor pop-up] Tubular reabsorption does not appear to be changed during pregnancy.
7	Text + pop-up	**Hepatic drug metabolism changes** Most drugs and other substances pass through the liver via portal vein, where they are metabolised in the hepatocytes. Pregnancy is an estrogenic state. Progesterone also rises dramatically. These changes are responsible, with other placental hormones, for the alteration in hepatic enzymatic activity. The activity of CYP3A4 and CYP2D6 is increased during pregnancy. CYP3A4 metabolizes about 50% of drugs and CYP2D6 is involved in 25% of drug metabolism, including anti-epileptics, anti-psychotics and SSRIs. The increases in enzyme activity reflects an increase in drug clearance. For prodrugs like codeine, increased activity of CYP2D6 reflects higher blood levels of one of the active metabolites- morphine-6-glucuronide. Did you know? [Doctor pop-up] **An interesting study** The pharmacokinetics of orally administrated methadone was studied by Pond et al, demonstrating no significant change in protein binding to plasma protein during pregnancy. The total clearance (renal clearance + liver clearance) of methadone is higher during pregnancy and although renal clearance was found to be twice as high compared to the postpartum period, the contribution is minimal to the total clearance. On the other hand, liver metabolism and clearance are increased by the increased activity of CYP3A4 with a major contribution to the total increased methadone clearance, hence lower drug concentrations during pregnancy. *(Pond SM, Kreek MJ, Tong TG, Raghunath J, Benowitz NL, 1985)*
8	Text + afbeelding	**The placenta** Until now we discussed pharmacokinetics and physiological maternal changes during pregnancy. Now we will explain how the placenta itself affects the passage of drugs from the mother to the fetus, and its effect on drug

		pharmacokinetics. Although the placenta is a barrier, for the most part, drugs and other substances given to the mother will be transferred to the fetus. Drugs cross largely by simple diffusion. Factors affecting drugs transfer are: 1. Molecular weight less than 600 Da. 2. Lipid solubility. 3. Protein binding. 4. Degree of ionization of the drug. Therefore, drugs with a molecular weight less than 600 Da, which are lipophilic, with less protein binding and that are uncharged or non-ionized, will easily traverse the placenta. Diffusion can also be active, with specific transporters. [Media 4.4 Figure 4 Placenta]  *(Roopenian DC, Akilesh S, 2007)*
9	Text	**The placenta and metabolism** Placenta can also function as an additional site for extra-hepatic metabolism that catalyse both Phase I (drug oxidation, reduction and hydrolysis) and Phase II (conjugation) reactions. The extent of placental drug metabolizing enzymes changes during pregnancy. Drugs which have been shown to undergo significant placental metabolism include structural analogues of endogenous compounds, such as zidovudine, but also other compounds such as oxcarbazepine, buprenorphine and methadone.

		It was indicated in several studies that methadone undergoes metabolism by CYP19 in human placenta. This could be an additional contributing factor for the increased metabolism of methadone during pregnancy, especially during the third trimester, and emphasizes appropriate methadone dosing to prevent maternal and foetal/neonatal withdrawal. *(Tetro N, Moushaev S, Rubinchik-Stern M, Eyal S, 2018)*
10	Text	**Postpartum changes** The cardiovascular changes of pregnancy are sustained as long as 12 weeks after delivery. Hepatic enzyme may either rapidly reverse within 24 hours of delivery or gradually return to normal during the first months after delivery. Pharmacokinetic studies during this period showed variability between subjects.

4A.3 Important steps in therapeutic drug monitoring (TDM) throughout pregnancy

Slide #	Work form	Content
1	Text + afbeelding	**Therapeutic drug monitoring (TDM) throughout pregnancy** As you have learned, physiological changes during pregnancy may influence pharmacokinetics of some drugs. In some circumstances, drug level monitoring and dose adjustments (therapeutic drug monitoring, TDM) may be required. Not all drugs require TDM, only those with significant pharmacokinetic changes that are correlated with a clinical effect. To understand the steps in TDM, Levetiracetam, an anti-epileptic drug, and Lithium will be used as examples.
2	Multiple choice question	Before you learn more about Leveriracetam and Lithium, try to answer the following question first. **Do you which one of these is the most common matrix for TDM?** a. Serum/plasma b. Saliva c. Dried blood spots *Feedback correct answer:* Yes, well done. The most common matrix for TDM is serum/plasma, but for some medications or exposures other methods might be explored such as saliva or dried blood spots. It is important to understand what exactly is measured – total concentration or only free (the unbound) concentration. Sometimes the pharmacologically active metabolite is measure. The reference range and the unit of measurement, is also important, since those might differ between the

		labs. *(Cecilie Johannessen Landmark, Svein I. Johannessen & Philip N. Patsalos, 2020)* *Feedback incorrect answer:* No, that's incorrect. The most common matrix for TDM is serum/plasma, but for some medications or exposures other methods might be explored such as saliva or dried blood spots. It is important to understand what exactly is measured – total concentration or only free (the unbound) concentration. Sometimes the pharmacologically active metabolite is measure. The reference range and the unit of measurement, is also important, since those might differ between the labs. *(Cecilie Johannessen Landmark, Svein I. Johannessen & Philip N. Patsalos, 2020)*
3	Text	**Levetiracetam concentration during pregnancy** Levetiracetam is a second-generation antiepileptic drug (AED), indicated for the treatment of generalized and focal seizures and is commonly used in pregnant women, due to its safety profile, with low teratogenic risk and favourable pharmacokinetic characteristics[1]. Studies have shown a reduction of Levetiracetam serum concentration during pregnancy, with a maximal reduction during the third trimester when compared with pre-pregnancy state. This reduction in blood levels is explained by the increased clearance rate of the drug during all stages of pregnancy. However, in a recent study of Berlin et al. (2019) the most significant increase in clearance was observed during the first trimester and not during the third trimester.
4	Text	**Levetiracetam concentration during pregnancy** Increased renal blood flow and glomerular filtration rate during pregnancy play a role in decreasing the drug serum levels. However, hormonal changes and increased estrogen levels may lead to accelerated drug glucuronidation early during pregnancy. This effect has been studied in pregnant women treated with lamotrigine as a possible explanation for decreased lamotrigine serum levels. Another physiological change during pregnancy is the increased peripheral hydrolysis of Levetiracetam. When adjusted to trimester, age and total daily dose, the decrease in Levetiracetam serum concentration was statistically significant during all three trimesters of pregnancy. These reductions in the first trimester are explained by the pharmacokinetic changes in metabolism during the first trimester. <u>Did you know?</u> [Doctor pop-up] **Pharmacokinetic properties of Levetiracetam** The pharmacokinetic properties of Levetiracetam include high oral bioavailability (>95%), low plasma protein binding (<10%), low risk of drug–drug interactions and it is not extensively metabolized. The major route of LEV excretion is through the urine. Due to these properties, this drug has a good safety profile and is frequently used during pregnancy.

5	Text + pop-up	**Is therapeutic drug monitoring recommended during pregnancy?** For many pregnant patients, literature demonstrates that serum concentrations during pregnancy are below the laboratory quoted reference range with an exposure to higher risk of seizures during pregnancy. Due to the higher risk of seizures it is crucial to follow a routine LEV serum monitoring while planning and commencing pregnancy and during all trimesters, with dose adjustment based on these serum levels. In conclusion, therapeutic drug monitoring of Levetiracetam is recommended during pregnancy. During the postpartum period, renal clearance and GFR are decreased. This reflects the increase in levels of Levetiracetam and serum concentration should be still monitored. Usually within two weeks after delivery, serum levels should be measured and dose adjustment should be made accordingly. Did you know? [Doctor pop-up] **Ampicillin and Amoxicillin** There are other drugs whose serum levels change during pregnancy due to physiological and pharmacokinetic changes, for example, antibiotics like Ampicillin and Amoxicillin. One study found lower peak levels in pregnant women compared to non-pregnant women. Both renal and total elimination clearance of ampicillin were increased by 50% during pregnancy and resulted in lower plasma concentrations. *(Philipson A, 1977)*
6	Text + pop-up text	**Lithium clearance during pregnancy** Lithium is the primary drug used for the treatment of bipolar disorder. In this chapter only pharmacokinetics will be discussed, teratogenic effects are not addressed. Dosing is guided by serum level, with a narrow therapeutic window of drug concentration. Lithium is well absorbed orally and excreted unchanged through the kidneys. During pregnancy lithium clearance is increased by 50-100% and clearance increases progressively requiring higher dosing and frequent level monitoring. Therapeutic drug monitoring should be tailored to the patient and should occur at least once per trimester. Renal function and GFR should be monitored as well. Did you know? [Doctor pop-up] **Discontinuation before delivery** Lithium crosses the placenta and reaches a concentration in the fetus that is similar to that of the maternal serum. Lithium clearance declines rapidly after birth; therefore the medication must be discontinued 24-28 hours before delivery.

4A.4 Acute disease - pain, fever, antibiotics, NVP/HG and allergy

Slide #	Work form	Content
1	Text	**What to do in case of an acute disease?** Acute disease requires an immediate response. Therefore we would now like to focus on common acute disease affecting pregnant women and medications. <u>Did you know?</u> [Doctor pop-up] Both symptomatic and asymptomatic UTIs are linked with adverse outcomes such as pyelonephritis and may lead to preterm labor and low birth weight.
2	Text	**Urinary tract infections (UTIs)** UTIs are one of the most common types of infection affecting pregnant women. Both symptomatic and asymptomatic UTIs are linked with adverse outcomes such as pyelonephritis and may lead to preterm labor and low birth weight. ***What is the appropriate treatment?*** Most of the antibiotics are compatible with pregnancy, but some are only allowed in certain gestational weeks. A urine culture should be taken in order to choose the right treatment and to avoid the above risks. Fluoroquinolones antibiotics were thought to be teratogenic for decades. Animal studies associated ciprofloxacin with arthropathy and other musculoskeletal problems. Several retrospective studies have refuted this hypothesis in humans. And yet, even though the FDA has also removed the Fluoroquinolone's warning from the leaflets, healthcare providers still think that these drugs are prohibited in pregnancy.
3	Multiple choice question	Fever is another common acute disease affecting pregnant woman. Do you know whether the following statement is true or false? **Prolonged fever in first weeks of pregnancy may result in a higher rate of miscarriages.** a. True b. False *Feedback correct answer:*

		Yes, well done. It may endanger the life of the fetus if a woman who is in the beginning of her pregnancy suffers from a high fever. Studies have indeed shown that prolonged fever in these weeks may result in a higher rate of miscarriages. Various antipyretic drugs are allowed to be used during the first trimester of pregnancy. Paracetamol is considered as a first-choice medicine to treat pain and fever in pregnancy. Therefore, the risk to the fetus of fever is much higher than the potential risk of these drugs. *Feedback incorrect answer:* No, that's incorrect. It may endanger the life of the fetus if a woman who is in the beginning of her pregnancy suffers from a high fever. Studies have indeed shown that prolonged fever in these weeks may result in a higher rate of miscarriages. Various antipyretic drugs are allowed to be used during the first trimester of pregnancy. Paracetamol is considered as a first-choice medicine to treat pain and fever in pregnancy. Therefore, the risk to the fetus of fever is much higher than the potential risk of these drugs.
4	Text + image + pop-ups	**Nausea and vomiting of pregnancy (NVP)** NVP has several negative impacts. Click on the icons to learn more. [Media 4A.4 Image Womans head + thought bubble] **Psychological** ● Quality of life is negatively affected. ● Depression/anxiety, isolation, frustration and helplessness. ● Time loss from work. ● [Media 4A.4 Image Womans full body] **Physical** ● Dehydration & electrolyte imbalance. ● Malnutrition and weight loss. ● Hospitalization. ● Longer recovery time from pregnancy, postpartum gallbladder dysfunction and muscle pain. ● Higher incidence of low birth weight, small for gestational age and premature babies. ● Due to the tremendous impact of NVP/HG, some women may choose to terminate an otherwise wanted pregnancy. <u>Did you know?</u> [Doctor pop-up] NVP affects up to 85% of pregnant women.
5	Text	**Treatment for NVP**

		The pharmacological treatment includes a few antiemetic medications such as: Doxylamine+Vit. B6, Ondansetron or Metoclopramide. These therapies are being administered (commenced) during the first trimester while embryogenesis is ongoing. In each case, a rational assessment of maternal and fetal risk should be determined according to the current circumstances. There is data that ondansetron is safe and effective but the consensus is controversial. Few studies suggest an association between ondansetron use during early pregnancy and an increased risk of cardiac defects and oral clefts. Recent publications claim that there is only a small excess risk of oral clefts corresponding to three additional cases of oral cleft for every 10 000 live-born children exposed to ondansetron in the first trimester of pregnancy. <u>Did you know?</u> [Doctor pop-up] Despite the existing risk, it should be remembered that nausea and vomiting that are not well treated also lead to pregnancy complications. In this case - because the risk of using ondansetron is minimal for the dangers of nausea and vomiting - the drug is recommended for use in women who need it.
6	Text	**Acute low back pain** Lower back pain is a very common example of acute pain that appears during pregnancy. The pain will be treated according to the gestational week of pregnancy in which it appeared. Safety profile of paracetamol during pregnancy was well studied. It is allowed in therapeutic doses up to the end of the pregnancy. ***Several key points before administration:*** ● Do not exceed the recommended daily dose (up to 4 g per day - for paracetamol). ● Avoid repeated doses. ● Use for a few days.
7	Text + pop-up	**What if NSAIDs are required?** If NSAIDs are required, treatment with old and well-known drugs such as Ibuprofen, Diclofenac, Naproxen should be preferred. The information regarding safety of selective COX-2 inhibitors (Etoricoxib, Celecoxib) is limited and therefore it is not recommended to use them. ***The use of NSAIDs should be restricted after week 20 of pregnancy.*** In any case, NSAIDs should not be used after week 28 of pregnancy due to the risk of in utero closure of the ductus arteriosus in the fetal heart. If NSAIDs treatment between the weeks 20-28 of pregnancy is essential, the lowest effective dose should be used for the shortest possible time. An ultrasound examination to assess the amount of amniotic fluid should be considered when a full therapeutic

		dose (anti-inflammatory) treatment exceeds 5 days. Discontinue treatment if amniotic fluid deficiency is found. Did you know? [Doctor pop-up] A woman who does not receive treatment may suffer from bothersome pain that will interfere with her daily routine. The pain may worsen and sometimes even cause damage that has future consequences for the mother's health.
8	Text	**Allergies** Pregnancy may worsen allergy symptoms such as rhinitis, rash, pruritus etc. There are several treatment options for controlling allergy symptoms: ● **Nasal irrigations** - nasal drops containing decongestants can be used for only two to three days to avoid addictions to these preparations. Those medications are effective and safe but sometimes the improvement is insufficient. ● **Oral antihistamines** - Second-generation antihistamines (Loratadine, Desloratadine, Cetirizine, Fexofenadine) are preferred over other oral treatments since its high safety profile and minimal sedative effect. ● **Intranasal steroid spray** - The absorption of steroidal sprays is minimal, does not increase risk and can be used for a long time. Oral steroids can also be administered after the 11th week of pregnancy. An earlier exposure may increase the risk of cleft lip and palate. The risk exists in doses exceeding 10 milligrams of prednisone per day.
9	Text + pop-up	**Chronic diseases** *#1/3 Inflammatory bowel diseases* Inflammatory bowel diseases are represented by Crohn's disease (CD) and ulcerative colitis (UC). The peak age onset of these diseases coincides with childbearing years. Management of IBD during pregnancy is essential due to an increased risk of obstetric complications including spontaneous abortions, preterm birth, babies small for gestational age and caesarean deliveries. Most women with active disease at the time of conception will have consistent flare-ups during pregnancy. Active inflammation from IBD may lead to a significant risk to the mother and fetus. The goal of the management of IBD during pregnancy is to keep the woman safe and to make sure the woman has a normal pregnancy with a healthy baby at the end. There is a known approach to discontinue treatment before or during pregnancy because of the concerns about drug safety, which may lead to increased risk of relapse and undesirable pregnancy outcomes. Did you know?

		[Doctor pop-up] Luckily, most of the medications used to treat IBD have not been associated with significant adverse fetal outcomes.
10	Text	**Medications IBD** As stated before, most of the medications used to treat IBD have not been associated with significant adverse fetal outcomes. Here are some examples: ● **Amino salicylates** (mesalazine, sulfasalazine) are considered safe (up to 3.2 g/day) during pregnancy. The mechanism of action is based on an intervention with folate synthesis; therefore the recommendation is that women on Amino salicylates should receive high-dose folic acid supplementation (5 mg/day) a month before conception and during the first trimester. ● **TNF- alpha inhibitors** - There is no evidence of teratogenicity as a result of the use of these drugs. Most of the drugs in this group cross the placenta at about 20 weeks of gestational age and up. Cetrolizumab has a different structure than other anti-TNF. Therefore it possesses minimal trans placental passage properties. Due to its mechanism, infants exposed to these drugs in utero may have an increased risk for immune system impairment (infections) at the beginning of life. Therefore, live attenuated vaccines should be avoided in the first 6 months of those exposed infant's lives.
11	Multiple choice question	The next chronic disease we would like to cover is anxiety and depression. Let's see if you can already answer the following question. **Which of the following statements is true?** a. A woman who is experiencing depression during her pregnancy is not at risk for preterm birth. b. Antidepressants can only be used at the early stages of pregnancy. c. Babies can have withdrawal symptoms if the mother's medication supply is cut after birth. d. Babies need special intervention if the mother's medication supply is cut after birth. *Feedback correct answer:* Yes, well done! Babies can have withdrawal symptoms if the mother's medication supply is cut after birth. However, babies will get better without special intervention. Furthermore, the mother is at risk for preterm birth if she experiences depression, and antidepressants can be used safely throughout all stages of pregnancy. Medications related to anxiety and depression during pregnancy are discussed further on the next slide. *Feedback incorrect answer:*

		No, that's incorrect. Babies can have withdrawal symptoms if the mother's medication supply is cut after birth. However, babies will get better without special intervention. Furthermore, the mother is at risk for preterm birth if she experiences depression, and antidepressants can be used safely throughout all stages of pregnancy. Medications related to anxiety and depression during pregnancy are discussed further on the next slide.
12	Text	**Chronic diseases** *#2/3 Anxiety and Depression* Studies that have reviewed referrals/enquiries to teratology centers have found that SSRIs are among the most common medications that are addressed. It is important to note that a woman who is having trouble with her mental health condition (especially anxiety and depression) is unbalanced during pregnancy; she is at increased risk for preterm birth, low birth weight and intrauterine growth restriction. Hundreds of studies have already demonstrated the safety of antidepressant use throughout all stages of pregnancy. Those drugs do not increase the risk of miscarriages and birth defects. Babies whose mothers are taking medications will be used to having the medication in their systems before they are born. When they are born this supply is cut, and some babies can have withdrawal symptoms (agitation, irritability, excess sleepiness, difficulty feeding). Most of these are very mild, and the baby will get better without any special intervention.
13	Text	**Chronic diseases** *#3/3 Epilepsy* Pre-pregnancy consultation and close collaboration between the gynecology and neurology providers as a multidisciplinary team are very important for a woman with seizures who becomes pregnant. Seizure frequency declines or remains the same in the majority of women during pregnancy. There are possible triggers that can explain increasing seizure frequency: hormone changes, sleep deprivation, stress, decreasing serum levels of antiepileptic medications, etc. Seizures during pregnancy can cause injury or problems for the mother and fetus including: trauma from falls, slowing of the fetal heart rate, placental abruption, premature labor, miscarriages and fetal growth restriction.
14	Text + pop-up	**Chronic diseases** ***Therefore, seizure control during pregnancy is crucial.*** Anti-epileptic drugs can affect the fetus. Birth defects such as neural tube defects, skeletal malformation, oral clefts and congenital heart defects are some examples for potential side effects associated with anti-seizure medications. The risk may be greater when there is polytherapy and high doses. ***Continued treatment during pregnancy is desirable for most women.*** It is important to note that folic acid helps prevent neural tube defects, serious abnormalities of the brain and spinal cord. Some seizure drugs affect the way the

		body uses folic acid. Therefore, a woman who uses anti- seizure medication should take a high dose of folic acid- 5 mg. <u>Curious for the major malformations caused by AED drugs?</u> **Major malformations** ● Valproic acid- neural tube defects (as spina bifida), ventricular and atrial septal defects, pulmonary valve atresia, cleft palate. ● Carbamazepine- neural tube defects, congenital heart defects, limbs malformations, urinary tract malformations. ● Phenytoin- congenital heart defects, facial clefts. ● Topiramate- hypospadias.
15	Text	**Cancer in pregnancy** Although it is a rare event, the last disease we want to discuss is cancer. The most common malignancies associated with pregnancy are, in order of decreasing frequency, melanoma and breast cancer, cervical cancer, lymphomas and leukemia. The case management depends on the location and type of the cancer, the stage of the cancer, the current gestational week and the urgency of the treatment.
16	Multiple choice question	Before we dive into the topic of cancer in pregnancy, can you answer the following question? **If a woman has cancer during her pregnancy, can the cancer affect the fetus?** a. Yes, cancer always affects the fetus. b. Yes, if the cancer spreads towards the breasts and/or uterus. c. No, but treatment might affect the fetus. *Feedback correct answer:* Yes, well done! Cancer itself rarely affects the fetus but diagnose tests and treatments can. *Feedback incorrect answer:* No, that's incorrect. Cancer itself rarely affects the fetus but diagnose tests and treatments can.
17	Text	**Cancer treatment during pregnancy** The case management depends on the location and type of the cancer, the stage of the cancer, the current gestational week and the urgency of the treatment. Imaging tests are essential to determine appropriate treatment. X-RAY and CT scans (especially PET CT) emit radiation that can do harm to the fetus.

		• **Radiation therapy** is known to teratogenicity, growth restriction, cognitive impairment and the gestational age plays an important role in determining the severity of the effect in consequence of radiation exposure. Exposures during the organogenesis stage are main risk factors for major malformations. • **Cytotoxic chemotherapy** - most chemotherapeutic drugs cross the placenta due to low molecular weight. Almost all of them are known to be teratogenicity according to in vitro studies. As in radiation therapy, the risk to the fetus depends on the pregnancy week that the drug was administered. Chemotherapeutic insult around ovulation and fertilization may lead to abnormal fetal development that will lead to miscarriage and spontaneous abortion. Exposure during the organogenesis may cause more malformations (central nervous system (CNS), genitals, eyes and the hematopoietic system) than at any other time. During the second and third trimester, exposure may lead to IUGR, low birth weight and preterm labor.
18	Text	**What can we conclude about chemotherapy?** According to retrospective studies, the incidence of major malformation in first trimester's exposure is about 4 times and up as the incidence during second and third trimester (14% Vs. 3%). Therefore, the recommendation is to avoid chemotherapy until the 13th gestational week. Chemotherapy during the second and third trimester is considered relatively safe. Yet, close monitoring of the mother and fetus is required as well as close monitoring of the newborn because the information regarding the safety of chemotherapy in pregnancy is still limited. To reduce hematological risk to the fetus, it is recommended to **stop chemotherapy 3 weeks before the expected date of delivery or after ≥ 35 weeks of pregnancy.** A multi-disciplinary team work is needed in those cases.

4A.5 Paternal exposure

Slide #	Work form	Content
1	Text	**Paternal exposure** Paternal exposure refers to exposure of the partner to the medications before pregnancy, around conception or during pregnancy. There are few main aspects of paternal exposure and pregnancy: ● Effect on male fertility. ● Possible effect of genetic alterations in exposed sperm. ● Possible effect of exposure to teratogenic medications through seminal fluid. ● Paternal transition of viral teratogens.
2	Text	**Effect on male fertility** There are medications that may reduce sexual function and semen quality and quantity that decrease the chance of the partner to get pregnant. These effects might be reversible when the medication stopped. If the effects persist, assisted pregnancy may be considered.
3	Text	**Possible effect of genetic alterations in exposed sperm** There are limited data available regarding the male exposure to known/suspected mutagens. Such substances could damage the sperm itself genetically or impair spermatogenesis. It is also possible that the substances may become attached to sperm and transported during fertilization. It is still recommended to wait 2 spermatogenic cycles (about 6 months) after the exposure to cytoxic or mutagenic medications prior to conception.
4	Text	**Exposure to teratogenic medications** There is currently no evidence suggesting an increased risk for teratogenic effects when exposed through semen fluids. There is no shared blood connection between the father and the fetus, so paternal medications do not reach the fetus. The exposure through the semen fluid is minimal.
5	Text	**Infections** Some viruses can be potentially transmitted to a pregnant partner during sexual intercourse if a man has an infection. A fetus might sometimes be affected. A Zika virus is an example of such transmission. If a pregnant person is infected with Zika virus, there is a chance of passing the infection to the developing fetus. Fetal infection increases the chance for birth

		defects caused by Zika virus. To date, there is no data to justify elective termination of otherwise wanted pregnancy because of paternal exposure to medications.

4A.6 Pregnancy Prevention Program

Slide #	Work form	Content
1	Text + pop-up	**Pregnancy Prevention Program** Remember the thalidomide tragedy from chapter 1? After this tragedy, regulatory agencies were concerned about teratogenic medication exposures during pregnancy. Risk minimization measures are interventions that aim to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur. Routinely required risk minimization measures are the Summary of Product Characteristics (SmPC), the package leaflet (PIL), pack size and legal (prescription) status, which are considered sufficient for most drugs. *(Ineke Crijns, Inge Zomerdijk, Miriam Sturkenboom, Lolkje de Jong-van den Berg & Sabine Straus , 2014)* However, some drugs contain serious important risks requiring an extra form of risk minimization, such as Pregnancy Prevention Program (PPP) to minimize the risk of exposure to teratogenic medications during pregnancy to prevent congenital anomalies. I-icon [Pop-up text Summary of Product Characteristics] **Summary of Product Characteristics (SmPC)** A document describing the properties and the officially approved conditions of use of a medicine. Summaries of product characteristics form the basis of information for healthcare professionals on how to use the medicine safely and effectively. I-icon [Pop-up text ppp elements and tools] **PPP elements and tools** Certification of prescribers and pharmacists, educational programs for health professionals and patients, patient counselling regarding contraception use and the need for pregnancy tests before and during treatment on a monthly basis and dispensing restrictions. Those programs can involve patients, prescribers, pharmacists, wholesalers and others. I-icon [Pop-up text the package leaflet (PIL)] **Package leaflet (PIL)** The leaflet in every pack of medicine that contains information on the medicine for end-users, such as patients and animal owners.
2	Text +	**Examples of PPP over the decades**

	tijdlijn + pop-ups	*Isotretinoin* Click on the timeline below to discover the stories of early PPS. First we take a look at Isotretinoin: a drug that was classified as pregnancy category X by the FDA due to concerns of teratogenicity identified by animal reproductive toxicology testing. [Media 4A.6 Timeline 1 PPP] **1982** [Pop-up text] **Introduction** The drug Isotretinoin was introduced in the US. **1983** [Pop-up text] **Congenital malformations** In 1983 the first reports of congenital malformations appeared despite the warnings about the risks in pregnancy. In the same year, Isotretinoin was introduced in the EU. **1988** [Pop-up text] **PPP for oral isotretinoin** In 1988 the marketing authorization holder implemented a Pregnancy Prevention Program (PPP) for oral isotretinoin, which was included in the product information worldwide. In the same year, the first PPP in the EU was established for isotretinoin. **2002** [Pop-up text] **'SMART' and 'iPledge'** Because of poor compliance, a stricter PPP for isotretinoin has been implemented in the US in 2002, 'SMART' and an even stricter PPP was implemented in 2006, 'iPledge'. **2003** [Pop-up text] **A new starting point in the development of PPP** The European Commission (EC) released a harmonized EU PPP for this drug. This PPP seems to be used as a starting point in the development of the PPP of the other drugs which resulted in similarities between the PPP. Interestingly, studies showed that a more stringent PPP does not guarantee better results with regard to pregnancy exposure rates, while it may place an unnecessary additional burden on the stakeholders. *(Brinker A, Kornegay C, Nourjah P, 2005), (Shin J, Cheetham TC, Wong L, et al., 2011), (Mitchell AA, Van Bennekom CM, Louik C., 1995)*

3	Text + tijdlijn + pop-ups	**Examples of PPP over the decades** *Valproate* Remember Valproate? This drug was discussed earlier in the first chapter. Sodium Valproate is an old medication, used in Europe since 1960s and licensed for treatment of epilepsy, bipolar disorder and migraine prophylaxis. Click on the timeline below to discover the stories of early PPP regarding this drug. [Media 4A.6 Timeline 2 PPP] **1960** [Pop-up text] **Introduction** The drug Valproate was introduced in the EU. **1970** [Pop-up text] **Teratogenic effects** The concern was raised about the teratogenic effects in animal studies. **1984** [Pop-up text] **Effect on children** A valproate foetal syndrome was described in children. **2004** [Pop-up text] **Growing body of evidence** Negative neurodevelopmental outcomes after in-utero exposure to Valproate were first reported in 2004 and since then a growing body of evidence confirmed behavioural teratogenicity of valproic acid. **2013** [Pop-up text] **PRAC review** Pharmacovigilance Risk Assessment Committee (PRAC), the committee that is responsible for assessing all aspects of the risk management of medicines for human use, started a review of Valproate use in pregnant women. **2014** [Pop-up text]

		Stronger restrictions PRAC recommended to strengthen the restriction for use in women. **2016** [Pop-up text] **Raised concerns** Concerns were raised regarding the lack of efficacy of RMM and another review was conducted by the PRAC. **2018** [Pop-up text] **New PPP** New PPP was released contraindicating the use of Valproate in women of childbearing potential unless they met the conditions of PPP. The program incorporates informed consent, an annual risk acknowledgement form, the use of highly effective contraception (but invasive or with possible health risks) and other requirements that vary between regulators. Some authors have raised concerns about the PPP in the context of vulnerable populations such as those who lack capacity to consent to the decision-making process (*Lance V Watkins, Hannah R Cock, Heather Angus-Leppan, Rohit Shankar., 2019)*. Others suggest that it is premature to ban the use of this drug in women of childbearing potential, since in rare cases the benefits of its use may outweigh potential harms *Macfarlane, A., Greenhalgh, T., 2018).*
4	Text	**Conclusion** As you have learned, physiological changes during pregnancy may influence pharmacokinetics of some drugs. In some circumstances, drug level monitoring and dose adjustments (therapeutic drug monitoring, TDM) may be required. Not all drugs require TDM, only those with significant pharmacokinetic changes that are correlated with a clinical effect. Furthermore you should pay close attention to pregnant women suffering from acute diseases as these require an immediate response. Paternal exposure might also influence the health of the fetus depending on the type of medication and the duration period. Pregnancy Prevention Program (PPP) help to minimize the risk of exposure to teratogenic medications during pregnancy to prevent congenital anomalies.

Chapter 4B: Principles of therapeutics in pregnancy (practice)

4B.1 Introduction to the chapter

Slide #	Work form	Content
1	Text	**Welcome to chapter 4B: Principles of therapeutics in pregnancy** After understanding the basic principles of therapeutics in pregnancy, we will try to discuss different maternal medical conditions and try to balance the benefits of treatment against potential risks posed by the medication. The intent is not to provide a formula or rigid “to do” list, but rather to facilitate a better understanding of risk assessments in different scenarios.
2	Text + pop-up	**Two important facts** According to the USA data- Center for disease Control and Prevention (CDC): ● Almost 1 in 4 pregnant women between 15-44 years of age reported using prescription medications in the last 30 days. ● 9 out of 10 women take at least one medicine during pregnancy. During pregnancy, underlying conditions can worsen, improve or remain the same. An uncontrolled maternal condition can lead to adverse perinatal outcomes including congenital anomalies, intrauterine growth restriction, preterm delivery, low birth weight and long-term neurodevelopmental impairment. On the other hand, some medications are known to be harmful if taken during pregnancy. Did you know? [Doctor pop-up] IBD (crohn and colitis) may lead to preterm birth. Anxiety and depression may lead to IUGR (intra uterine growth restriction) and SGA (small for gestational age). Diabetes mellitus may lead to cardiac anomalies and neural tube defects. *(Nørgård B, Fonager K, Sørensen HT, Olsen J, 2000)* *(Pinto TM, Caldas F, Nogueira-Silva C, Figueiredo B, 2017)* *(Ornoy A, Reece EA, Pavlinkova G, Kappen C, Miller RK, 2015)*
3	Text	**The problem of “contraindicated” medicines** In the absence of a sufficient evidence base addressing the safety of medicines in pregnancy, many medicines are designated as "contraindicated". Lack of access to information on the safety of medicines in pregnancy may result in pregnant women being reluctant to use medicines in pregnancy. This may lead to inadequate control of the disease and

		adverse pregnancy outcomes. What are the risks that drugs are known to pose to pregnant women or their unborn babies? What are the risks of untreated maternal conditions? [Media 4B.1 Image Overview]  *(Image based on an infographic from cdc.gov)*

4B.2 Formulate a treatment plan/option for a patient case

Slide #	Work form	Content
1	Text	**How can you formulate a treatment plan/option for a patient case?** In this course you have come across different scenarios related to pregnant women in need of medication. As a health professional it is important you know how to work with the ethical issues, but also how to formulate a treatment plan/option for a patient case. Ethical issues are important, but there is still a need for a plan.
2	Text + image + pop-ups	**Important factors** To formulate a treatment plan/option for a patient case, take the following factors into account. Click on the images to learn more. [Media 4.7 Image Woman (not pregnant)] **Woman related:** ● Demographics – age, BMI, education (if possible), substance use – smoking, alcohol, drugs, folic acid supplementation. ● Pregnancy (planned/spontaneous/IVF), LMP date. ● Prior obstetric history – pregnancies, miscarriages, pregnancy terminations (medical or social), previous malformations. ● Supportive environment – family [Media 4.8 Image Disease or Medication] **Disease/treatment related:** ● Status of the disease – controlled/not controlled. ● Medication (new treatment /ongoing treatment). ● Teratogenic risk. ● Polytherapy. ● Other possible treatment options. [Media 4.9 Image Talking bubbles] **Pre-conceptional Counselling** ● Is the disease stable? ● What are the risks of the suggested treatment? ● Are there other possible treatment options that have a more favourable profile? ● What is the risk of the untreated disease?

3	Text + image _ pop-up	**In case of a favourable safety profile** If the woman is already pregnant and the treatment medication has a favourable safety profile, it is suggested to think about the following questions. [Media 4.10 Image Woman pregnant] **Pregnant and treatment medication has a favourable safety profile:** ● What is the period of exposure? ● What are the risks of medication used? ● What is the prognosis of the disease during pregnancy? (Is it more stable or might be worse?) ● What is the medical follow up needed during pregnancy, including the prenatal tests, specialist follow up, specific tests e.g. therapeutic drug monitoring?
4	Meerdere antwoorden mogelijk	Now imagine a case in which the woman is already exposed to possible teratogenic medication. **What additional questions should be considered?** Multiple answers possible. a. What is the medical follow up needed during pregnancy, including the prenatal tests, specialist follow up, specific tests e.g. therapeutic drug monitoring? b. Is there a critical exposure window, eg. Warfarin? c. Is there a possibility of accelerated washout, eg. Leflunomide/ teriflunomide? *Feedback correct answer:* Yes, well done! In fact, all these questions should be considered. What is the period of exposure? What are the risks of medication used? What is the prognosis of the disease during pregnancy? Is there another treatment option with a better safety profile? What is the medical follow up needed during pregnancy, including the prenatal tests, specialist follow up, specific tests e.g. therapeutic drug monitoring? Is there a critical exposure window, eg. Warfarin? Is there a possibility of accelerated washout, eg. Leflunomide/ teriflunomide? These are all important questions. *Feedback incorrect answer (there is no incorrect answer):* Yes, well done! In fact, all these questions should be considered. What is the period of exposure? What are the risks of medication used? What is the prognosis of the disease during pregnancy? Is there another treatment option with a better safety profile? What is the medical follow up needed during pregnancy, including the prenatal tests, specialist follow up, specific tests e.g. therapeutic drug monitoring? Is there a critical exposure window, eg. Warfarin? Is there a possibility of accelerated washout, eg. Leflunomide/ teriflunomide? These are all important questions.
5	Text	**Conclusion**

		Keep in mind… It is ok not to have the answer immediately. People appreciate it when you are making an effort to get a comprehensive answer for them. Do not try to give the answer to the question – what should I do? Instead, present information in a clear way that will inform shared decision making and balancing benefits and risks of the treatment. Remember that each case comes with a woman, partner, family, medical and personal history, religious beliefs and culture differences. We are here to present the benefits and risks of medicines in pregnancy in the most simple and accessible way.

4B.3 Ethical considerations that may arise in making decisions around therapeutics in pregnancy

Slide #	Work form	Content
1	Multiple choice question	Imagine the following scenario: a 28-year-old woman, married with 2 children, was diagnosed with cervical cancer on the 29th week of her third pregnancy. Evaluation includes PET-CT, followed by treatment with chemotherapy. **Which of the following statements are always true based on this scenario?** Multiple answers are possible. a. Compromising with the radiological method might misdiagnose the staging of the mother. b. Chemotherapy should always be administered immediately for the safety of the mother and the infant. c. Postponing the chemotherapy too long, after delivery, may endanger the mother, negatively affecting her prognosis. d. Radiological evaluation might expose the fetus to high-dose radiation, which might affect the infant later on in life. *Feedback correct answer:* Yes, well done. Diagnosis and staging of the disease are crucial. The woman is 29-weeks pregnant and evaluation and/or treatment cannot be postponed until after delivery. However, chemotherapy, if administered late toward delivery, will affect not only the mother, but the infant as well. This part of the course will focus on the ethical considerations that may arise in decisions around therapeutics in pregnancy. *Feedback incorrect answer:* No, that's incorrect. Diagnosis and staging of the disease are crucial. The woman is 29-weeks pregnant and evaluation and/or treatment cannot be postponed until after delivery. However, chemotherapy, if administered late toward delivery, will affect not only the mother, but the infant as well. This part of the course will focus on the ethical considerations that may arise in decisions around therapeutics in pregnancy.

2	Text	**The most important factors to consider** *In short…* Several factors should be taken into consideration: diagnosis and staging of the disease are crucial. The woman is 29-weeks pregnant and evaluation/treatment cannot be postponed until after delivery. The needs of the mother and the unborn fetus should be considered. Radiological evaluation might expose the fetus to high-dose radiation, which might affect the infant later on in life. Compromising with the radiological method might misdiagnose the staging of the mother. Appropriate staging of the cervical cancer (dissemination to other organs) is the mainstay of the treatment. PET-CT is associated with high radiation, and the effect on the fetus, at this stage of pregnancy, is probably low-risk. High-dose radiation at 29 weeks of pregnancy might increase the risk of malignancy in the fetus later on during lifetime, though, with low risk. *The mother likely will need chemotherapy. The real question is <u>when</u> to start the administration of chemotherapy.*
3	Text	**When would you suggest to start chemotherapy?** *Always consider the following…* If administered late toward delivery, chemotherapy will affect not only the mother, but the infant as well. Postponing the chemotherapy too long, after delivery, may endanger the mother, negatively affecting her prognosis. This case is an example of ethical considerations where several parties are involved: the mother, the fetus, the woman's family, and the gynecological oncologist. The mother needs a thorough evaluation and initiation of chemotherapy as soon as possible. However, as stated before, that means the fetus might be exposed to high radiation and to chemotherapy.
4	Text + pop-up	**Is there another option?** Inducing labour earlier than the expected date of delivery is a possibility, but the gynecologist should be involved. Early delivery might be associated with prematurity with all consequences of prematurity. In short, there is no one good solution in this case. The mother should have the right to do the best for herself, i.e; accomplish the staging of her disease and initiating treatment as soon as possible. Not all partners will accept this attitude. Some will ask the mother to postpone everything after delivery of the baby. <u>Did you know?</u> [Doctor pop-up]

		Usually, gynecologists would not accept this solution. If this is going to be the decision of both the woman and her partner, can the medical team interfere to change this decision?
5	Text	**The need for more research** A concerning reality is that for the majority of the therapeutics these women are exposed to, the relevant safety and efficacy have never been tested in prospective clinical trials. Most evidence has been obtained through retrospective cohort studies or from case studies of off-label use. <u>Did you know?</u> [Doctor pop-up] In a study of over 9000 pregnant women in Europe, Australia, and the Americas published in 2014, more than 80% used at least one medication during pregnancy.
6	Text	**Ethical issues in maternal-foetal medicine** There are many ethical issues concerning the topic of maternal-foetal medicine. Luckily, there are central values we can focus on. The Code of Ethics for Lamaze Certified Childbirth Educators (Lamaze International, 2006) include these central values: ● The childbirth educator's primary responsibility is to promote the well-being of the childbearing woman. ● The childbirth educator should respect and promote the right of childbearing women to make informed decisions and assist childbearing women in their efforts to identify and clarify their goals. In addition, childbirth educators should provide full, accurate, up-to-date information upon which childbearing women are able to make an informed decision, whether it be informed consent or informed refusal.
7	Text	●
8	Multiple choice question	Let’s take a look at one more case A 32-year-old woman has been treated with Fluoxetine for depression for more than 3 years. During her third pregnancy, her prescriber instructed her to stop the medication in week 28 in order to prevent a possible withdrawal

		syndrome in the baby after birth. **Do you know which one of the following related statements is false?** a. Anxiety and depression are common medical conditions in the western world. b. Very rarely, after delivery, the infant may present with symptoms such as dyspnea, hypotonia, convulsions, hypoglycemia, or apnea. c. Many studies have shown the safety of this group of medications during pregnancy. d. This is not an ethical issue and should not be treated as such. *Feedback correct answer:* Yes, well done. This is an ethical issue, where appropriate education and explanation to the psychiatrists practicing this approach, will prevent them from protecting the newborn while the mother's psychological condition may deteriorate. We will now discuss the case in more detail. *Feedback incorrect answer:* No, that's incorrect. This is an ethical issue, where appropriate education and explanation to the psychiatrists practicing this approach, will prevent them from protecting the newborn while the mother's psychological condition may deteriorate. We will now discuss the case in more detail.
9	Text + pop-up	**How do we tackle the ethical issue in this case?** Anxiety and depression are common medical conditions in the western world. Many women may need medical treatment. Fluoxetine belongs to the family of SSRI's (Selective Serotonin Reuptake Inhibitors). Many studies have shown the safety of this group of medications during pregnancy. Very rarely, after delivery, the infant may present with symptoms such as dyspnea, hypotonia, convulsions, hypoglycemia, or apnea. These symptoms are defined as PNA- Poor Neonatal Adaptation. Did you know? [Doctor pop-up] Some psychiatrists believe that discontinuation of SSRIs toward the beginning of the third trimester of pregnancy, may alleviate these symptoms. However, there are no published studies to support this approach.
10	Text	**That does not mean there are no risks at all..** There are reports on increased risk of postpartum psychosis among mothers who stopped the medication before delivery. This is an example where the physician took into consideration the medical condition, trying to protect the newborn, but, at the same time, may unnecessarily endanger the mother.

		This is an ethical issue, where appropriate education and explanation to the psychiatrists practicing this approach, will prevent them from protecting the newborn while the mother's psychological condition may deteriorate. *(Andrea L. Kalfoglou, 2016), (J Obstet Gynaecol Can, 2022)*

4B.4 How to support an appropriate therapeutic decision with a pregnant woman

Slide #	Work form	Content
1	Text + video	**How to support an appropriate therapeutic decision with a pregnant woman** Previously, you have learned about the difficult decisions that need to be made related to pregnancy and medication. In this part of the course we will take a deeper look at how to support such decisions. Take a look at the following video. **[Media 4B.4 Video]** **Case (video):** A 28-year old woman calls a TIS – she has just found out that she is pregnant, she is about 5 weeks pregnant. She was once treated with **Lamotrigine** but it gained poor seizure control, so the neurologist changed the medication to Valproic acid 500 mg daily. Afbeelding: Poppetje _____ **Lamotrigine** Studies have not found that lamotrigine is associated with a higher chance for miscarriage or major malformations over the background risk. It is recommended that all women taking anti-epileptic medicines also take high dose folic acid (5 mg/day) whilst trying to conceive and during the first trimester of pregnancy. Lamotrigine is cleared from the body faster during pregnancy, especially during the last trimester. It is recommended to monitor Lamotrigine serum levels during pregnancy, at least once during each trimester and adjust dosage of Lamotrigine accordingly. _____ **Valproic acid** Studies have shown that Valproic acid use during pregnancy is associated with a 1-2% incidence of neural tube defect, heart defects, cleft lip and palate and hypospadias. The chance of a birth defect seems to be greater with higher doses of Valproic acid or with taking more than one seizure medication. Dosage of Valproic acid during pregnancy above 1000 mg daily was reported to be associated with neurodevelopmental delay. There are ways to screen for neural tube defects in pregnancy. A blood test can be done to measure the amount of a protein called alpha fetoprotein (AFP) in the blood of the person who is pregnant. If the AFP is higher than usual in the blood

		test, more testing or screenings may be offered to you to find out if the baby has birth defects. An ultrasound can be used to screen for spina bifida. Ultrasounds can also screen for some other birth defects, such as a heart defect or cleft lip. Some valproate-exposed babies may have just one of these malformations, while others have more than one, or none at all. _____ **Vraag:** Ask the patient some questions to find out more. Please note: not all questions are relevant. Poppetje patiënt om vragen aan te stellen. Opties: **Is your epilepsy stable?** Yes, my epilepsy is stable. I am seizure free for the last 2 years. **Do you take other medications?** No, valproic acid is the only medication I'm currently on. **What is your last menstrual day?** I took a home pregnancy test when my period was late; I suppose I am about 5 weeks pregnant. **Do you take folic acid?** I have regular appointments with my neurologist and she gave me a recommendation to take folic acid 5 mg a day for the last 6 months. **For how long have you been suffering from epilepsy?** I had my first seizure when I was 10 years old, why does that matter? **Vraag:** What would you advise the patient? Optie 1 (correct): Although, the risk in your situation for major malformations is higher than average, there is still a big chance for a healthy baby. Most of the malformations may be detected via prenatal screening, except for the neuro-developmental effects. Optie 2 (incorrect): The risk in your situation for major malformations is higher than average, so I recommend you talk to your neurologist about pausing your medication. Optie 3 (incorrect): Lamotrigine gives a smaller chance for malformations or neuro-developmental effects. I recommend that you discuss switching back to this medication with your neurologist. **Feedback:** This case is a matter of weighing different matters. The medication can have its effects on the unborn baby, but having a seizure while pregnant could also be harmful to a pregnancy. Therefore, the correct answer is that the risk for major malformations is higher than average, but there is still a big chance for a healthy baby.

		Also don’t forget to tell your patient to notify the medical personnel regarding medication use when she is in labor.
2	Text	**Conclusion** This chapter gave you a better understanding of risk assessments in different scenarios and showed you how to formulate a treatment plan/option. There are many ethical issues that may arise when prescribing medicine to pregnant women, but focusing on central values will steer you towards the best decision.

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Additional materials:

EMA resources:

- Read: https://www.ema.europa.eu/en/documents/referral/valproate-related-substances-article-31-referral-review-started_en.pdf

- Read: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices#final-gvp-annex-i---definitions-section
- Read: https://www.ema.europa.eu/en/documents/referral/valproate-related-substances-article-31-referral-prac-recommends-strengthening-restrictions-use_en.pdf
- Read: https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-review-started_en.pdf
- Read: https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-prac-recommends-new-measures-avoid-valproate-exposure-pregnancy_en.pdf

4B.3 Ethical considerations that may arise in making decisions around therapeutics in pregnancy

- Watch: "Maternal-Fetal Decision Making: Ethical Issues in Pregnancy" by Dr. Christy Cummings" (https://youtu.be/nGrcrVnXYQA)

Chapter 5: Medications and breastfeeding

5.1 Introduction to the course

Slide #	Work form	Content
1	Text	**Welcome to chapter 5: Medications and breastfeeding** You have just completed the principles of therapeutics in pregnancy. Now, you know the basics of pharmacokinetics and pharmacodynamics in pregnancy. In this chapter, you will learn about the principles of therapeutics during breastfeeding. The lack of knowledge on medication during breastfeeding among health care professionals may result in unnecessary cessation of breastfeeding in women who need to take medication. This happens regularly, even when there is good information on the safety of the medicine during breastfeeding. Most medication can be used by breastfeeding women. In most cases, the medication amount transferred to the breast milk is too small to exert any effects on the infant. Often, the combination of available information and clinical experience is sufficient to provide specific advice.
2	Text	**What are the learning objectives?** This chapter will be structured around different clinical scenarios to clarify the benefits and risks of breastfeeding while the

		mother is on medication. In this chapter, you will learn about: ● Clinical scenario: mother on levetiracetam wishing to breastfeed. ● Breastfeeding benefits ● Medication transfer from mother to infant. ● Assessing the safety of medications with breastfeeding. ● Adverse drug reactions via breast milk. ● Advances in human lactation studies. Good luck!

5.2 Clinical scenario: mother on levetiracetam wishing to breastfeed

Slide #	Work form	Content
1	Text	**Risk assessment** As a health professional, it is important you know the right questions to ask patients to correctly assess the benefit and risk of using medications in breastfeeding. On the next slide you will be able to see a conversation taking place between a mother and her neurologist. She is on levetiracetam for epilepsy and has given birth to a preterm baby. She is concerned about giving her breast milk to her baby while on levetiracetam. Do you know which questions to ask in this scenario?
2	Text + video	**What is your opinion on the following conversation?** Please watch the video below. [Media 3.1 Video 1:38, 208 words] **Mother:** I do not understand. I was on levetiracetam throughout my pregnancy. I had my blood levels regularly tested and you adjusted the levetiracetam doses. My little Anna was born prematurely yesterday and I am really upset to learn that I cannot breastfeed her. Could I stop the levetiracetam to let me breastfeed her? I did not have any seizures during all my pregnancy. **Neurologist:** Why are you saying that you cannot breastfeed her? **Mother:** The nurse read the patient information leaflet. It said that Levetiracetam is excreted in human breast milk. Therefore, breastfeeding is not recommended. But, I thought breast milk was essential for preterm babies! **Neurologist:** OK. Please, do not stop your medication. You will risk seizure relapse if you stop it suddenly. We can measure the levetiracetam concentration in your blood to adjust the dose if necessary. Let's go through the patient information leaflet together…Oh, you did not mention this part: "However, if levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding." I need to talk with the neonatologist who is looking after Anna to be able to assess the benefit/risk of the breastfeeding in this particular context. I will get back to you shortly with further information.
3	Open vraag	**It's your turn** Could you write questions that help assess the benefit and risk of using medications in breastfeeding based on the conversation you have just seen? Take a moment to reflect.

		Consider the following: ● Medication factors ● Infant factors ● Maternal factors
4	Text + visual	**Did you think of these examples?** Click on the images to learn more. [Media 3.2 Three images: medication, mother, baby] [Image medication] **Medication factors:** ● Is the medication formally contraindicated with breastfeeding? ● Are there any alternative medications that would be safer for the infant? ● How much medication will the infant ingest via breast milk? What is the mother's medication dose? The frequency of administration? The route of administration? ● Is it possible to compare this medication dose to a therapeutic dose for infants? ● Have any side effects been previously reported in breastfed infants? [Image mother] **Maternal factors:** ● What are her breastfeeding intentions? ● Is the infant fully breastfed? ● How necessary is this medication for the mother? ● How long will the mother be using the medication for? [Image baby] **Infant factors** ● How old is the infant? ● Was the infant born prematurely? ● Is the infant healthy? *For more background information, see the Drug use and breastfeeding reference in the additional materials.*
5	Text	**Conclusion** Health professionals should be able to correctly assess the benefit and risk of using medication in breastfeeding during a

		conversation with a mother wishing to breastfeed. Important questions to ask relate to information on the available information on effects and intended use of the medication, the breastfeeding wishes of the mother, and the health of the infant.

5.3 Breastfeeding benefits and prevalence

Slide #	Work form	Content
1	Text	**Breastfeeding is recommended** Given the range of benefits of breastfeeding, the World Health Organization recommends that children be exclusively breastfed for the first 6 months of life and is working on increasing the rate of breastfeeding. <u>Did you know?</u> [Doctor pop-up] **Mutual benefits** Breastfeeding does not only have beneficial effects for the infant. Breastfeeding offers many advantages to mothers too.
2	Text + visual	**What are the benefits?** Click on the image below to examine the range of benefits for both infant and mother. [Media 3.3 Image infant, image mother] [Image infant] **Infant benefits** ● Provides fundamental nutrients. ● Reduced sudden infant death. ● Lower incidence and severity of infections. ● Lower incidence of allergic disease. ● Greater bonding experience with the mother. ● Better performance on tests of cognitive development. ● Lower incidence of obesity during childhood and adolescence. [Image mother] **Mother benefits**

		• Decreased risk of postpartum depression. • Decreased risk of breast and ovarian cancers. • Weight loss. • Money savings on formula and associated equipment. *(Victora CG, Bahl R, Barros AJ, França GV, Horton S, Krasevec J, Murch S, Sankar MJ, Walker N, Rollins NC; Lancet, 2016).* *(Yngve A, Sjöström M, 2001)*
3	Text	**What can we do to support breastfeeding?** *The need for more research* Despite breastfeeding being actively promoted, the issue of the use of medication by breastfeeding women is an area with significant research gaps. In 2004, a Dutch survey highlighted that 66% of breastfeeding women had at least used a medication at any time during the first 6 months after birth vs 80% of non-breastfeeding women. A recent systematic review reveals several limitations to have reliable data on prevalence of medication use during breastfeeding: • Breastfeeding information is often not available in the large medico-administrative databases. • Studies mainly focus on medication use during pregnancy. • Medication use information is often restricted to a limited period, not the breastfeeding period itself (e.g., 3 months postpartum). • Populations of cohort studies are often biased and do not represent the diverse range of medication used by women for chronic diseases.
4	Text	**The impact of a lack of research** However, taking medication is an established risk factor for breastfeeding discontinuation. Thus, the significant increase of chronic disease prevalence during pregnancy and the postpartum periods in the last three decades may have impacted on breastfeeding. In addition, the lack of evidence-based knowledge of health care professionals on the breastfeeding compatibility of many commonly used medications may contribute to failure to start or to premature cessation of breastfeeding.

		Several studies on health professionals' knowledge of medicines and breastfeeding in different countries showed, for example, that: ● 50% of health professionals in the United States were unaware that women taking most anti-epileptic medications could safely breastfeed. ● About 1/3 of Australian general practitioners and community pharmacists were unaware that ibuprofen was compatible with breastfeeding. *(Schirm, E., Schwagermann, M., Tobi, H. et al, 2004)* *(Saha, M.R., Ryan, K. & Amir, L.H, 2015)*
5	Text	**Conclusion** Different factors such as societal influences, socio-demographic status, psychosocial or healthcare-related characteristics may influence the initiation and duration of breastfeeding, but research suggests that more adequate education on medication use for mothers wishing to breastfeed is needed to increase breastfeeding prevalence.

5.4 Medication transfer from mother to infant

Slide #	Work form	Content
1	Text	**Infant medication exposure** You will see that preterm babies, neonates or infants are more vulnerable to medications than adults. However, the different steps in the medication pathway from mother to infant allow the medication to be filtered, metabolized or eliminated, which often significantly reduces the infant dose. Earlier on in the course, you have studied how to assess the benefit and risk of using medication in breastfeeding. Are you also aware of the correct questions to help assess the degree of infant medication exposure?
2	Text + image + pop-up	**Key questions** Click on the images below for key questions to help assess the degree of infant medication exposure. [Media 3.4 Image medication, mother, infant] [Image medication] **Medication factors** ● How much medication will the infant ingest via breast milk? ● What is the mother's medication dose? ● What is the frequency of administration? ● What is the route of administration? ● How long will the mother use the medication for? [Picture mother] **Maternal factors** ● Is the infant fully breastfed? [Picture infant] **Infant factors** ● How old is the infant? ● Was the infant born prematurely? ● Is the infant healthy?
3	Text	**How medication is transferred to breast milk**

		Most medications are transferred to breast milk in amounts well below a level that would exert any pharmacological effect on the infant. But what are the physiochemical properties of medication that most easily diffuse into the breast milk? How does medication transfer from the mother to the infant through the breast milk? What are the important steps? Click on the image below to learn more about the medication pathway. [Media 3.5 Image timeline Medication pathway in the mother and infant] [Step 1] **Step 1** Maternal administration and metabolism of medication. [Step 2] **Step 2** Maternal distribution of medication. [Step 3] **Step 3** Breastfeeding. [Step 4] **Step 4** Infant absorption and metabolism of medication. [Step 5] **Step 5** Infant distribution of medication. [Step 6] **Step 6** Infant response to medication.
4	Text + pop-ups	**Determinants of the medication concentration** Click on the terms below to learn their definitions. The route of medication administration influences two determinants of the medication concentration in the breast milk: the time of medication peak concentration and medication bioavailability in the systemic circulation.

		Passage from the mother's blood to her milk is generally based on principles of passive diffusion through lipid membranes. It invariably follows a gradient from a high to a low concentration of free (unbound) medication. Peak medication level in breastmilk occurs shortly after the plasma peak. Thus, the breastfeeding timing relative to the medication administration is a key determinant for the infant dose. After 5 half-lives, all of the medication is considered eliminated from mother's plasma, and thereby from her milk. In addition to breastfeeding timing, breastfeeding type (partial or full) is an important determinant of the infant's ingested medication dose. I-icon [Pop-up Time of medication peak concentration] **Time of peak concentration (T_{max})** The time it takes for a medication to reach the maximum concentration (C_{max}) after administration of a medication that needs to be absorbed. T_{max} is determined by the rate of medication absorption and the rate of medication elimination. I-icon [Pop-up Bioavailability] **Bioavailability** Fraction (%) of an administered medication that reaches the systemic circulation intact. By definition, when a medication is administered intravenously, its bioavailability is 100%. The greatest variability in drug absorption is seen with the orally administration route. It is affected by, among other things, the amount of medication absorbed across the intestinal epithelium, as well as first-pass metabolism as the drug crosses the intestine and the liver on its way to the systemic circulation.
5	Text + pop-up	**Properties and diffusion of medication** The physiochemical properties of medications that diffuse most easily into the breast milk are: ● High concentration in maternal plasma. ● Fat-soluble. ● Relatively low molecule weight (< 500 Dalton). ● Relatively low degree of protein binding in the plasma. Did you know? [Doctor pop-up] **A dynamic equilibrium** Medication does not remain in breast milk as in a reservoir. There is a dynamic equilibrium between the breast plasma and the breast milk: as the plasma concentration in medication declines, the substance diffuses from breast milk back into the

		plasma. The active diffusion allows certain medications to be transferred to the breast milk via active transport through lipid membranes. It is the transcellular transport (nitrofurantoin, cimetidine, ranitidine, acyclovir).
6	Text	**Age as an important factor** Premature neonates and infants have physiological characteristics and may absorb, metabolise and excrete medicines differently to older children and adults. Their hepatic and renal functional immaturity can also make them more vulnerable to adverse effects of medications. Infant absorption and metabolism of medication are largely affected by the maturation process of the gastrointestinal tract and liver. In preterm babies and newborns, the metabolism of medication is reduced because the first pass metabolism is not or not very efficient and many liver enzymes are not expressed. Medication is distributed into tissues via the bloodstream. It relies on factors that mature with age. For instance, in younger infants, there is a lower plasma protein binding concentration as compared to older children. It leads to a higher unbound/free medication in the plasma with a pharmacological effect on the infant target site. Let's dive deeper into these contributing factors. *(Allegaert K, van de Velde M, van den Anker J, 2014)* *(Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE, 2003)*
7	Text	**The first pass metabolism** Medication absorbed from the gastrointestinal tract is first delivered to the liver by the portal vein. A fraction of the medication can be metabolized in the gastrointestinal tract or liver before it even reaches the systemic circulation. For adults this first pass metabolism may thus greatly reduce the bioavailability of the medication. Nevertheless, in preterm babies and newborns, this first pass metabolism is very low resulting in a very high bioavailability of the medication.
8	Text + afbeelding	**Maturation of hepatic function** Take a look at the graphic below. [Media 3.6 Graphic Changes in metabolic capacity] Hepatic enzyme function matures as infants and children age. Thus, the bioavailability of many medications is higher in the youngest infants and lower in older children.

9	Text	**The plasma binding protein** In preterm babies, neonates and young infants, the plasma binding protein concentration is low and combined with an increased competitive binding with endogenous compounds (eg, bilirubin, free fatty acids). This leads to higher levels of unbound/free medication distributed through the body. The unbound fraction is free to exert its pharmacological effect.
10	Text	**The blood-brain barrier** Furthermore, the blood-brain barrier is more permeable in newborns and youngest infants. The blood-brain barrier serves as a protective mechanism for the brain by preventing potentially harmful substances from gaining free access to the central nervous system. Endothelial tight junctions, associated with efflux transporters, are scarcer at birth as compared to older infants. The blood-brain barrier is therefore more permeable in newborns and youngest infants.
11	Text + visual + pop-up	**Factors increasing risk of side effects** It is very important to assess the infant's ability to handle small amounts of medication in the breast milk. Some infants, such as preterm babies or sick infants, may tolerate less well these medications compared to older and health infants. Several factors may increase the risk of side effects of these medications in breastfed infants: [Media 3.8 Image medication and infant] [Image medication] **Medication factors** ● Narrow therapeutic index ● Long half-life ● Long-term therapy ● High concentration in breast milk [Image infant] **Infant characteristics** ● Age ● Hepatic function ● Renal function ● Concurrent conditions ● Co-medication

		There is risk of accumulation if the ingested amount of medication through breastmilk is larger than the infant's capacity for metabolizing/excreting the medication.
12	Text	**Preterm babies and newborns** Preterm babies and newborns are populations particularly vulnerable to adverse effects of medicaton. They can accumulate several risk factors: ● Developmental immaturity (liver, kidney, etc). ● Disease (icterus, sepsis, organ failure). ● High medication burden (for preterm babies), lack of licensed-formulations, limited evidence-based dosing).
13	Text	**The neonatal period** During the neonatal period, hyperbilirubinemia is a common and part of normal developmental physiology. The presence of fetal proteins and endogenous substrates known to interfere with medication binding, can lead to adverse medication effects due to a higher than expected 'free' medication fraction. Furthermore, a decrease in the affinity of albumin for bilirubin during this period may lead to bilirubin displacement by medication resulting in clinical icterus. This would not occur beyond the neonatal period (diazepam, salicylates) *(Nordeng H, Havnen GC, Spigset O, 2012)* *(Allegaert K, van den Anker J, 2021)* *(Allegaert K, van de Velde M, van den Anker J, 2014)*
14	Text + video	**Case study** You have already watched a video about a mother on levetiracetam for epilepsy who has given birth to a preterm baby. She was concerned about breastfeeding her baby while on levetiracetam and discussed it with her neurologist. Now, you will watch the discussion between the neurologist and the neonatologist about the benefits and risks of breastfeeding in her case. [Media 3.8 Video, 1:30, 196 words] **Neurologist:** Hi, could you please give me information about Anna who is born yesterday and whose mother is on levetiracetam?

		Neonatologist: Anna was born at 32 weeks' gestation yesterday. Her birth weight is appropriate for her gestational age. She has lost some weight, but that is normal. She is on oxygen and caffeine and copes well for the moment. She had no complications so far. She is receiving phototherapy right now. **Neurologist:** Anna's mother would like to give her breast milk. What do you think? **Neonatologist:** Great news. She needs to express her milk as Anna is too young to suckle. We will increase the breast milk amount steadily over the time according to Anna's digestive tolerance. As usuall we will monitor her tone, awareness and weight gain. It is even more necessary in this context. We will also notify the mother that we might recommend her to stop giving breast milk if we suspected an adverse drug reaction. It rarely happens, but it is always better when parents are informed. Sometimes, this is only a temporary pause in breastfeeding if the suspicion is not confirmed. Some complications or medication interactions can predispose Anna to adverse drug reactions. **Neurologist:** What are the complications or interactions that may lead to stopping breastfeeding?
15	Text	**It's your turn** Given what you learned, how would you answer the neurologist? In other words, what are the complications or interactions that may necessitate cessation of breastfeeding in this particular context? Take a moment to reflect. Levetiracetam is rapidly and completely orally absorbed with linear dose kinetics, a minimal degree of protein binding, and predominantly renal excretion. Because of the lack of hepatic metabolism and low protein binding, the risk of interaction with other drugs is considered low. *(Radtke RA, 2001)*
16	Text	Check your knowledge Clinically: severe symptoms suggesting an adverse drug reaction: ● For instance, sedation or poor weight gain with levetiracetam could suggest an adverse drug reaction. ● The causality of the adverse drug reactions is difficult to determine given the multiple causes that may result in these symptoms (especially for hospitalized preterm babies). A transient breast milk weaning test can help to determine if the medication in the breast milk is the cause of symptoms. **Exposure to medication via breast milk may result in:** ● Levetiracetam is not appreciably protein-bound, nor does it affect the protein binding of other drugs. Thus, because of its minimal protein binding and lack of hepatic metabolism, the risk is very low.

		Infant factors which may increase the risk of adverse drug reactions: ● Sepsis: risk of kidney failure, see below. ● Kidney failure: Total body clearance of levetiracetam is decreased in patients with renal impairment. ● Liver failure: see above. Levetiracetam is not significantly impacted by hepatic metabolism.
17	Text	Conclusion More research may improve knowledge on medication and breastfeeding in Europe. They offer the opportunity to estimate the amount of medication in the human breast milk. Furthermore, it is very important to assess the infant's ability to handle small amounts of medications in the breast milk.

5.5 How to assess the safety of medications with breastfeeding

Slide #	Work form	Content
1	Text	**Case study: Package leaflets** You know the basic principles for medication transfer from mother to infant. You know the risk factors for side effects among vulnerable populations. You saw with the first video that the package leaflet can be ambiguous about taking the medication while breastfeeding. Breastfeeding was not recommended but it could outweigh the risks related to the treatment… In this part of this chapter, you will listen to 2 audio clinical scenarios: 2 mothers wishing to breastfeed who were confused by the package leaflet. You will read about the limitations of summary product characteristics mentioned in the package leaflets. You will see how to answer to these following questions: ● Is the medication formally contraindicated with breastfeeding? ● Are there any alternative medications that would be safer for the infant? ● Have any side effects been previously reported in breastfed infants? You will be able to find complementary information sources and what the medications formally contraindicated are.
2	Text + audiofragment	**Inside the rheumatologist's office** A mother has a relapse of rheumatoid arthritis 2 months after the birth of her baby boy. Her rheumatologist confirms the diagnosis and quickly schedules a rituximab infusion. The mother mentions she breastfeeds her little boy. Listen to the discussion. [Media 3.9 Audiofragment, 2:00, 296 words] Mother: Doctor, are you sure this is a relapse of the rheumatoid arthritis? I was really stable during my pregnancy... the pain might be due to the moving into my new house: I carried too many boxes the past few days. Rheumatologist: I am certain of the diagnosis. We are going to help you to get better control of the disease. The rituximab worked well before your pregnancy. We should consider scheduling one as soon as possible. Mother: Oh, that's really bad news! Little Matheo is only 2 months. I hoped to breastfeed him until he is at least 6 months to protect him from allergies. It was difficult to start breastfeeding and now when it has eventually worked well for me, I have to stop … I would like to wait before considering rituximab again. Or, is there any medication that could be effective and compatible with breastfeeding. Rheumatologist: Why would you stop breastfeeding Mother: I read the rituximab package leaflet. It explained that breastfeeding is not recommended during treatment with

		rituximab and for 12 months afterwards. Rheumatologist: I understand. This drug package leaflet is not in line with recent guidelines. The scientific societies, organisations that represent the consensus opinion of groups of specialists, recently recommended to maintain breastfeeding during rituximab treatment given all the benefits of breastfeeding. The passage of rituximab into breast milk is really low. Rituximab is probably largely destroyed and not absorbed in the gastrointestinal tract, which makes significant exposure of Matheo via milk unlikely. In addition, no particular adverse events have been reported in infants breastfed by mothers on rituximab. Mother: Are you sure? I want to protect Matheo and don't want him to have adverse effects from rituximab.
3	Open vraag	**Take a moment to reflect on the following questions.** ● Do you think the mother is completely reassured at the end of the visit with the neurologist? ● What is the summary of product characteristics (SmPC)? ● How did the American College of Rheumatology make the guidelines for rituximab use while breastfeeding? *(Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, Marder W, Guyatt G, Branch DW, Buyon J, Christopher-Stine L, Crow-Hercher R, Cush J, Druzin M, Kavanaugh A, Laskin CA, Plante L, Salmon J, Simard J, Somers EC, Steen V, Tedeschi SK, Vinet E, White CW, Yazdany J, Barbhaiya M, Bettendorf B, Eudy A, Jayatilleke A, Shah AA, Sullivan N, Tarter LL, Birru Talabi M, Turgunbaev M, Turner A, D'Anci KE, 2020).*
4	Text	**Here is our response…** She is probably confused by receiving conflicting information. The rituximab leaflet package advises against breastfeeding for 12 months after the last use of rituximab, while her practitioner tries to reassure her that she can continue breastfeeding. Summary of product characteristics: a document describing the properties and the officially approved conditions of use of a medicine. Summaries of product characteristics form the basis of information for healthcare professionals on how to use the medicine safely and effectively. The package leaflet includes the summary of product characteristics. The American College of Rheumatology performed: ● A systematic literature review on the treatments of rheumatic and musculoskeletal diseases during pregnancy and breastfeeding. They graded their guidelines following the Grading of Recommendations Assessment, Development and Evaluation methodology.

		• When no direct data on rheumatic and musculoskeletal disease patients were available from the systematic literature review, discussion and voting were supplemented with indirect data collected in additional, less formal literature reviews. For Rituximab use during the breastfeeding: A strong recommendation was voted, meaning that most informed patients would choose the recommended management. Nevertheless, individualized risks and benefits need to be reviewed with each patient. *(Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, Marder W, Guyatt G, Branch DW, Buyon J, Christopher-Stine L, Crow-Hercher R, Cush J, Druzin M, Kavanaugh A, Laskin CA, Plante L, Salmon J, Simard J, Somers EC, Steen V, Tedeschi SK, Vinet E, White CW, Yazdany J, Barbhaiya M, Bettendorf B, Eudy A, Jayatilleke A, Shah AA, Sullivan N, Tarter LL, Birru Talabi M, Turgunbaev M, Turner A, D'Anci KE, 2020).* *(SmPC, 2009)*
5	Text + audiofragment	**Inside the general practitioner's office** Let's listen to the second audiofragment. In this scenario, a mother feels bad because of her allergies. She breastfeeds her infant. She asks advice from her general practitioner. [Media 3.10 Audiofragment, 2:15, 296 words] **Mother:** Doctor, I feel really bad. It is the spring and all my allergies are back. I am worried about my asthma as pollen season approaches. In addition, I am tired because of the breastfeeding. Could you do something for me? **General practitioner**: An antihistamine could help with your allergy symptoms. **Mother**: But, I read the cetirizine package leaflet and I did not understand anything. I brought it and I can read it to you. "Cetirizine is excreted in human milk at concentrations representing 25% to 90% those measured in plasma, depending on sampling time after administration. Therefore, caution should be exercised when prescribing cetirizine to lactating women." What does "caution" mean? **General practitioner**: I agree with you this sentence is ambiguous and I do not know how to interpret it. Let us have a look in the Breastfeeding Network. Let us search antihistamine. Ah here it is… I found it. The British Society for Allergy and Clinical Immunology recommends Cetirizine, it reaches low levels in breast milk. Perfect! **Mother**: Why does the leaflet package mention that it should be prescribed with caution? **General practitioner**: Really good point. You have the answer here. We can read on the website: "Most of the drugs to treat allergies are available to buy over the counter but the leaflets may say that they are not suitable to take whilst you are breastfeeding. This does not necessarily mean that they are dangerous, merely that the drug company has not undertaken trials itself and has chosen not to recommend its use in this situation." If you agree, I am going to prescribe you cetirizine.
6	Text	**Take another moment to reflect on the following questions.** • Who writes the summary of product characteristics (SmPC)? Who validates it?

		• What should appear in the section lactating women in the summary of product characteristics? Can you compare it to the leaflet package read by the patient?
7	Text	**Here is our response…** The SmPC is initially drafted by the applicant based on the results of the studies performed to support a marketing authorization for the medication. Competent Authorities (e.g., in Europe, the European Medicines Agency) review the proposal during the assessment process before adopting it as part of the marketing authorization. This assessment of the SmPC is reflected in the public assessment report. The information should be in the section related to the use of medication in pregnant and lactating women: • Secretion of the medications into milk. • The existence of preclinical and clinical studies. • Clinical experience describing the use of the medication during breastfeeding. • Specific recommendations for use during breastfeeding. At the time of marketing authorization, the large majority of medications will have data on breastfeeding as ”missing information”. This consequently has an impact on the wording in the medication label. *(Arguello B, Salgado TM, Fernandez-Llimos F, 2015).* *(Drelich E, Religioni U, Chung K, Kaźmierczak J, Blicharska E, Neumann-Podczaska A, Krysiński J, Merks P, 2022)*
8	Text + pop-up	**Limitations of summary of product** You saw that the main document supposed to provide key information for health care professionals on the safety and efficacy of the medication has limitations. It is submitted by the marketing authorization holders who can decide to not conduct trials for lactating women. According to the regulations, they cannot recommend breastfeeding without supporting data. **Limitations:** • Unfrequent updates of product information. • Rare human lactation studies • Medication use is restricted in more than 90% of the summary of productive characteristics in both pregnancy and breastfeeding sections due to lack of data.

		● Lack of clear recommendations, wording open to individual interpretation (e.g., use with caution…). **Consequences:** ● It does not provide clinically useful and comprehensible information about medication for healthcare professionals, especially concerning the pregnancy and breastfeeding section. ● A small number of primary care physicians use this document as a source of information on the medication. ● Patients may be confused and anxious about contradictory information if information sources diverge in the recommendations about breast feeding. <u>Did you know?</u> [Doctor pop-up] A review of the labels of 213 medications approved by the FDA between 2003 and 2012 found that there was no data on breastfeeding in 48% of labels, animal data was available in 43% of labels, whereas human breast milk data was available in less than 5% of the labels. *(Arguello B, Salgado TM, Fernandez-Llimos F, 2015).* *(Drelich E, Religioni U, Chung K, Kaźmierczak J, Blicharska E, Neumann-Podczaska A, Krysiński J, Merks P, 2022)*
9	Text	**Resources available to assess the safety of medications with breastfeeding** Let us see the available resources verifying the compatibility of drugs with breastfeeding, other than the summary product characteristics. Have you for example heard of the Drugs and Lactation Database (LactMed)? **The LactMed® database is free and contains information on:** ● Medications to which breastfeeding mothers may be exposed. ● The levels of such substances in breast milk and infant blood. ● The possible adverse effects in the nursing infant. ● Therapeutic alternatives to those drugs, where appropriate. All data are derived from the scientific literature and fully referenced. A peer review panel reviews the data to assure scientific validity and currency.
10	Text	**Another option is the site Hale's Medications & Mothers' milk** This is a fee-paying site with similar information. You can find both sites in the additional resources for later review. If you have persisting doubt, there are specialist medication information services in your country. For help or more

		detailed information, do not hesitate to contact them. Health care professionals should not stop breastfeeding merely because of heightened anxiety or lack of knowledge on their part.
11	Text	**Medications formally contraindicated with breastfeeding** Few medications are considered contraindicated for use among breastfeeding women by clinical data sources (the list is not exhaustive): ● Chemotherapeutic drugs (methotrexate, anthracyclines): risk of leukopenia and bone marrow suppression. ● Radioactive substances: a transient breastfeeding stop is required (10 half-lives of the radiopharmaceutical): During this interruption period, the mother may express and store her milk to be used after the milk is no longer radioactive. Alternatively, the nursing mother may choose to discard the expressed radioactive milk. ● Amiodarone (antiarrhythmic): a iodine-containing molecule with a long half-life that may affect thyroid function in infants. *(Hotham & Hotham, 2015)*
12	Text	**Medications requiring precautions with breastfeeding** Some medications require close follow-up of the breastfed infant. These are, for instance, lithium, cyclosporine, lamotrigine and levetiracetam. When possible, for some medication, alternative medication should be preferred to some others: ● Z-hypnotics (zopiclone) or short acting benzodiazepines (oxazepam) are preferred ● Paroxetine, sertraline are preferred to fluoxetine given the longer half life and active metabolite of fluoxetine, in additional to more adverse effects reported among breastfed infants with fluoxetine (lowest excretion of sertraline in the breast milk). *(Kronenfeld N, Berlin M, Shaniv D, Berkovitch M, 2017)* https://www.ncbi.nlm.nih.gov/books/NBK501922/
13	Text	**Conclusion** Using medication is a risk factor of breastfeeding discontinuation. But, most medications are transferred to breast milk in

		amounts well below a level that would exert any pharmacological effect on the infant. Few medications are formally contraindicated.

5.6 Adverse drug reactions via breast milk

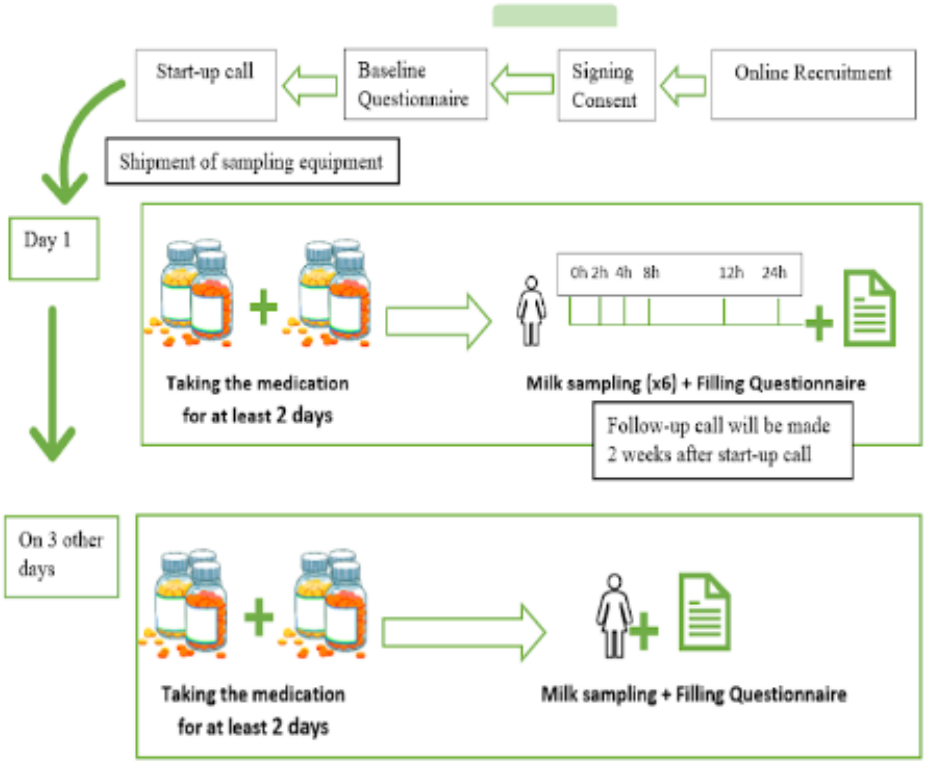
Slide #	Work form	Content
1	Text	**Breast milk medication can cause adverse drug reactions** Previously in this chapter, you learned how to search whether any side effects in breastfed infants have previously been reported for a medication. What are these adverse drug reactions? Adverse drug reactions in breastfed infants are rarely reported due to low awareness and low occurrence of adverse drug reactions via breast milk. Mild adverse drug reactions (e.g, gastro-intestinal events with antibiotics) are common. However, central nervous system acting medications with more severe symptoms (such as sedation, lethargy) account for approximately 50% of all published suspected adverse drug reactions among breastfed infants. In approximately 80% of reported cases, the adverse drug reactions appeared in infants < 2 months of age. *(Allegaert K, van de Velde M, van den Anker J, 2014)* *(Anderson PO, Pochop SL, Manoguerra AS. Adverse, 2003)* *(Soussan C, Gouraud A, Portolan G, Jean-Pastor MJ, Pecriaux C, Montastruc JL, Damase-Michel C, Lacroix I, 2014)*
2	Text	**Adverse drug reaction?** When an adverse drug reaction is suspected, it may be useful to have: ● Analysis of the serum concentration of the medication of the mother and in the infant, and possibly also in the milk. ● A period without breastfeeding to observe whether the infant's symptoms disappear. The mother pumps out and discards her milk. If the symptoms return when the breastfeeding is resumed (for mild adverse drug reactions), this would give even stronger indications of causality. Suspected adverse drug reactions should be reported to the nearest medication information center or national medication regulator. For signal detection, as well as for causality and severity assessment, disentangling confounders from adverse drug events remains a major challenge. *(Nordeng H, Havnen GC, Spigset O, 2012)*
3		**A major challenge to establish causality of adverse drug events** Historically, surveillance of spontaneous reports and published case reports/case series has been the main

		pharmacovigilance activity to assess medication safety during breastfeeding. Published case reports of possible ADRs in breastfed infants, however, often suffer from severe methodological limitations that impair causal inference: ● It is often not possible to separate potential drug effects from the infant's normal state or from concurrent disease (e.g., rash, sedation, irritability, weight gain, and gastrointestinal events are not specific to adverse drug reactions). ● Reports are often confounded by in utero exposure, i.e. the breastfed infant was also exposed to the medication during pregnancy. Effective detection of a signal of an adverse drug reaction requires comparison of outcomes between medication exposed and unexposed populations (i.e., comparing "abnormal" and "normal" events). To have data for creating such groups, a potential perspective would be, in registries, to encourage health professionals to record breastfeeding periods and possible adverse drug reactions in infants when they occur. *See the additional materials for the guideline on good pharmacovigilance practices (GVP) from the European Medicines Agency.*
4	Text	**Conclusion** The developmental immaturity of young infants with vulnerabilities of some key organs/systems can predispose to adverse drug reactions. In approximately 80% of reported cases, the adverse drug reactions appeared in infants < 2 months of age. Central nervous system acting medications with severe symptom events account for 50% of all suspected adverse drug reactions among breastfed infants.

5.7 Human lactation studies

Slide #	Work form	Content
1	Text	**Human lactation studies** Breastfeeding women and their health care providers often must make decisions about medication treatment and continuation of breastfeeding during therapy. For that decision to be evidence based, they would need information on the amount of medication in human milk and adverse drug event data in breastfed infants. In this chapter, you will learn how with a sample of breastfeeding women, human lactation studies can provide these crucial data. As a healthcare professional, your main concern is how to interpret these data in the literature for a medication in order to assess the breastfeeding continuation. This chapter will answer to three key questions: ● How much medication will the infant ingest via mother's milk (based on findings of human lactation studies)? ● Is it possible to compare this medication dose to a therapeutic dose for infants? ● Have any side effects been previously reported in breastfed infants? Good luck!
2	Text + pop-up	**Lack of data on the benefit/risk of medications used during breastfeeding** You previously understood that many pharmaceutical companies restrict the use of most medications in pregnant and lactating women in the summary product characteristics. Why? A lack of evidence on the safety of maternal medication during breastfeeding.. So far, human data are scarce as studies in this context are often expensive, time-consuming and face many practical and ethical limitations. Several non-human models were used to understand the amount of medication in breast milk. However, they have limitations. Click on the following models to discover their specific limitations. *In vitro* [Pop-up text] To quantify medication transport data across the *in vitro* blood-milk barrier.

		Animal *in vivo* [Pop-up text] To quantify medication transport data across the *in vitro* blood-milk barrier. Prediction based on physicochemical characteristics [Pop-up text] The role of transporter proteins and several physiological factors are not addressed.
3	Text	**Human lactation studies** Human lactation studies can offer the opportunity to: ● Estimate the amount of medication in the human breast milk. ● Understand the risks posed by the medication on the breastfed infant. The US Food and Drug Administration recently developed guidance for human lactation studies to facilitate the conduct of this type of research. Furthermore, the European Medicines Agency published guidelines recommending post-marketing studies among breastfed infants. This may include a clinical lactation study and/or a prospective study following up infants exposed to a specific medication through breast milk. Use of pregnancy registries to follow-up breastfed infants is also possible. These European Medicines Agency guidelines and Europe Union initiatives such as ConcePTION, may increase post-marketing studies among breast fed infants. It may improve knowledge about medication and breastfeeding in Europe. You can find more information on these guidelines from the link in our additional resources. *(Nauwelaerts N, Deferm N, Smits A, Bernardini C, Lammens B, Gandia P, Panchaud A, Nordeng H, Bacci ML, Forni M, Ventrella D, Van Calsteren K, DeLise A, Huys I, Bouisset-Leonard M, Allegaert K, Annaert P, 2021)*
4	Text	**A cetirizine demonstration project in ConcePTION** Europe Union initiatives such as ConcePTION may increase post-marketing studies among breastfed infants to improve knowledge about medication and breastfeeding. One demonstration project for human lactation studies in ConcePTION focuses on Cetirizine, a common antihistamine used in allergies. Take a look at the set-up of the study on the following slide.
5	Text + infographic	**Example of a single-dose design of human lactation study**

	+ pop-up	This figure describes the protocol of this study (breastfeeding women participants, N=37). One of the aims of ConcePTION is to establish a human milk biorepository to provide researchers, pharmaceutical industry and regulators with a system to perform human lactation studies, and establish the standards to do so. Several clinical lactation demonstration projects are ongoing, both as “milk only” and “blood & milk” human lactation studies. Traditional pharmacokinetics calculations and/or population based pharmacokinetics modelling are being used. [Media 3.11 Infographic Human Lactation Study] 
6 **ADVANCED**	Text	**How to calculate the relative infant dose in the breast milk?** Click on the text to learn more about relative infant dose calculations.

		First, for each breastfeeding woman, you calculate <u>the average medication concentration in the breast milk</u>: You take the highest concentration of the medication in the breast milk (µg/L). Alterntively: you calculate the area under the curve (AUC) determined by the medication concentrations in the breast milk (µg/L) during the 24-hour sampling period and divide this AUC by 24. (see Pop up 1 for more details). Second, with the highest concentration in the breast milk, you can now calculate the infant's theoretical dosage and the relative infant dose for each breastfeeding woman. **The infant's theoretical dose (mg/day**) = the medication concentration in the breast milk (mg/L) × 0.15 (L/kg/day)* × the infant's weight (kg). **The relative infant dose (%)** = the infant's theoretical dose (mg/day) × 100 / (the mother's dose (mg/kg) x the infant's weight (kg)) **A fully breast-fed infant (from 5 days to 3 months of age) ingests approximately 150 ml of breast milk per kilogram per day* The averages of these parameters obtained from the sample of breastfeeding women will serve as references in the literature for this specific medication. Let's see how to interpret it. *(Sachs HC, 2013)* <u>I-icon</u> [Pop-up text The average medication … breast milk] **How to calculate AUC** For more details on how to calculate the area under the milk concentration curve, you can find a link to a short video (8 minutes) on YouTube in our additional materials.
7 **<u>ADVANCED</u>**	Text	**How to interpret the relative infant dose and the infant's theoretical dosage** The transfer to breast milk is considered as: ● Minimal when the **relative infant dose** <2%. ● Small when the relative infant dose is between 2% and 5%. ● Moderate when the relative infant dose is between 5% and 10%. ● High when the relative infant dose >10% with a risk of pharmacological effects in the infant.

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<td>With relative infant dose <10%, breastfeeding is assumed to be safe – unless very toxic drugs such as cytostatics are involved.

Pragmatically, to assess the risk of side effects, the infant's theoretical dosage can be compared to the recommended pediatric dosage (if known) for individuals of the same age/with the same body weight.

(Sachs HC, 2013).</td>
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<td>8
<u>ADVANCED</u></td>
<td>Text + graphic + hyperlink</td>
<td>Calculating the relative infant dose for cetirizine

Earlier on in the course, you saw the protocol of cetirizine demonstration project in ConcePTION. A breastfeeding mother on cetirizine expressed her milk over 24 hours after having taken 10 mg of cetirizine for the day. She sent the breast milk samples to the laboratory where cetirizine concentrations were measured.

Take a look at the corresponding table.

<table>
<tr><th>Hours</th><th>Cetirizine concentrations (ng/mL)</th></tr>
<tr><td>0:00</td><td>2.1</td></tr>
<tr><td>2:00</td><td>33.6</td></tr>
<tr><td>4:10</td><td>26.4</td></tr>
<tr><td>8:01</td><td>16.6</td></tr>
<tr><td>12:01</td><td>8.1</td></tr>
<tr><td>24:00</td><td>2.8</td></tr>
</table>

Take a look at this YouTube video and calculate the AUC with Excel using the slide shown at 3:20 and the information on the next slide.</td>
</tr>
<tr>
<td>9
<u>ADVANCED</u></td>
<td>Text</td>
<td>More information

The final result of AUC was 296.5 ng/mL (or µg/L).

Could you give the relative infant dose (%) for this breastfeeding mother?</td>
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Assuming this fully breast-fed infant ingests approximately 150 ml of breast milk per kilogram per day.
Mother weight=64 kg, Infant weight =5,5 kg, cetirizine 10 mg a day.

You replicate these calculations for the 36 other breastfeeding women in the sample. The average relative infant dose (and its 95% confidence intervals) is 1.5% [1.2; 1.7]. Think about how you consider the cetirizine transfer the breast milk.
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<td>9
<u>ADVANCED</u></td>
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Here is our response…

<table>
<tr><th>Hours</th><th>Cetirizine concentrations (ng/mL)</th><th>ng/mL</th><th>ng/mL</th></tr>
<tr><td>0:00</td><td>2.1</td><td></td><td></td></tr>
<tr><td>2:00</td><td>33.6</td><td>2 x (2.1+33.6)/2</td><td>35.7</td></tr>
<tr><td>4:00</td><td>26.4</td><td>(4-2) x (33.6+26.4)/2</td><td>60.0</td></tr>
<tr><td>8:00</td><td>16.6</td><td>(8-4) x (26.4+16.6)/2</td><td>86.0</td></tr>
<tr><td>12:00</td><td>8.1</td><td>(12-8) x (16.6+8.1)/2</td><td>49.4</td></tr>
<tr><td>24:00</td><td>2.8</td><td>(24-12) x (8.1+2.8)/2</td><td>65.4</td></tr>
</table>

The relative infant dose (%) = the average medication concentration in the breast milk (mg/L) × 0.15 (L/kg/day) × 100 / (the mother’s dose (mg/kg). We can calculate it without the infant’s weight because it is in the numerator and in the denominator. Be careful with the units!

That makes the following calculation: (296.5 /(24*1000)) x 0.15 x 100 x 64 / 10 =1,186%

You replicate these calculations for the 36 other breastfeeding women in the sample. The average relative infant dose (and its 95% confidence intervals) is 1.5% [1.2; 1.7]. We consider the cetirizine transfer to breast milk to be minimal.
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<td>Text + visual + pop-ups</td>
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Conclusion

Click on the images to learn the take home messages from this extensive chapter.

[Media 3.12 Images Health care professional, laptop, leaflet package, medicine, pig, magnifying glass, lactation bottle, infant]
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		[Pop-up text Health care professional] **Health care professionals** Health care professionals should not stop breastfeeding because of anxiety or ignorance on their part. Key questions allow to asses the benefit/risk of using medications in breastfeeding. [Pop-up text Laptop] **Resources other than the summary product characteristics** LactMed is a resource verifying the compatibility of medication with breastfeeding. There are reference sites for medication and breastfeeding [Pop-up text Leaflet package] **Leaflet package** At the time of marketing authorization, the large majority of medications will have data on breastfeeding as “missing information” in their risk management plans. This consequently has an impact on the wording in the medication label. [Pop-up text Medicine] **Medication** Using medication is a risk factor of breastfeeding discontinuation. But, most medications are transferred to breast milk in amounts well below a level that would exert any pharmacological effect on the infant. Few medications are formally contraindicated. [Pop-up text Pig] **Non-human models** Several non-human models used to understand the amount of medication in breast milk have limitations. [Pop-up text Magnifying glass] **Adverse drug reactions – causality** For causality and severity assessment: disentangling confounders from adverse drug reactions remains a major challenge. [Pop-up text Lactation bottle] **Human lactation studies on medication** More research may improve knowledge on medication and breastfeeding in Europe. They offer the opportunity to estimate the amount of medication in the human breast milk. [Pop-up text Infant] **Preterm babies, newborns, infants** The developmental immaturity of young infants with vulnerabilities of some key organs/systems can predispose to adverse drug reactions. In approximately 80% of reported cases, the adverse drug reactions appeared in infants < 2

		months of age. Central nervous system acting medications with severe symptoms events account for 50% of all suspected adverse drug reactions among breastfed infants.

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Additional resources

- Read: Summary Product Characteristics EMA (https://www.ema.europa.eu/en/glossary/summary-product-characteristics)
- Visit: Drugs and Lactation Database (LactMed) - NCBI Bookshelf (nih.gov)
- Visit: HalesMeds (https://www.halesmeds.com/)
- Read: Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (europa.eu)
- Read: Clinical Lactation Studies: Considerations for Study Design Guidance for Industry (fda.gov)
- Read: Guideline on good pharmacovigilance practices (GVP) - Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (europa.eu)
- Video: How to Calculate AUC (https://www.youtube.com/watch?v=HJkInJV29t8)

Chapter 6: Information sources

6.1 Introduction to the chapter

Slide #	Work form	Content
1	Text	**Welcome to chapter 6: Information sources** Imagine you want to assess whether a drug can be prescribed during pregnancy or breastfeeding. Where do you start to find information? It is often not feasible to read all the scientific studies and it can be challenging to stay up-to-date. Luckily, some information sources offer overviews of the most important scientific literature on the topic.
		What are the learning objectives?

		In this chapter, you will learn: ● The sources that offer information on the safety of drug use during pregnancy and breastfeeding. ● The strengths and limitations of different study designs that will help you to critically assess the scientific literature and to better interpret the data. Good luck!

6.2 Publicly accessible and subscription based information sources

<table>
<tr><td>Slide #</td><td>Work form</td><td>Content</td></tr>
<tr><td>1</td><td>Text</td><td>Information sources

Before prescribing or dispensing a drug, it is important to check the summary of product characteristics (SmPC) of that specific medication. The pharmaceutical companies describe what is known about the safety of using the product during pregnancy or breastfeeding. Oftentimes, this information is limited to the available animal studies and clinical trials and cautiousness is recommended. To get a broader perspective on the possible teratogenicity of the drug, it is useful to consult sources of information that summarize the relevant safety studies that were published in scientific literature.

Below you can find an overview of sources that offer information on the safety of a wide range of exposures during pregnancy and breastfeeding. You can use this overview to decide what information sources are relevant to you in your daily practice. You can also download the overview [here], and easily have access to it when you need additional resources.

Take a look at the table at the following slides to learn more about available information sources.</td></tr>
<tr><td>2</td><td>Table</td><td>
<table>
<tr><th colspan="6">Information sources for safety of exposures during pregnancy and breastfeeding</th></tr>
<tr><th>Information source</th><th>Type</th><th>Language</th><th>Directed towards</th><th>Access</th><th>Website</th></tr>
<tr><td>Reprotox</td><td>Overview of all scientific studies on the safety of medications, chemicals, physical agents, and biologics, during pregnancy and breastfeeding. For some drugs, paternal use is also described. References are included.</td><td>English</td><td>Healthcare professionals</td><td>Subscription based</td><td>https://www.reprotox.org/</td></tr>
<tr><td>TERIS</td><td>Overview of all scientific studies on the safety of medications, chemicals, physical agents, and biologics, during pregnancy and breastfeeding. For some drugs, paternal use is also described. References are included.</td><td>English</td><td>Healthcare professionals, researchers and the pharmaceutical industry</td><td>Subscription based</td><td>https://deohs.washington.edu/teris/</td></tr>
<tr><td>Drugs in Pregnancy and</td><td>(Online) textbook with an overview of</td><td>English</td><td>Healthcare professionals</td><td>The online version of</td><td>https://wolt</td></tr>
</table>
</td></tr>
</table>

		Lactation by Gerald G. Briggs et al.	the scientific literature.			the textbook is subscription based	erskluwer.vitalsource.com/#/user/signin
		Pregnancy and Breastfeeding Medicine Guide (Australia)	Summary of the scientific literature of medication use during pregnancy and breastfeeding.	English	Healthcare professionals and general population	Subscription based	https://thewomensphbmg.org.au/
3	Table						

Information sources specific for safety of exposures during breastfeeding

Information source	Type	Language	Directed towards	Access	Website
Medications and Mother's Milk by Thomas W. Hale	(Online) textbook with an overview of the scientific literature. Includes pharmacokinetics.	English	Healthcare professionals Professionals	The online version of the textbook is subscription based	https://www.halesmeds.com/
LactMed (The Drugs and Lactation Database)	Overview of all scientific research on the safety of the medication and other chemicals during breastfeeding. Peer reviewed.	English	Healthcare professionals Professionals	Publicly accessible	https://www.ncbi.nlm.nih.gov/books/NBK501922/
E-lactancia	Summary of the scientific literature. Includes pharmacokinetics.	English and Spanish	Healthcare professionals Professionals	Publicly accessible	https://www.e-lactancia.org/
UKDilas	Summary of the scientific literature. It includes advice on individual medicines, therapeutic groups, as well as more detailed information on the most frequently asked questions.	English	Healthcare professionals Professionals	Publicly accessible	https://www.sps.nhs.uk/articles/information-resources-that-give-advice-on-medicines-and-breastfeeding/#:~:text=UKDilas

4 Table

Teratology Information Services (TIS) 1/2

Information source	Type	Language	Directed towards	Access	Website	
Many countries have their own Teratology information service (TIS)	The TIS provides free teratology information, based on…. often on their national website, and answers questions by phone or email.		Healthcare professionals Professionals and general population	Publicly accessible	Specific for each country. Find a TIS nearby on http://www.entis-org.eu/centers	
Embryotox (German Teratology Information Service)	Summary of the scientific literature and recommendations for use during pregnancy and breastfeeding. References are not included.	German	Healthcare professionals Professionals	Publicly accessible	https://www.embryotox.de/	
UKTIS (UK Teratology Information Service)	Interpretation of scientific literature on various exposures in abstract form	English	Healthcare professionals Professionals	Publicly accessible	www.uktis.org	
	More detailed information on various exposures	English	Healthcare professionals Professionals	Subscription based	www.toxbase.org	
	BUMPS: Leaflets with a summary of patient information on various exposures	English	General population	Publicly accessible	www.medicinesinpregnancy.org	

		Netherlands Pharmacovigilance Centre Lareb (Dutch Teratology Information Service)	Summary of the scientific literature of medication use during pregnancy and breastfeeding. References are often included.	Dutch	Healthcare professionals Professionals and general population	Publicly accessible	https://www.lareb.nl/mvm-kennis
		Janus (Sweden)	Assessment of potential risks to the fetus when medicines are used during pregnancy.	Swedish	Healthcare professionals Professionals and general population	Publicly accessible	https://www.janusinfo.se/beslutsstod/janusmedfosterpaverkan.4.72866553160e98a7dc

5 Table

Teratology Information Services (TIS) 2/2

Information source	Type	Language	Directed towards	Access
MotherToBaby (Organization of Teratology Information Specialists USA)	Factsheets and easy to understand information, directed towards pregnant or lactating women.	English and Spanish	General population	Publicly accessible
Le Centre de Référence sur les Agents Tératogènes, CRAT (France)	Information service on the risks of medications, vaccines, radiation and addictions during pregnancy and breast- feeding. For some drugs, paternal use is also described.	French	Healthcare professionals Professionals	Publicly accessible
metaPreg (France)	MetaPreg gives direct access to all the studies about the impact of drugs during pregnancy on fetal development and risk of malformations, birth defects or bad pregnancy outcomes. Results are	French	Healthcare professionals Professionals	Publicly accessible

			synthesized by meta-analysis and continuously maintained up-to-date (dynamic meta-analysis).		Not designed for the general public		
		Trygg Mammamedisin (Norway)	Information on medications for some common conditions during pregnancy and breastfeeding.	Norwegian	General population	Publicly accessible	https://t

6 Table

Information sources for drug information

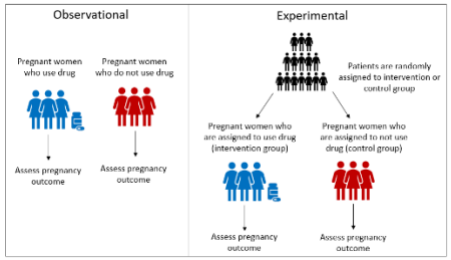
Information source	Information	Language	Directed towards	Access	Websit
DrugBank	A comprehensive, free-to-access, online database containing information on drugs and drug targets.	English	Healthcare professionals Professionals and users	Publicly accessible	https://gc
EMA	Summary of product characteristics (SmPC). Drug and safety information provided by the pharmaceutical company. Often limited to basic information and quite conservative. Often difficult to translate to the individual patient.	English	Healthcare professionals Professionals and users	Publicly accessible	https://w
Electronic medicines compendium (EMC)	Information about medicines licensed for use in the UK. SmPC and Patient Leaflet.	English	Healthcare professionals Professionals and users	Publicly accessible	https://w the-emc

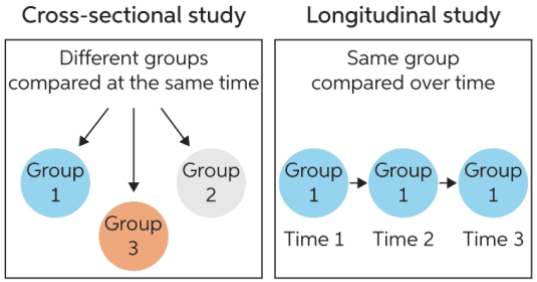
7 Text

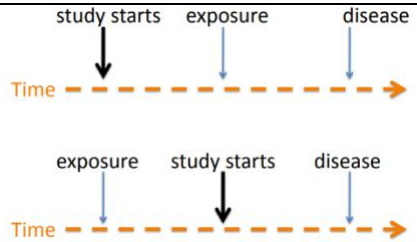
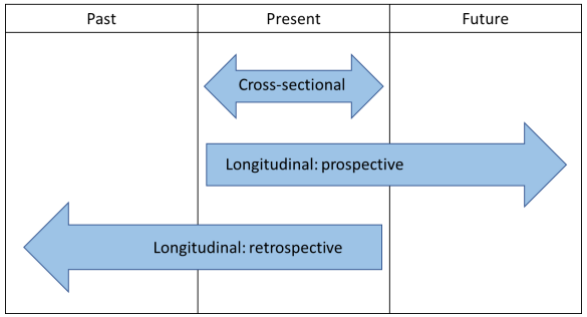
Conclusion

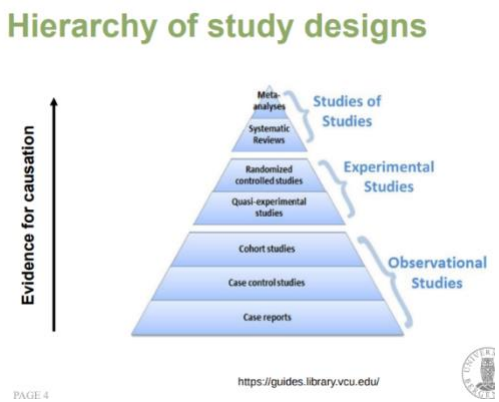
You just learned about the information sources you can use to get information on the safety of a certain exposure during pregnancy or breastfeeding. These sources reviewed the scientific literature and summarized the most important findings. Sometimes you may need to read scientific articles for more in-depth knowledge. Some studies are of better quality than others. It is important to be able to correctly understand and interpret the data.

6.3 Epidemiological research

Slide #	Work form	Content
1	Text + pop-up	**Epidemiological research** This part will explain basic principles of epidemiological research in relation to teratology. This will help you to better understand and interpret the scientific literature. We will discuss the different study designs and give examples from the literature. I-icon [Pop-up text] **Epidemiological research** Epidemiology is the study of the distribution and determinants of health and disease conditions in a specified population. In other words, it is the study of how often and why diseases or conditions occur in specific groups of people.
2	Text + afbeelding	**Experimental versus observational research** In *experimental studies*, the researcher intervenes by making a change (e.g., giving a medical treatment of part of the population) and then observes what happens. The study population is split into an intervention group and a control group that does not undergo the intervention. This intervention manipulates one or more variables of interest. To study the effect of a certain intervention, the outcome of the intervention group is compared to the outcome of the control group. The best-known example of an experimental study is a randomized controlled trial (RCT). However, in pregnant women it would not be ethical to conduct such a study. Therefore, for studies on teratogenic outcomes we mostly rely on *observational studies*. In observational studies, the researcher observes but does not intervene in the study population. This study type cannot establish causation but can observe associations. [Media 6.1 Afbeelding Observational vs. Experimental]  *(Image based on an image from Research Hubs. See the additional materials for the full source.)*

3	Text + afbeelding	**Cross-sectional versus longitudinal research** ● A cross-sectional study is an observational study that measures the outcome and the exposure of interest at the same time. Thus, in each individual, there is only one moment of data collection. There is no data collection from the past and no follow-up. ● In longitudinal research, researchers collect data at multiple time points. The study outcome is assessed at a different time point than the exposure(s) or determinants of interest. [Media 6.2 Afbeelding Cross-sectional vs. Longitudinal]  *(Based on an image from Chegg)*
4	Text + afbeelding	**Two type of longitudinal studies** Longitudinal studies can be divided into prospective and retrospective studies. ● In a prospective study, participants are included in the study and are followed over time. Prospective studies are very time consuming and therefore expensive. ● In a retrospective study, participants are included in the study and data is collected about their past. Retrospective studies are less time consuming and therefore relatively inexpensive to perform. [Media 6.3 Afbeelding Prospective vs. Retrospecitive. In de afbeelding titel van study soort meenemen. Prospetive boven, Retrospective beneden]

		
5	Text + afbeelding	**An overview of focus in time** In teratology, longitudinal studies are mostly used, but sometimes cross-sectional studies are applied. The different study designs can focus on the past, present or future. [Media 6.4 Afbeelding Summary study designs] 
6	Text	**Data gathering** When a new drug enters the market, very little is known about the safety of its use during pregnancy. Most of the time, there is only data from mandatory animal studies and from unplanned pregnancies that occurred in clinical trials during drug development. However, results of animal studies are difficult to extrapolate to humans due to inter species variability and data on unplanned exposed pregnancy are scarce. Based on this limited data, usually nothing can be said about possible risks during pregnancy. Data on the safety of use during pregnancy will therefore have to be gathered after the drug has entered the market. These

		data will be collected through observational studies. First, there will be case reports and (small) case series. This will be followed by cohort studies and case-control studies. This also includes the large registry or database studies. When enough data are gathered, systematic reviews and meta-analysis will be performed. The various study designs will be discussed in the following sections. It takes many years before a risk assessment is possible, if at all. One study found that it takes an average of 27 years for a drug to change from risk unknown to a risk classification *(Adam et al, 2011)*. For drugs that are rarely prescribed to women of childbearing age, it may never be possible to clearly assess safety of use in pregnancy.
7	Text + afbeelding	**Level of evidence of different study designs** Different study types can offer different quality of information. As you can see in the figure, the study designs can be ranked based on their quality of information. This is the so-called level of evidence. This indicates the quality and reliability of the study results. A meta-analysis offers the highest quality of information, while case reports and case series are considered to have a low level of evidence. [Media 6.5 Hierarchy of study designs. Note: Change "quasi experimental studies" to "experimental studies"]  *(Source?)*
8	Text + afbeelding	**Why you need to know about different study designs** As you could see in the pyramid, ideally, experimental studies are preferred over observational studies. The higher you go up in the pyramid, the higher the quality of study design will be. Since experimental studies are often not ethically justified

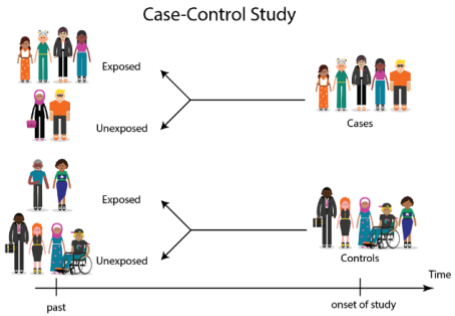
		in teratology, we are dependent on observational studies. In order to interpret the data from scientific studies, it is important to know the strengths and limitations of the different study designs. In every study there is a risk of bias and confounding. You should keep this in mind when interpreting scientific studies. This will help you to critically assess the study outcomes and to put them in a broader perspective. We will now discuss each study design in more detail. In this section we will explain the difference between study designs, and describe their pros and cons. We start with the lowest level of evidence and work our way up. Click on the bottom section of the pyramid to start. *(Bouter, LM and van Dongen, 2006),* *(Adam MP, Polifka JE, Friedman JM, 2011)* *(Källén B, 2012)* I-icon [Pop-up text Bias] **Bias** Bias is any systematic error in an epidemiologic study that results in an incorrect estimate of the association between exposure and the health outcome. I-icon [Pop-up text Confounding] **Confounding factor** A confounder or confounding factor is an external variable that is associated with both your outcome of interest and your determinant of interest. This confounder distorts the association between the exposure and the outcome. Imagine the following example in which the association between a drug and the risk of miscarriage is studied. The use of the specific drug increases when maternal age increases. The risk of having a miscarriage also increases when maternal age increases. The study finds a significant association between the drug use and an increased risk of having a miscarriage. However, this increased risk is likely caused by the maternal age and not by the drug.
9	Text + tabel	**#1 Case report and case series** *Definition, strengths and limitations* ● A **case report** is a detailed description of the symptoms, treatment and outcome of an individual patient. In this case the patient refers to a pregnant woman. The outcome refers to the outcome of the pregnancy: a healthy child or a child with a birth defect. A case report of a birth defect may be an indication for teratogenicity. However it may well be a coincidental finding. A single case report is not suited to prove an association or causality.

<table>
<tr><td></td><td></td><td>
A case series is a detailed description of the treatment and outcome of multiple patients (in this case pregnant women). Often, these pregnant women have used the same drug. The case series reports the pregnancy outcomes of the included women.
Take a look at the table to compare their strengths and limitations.
<table>
<tr><th>Strengths</th><th>Limitations</th></tr>
<tr><td>Starting point for discovering teratogenicity of an exposure - can be hypothesis generating</td><td>Cannot prove an association or causality between the exposure and outcome</td></tr>
<tr><td>First form of publication - it can raise concern and awareness for a specific exposure</td><td>Often the combination of exposure and congenital anomaly is coincidental</td></tr>
<tr><td>Quick and inexpensive</td><td>No control group</td></tr>
</table>
</td></tr>
<tr><td>10</td><td>Text + pop-up</td><td>
Discoveries through case reports and series

Some teratogens were discovered by astute clinicians, who linked a unique pattern of malformations to a rare pregnancy exposure. These patterns were first described in a case report or case series. However, it is difficult to link malformations described in case reports to a specific drug. Clinical reports from a case or case series on a specific outcome after maternal exposure can raise a hypothesis that needs to be confirmed by further epidemiological research.

A well-known example of a drug whose teratogenicity was discovered through case reports is thalidomide as discussed early in the course.

<u>Did you know?</u>
[Doctor pop-up]
Mycophenolate mofetil (MMF)
A more recent example is mycophenolate mofetil, a drug used for prophylaxis against acute organ rejection in transplantation. After entering the drug market, publications appeared about a very specific pattern of abnormalities, which was the first indication of teratogenicity of the drug. As a result of these case reports and case series, it is believed that MMF is teratogenic and should not be given to women of childbearing age.
</td></tr>
<tr><td>11</td><td>Text</td><td>#2 Case-control studies</td></tr>
</table>

		In this type of study, the study population is selected based on the outcome of interest. In teratology, an outcome of interest may be having a child with a birth defect. The study population is subdivided into cases (infants with the outcome) and controls (infants without the specific outcome). Information is collected on whether the study participants have been exposed to certain variables of interest in the past. This study design is therefore retrospective. The frequency of exposure among cases is compared with the frequency of exposure among controls. In the field of teratology, cases are often selected from birth registers. However, there are no controls in these registers and it can be difficult to select a comparable control population. Another problem is that people do not remember everything that happened in the past (recall bias) and that cases may remember more details than the controls. This can have an effect on the results of the study. [Media 6.6 Image Case-control study]  I-icon [Pop-up text] **Recall bias** Recall bias is an error that is caused by incomplete or inaccurate data regarding the past. This is mainly a concern in retrospective studies. For example, it can be difficult to remember all the medications or exposures in the last six months. Also, cases (e.g. patients that have a child with a birth defect) might be more accurate and complete in reporting their past exposures than control patients. This can lead to biased results.
12	Multiple answers	Each study design has its own strenghts and limitations. **Can you select the strengths of a case-control study?** Choose three answers. a. Different/multiple exposures can be studied b. Does not require a huge sample size

<table>
<tr><td></td><td></td><td>c. Can be used to estimate incidences and risks of developing the outcome
d. Suitable for studying rare outcomes or outcomes with a long latency period

Feedback correct answer:
Yes, well done. Case-control studies allow to study different/multiple exposures, does not require a huge sample size and is suitable for studying rare outcomes or outcomes with a long latency period. On the next slide, we provide an overview of all strengths and also the limitations of this study design.

Feedback incorrect answer:
No, that’s incorrect. Case-control studies allow to study different/multiple exposures, does not require a huge sample size and is suitable for studying rare outcomes or outcomes with a long latency period. On the next slide, we provide an overview of all strengths and also the limitations of this study design.</td></tr>
<tr><td>13</td><td>Text + tabel + pop-up</td><td>Strenghts and limitations
Case-control studies

Take a look at the table below to learn more.

<table>
<tr><th>Strengths</th><th>Limitations</th></tr>
<tr><td>Suitable for studying rare outcomes or outcomes with a long latency period</td><td>May be difficult to find enough cases when the outcome is rare</td></tr>
<tr><td>Different/ multiple exposures can be studied</td><td>Only one outcome can be studied</td></tr>
<tr><td>Can identify associations and risk evaluation</td><td>Risk of bias, especially recall bias due to retrospective design</td></tr>
<tr><td>Relatively inexpensive, efficient in resources and time</td><td>Not suitable for studying rare exposures</td></tr>
<tr><td>Does not require a huge sample size</td><td>Studies can test different hypotheses from one dataset. Multiple testing can induce bias.</td></tr>
<tr><td></td><td>Selection of suitable controls is challenging</td></tr>
<tr><td></td><td>Quality of data can be low due to missing data</td></tr>
</table>

I-icon
[Pop-up text]</td></tr>
</table>

<table>
<tr><td></td><td></td><td>Multiple testing
Multiple testing is simultaneously testing multiple hypotheses. The more hypotheses are tested, the higher the probability of finding a significant result due to chance (false-positive). When 20 tests are performed in one study, there is a high chance of finding at least 1 significant result even if this test is not actually significant.</td></tr>
<tr><td>14</td><td>Text</td><td>An interesting example

There is an interesting example of a case-control study from a birth defects registry, the NBDPS. In this study, 7 antidepressants are examined for associations with 43 specific birth defects. Because of the multiple comparisons, the risk of bias due to multiple testing is present. (Benevent J, Hurault-Delarue C, Araujo M, Revet A, Sommet A, Lacroix I, Damase-Michel C, 2022)

You can find the full source in the additional materials.</td></tr>
<tr><td>15</td><td>Text</td><td>#3 Cohort studies

In this type of study, the study population is selected based on the exposure of interest. The study population is subdivided into an exposed and an unexposed group. Both the exposed and the unexposed group must be selected from the same source population. All participants must be at risk of developing the outcome. To find women who are exposed to a certain drug, studies often use a cohort of pregnant women with the same disease.

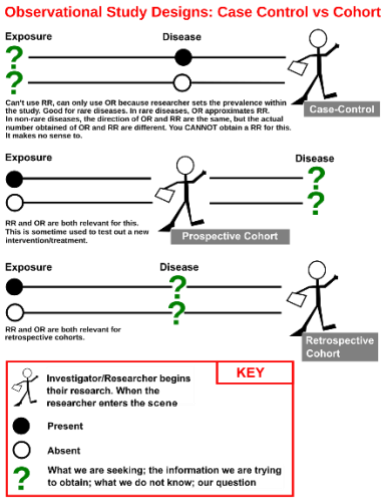
There are two types of cohort studies:

● Retrospective
● Prospective</td></tr>
<tr><td>16</td><td>Text + tabel + pop-up</td><td>Strengths and limitations
Cohort studies

A problem with cohort but also case-control studies is confounding by indication. This means that the condition itself can also cause the outcome. For example, diabetes can give a higher risk of birth defects. It is not always possible to correct for this in the analysis. The severity of the indication can also play a role in the outcome.

<table>
<tr><th>Strengths</th><th>Limitations</th></tr>
<tr><td>Suitable for studying uncommon and rare exposures</td><td>Not suitable for studying rare outcomes</td></tr>
</table>
</td></tr>
</table>

		<table><tr><td>Different and multiple outcomes can be studied</td><td>Only one exposure can be studied</td></tr><tr><td>Can be used to estimate incidences and risks of developing the outcome</td><td>It can be challenging to find women that were exposed to a specific drug to include them in the study</td></tr><tr><td></td><td>Can be time consuming and costly</td></tr><tr><td></td><td>Risk of bias due to recall bias (retrospective design) or loss to follow-up (prospective design)</td></tr></table> I-icon [Pop-up text] **Loss to follow-up** Loss to follow-up happens when a study participant drops out of the study and the outcome data for this participant are missing. Participants who are lost to follow-up (and thus have missing data) may differ systematically from the participants that remain in the study. For example, participants who had a miscarriage may drop out of the study more often than participants with ongoing pregnancies. This can lead to biased results.
17	Text + afbeelding	**Case control vs. cohort studies** *Can you tell the difference?* The following figure might help to visualize the difference between case-control studies and (prospective and retrospective) cohort studies. [Media 6.7 Afbeelding Obersational study designs: case control vs cohort. Suggestie: Het zou misschien consequenter zijn om in plaats van 'disease' te kiezen voor 'birth defect', zodat het goed overeenkomt met de eerdere figuren.]

		
18		**#5 Randomized controlled trial** The most ideal study design to evaluate a causal relationship would be a randomized controlled trial. This type of study minimizes bias by controlling for confounding variables by randomly distributing these characteristics among the treatment and control groups. However, as was discussed in the previous chapter, most of the time it is not ethical to conduct an experimental study on pregnant women. Therefore this study design is rarely used in humans in the field of teratology. The exception is when the treatment of interest is specifically used for pregnant women, such as the treatment of morning sickness, preeclampsia or gestational diabetes.
19		**Strength and limitations** *Randomized controlled trials* Compare the strengths and limitations below.

<table>
<tr><td></td><td></td><td>
<table>
<tr><th>Strengths</th><th>Limitations</th></tr>
<tr><td>Ideal study design to study causal effects</td><td>Most of the time not ethical to study teratogenic outcomes in an experimental study design</td></tr>
<tr><td>Minimal bias and confounding due to randomization and control group</td><td>Risk of bias due to loss to follow-up</td></tr>
<tr><td></td><td>Costly</td></tr>
</table>
</td></tr>
<tr><td>20</td><td>Text</td><td>Study examples

In the additional materials you will find study examples of RCTs for the treatment of pregnancy related diseases. The drug may be compared to a placebo or to other medications for that condition.

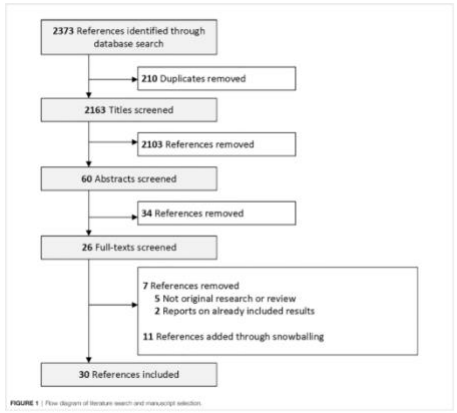
(Guttuso T Jr, Messing S, Tu X, Mullin P, Shepherd R, Strittmatter C, Saha S, Thornburg LL, 2021)
(Livingston JC, Livingston LW, Ramsey R, Mabie BC, Sibai BM, 2003)
(Najafian, Mahin & Barati, Mojgan & Masihi, Sara & Fardipor, Ailin, 2016)</td></tr>
<tr><td>21</td><td>Text</td><td>#5 Systematic reviews

A systematic review systematically summarizes and compares the available literature on a specific topic. Often a critical appraisal of the studies is performed, which provides insight in the quality of the data. Frequently, a systematic review is combined with a meta-analysis.</td></tr>
<tr><td>22</td><td>Text + tabel + pop-ups</td><td>Strength and limitations
Systematic reviews

Compare the strengths and limitations below.

<table>
<tr><th>Strengths</th><th>Limitations</th></tr>
<tr><td>Efficient way to evaluate large amounts of information, no need for professionals to read all the literature</td><td>The studies included may be subject to publication bias. This will result in biased results of the systematic review.</td></tr>
<tr><td>Reliable conclusions</td><td>Very time consuming and methodologically challenging</td></tr>
</table>
</td></tr>
</table>

		<table><tr><td>Enables comparison of individual studies</td><td></td></tr><tr><td>Explicit methods, allows the reader to assess how review was compiled</td><td></td></tr></table> I-icon Studies with statistically significant results have a higher chance of being published. Studies that did not find significant results are underrepresented in the literature. This can lead to an overestimation of an effect.
23	Text	**Study example** During the COVID-19 pandemic, information about vaccination during pregnancy or breastfeeding was important. This systematic review provides a comprehensive overview of the available literature. *(Muyldermans J, De Weerdt L, De Brabandere L, Maertens K, Tommelein E, 2022)*
24	Text + pop-ups + visual	**Flow diagrams and overview tables** Systematic reviews always include a flow diagram of the literature search and the study selection. This way, the process of study selection is transparent and can be reproduced by others. Systematic reviews also present the most relevant methods and results of the selected studies in an overview table. This way, the reader can quickly find a summary of the most important findings. [Pop-up Text + image] **Example of a "flow diagram"** [Media 6.8 Flow diagram]

		 *(Source?)* [Pop-up text+image] **Example of an "overview table"** [Media 6.9 Overview table]  *(Source?)*
25	Text	**#6 Meta-analysis** A meta-analysis is a type of systematic review, containing a statistical analysis that combines the results of multiple individual studies. Merging of different studies results in a higher number of cases and more reliable conclusions. Therefore, a meta-analysis is considered to have the highest quality of evidence of all study types.

<table>
<tr>
<td>26</td>
<td>Text + tabel</td>
<td>
Strengths and limitations
Meta-analysis

Take a look at the table below to learn more.

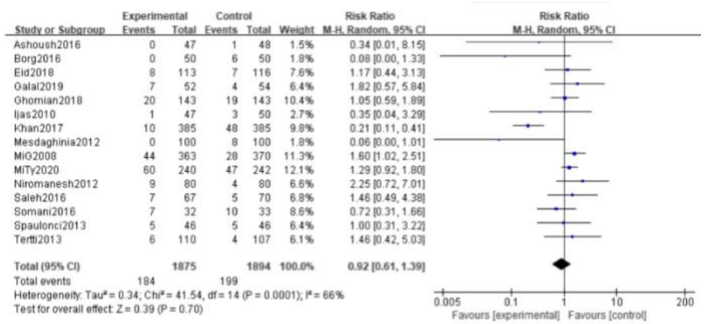
<table>
<tr><th>Strengths</th><th>Limitations</th></tr>
<tr><td>Enables a more precise estimate of the effect or risk than the individual studies in the analysis</td><td>A meta-analysis is as good as the included studies. A good meta-analysis of badly designed studies will still result in bad statistics</td></tr>
<tr><td>Provides more statistical power; useful for studying rare outcomes or small effects</td><td>Studies can be very heterogeneous in their design, quality and patient populations. A meta-analysis can only be performed on a selection of comparable studies, which often leads to exclusion of (smaller) studies or case reports</td></tr>
<tr><td></td><td>Very time consuming and methodologically challenging</td></tr>
</table>
</td>
</tr>
<tr>
<td>27</td>
<td>Text + afbeelding + pop-up</td>
<td>
Study examples

An example is the systematic review with meta-analysis by Zhao and his team in which the efficacy and safety of metformin is tested. The underlying maternal disease may be relevant to take into consideration in this kind of study. In the first example the indication for metformin is PCOS, in the second example it is diabetes.

Another example includes the meta-analysis by He and team to compare metformin to insulin. In the meta-analysis, a flow-chart shows the selection process and the number of studies included. There is a statistical analysis to get the pooled result from all studies combined. These results are shown in a forest plot.

(He K, Guo Q, Ge J, Li J, Li C, Jing Z, 2022)
(Zhao Q, He J, 2022)

Pop-up text + image
Forest plot
[Media 6.10 Forest plot]
</td>
</tr>
</table>

		 FIGURE 3 Risk ratio for preterm birth between the metformin and insulin arms *(Source?)*
28	Text	**Study outcomes** *Relative risk (RR), odds ratio (OR) and hazard ratio (HR)* When reading publications of cohort studies and case-control studies, you will notice that the study outcomes are often reported as relative risks (also called risk ratios) or odds ratios. These are two different outcome measures and it is important to interpret these correctly. To understand the difference, we will explain the terms risk and odds on the next slides.
29	Text + pop-up + tabel	**Relative Risk** Imagine you are tossing a coin. The probability (risk) that it will be heads is 0.5. The odds that it will be heads is 1. Similarly, a risk (incidence) is calculated by dividing the number of people that develop the outcome by the total number of people in that group. Meanwhile, an odds is calculated by dividing the number of people that develop the outcome by the number of people that do not develop the outcome. When dividing the risk or the odds of the two study groups, you get the relative risk or the odds ratio. Interpretation: ● RR = 1 → the incidence in the exposed is equal to the incidence in the unexposed. No increased risk. ● RR > 1 → the incidence in the exposed is larger than the incidence in the unexposed. Increased risk.

<table>
<tr>
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RR < 1 → the incidence in the exposed is smaller than the incidence in the unexposed. Decreased risk.

<u>Click here to learn more about how to calculate a RR (advanced)</u>
[Pop-up text]
Calculation RR
A 2x2 contingency table to show the exposed and unexposed participants with and without the outcome of interest.
<table>
<tr><td></td><td>Develop the outcome</td><td>Do not develop the outcome</td></tr>
<tr><td>Exposed</td><td>a</td><td>b</td></tr>
<tr><td>Not exposed</td><td>c</td><td>d</td></tr>
</table>
RR = incidence in exposed / incidence in unexposed = (a / (a + b)) / (c / (c + d))
</td>
</tr>
<tr>
<td>30</td>
<td>Text + pop-up + tabel</td>
<td>
Odds Ratio

Interpretation:

OR = 1 → The odds of having the outcome in the exposed is equal to the odds of having the outcome in the unexposed. No increased risk.
OR > 1 → The odds of having the outcome in the exposed is larger than the odds of having the outcome in the unexposed. Increased risk.
OR < 1 → The odds of having the outcome in the exposed is smaller than the odds of having the outcome in the unexposed. Decreased risk.

<u>Click here to learn more about how to calculate an OR (advanced)</u>
[Pop-up text]
Calculation OR
A 2x2 contingency table to show the exposed and unexposed participants with and without the outcome of interest.
<table>
<tr><td></td><td>Develop the outcome</td><td>Do not develop the outcome</td></tr>
<tr><td>Exposed</td><td>a</td><td>b</td></tr>
</table>
</td>
</tr>
</table>

		<table><tr><td>Not exposed</td><td>*c*</td><td>*d*</td></tr></table> **OR** = odds that exposed person has the outcome / odds that unexposed person has the outcome = (a / b) / (c / d) = a*d / b*c
31	Text + pop-up + tabels	**When are RRs and ORs used?** An RR can be calculated only if we can estimate the probability (prevalence) of an outcome in both groups. This is not true in case control studies, since the researchers choose how many cases and controls they include in the study. In other words, the researchers set the prevalence of the outcome within the study. Therefore, RR cannot be used in case control studies. The RR can be used in cohort studies. An OR on the other hand can be used when we do not know the prevalence of the outcome. Therefore, ORs can be used in case control studies as well as cohort studies. With rare outcomes, the odds ratio is an estimate of the relative risk. With common outcomes (e.g. the outcome occurs in more than 10% of the population), the odds ratio tends to overestimate the relative risk. Click here to learn more about the difference between RR and OR (advanced) [Pop-up text + tabel] **Difference between RR and OR** First, we show you an example of a 2x2 table of a study that has a rare outcome of interest. Less than 10% of the participants develop the outcome of interest. <table><tr><td></td><td>Develop the outcome</td><td>Do not develop the outcome</td></tr><tr><td>Exposed</td><td>*8*</td><td>*92*</td></tr><tr><td>Not exposed</td><td>*5*</td><td>*95*</td></tr></table> RR = (8/(8+92)) / (5/(5+95)) = 1.60. The incidence in the exposed group is 1.6 times the incidence in the unexposed group. OR = (8/92) / (5/95) = 1.65. The odds of having the outcome in the exposed group is 1.65 times the odds of having the outcome in the unexposed group.

<table>
<tr>
<td></td>
<td></td>
<td>The RR and the OR are very similar in this situation. For rare outcomes, the OR is an estimation of the RR.

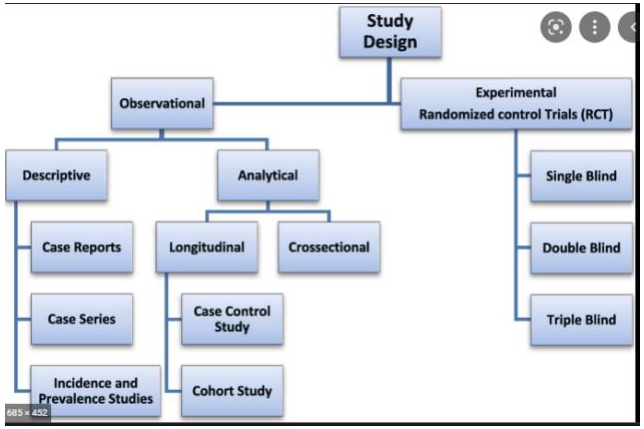
Second, we show an example of a 2x2 table of a study that has a more common outcome of interest. Almost half of the population develop the outcome of interest.
<table>
<tr><th></th><th>Develop the outcome</th><th>Do not develop the outcome</th></tr>
<tr><td>Exposed</td><td>50</td><td>50</td></tr>
<tr><td>Not exposed</td><td>40</td><td>60</td></tr>
</table>
RR = (50/(50+50)) / (40/(40+60)) = 1.25. The incidence in the exposed group is 1.25 times the incidence in the unexposed group.
OR = (50/50) / (40/60) = 1.5. The odds of having the outcome in the exposed group is 1.5 times the odds of having the outcome in the unexposed group.

As you can see by the numbers, the OR is much higher than the RR. For common outcomes, the OR is an overestimation of the RR.</td>
</tr>
<tr>
<td>32</td>
<td>Text</td>
<td>Hazard ratio (HR)

Another measure of outcome that is often confused with the RR is the hazard ratio (HR). The HR is a measure of an effect over time. This measure is useful when the risk is not constant over time. The HR is often used to estimate the risk of a miscarriage or stillbirth. To learn more about HR calculations, we added an interesting tutorial from Albarqouni in the additional materials.

Interpretation:
● HR < 1: at any given time, less patients in the treatment group experience the outcome compared to the control group.
● HR = 1: at any given time, event rates are the same in both groups.
● HR > 1: at any given time, more patients in the treatment group experience the outcome compared to the control group.

<u>Click here to learn the difference between HR and RR (advanced)</u>
[Pop-up text]
Difference between HR and RR
While the RR estimates the risk at a certain time point, the HR estimates the risk of an event over the entire study duration. The RR can be different at different time points, but the HR is constant over time.</td>
</tr>
</table>

		The easiest way to understand the difference between the HR and RR is by assessing the risk of death. Eventually everyone dies, so the RR will approach 1 with time. However, the HR remains constant over time. *Confidence intervals (CI)* When interpreting RR, OR and HR, it is important to take into account the confidence interval. If the p value is larger than 0.05 or if the confidence interval includes the 1, the RR, OR or HR is not statistically significant. That is why you should always look closely at the lower and upper boundary of the confidence interval in the interpretation of statistical study results. *(Viera AJ, 2008)* *(Stare, Janez & Maucort-Boulch, Delphine, 2016)*
33	Text + afbeelding	**Conclusion** In this chapter you learned about available information sources and different study designs in epidemiological research. To summarize, take another look at the overview below. [Media 6.11 Afbeelding Study design overview]  Thank you for your participation!

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Livingston JC, Livingston LW, Ramsey R, Mabie BC, Sibai BM. Magnesium sulfate in women with mild preeclampsia: a randomized controlled trial. Obstet Gynecol. 2003 Feb;101(2):217-20. doi: 10.1016/s0029-7844(02)03053-3. PMID: 12576241.

Najafian, Mahin & Barati, Mojgan & Masihi, Sara & Fardipor, Ailin. (2016). Investigation the Effects of Metformin versus Insulin on Neonatal and Maternal Outcomes in Women with Gestational Diabetes Mellitus: A Randomized Clinical Trail. Global Journal of Health Science. 9. 272. 10.5539/gjhs.v9n4p272.

Stare, Janez & Maucort-Boulch, Delphine. (2016). Odds Ratio, Hazard Ratio and Relative Risk. Advances in Methodology and Statistics. 13. 59-67. 10.51936/uwah2960

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Zhao Q, He J. Efficacy and safety of metformin in pregnant women with polycystic ovary syndrome: a systematic review with meta-analysis of randomized and non-randomized controlled trials. Gynecol Endocrinol. 2022 Jul;38(7):558-568. doi: 10.1080/09513590.2022.2080194. Epub 2022 May 27. PMID: 35621312.

Additional resources

- Read: Benevent J, Hurault-Delarue C, Araujo M, Revet A, Sommet A, Lacroix I, Damase-Michel C. Prenatal Drug Exposure in Children With a History of Neuropsychiatric Care: A Nested Case-Control Study. Front Psychiatry. 2022 Mar 22;13:795890. doi: 10.3389/fpsyt.2022.795890. PMID: 35392389; PMCID: PMC8980541. (https://pubmed.ncbi.nlm.nih.gov/35392389/)
- Read: Muyldermans J, De Weerdt L, De Brabandere L, Maertens K, Tommelein E. The Effects of COVID-19 Vaccination on Lactating Women: A Systematic Review of the Literature. Front Immunol. 2022 Apr 8;13:852928. doi: 10.3389/fimmu.2022.852928. PMID: 35464406; PMCID: PMC9024041. (https://pubmed.ncbi.nlm.nih.gov/35464406/)

- Read: Tutorial about Hazard Ratios, Loai Albarqouni (*https://s4be.cochrane.org/blog/2016/04/05/tutorial-hazard-ratios/#:~:text=One%20of%20the%20main%20differences,end%20of%20the%20study%20period)*
- Image: Research Hubs (https://researchhubs.com/post/ai/data-analysis-and-statistical-inference/observational-studies-and-experiments-sampling-and-source-bias.html)

Chapter 7: Risk communication

7.1 Introduction to the chapter

Slide #	Work form	Content
1	Text + pop-up	**Welcome to chapter 7: Risk communication** Women and their health professionals perceive risk differently with frequent overestimation of risk by women. There is frequently a lack of awareness of back risks in pregnancy, which causes the decision making process to be troubled. Patients need clear information to enable shared decision making. Risk perception may be influenced by how the risk is framed (negative framing vs. positive framing. *(Jasper, 2001)* This causes conflict between the scientific statement of available data and uncertainties, and the patient's desire for a definite answer – is this medicine safe for my babe? In this chapter, we try to battle collective statistical illiteracy. [Pop-up text Collective statistical illiteracy] **Collective statistical illiteracy** Collective statistical illiteracy refers to the widespread inability to understand the meaning of numbers. For instance, many citizens are unaware that higher survival rates with cancer screening do not imply longer life, or that the statement that mammography screening reduces the risk of dying from breast cancer by 25% in fact means that 1 less woman out of 1,000 will die of the disease. *(Gigerenzer, 2007)*
2	Multiple choice question	Taking medicines in pregnancy is a "high-stakes" decision. However, as you know, available information might be limited or even conflicting.

		What do you think is a common response from health professionals and their patients when presented with limited and conflicting information? a. The stakes are high, thus a decision is made nonetheless **b. The information is limited and confliction, thus no decision is made** *Feedback correct answer:* Yes, well done. Limited and/or conflicting information when presented with a "high-stakes" decision can lead to risk aversion in patients and healthcare professionals. Sometimes, the uncertainties and limited or conflicting information leads to no decision being made about medication use in pregnancy. However, doing nothing is still a decision. *Feedback incorrect answer:* No, sorry. Limited and/or conflicting information when presented with a "high-stakes" decision can lead to risk aversion in patients and healthcare professionals. Sometimes, the uncertainties and limited or conflicting information leads to no decision being made about medication use in pregnancy. However, doing nothing is still a decision.
3	Text/Quote	**'The single biggest problem in communication is the illusion that it has taken place'** *-George Bernard Shaw*
4	Text	**What are the learning objectives?** In this chapter, we describe general principles of risk communication in healthcare, outline challenges unique to medicines in pregnancy/breastfeeding, learn how to use available risk communication materials/techniques to communicate risk effectively in the context of medication use in pregnancy and breastfeeding to facilitate shared decision making. You will furthermore learn how to apply risk communication skills to a real life scenario and describe novel decision aids that aim to reduce decisional conflict when deciding on treatment options during pregnancy and breastfeeding. Good luck!

7.2 General principles of risk communication

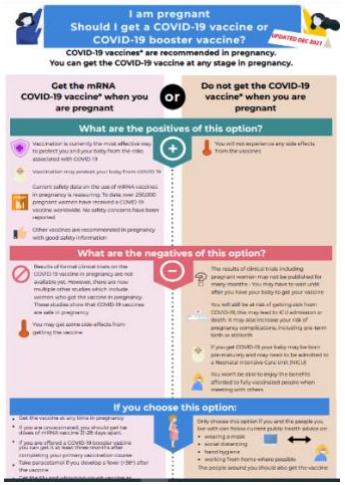
Slide #	Work form	Content
1	Text	**How to communicate risks?** Health professionals and patients may struggle to understand the probability of risks when learning more about medication use during pregnancy. It is there for best to avoid using verbal expressions of risk - use numbers if you have them. How would you interpret the level of risk with terms like: rare, unlikely, frequent? Leave little room for interpretation and avoid using broad terms. You may also want to use a common denominator when communication risks. For example, use x in 100 instead of 1 in x. The first option will be easier to understand for most people, e.g. 2-3 babies in 100 are born with a congenital anomaly and 20 in 100 pregnancies end in miscarriage. Another best practice would be to use visual risk communication as much as possible, as it may help to overcome challenges of limited health literacy or numeracy.
2	Text	**General strategies** When communication risks, use the following general strategies: • Distinguish between relative and absolute risks • Clearly describe the risk and who it applies to • Explain risk in terms that the patient will understand • Give balanced information • Explain the uncertainties Take a look at the following example in which one of these general strategies has not been followed.
3	Text	**An example from the media** A good source to study general strategies of communication risks are media reports on health-related problems. ProPublica published an article with the following title: **Most Drugs Aren't Tested on Pregnant Women. This Anti-nausea Cure Shows Why That's a Problem**.

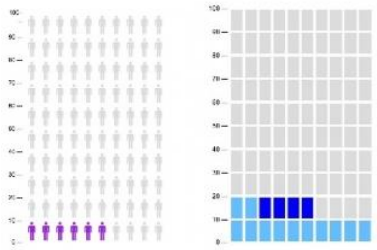
		In the article, they stated that *"One [study] found no difference in birth defects between the Zodran-exposed and unexposed babies; another found an elevated risk – up to twice as high – of hole-in-the-heart defects."* This is a perfect example of how focusing on relative risk can lead to over-estimation of risk. Therefore you should always use absolute risk in risk communication materials. In the next slide we will learn more about the difference. *(www.propublica.org)*
4	Text	**Absolute vs. relative risk** In a study from Huybrechts and team (2018) on ondansetron exposure during pregnancy and cardiac malformations and oral clefts in offspring. They reported the following relative and absolute risks: • **Relative**: ondansetron exposure in the first trimester is associated with a 26% increase in the risk of oral clefts • **Absolute**: among exposed pregnancies, the risk of oral clefts were 14.0 (95% CI, 11.6-16.5) per 10,000 vs. 11.1 (95% CI, 10.6-11.6) per 10,000 unexposed pregnancies. The statement of relative risk might make patients hesitant to use the medication, and the absolute numbers might be difficult to understand. This is where visual communication is useful. Take a look at the next slide for an example.
5	Text + afbeelding	**Visual representation** Please compare the following two visual graphs. How would you feel about the risk related to ondansetron exposure during pregnancy after being presented with these visual graphs? [Media 7.1 Image graph 1]

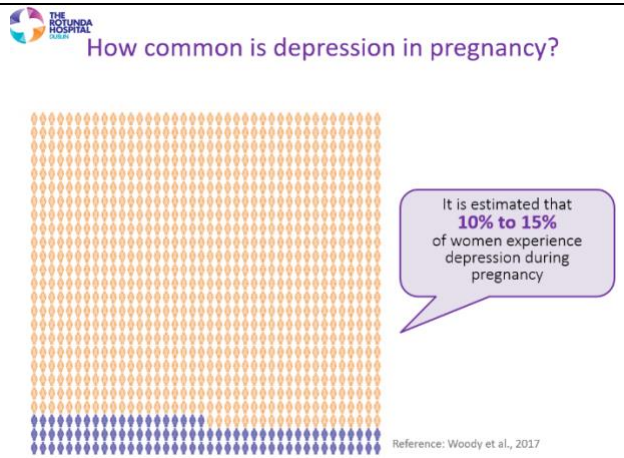
		 Risk of oral clefts- 11.4 (95% CI, 10.6-11.6) per 10 000 among unexposed pregnancies [Media 7.2 Image graph 2] *Risk of oral clefts- 14.0 (95% CI, 11.6-16.5) per 10 000 among ondansetron-exposed pregnancies* *(Huybrechts et al, 2018)*
6	Multiple choice question	It is time for some critical thinking. Answer the following questions using what you have learned so far. Also think about the visual representations you just studied. **Which of these principles should be applied when communicating about the risk of oral clefts in pregnancy?** Multiple answers are correct. a. Use numbers if you have them, not verbal expressions of risk b. Use visual risk communication to address health literacy/numeracy challenges

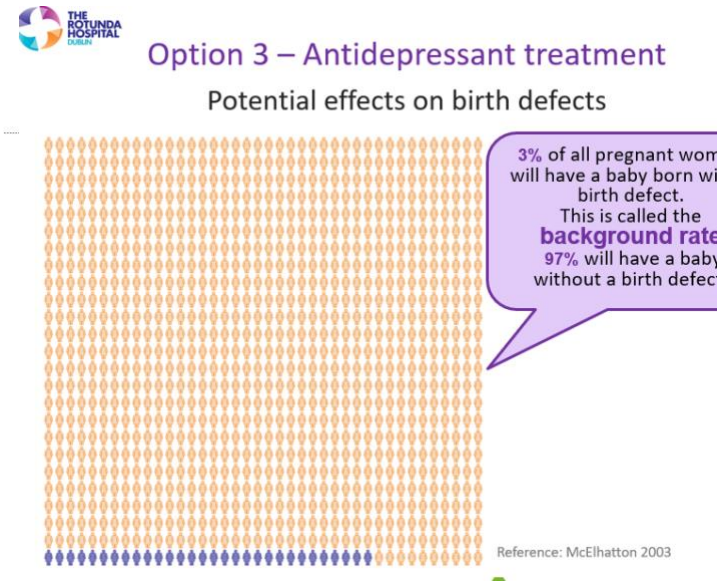
		c. Use positive framing and avoid negative framing as much as possible d. Provide absolute risks of adverse outcomes with and without exposure *Feedback correct:* Yes, well done! Based on our knowledge so far, we can conduct some general principles of risk communication in pregnancy. For example, it is wise to communicate background risks of adverse pregnancy outcomes using numbers and to provide absolute risks of adverse outcomes with and without exposure. You can share that e.g. 2-3 babies in 100 are born with a congenital anomaly and 20 in 100 pregnancies end in miscarriage. This paints a clear picture. *Feedback incorrect:* No, sorry. Let's take a look at the general principles of risk communication in pregnancy. For example, it is wise to communicate background risks of adverse pregnancy outcomes using numbers and to provide absolute risks of adverse outcomes with and without exposure. You can share that e.g. 2-3 babies in 100 are born with a congenital anomaly and 20 in 100 pregnancies end in miscarriage. This paints a clear picture.
7	Text	**General principles of risk communication in pregnancy** • Provide absolute risks of adverse outcomes with and without exposure • Use numbers if you have them, not verbal expressions of risk • Use positive and negative framing • Use visual risk communication to address health literacy/numeracy challenges • Communicate uncertainties or information gaps • Communicate available information on the risk of maternal disease
8	Multiple choice question	One of the general principles was to communicate uncertainties or information gaps, but this is not always easy to do. Luckily, there are a few communication strategies that you can use. **Which of the following options would be your go-to strategy for communicating uncertainty?** a. Communicating the best summary of the current scientific consensus b. Address conflicting findings c. Describing limits of knowledge and outcomes with less data e.g. long term neurodevelopmental outcomes

		Feedback correct: Yes, well done! To communicate uncertainties, there are several strategies you can try. For example, flag that there are information gaps. Describe limits of knowledge and outcomes with less data e.g. long term neurodevelopmental outcomes. Address conflicting findings. Communicate the best summary of the current scientific consensus. Also give appropriate caveats on available information, including the benefits and harms of doing nothing. *Feedback incorrect:* [There is no incorrect answer, feedback is always 'Feedback correct']
9	Text + afbeelding + pop-up	**Balanced communication** Information materials are an important tool in communication and should therefore always be balanced. Take a look at this information poster on COVID vaccination in pregnancy. **Do you think it is an effective way to present the information?** Click on the poster to learn more about our thoughts on this specific information poster.

		[Media 7.3 Covid information poster]  [Pop-up Covid information poster] **A good example** This information poster is balanced: it presents both the positives and the negatives. The magnitude of safety data is presented. The limitations of available data is acknowledged. Furthermore, the public health recommendations are clear and practical advice regardless of decision is outlined.
10	Text + afbeelding + pop-up	**Why icon arrays and pictographs are always a good idea** Extensive testing by CBSSM investigators of icon arrays and pictographs indicates that they accurately communicate risk and are easier to interpret than other risk communication materials. Click on the icon arrays below to discover their benefits.

		[Media 7.4 Icon arrays]  [Pop-up text Icon arrays] **Benefits of icon arrays and pictographs** Icon arrays inherently present absolute risk and balanced framing. Furthermore, they score well in empiric studies in terms of communicating gist and verbatim knowledge in low numeracy individuals *(Hawley, 2007)*. Therefore, icon arrays/pictographs should be further assessed as a risk communication tool in the context of medication use in pregnancy.
11	Text + afbeelding	**Communicating background information** Let's now take a look at an example of the importance of communicating background information on conditions. As you can see in the following figure, it is estimated that 10 to 15% of women experience depression during pregnancy. [Media 7.5 Icon array from the image below]

		 *(Woody et al., 2017)*
12	Multiple choice question	Now answer the following question. **Do you know how many of these women still experience depression when their child is 1 years old?** a. 25% b. 65% c. 95% *Feedback correct answer:* Yes, well done! Around a quarter of the women who experience depression during pregnancy still experience depression when their child is 1 years old. This leaves medical professionals with two options: watchful waiting or antidepressant treatment. *Feedback incorrect answer:* No, sorry. Around a quarter of the women who experience depression during pregnancy still experience depression when their child is 1 years old. This leaves medical professionals with two options: watchful waiting or antidepressant treatment.
13	Text	**Watchful waiting**

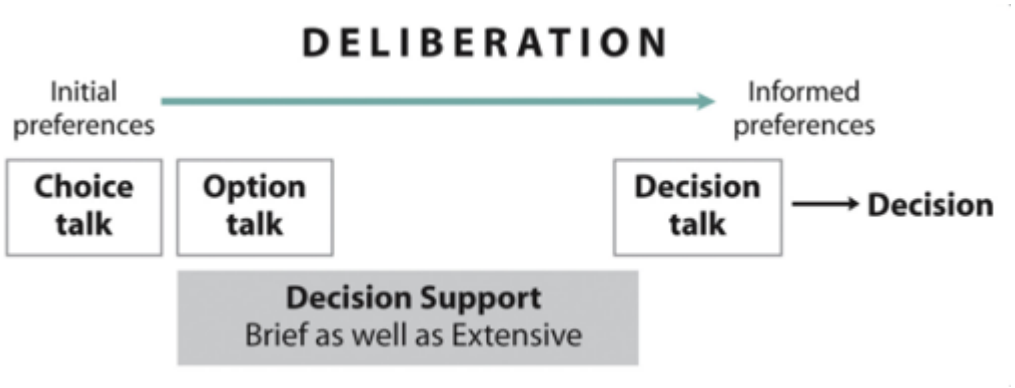
		If treatment is not started right away, it is important to address the risk of not treating the maternal condition. Depression can have an impact on women's experience of motherhood. It can strain their relationship with their baby and partner. They may not look after their baby or themselves as well as they would without the experience of depression. Furthermore, postnatal depression can affect the child's development and behavior even after the depression has ended. *(Goodman, 2014, Stein et al., 2014)*
14	Test + afbeelding + pop-up	**Antidepressant treatment** If treatment is started right away, it is important to address background information on the risk of adverse outcomes. Click on the icon array to discover the background rate. [Media 7.6 Icon array Antidepressant treatment]  [Pop-up text] **The background rate** 3% of all pregnant women using antidepressant treatment will have a baby born with a birth defect. There are for example

		concerns about cardiac septal defects. On the next page you can read more about this specific condition and the importance of background populations.
	Text	**Background risks and cardiac septal defects** Cardiac septal defects are problems with the hole in the septum in the heart closing during pregnancy. A Danish national registry study shows 0.57% of pregnant women who were exposed to SSRI did had a baby with a cardial septal defect. So 99.5% of the pregnant women of women who were exposed to the treatment did not have a baby with this adverse outcomes - that is the background population.
15	Text	**Can treatment be paused during pregnancy?** It is interesting to note that a study from Jimenez-Solem et al. (2012) found that 1.17% of pregnant women who were taking an SSRI antidepressant had a baby with a cardiac septal defect, 98.8% did not. However, only 1.36% of pregnant women who paused their treatment had a baby with a cardiac septal defect, 98.6% did not. This poses an interesting question: should treatment be paused when there is no increase in risk of cardiac septal defects?
16	Text	**Pausing treatment is not completely without risk** Patients receive antidepressants for a reason. If we stop treatment, what is the impact on the mother's well-being during pregnancy? On her engagement with natal care, on her dietary and lifestyle choices during pregnancy? On her experience of new motherhood and her ability to bond with her new child? There may also be very rare adverse outcomes like suicidality and maternal death as a result of severe mental health disorders. So pausing treatment is not without its risks. Therefore, it is even more important that we use all risk communication tools that are available to us.
17	Text	**Get familiar with your local Pregnancy Prevention Program** You should become familiar with your local Pregnancy Prevention Program for valproate and the kind of risk communication tools. For example, regulators are now mandating the use of risk communication tools to minimize the risk of exposure to teratogens.

		This is an example of an information card by the Valproate Pregnancy Prevention Progam, which is being rolled out by multiple regulators internationally. This image is from the Irish regulator. [Media 7.7 Image VPPP Irish regulator Front + Back]  
18	Text	**Conclusion** There are general principles and strategies that can help us increase knowledge and decrease anxiety and decision conflict for the patients. These include balanced framing and communicating in terms of absolute risk rather than relative risk. Furthermore, icon arrays and pictographs, as well as decision support tools, can help us to communicate clearly.

7.3 Shared decision making

1	Text + pop-up	**A shared decision making model** It is recommended to use a shared decision making model and also to address language and numeracy or health literacy barriers by using appropriate communication techniques. That way we can prioritize patient values and acknowledge autonomy to make decisions. The goal is to move from initial preferences to informed preferences. [Pop-up text] **Did you know?** Awareness of options leads to the development of initial preferences. The goal is to arrive at informed preferences based on 'what matters most to patients', predicated on an understanding of the most relevant benefits and harms.
2	Text + image + pop-ups	**Different stages** There are stages to this process of moving from the initial preferences to the informed preferences. These stages include choice, talk, option, talk and decision talk and then highlight the definition of each of these stages. Click on the image below to learn more about this process. [Pop-up text] **Delibiration** A process where patients become aware of choice, understand their options and have the time and support to consider 'what matters most to them': may require more than once clinical contact not necessarily face-to-face and may include the use of decision support and discussions with others. [Pop-up text] **Choice talk** Conveys awareness that a choice exists – initiated by either a patients or a clinician. This mat occur before the clinical encounter. [Pop-up text] **Option talk** Patients are informed about treatment options in more detail. [Pop-up text] **Decision talk** Patients are support to explore 'what matters most to them', having become informed.

		[Pop-up text] **Decision Support** Decision support as designed in two formats: 1) brief enough to be used by clinician and patient together and 2) more extensive designed to be used by patients either before or after clinical encounters (paper, web) [Media 7.8 Image Shared-decision making model]  *Based on Society for Maternal-Fetal Medicine. SMFM Consult Series #55: Counseling women at increased risk of maternal morbidity and mortality. Am J Obstet Gyneacol 2021.*

3	Text +	**Time for an example** On the next page you will find a video in which a health profession will apply the collaboration talk model for a clinical scenario. Please ask yourself the following questions while watching the video: ○ Health literacy- can the patient teach back the content discussed? ○ What is their level of understanding? ○ Did their decisional conflict decrease as a result of the conversation? ○ Do they ask appropriate questions and can they apply the information provided to their decision making process? ○ How can HCPs build trust and credibility, what reliable resources can be used?
4	Text + video	**A video for shared decision making** Click play to watch the video. [Media Video 7.9 Collaboration Talk Model] Video/images with audio required for worked example of the Collaboration Talk Model- Dr. Jen Donnelly & Patient
5	Open question	**Take a moment to reflect on your own experiences** Select a recent case or example from your practice or from anywhere in the course and write some reflective notes below on how you would use the collaborative talk model to support a patient who's concerned about taking medicines in pregnancy. [Answer box]
6	Text	**Recent research** The next part of this module will focus on recent research addressing risk communication and risk perception in practice in pregnancy. It's important as you work through these examples, to think about how these novel techniques could be applied to your practice. Let’s start with vaccines.
7	Text	**Skewed risk perceptions in pregnant women**

		One research by Bödeker et al (2015) found that there are skewed risk perceptions in pregnant women around the influenza vaccination. The findings included that the patient's perceived risk of disease was higher than the perceived risk of the vaccine for childhood vaccines, but not for influenza vaccine in pregnancy. People seem to apply different standards to decisions around vaccination in pregnancy.
8	Multiple choice question	There was one reason quoted most for not taking the influenza vaccination during pregnancy. **Which reason do you think that is?** a. Women had the perception that the vaccine was unnecessary b. Women were afraid it would counteract their current mediciation c. Women deemed the vaccine to be very dangerous *Feedback correct answer:* Yes, well done! The most frequent quoted reason for not taking a vaccine in pregnancy was the perception that it was unnecessary. There was no awareness of the recommendation from public health authorities that they should be vaccinated. *Feedback incorrect answer:* No, sorry. The most frequent quoted reason for not taking a vaccine in pregnancy was the perception that it was unnecessary. There was no awareness of the recommendation from public health authorities that they should be vaccinated.
9	Text	**What increases vaccine uptake?** Researchers found that uptake was independently associated with being aware that there was a public health recommendation that you should get the influenza vaccine during pregnancy. Uptake was furthermore associated with higher perceived attitude of their obstetrician and gynecologist towards vaccination in pregnancy. And finally, women in the study were aware of the increased risk of influenza infection during pregnancy to their health and the health of their baby.
10	Text	**Practical implications** What do these findings mean for practice? We need to address the risk of influenza in pregnancy for pregnant persons. We need to address the safety data that are available for vaccination during pregnancy. We need to highlight public health recommendations that advocate for vaccination in pregnancy. And we should also have health care professionals clearly endorsing vaccination. The health professionals attitude to

		vaccination in pregnancy is a very strong determinant of vaccine uptake among pregnant people. However, another study by Karafillakis et al (2021) implies that there is a problem in terms of getting health professionals consistently recommending vaccines during pregnancy.
11	Text + pop-up	**A recommendation problem** A study by Karafillakis et al (2021) shows that characteristics associated with vaccine uptake and future vaccine intentions included awareness about vaccines and their safety and efficacy, getting recommendation from their health professional, being pregnant and having a higher household income. All of these things were associated with more likeliness to decide positively on getting a vaccine. However, the strongest predictor of vaccine uptake was health care professional recommendation. Yet only a third of the participants received a recommendation for vaccination during pregnancy. So it's evident that there's a problem in terms of getting health professionals consistently recommending vaccines during pregnancy. <u>Did you know?</u> [Pop-up text] People were more positive about vaccines generally than about vaccines in pregnancy specifically. So, again, people seem to apply different standards to decisions around vaccination and pregnancy and medication use and pregnancy generally.
12	Text	**An important take-away** Awareness around the need for maternal vaccination during pregnancy shows that there's a missed opportunity to influence vaccine uptake in pregnancy. Perceptions of risk are complex, and health professionals need to listen and address the real concerns that patients have.
13	Text	**Antiepileptic drugs** The importance for communication also becomes clear in a study by Widnes et al (2012) focusing on pregnant women in need of antiepileptic drugs. The researchers found that all participants felt that the benefits of antiepileptic drugs clearly outweighed the teratogenic risks of antiseizure medications. Women were concerned about teratogenic effects as doses increased, with higher doses being more associated with adverse outcomes.
14	Multiple choice question	There are several factors that can influence risk perception among pregnant women. **Which of these factors do you think are influential?** Multiple answers can be correct.

		a. The age of the patient b. The time spent communicating up-to-date information around the medication safety c. The number of previous pregnancies *Feedback correct answer:* Yes, well done! In the study by Widnes et al (2012) health professional credibility was enhanced when the health professionals spent time communicating up-to-date information around the safety of antiseizure medications during pregnancy. Furthermore, patients found it difficult to understand some of the written materials around the safety of medicines in pregnancy emphasizing the importance of the time spent communicating. There was also a lower risk perception among those women who had previous pregnancy and who had received preconception counseling. *Feedback incorrect answer:* No, sorry. In the study by Widnes et al (2012) health professional credibility was enhanced when the health professionals spent time communicating up-to-date information around the safety of antiseizure medications during pregnancy. Furthermore, patients found it difficult to understand some of the written materials around the safety of medicines in pregnancy emphasizing the importance of the time spent communicating. There was also a lower risk perception among those women who had previous pregnancy and who had received preconception counseling.
15	Text	**Support and collaboration** It is important to explain in advance that the doses of antiepileptic drugs or antiseizure medications may change during and after pregnancy and address unnecessary concerns for women who haven't had a prior pregnancy or who need further support. Peer support can be very useful and offer to individually tailored medicines information, preferably by a neurologist, and also with sufficient time to address questions. Collaboration between neurology services and obstetric services could lead the development of effective risk communication and shared decision making materials that would support such consultations.
16	Text + pop-up	**Work to do** Although much work has been done in the field of risk communication, we are not there yet. In a study by Dierking et al (2017) the researchers found that about 40% of the population who were on Valproate were <u>not</u> aware of it being highly dangerous. <u>Did you know?</u> [Pop-up text] In the survey around 45% of pregnancy related knowledge questions were answered correctly. Women who had been counseled by their neurologists gave more correct answers. Yet there were still information needs among the survey participants, with 71% of women wanting further information on antiepileptic drugs and epilepsy in pregnancy.

17	Text	**Help solve the adherence problem** Ceulemans et al (2019) found that women are often reluctant to use medicines in pregnancy and tend to overestimate teratogenic risk of medications, especially women with lower literaxy and education levels. Maternal characteristics (incl. age, parity, smoking, lack of folate use, personality traits), beliefs and perceptions about medication exposure and specialist counselling about continuation of medicines in pregnancy were determinants of medication adherence. Only one study demonstrated high adherence rates among more than 80% of participants. Unfortunately, medicines won't work if patients don't take them. Luckily, you are a part of the solution.
18	Text+ pop-up	**Change the focus of pregnant women** Research also shows women who are expecting tend to focus on the health of the baby (Ralston et al, 2021). They are worried that vaccines might harm the baby. As a health care professional you can direct their focus to the mother's health. If the mother gets ill from a illness that could be prevented by a vaccine, it impacts the health of <u>both</u> the mother and the baby. <u>Did you know?</u> [Pop-up text] Women are driven to focus exclusively on risks to baby with minimal consideration of risks to self. This is because these risks are seen as separate as opposed to intertwined.
19	Text	**New directions in risk communication on medicines and pregnancy** There are two new directions in risk communication: vaccines and presumptive recommendations and motivational interviewing and patient decision aids on medicines and pregnancy. A study by Brewer et al (2020) shares a motivational interviewing technique that has been demonstrated to increase the uptake of HPV vaccine in teenagers. This is a person centered conversation to leverage intrinsic motivations to address ambivalence or hesitancy. Open ended questions are used focusing on affirmation, reflection, autonomy, support and permission. Seeking to inform these approaches may be appropriate for public health interventions such as vaccines, where it is clear recommendations on use but might not be suitable for other medicines for guidance on the use during pregnancy is not as clear cut.
20	Text	**Interesting research is being done** Finally, there is a pilot study in the UK assessing feasibility of RCT to evaluate the efficacy of an electronic patient decision aid on antidepressant use in pregnancy. Patients reported good satisfaction ratings. There was a small improvement in decisional conflict and the full scale randomised controlled trial is ongoing and will hopefully be published upon completion. *(Khalifeh et al, 2019)*

		And this leads us to the question: what other conditions could decision aids be useful for regarding the safe and effective use of medications in pregnancies?
21	Text	**Real Risk Tool** Try using the Real Risk tool to develop communication materials on the risk of valproate exposure in pregnancy and complete the exercise on the next page. You can find the tool here: https://realrisk.wintoncentre.uk/
22	Open question	**An exercise for you** Use a sample exposure e.g. valproate and a single outcome of interest e.g. congenital anomalies. Apply the odds ratio in the Real Risk tool and look at the impact assuming a background rate of 2.5% for congenital anomalies. **What results did you find?** [Open answer box]
23	Text	**Conclusion** Studies have shown that it is possible to reduce decisional conflict through improved patient knowledge and more accurate risk perception. We can build enhanced relationships with patients by engaging in shared decision making processes. Engaging patients in decisions that can improve their pregnancy outcomes is important as it makes them a powerful agent of change in their own health care. Reducing the risk of adverse perinatal outcomes and maternal deaths could be possible. There is still much work to do, but you are part of the solution.

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Additional resources

- Read: University of Cambridge – Winton Centre for Risk and Evidence Communication
- Read: Communicating potential harms and benefits: obstetrics and gynaecology version (https://moodle.wintoncentre.uk/)
- Read: Risk and Evidence Communication in Public Health (https://moodle.wintoncentre.uk/)
- Read: Teratology Primer- Teratology Communication: How Can I Provide Information in a Way That Supports Effective Decision Making? (https://www.birthdefectsresearch.org/primer/Teratology-Communications.asp)
- Real Risk Tool: https://realrisk.wintoncentre.uk/

Chapter 8: Reporting information

8.1 Introduction to the chapter

Slide #	Work form	Content
1	Text	**Welcome to the chapter 8: Reporting information** A 25 year old woman, pregnant for the first time, was examined by an Obstetrician. She is currently at 15 weeks' gestation. She was diagnosed with Multiple Sclerosis (MS) and has failed on several treatments. Her current treatment is fingolimod at a dose of 0.5 mg daily. She asks her doctor about the safety of this drug for the fetus. The doctor calls a Teratology Information Service to enquire. There is very little information about this drug during pregnancy. A literature search reveals limited and conflicting results.
2	Text	**What are the learning objectives?** In this chapter, you will learn: • **Why reporting is important** • What to report • How to report

		Good luck!

8.2 The importance of recording exposure to drugs, timing and pregnancy outcome

Slide #	Work form	Content
1	Text	According to the WHO, Pharmacovigilance (PV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine related problem. Information collected during the pre-marketing phase of the drug development process is incomplete with regard to adverse drug reactions. This is mainly because: • Patients enrolled in clinical trials are limited in number and are not representative of the public at large. • The conditions of use of medicines differ from those in clinical practice. • Duration of treatment is limited. • Information about rare but serious adverse reactions, chronic toxicity, and use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete. Therefore, post-marketing surveillance is important to permit detection of less common but sometimes very serious adverse drug reactions (ADRs).
		Objectives of Pharmacovigilance • To improve patient care and safety in relation to the use of medicines, and all medical and paramedical interventions. • To improve public health and safety in relation to the use of medicines. • To detect problems related to the use of medicines and communicate the findings in a timely manner, • To contribute to the assessment of benefit, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use. • To promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public.
		Why? The importance of reporting As explained in the previous chapters, we are limited in conducting RCTs and conducting research on medication exposures during pregnancy. Therefore, active reporting is required to assess drug safety in pregnancy. By reporting side effects, one can help to provide more information about medications, which will ultimately help to

		make them safer. Every report- prospective or retrospective is important. Information from professional sources will usually be more reliable and detailed. Individual reporting is not as impactful as accumulating reports. A high number of reports enables more rapid signal detection.
		What? • Information on the person exposed (such as age, gestational age, medical/surgical history); • the dose and the name of the medicine exposed (brand name as well as active ingredient) • the timing and duration of exposure during pregnancy • the batch number of the medicine; • the description of the outcome of exposure; • any other medicines being taken around the same time (including non-prescription medicines, herbal remedies and contraceptives) • any other health conditions that the person who experienced the side effect may have.
		By whom? • Pregnant women or family members • Healthcare providers (obstetrician, GP, midwife, pharmacist) • QPPV (Qualified Person Responsible for Pharmacovigilance)
		To Whom? • National authorities (regulators). For EU & EEA countries the list can be found here: https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states/national-competent-authorities-human • Pharmaceutical companies – to the Marketing Authorization Holder of the product • National Pharmacovigilance centres, who collect spontaneous reports of adverse drug reactions. Monitoring of the safety of drug use during pregnancy is a special topic of interest in PV and requires a distinct approach. To support other pharmacovigilance (PV) centres in the practice of PV specific to the

		use of drugs during pregnancy, a comprehensive Pregnancy PV toolkit has been developed by the Netherlands Pharmacovigilance Centre in Lareb. • A national TIS- Teratology Information Service, the list of services available in different countries could be found here: https://www.entis-org.eu/centers • The IMI ConcePTION project is developing an app that will allow women to report the medicines they use, and provide pregnancy information: using a simple and straightforward interface. The first version of the app will be launched in the UK, in collaboration with the UK Medicines and Healthcare products Regulatory Agency, MHRA. Versions for other European languages and countries will follow. More information available: https://www.imi-conception.eu/news-details/?news_id=957

8.3 Existing registries

Slide #	Work form	Content
1	Text	It is well known that drug-labelling documents, such as Summaries of Product Characteristics (SPCs) and Patient Information Leaflets (PILs), contain limited information about safety in pregnant and breastfeeding women exposed to medicines. Pregnant women are typically not enrolled in clinical trials to assess the safety and efficacy of new medicinal products. There is a need to identify effects on pregnant women and their children post-licensure. The EMA published the Good Pharmacovigilance Practices guide that advocates for adequate data collection and data assessment through existing pregnancy exposure registries/databases, product-specific registries, or even a hybrid approach to enable patients and prescribers to have relevant information to make informed decisions about using medicines during pregnancy or breastfeeding. There are several ways in which information can be collected: 1. Registry 2. Database 3. TIS- Teratology Information Service

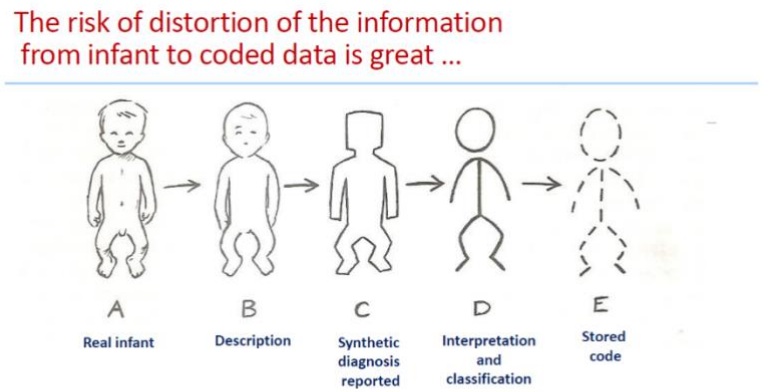
		Registry- established by pharmaceutical companies with set inclusion criteria. Therefore, in this way there is a bias in patients' recruitment. Registries may miss important information and there is a limitation to identify the reporter. Data quality, enrollment size/retention, selection bias, lack of appropriate comparator group (e.g., a valid unexposed comparator cohort) and missing information may be among the challenges associated with these observational studies. Database- established by various entities including national health services or health insurance/health maintenance organizations. Collection of relevant information on medication exposures and pregnancy outcomes. One of its limitations is that conducting multiple comparisons on so much information may result in finding false associations. Adherence with prescribed medications is also uncertain. Outcome information may be limited to observations in the immediate peripartum period in many cases. The increasing availability of electronic health records (EHR) has boosted interest in assessing whether these can be used to replace or complement existing systems given their ability to overcome some registry design limitations. Spontaneous reporting databases from Pharmacovigilance centres contain ADRs, reported by health professionals or consumers. The pregnancy-specific information needed is provided by applying a special reporting form, or by asking pregnancy-related follow-up questions. Usually, pregnancy exposure needs to be reported to the national authorities only if there is a known or suspected adverse pregnancy outcome to the mother or the fetus. Additionally, there is a pregnancy specific section in the PBRER (Periodic Benefit-Risk Evaluation Report) that presents overall documented exposure (including spontaneous reports, literature reports and clinical trials reports) and all the known outcomes and provides the assessment of presented information. TIS- several ways of consulting in the TIS exist: by phone or face to face consultation, through written consultation or via chat/messaging, and by providing a written safety information summary on specific topics. It is not only a system for consulting regarding drug exposure during pregnancy, but also recording information and safety monitoring, e.g. follow-up after expected date of delivery. Moreover, these services undertake research to improve the use of medicines in pregnancy. Benefits of TIS monitoring: • Detailed information on exposure and outcomes • Specifically designed for pregnancy PV • Speed • ENTIS expertise Prenatal exposure to drugs with known teratogenic risks is a significant concern for regulatory agencies globally. Risk management strategies such as pregnancy prevention programmes are utilized by national regulatory authorities.

		Nevertheless fetuses continue to be exposed to definite or potential teratogenic medications during pregnancy. Within the ConcePTION project – a data sources catalogue was prepared by WP1: “Spreadsheet containing all additional data sources for the ConcePTION Data Source Catalogue (D1.1)”. https://zenodo.org/record/5824739
		Reports of infant malformations after maternal drug use may act as signals for further investigations, but coincidental associations between rare drugs and rare congenital malformations will occur by chance; it is impossible to evaluate the probability for the association to be random. There are formal ways in which such associations can be reported to central agencies, where the reports can be evaluated and stored. If the same rare drug appears repeatedly with the same rare malformation, the chances for a causal association increase. The ‘alert clinician’ is most effective in situations where a sudden increase of a previously rare malformation is noticed. One of the first identified clear-cut human teratogens was rubella. This was the result of clinical observation, e.g. the ‘alert clinician’. **Rubella** In 1941, Norman Gregg, an ophthalmologist from Australia, reported on 78 newborns who were born with congenital cataract, after their mother had rubella during pregnancy. [NM Gregg. Congenital cataract following German measles in the mother. TRANSACTIONS OF THE OPHTHALMOLOGICAL SOCIETY OF AUSTRALIA. 1941; 3:35-46.] In the introduction of his paper, he have thanked his colleagues for their contribution. "I am indebted to many of my colleagues in New South Wales, Victoria and Queensland for particulars of very many of the cases reviewed. These, for the most part, conform very closely to the general features noted in my own series of cases on which the following description is based. The total number of cases included in this review is seventy-eight. My own cases total thirteen, and in addition I have seen seven others included in my colleagues' lists." Gregg hypothesized that measles could alter fetuses as they developed, but he encountered initial opposition to that claim. Doctors characterized rubella as a mild infection consisting of a slight cough, fever, and rash that disappeared within two weeks. Few accepted that the mild rubella virus could be connected to severe birth defects, as many doctors claimed that congenital defects could only be inherited. Gregg's findings received mixed reviews from his peers in scientific and medical fields. In Australia, The National Health and Research Council of Australia arranged for Charles Swan, a medical researcher in South Australia, to corroborate Gregg's conclusions. Swan studied forty-nine cases of women who contracted the German measles during pregnancy. Many in the US accepted Gregg's findings, while many in the UK were more cautious, even after Swan's corroboration. A 1944 Lancet editorial stated that Gregg's conclusions were weak, while a 1946 British Medical Journal editorial accepted Gregg's conclusion as possible. Medical professionals later classified German measles as teratogenic. Vaccination subsequently mitigated the teratogenic effect of German measles in the developed world. **Thalidomide**

		First synthesized in 1953 by "Chemie Grünenthal" in West Germany. It was synthesized as part of research to find methods for the production of antibiotics from peptides. Studies with the drug in mice and rats demonstrated low acute toxicity. In early human studies thalidomide was reported to aid restful sleep. It was first marketed in 1957 in West Germany, marketed over the counter as part of a cough and cold remedy. Over the following years it was prescribed for a variety of indications including anxiety, insomnia, and "Morning sickness". Reports of an association between long term thalidomide exposure and peripheral neuritis began to emerge in 1960. In December 1961, William McBride- an Australian obstetrician published a letter to the editor in The Lancet entitled- "Thalidomide and congenital abnormalities" (Lancet 1961;ii:1358). In this letter, McBride reported an increase in the number of cases of congenital abnormalities associated with use of thalidomide. Widukind Lenz, a German paediatrician also published on the association between the use of thalidomide during pregnancy and congenital malformations [Lentz W, Child malformations after drug use during pregnancy? Dtsch Med Wochenschr 1961; 86:2555-2556.(In German)].
		Valproate (VPA) during pregnancy and the delay in detecting neurodevelopmental impairment Although valproate was already suspected as a cause of congenital anomalies in the late 1960s, it was not proven until the early 1980s, when the drug was verified as a teratogen in humans by Elizabeth Robert. Robert interviewed women who had infants with spina bifida, noting a high rate of valproic acid use. This finding led to the other teratogenic properties of valproate. This is an example of finding signal through clinical observations made over years and not from established epidemiological information. Years later, although it was known that valproate has teratogenic properties, there was again a significant delay in the detecting of the neurodevelopmental impairment from valproate. It took almost 30 years for the dose–response associations between in utero exposure to valproic acid and altered neurodevelopment trajectories to become apparent and for scientific consensus to develop.
		Case report or case series: Spontaneous reporting is an important tool to generate signals on new or rare ADRs, published as a case report or case-series. The collection of spontaneous reports by (collaborating) Pharmacovigilance centres enables early drug safety monitoring. Retrospective data-collection and under-reporting are important limitations to keep in mind with this system. **The case-control study:** In the case-control or case-referent approach, the exposure rate among cases (infants with a congenital malformation) is compared with that among controls- usually non-malformed infants. First, it starts with the identification of cases and controls and then continues with a study of many different exposures, such as different drugs used by the mothers. Cases can be ascertained in different ways: Cases can be identified at treating hospitals. Cases can be identified from existing registers of congenital malformations. In some congenital malformation registers,

		exposure information is obtained by interviews of the mothers soon after the birth of infants with congenital malformations and selected controls, such as next non-malformed newborn of the same sex as the affected infant. Sometimes, collaboration between different registers can increase the statistical power of the studies. An example for that are the collaborative studies of ENTIS on specific medications. **The cohort study:** It starts with a group of exposed individuals and studies the outcomes. Exposure is defined and different outcomes can be studied, such as different malformations or other birth defects. ENTIS and OTIS are collaborating on cohort studies, using the registers in the Teratogen Information Services. The Pharmaceutical industry: Prospective cohort data have been collected by the pharmaceutical industry, usually as a post-marketing surveillance of new drugs. These pregnancy registries are based on spontaneous reports of drug exposure, reported before the outcome of the pregnancy is known. **Studies of total populations:** Greater statistical power can be obtained if no sampling had to be made, but all infants in a defined population could be studied. This could be done using different methods: *Special research projects*- for example, The Collaborative Perinatal Project published by Heinonen OP et al. (The Collaborative Perinatal Project, Heinonen OP et al. Birth Defects and Drugs In Pregnancy. Publishing Science Group. Inc., Littleton, Mass. 1977). This is one of the largest studies on the possible association between maternal drug use and congenital malformations. It was started in 1958 as part of The Collaborative Perinatal Project, which collected information from 12 American hospitals. Data collection ended in 1965 and a full report of the study was published in 1977. The study described drug use and pregnancy outcome in more than 50,000 pregnancies. Exposure data were obtained by interview or questionnaire data obtained during pregnancy and were prospective. Follow-up was performed in cases where infant was born with anomaly. *Use of data computerized for other purposes*- Studies in North America and Europe have used registers from various health insurance programs, linking data on drug prescription and data on delivery outcome (Rosa F. Database in the assessment of the effects of drugs during pregnancy. J Allergy Clin Immunol 1999;103:S360-361). *Use of medical birth registers*- Some registers collect exposure data in connection with deliveries. They use data independent of exposure during pregnancy. For example, in the Swedish Medical Birth Register (National Board of Health and Welfare 2003), data on drug use are recorded at the first visit of the pregnant woman to the antenatal clinic when nothing is yet known about outcome. The data set continues to grow as long as the register is active. More on epidemiological studies in Chapter 6.
		<u>The Data</u> The illustration reflects the available data from each of the above-mentioned information sources where "A" represents a real infant, whereas "E" reflects the outcome from data storage.

We can see the decrease in the level of details and the magnitude of the data available.
The more accurate and extensive information we have, the clearer and more reliable details of the case will be.



Reports of infant malformations after maternal drug use may act as signals for further investigations, but it must be realized that coincidences between rare drugs and rare congenital malformations will occur by chance; therefore, epidemiological studies with advanced and robust methodology are need.

Examples of evolving pharmacoepidemiological research on medicines in pregnancy:

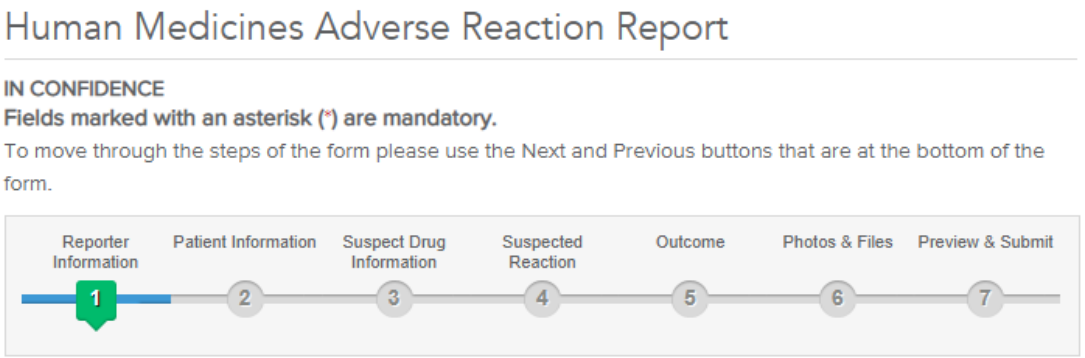
SSRIs & Cardiac defects
In 2005, the FDA issued a warning about the occurrence of cardiac defects in babies exposed to the SSRI paroxetine during

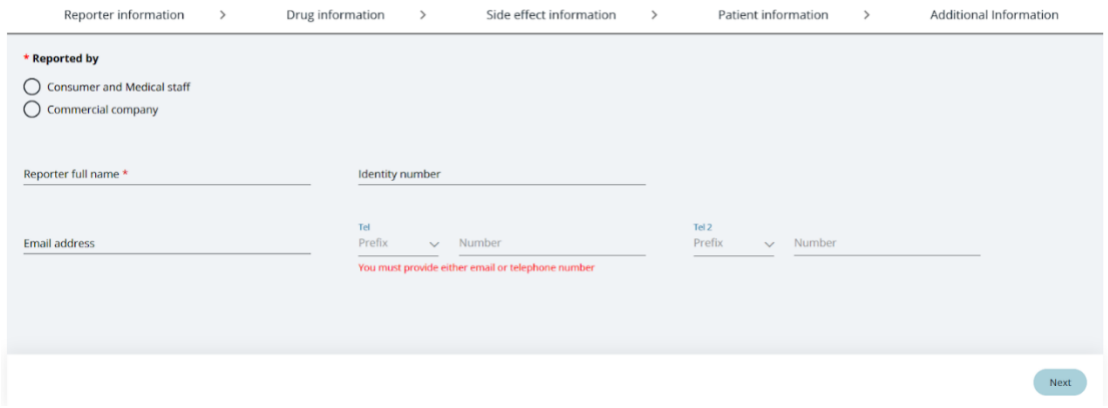
		pregnancy. The publication was supported by early results of two pharmacoepidemiologic studies. Later, in 2010, the EMA issued a similar warning for fluoxetine. More recently, several studies have demonstrated that there is no association between the use of SSRIs during pregnancy and cardiac defects in the fetus. The possible association between paroxetine and fluoxetine and cardiac septal defects was mainly observed in older studies which may have been affected by residual confounding. Two sample studies include Jimenez-Solem et al (2012) and Huybrechts et al (2014). Both of these studies compared the risk of major cardiac defects in babies born to women who used antidepressants in pregnancy compared to those who were not exposed. In contrast to earlier studies, the authors used comparison groups of women with depression that did not take SSRIs during pregnancy. Statistical analyses were also used to adjust for confounding by indication. In both studies the association between SSRI exposure and cardiac defects disappeared with appropriate adjustment for confounding by indication. Cross reference to Risk Communication chapter? Visual risk communication slides
		SSRIs & ASD Several studies have demonstrated the association between SSRIs exposure during pregnancy and the onset of ADHD and ASD in children. In 2015, Clements et al found that antidepressant exposure prior to and during pregnancy was associated with higher risk for ASD and ADHD. With adjustment for maternal major depression and sociodemographic characteristics the association with ASD disappeared. Antidepressant exposure during but not prior to pregnancy was associated with ADHD risk, even after adjustment for maternal depression. A more recent study by Sujan et al proposed that earlier studies may not have adequately accounted for confounding. In analyses that compared siblings while adjusting for pregnancy, maternal, and paternal traits, first-trimester antidepressant exposure was not associated with ASD or ADHD. This is demonstrated in the figure.
		A systematic review examined the association between the use of antidepressants and neurodevelopmental outcomes in children. A total of 15 studies evaluated ASD, included more than 40,000 cases and above 3,500,000 unexposed children and 7 studies evaluated ADHD (involving more than 2,700,000 unexposed children and about 52,000 cases). Studies evaluating the risk of ASD and ADHD with antidepressant exposure were heterogeneous in their design and had a high risk of residual confounding. Alternative comparisons and sibling designs may aid the interpretation of causality, including understanding potential limitations of undertaking meta-analyses with such data.

8.4 Data interpretation

Slide #	Work form	Content
1	Text	xx

8.5 How to report drug exposure during pregnancy or lactation

Slide #	Work form	Content
1	Text	The physician was asked to report the exposure to the Health insurance registry / the national registry or the national Pharmacovigilance Centre. Simultaneously, the Teratology Information Service contacts the Pharmacovigilance department of the marketing authorization holder (MAH) of the medication to seek additional information. The MAH will report the exposure to the national health authorities, eventually will appear in the WHO database – Vigibase. After the expected delivery date, the TIS will contact the woman/HCP in order to obtain outcome data. This data collection will be later incorporated in the ENTIS study on fingolimod safety, helping for future similar cases consultations. **Example on human medicines adverse reaction report** HPRA  Pharmacovigilance

		Israeli Ministry of Health 

Chapter 9: Course summary

Slide #	Work form	Content
1	Text	**Time for a recap** In this chapter we summarize the most important findings of the course in preparation for the test. If you feel the need to catch-up on any of the topics, please refer back to the corresponding chapter. We will go over the chapters one by one.
2	Text	**Chapter 1** Chapter 1 introduced the historical context of medication use in pregnancy. You learned about definitions of teratology and how it developed as a science. The lessons of previous tragedies with medications such as thalidomide, diethylstilbestrol or valproic acid were explored in detail. Interactive timelines allowed you to explore how the field of teratology developed and how specific medications such as valproate were identified as teratogens.
3	Text	**Chapter 1** The consequences for governments and regulators were explored as well as the impact on individuals and healthcare professionals. Reviews of maternal deaths were also described along with patient stories describing tragic maternal deaths that occurred where essential medications were not used during pregnancy. Additional reading materials allowed you to explore the involvement of individual clinicians such as Frances Kelsey in the thalidomide tragedy and also to read about the personal experiences of thalidomide survivors and their families.
4	Text	**Chapter 2** In this chapter you have become familiar with the principles of teratology. You now know that the basic background risk of a major malformation at birth is 2-4%. For most birth defects the cause is unknown. A small proportion (5-10%) of major malformations are caused by exposure to a teratogen (like maternal medication) during pregnancy. In addition to the risk of birth defects, teratogenic substances can also cause other effects. You are able to summarize different teratogenic effects. You have been introduced to the six basic principles of teratology by Wilson. With these basic principles Wilson tries to explain the development of birth defects and to provide biologic plausibility for a teratogenic effect.
5	Text	**Chapter 2** In this chapter you have learned more about his first, fourth and third principle. **First principle**: Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with environmental factors. High variability between species causes differences in susceptibility to teratogens.

		Some drugs are shown to be teratogenic in animals but not in humans, and vice versa. Genetic differences between humans explains why only a (small) proportion of foetuses will develop a malformation. **Third principle**: Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis). For most teratogens this mechanism is unknown. **Fourth principle**: The final manifestations of abnormal development are death, malformation, growth retardation, and functional disorder.
6	Text	**Chapter 3** In this chapter you have learned more about the second, fifth and sixth principles of teratology. **Second principle**: The susceptibility to a teratogenic agents varies with the gestational period at the time of exposure. Depending on the gestational period, the effect of a teratogen will be different. Exposure in the first trimester can lead to a major malformation while exposure in the second or third trimester can give growth retardation or functional- and pharmacological effects. **Fifth principle**: In order to affect the development of the embryo or fetus, the medication must be able to enter the maternal bloodstream and cross the placenta. Route of administration, pharmacokinetics of the drug in the pregnant woman and physical and chemical properties of the drug play a major role in the fetal exposure. Small drugs can cross the placenta through passive diffusion. Some drugs can transfer through an active transport mechanism. **Sixth principle:** Manifestations of deviant development increase in degree as dosage increases from the no-effect to the totally lethal level. Chronic exposure can also lead to increased fetal risk. When dealing with a question about medication during pregnancy, you know what the main considerations are: 1. Severity of illness. Is it necessary to treat the disease? 2. What is the gestational age? Exposure in the first trimester may give an increased risk for structural malformations. Exposure in the second and third trimester may give other effects such as functional- and pharmacological effects. 3. What is the degree of systemic exposure? Consider the route of administration and pharmacokinetics of the drug. 4. Is transfer across the placenta possible? The physical and chemical properties such as the molecular weight and the plasma protein binding of the drug are important. **5.** What dosage is given and for how long? Use the lowest effective dose of the drug and treat for the shortest duration possible. Do not treat when not necessary **6.** How much -reliable- information is available on the use of the drug during pregnancy
7	Text	**Chapter 4**

		In this chapter we learned about the factors that influence the determination of the safety of the medication use during pregnancy. We overviewed some physiological changes during pregnancy which might influence the pharmacokinetics and pharmacodynamics of some drugs and their effects. The changes exist in a variety of different systems of the body such as the digestive system, heart and blood vessels, kidney and urine and more.
8	Text	**Chapter 4** Moreover, we evaluated the risk and benefits of treatment during pregnancy. A potential risk to the mother and the fetus can also be from an untreated maternal condition and not only by administration of a "dangerous" medication. Also, we reviewed a number of other parameters that influence the decision to administer the drug during pregnancy, such as ethical considerations and the need for TDM.
9	Text	**Chapter 5** In this chapter you find an overview of the principles of therapeutics during lactation. The lack of knowledge on medications during breastfeeding among health care professionals may result in women who need to take medication to not breastfeed their infant. It regularly occurs even if the used medication will not be harmful for the infant. Most medications can be used by breastfeeding women. In most cases, the medication amount transferred to the breast milk is too small to exert any effects on the infant. Often, the combination of available information and clinical experience is sufficient to provide a specific advice.
10	Text	**Chapter 6** In this chapter you find an overview of possible sources that offer information on the safety of a wide range of exposures during pregnancy and breastfeeding. It is often not feasible to read all the scientific studies and it can be challenging to stay up-to-date. Luckily, some information sources offer overviews of the most important scientific literature on the topic.
11	Text	**Chapter 6** Research in the field of teratology is complex and has many limitations. It often takes many years to obtain sufficient data to make a statement about the potential risks of a drug to pregnancy. This chapter explained the basic principles of epidemiological research in relation to teratology. In teratology, usually observational studies are performed, but occasionally RCTs may be used. All studies are valuable in teratology, if done correctly. In this chapter you have become familiar with the different study designs used in teratology. You have learned their strengths and limitations. This will help you to better understand and interpret the scientific literature. The most important study designs in teratology are:

		• Case reports/ Case series • Case-control study • Cohort study • Randomized controlled trial (RCT) • Systematic review • Meta-analyses In every study there is a risk of bias and confounding. You should keep this in mind when interpreting scientific studies.
12	Text	**Chapter 7** In this chapter you learned about general principles of risk communication in healthcare. These principles were then expanded with an outline of the challenges unique to risk communication in the context of medicines in pregnancy/breastfeeding. Principles of risk communication specific to pregnancy were then addressed. These can be translated into approaches to risk communication and shared decision making that help overcome challenges unique to this setting.
13	Text	**Chapter 7** In this chapter you also worked through practical examples of shared decision making using novel techniques such as icon arrays/pictographs and patient decision aids. These communication materials and techniques empower you to communicate risk effectively and facilitate shared decision making. A practical worked example of using a shared decision making model was then used to help you to apply your learning to a relevant clinical scenario. Practicing using this model with potential scenarios that may arise in your clinical work will help to consolidate this learning. Finally you saw examples of studies assessing risk perception in pregnancy, risk communication and shared decision making. Now you can describe novel decision aids that aim to reduce decisional conflict when deciding on treatment options during pregnancy and breastfeeding. You should now be able to advocate for the safe and effective use of medicines in pregnancy and ensure that essential medicines are used where indicated.
14	Text	**Chapter 8** In this chapter, you understand what is Pharmacovigilance and the importance of reporting exposure to medication during pregnancy and breastfeeding. First, it is important to record exposure to drugs, timing and pregnancy outcome, reason of exposure. These data are important to record for research.
15	Text	**Chapter 8** You also found an overview of possible ways to report the exposure and the description of the registries that exist (Industry, local Pregnancy registries, population registries), their benefits and limitations.

		Data interpretation - reports of infant malformations after maternal drug use may act as signals for further investigations, but it must be realized that coincidences between rare drugs and rare congenital malformations will occur by chance. Discussion based on rubella, thalidomide and valproate examples. Here we present some current controversies in teratology that started with reported association, but in the better study setups these association were refuted, such as SSRIs' and cardiac defects and SSRIs' and ASD/ADHD.
16	Text	**Ready for the test?** You have now completed all the chapters. In the next module you will can test your understanding. You will need to get a score of 70% or higher to pass the course and receive your certificate. Don't worry if you don't pass the first time, you can take the exam a maximum of three times. Good luck!

Chapter 10: Test your knowledge

Slide #	Work form	Content
1	Text	**Welcome to the final test** On the next slides you will find 25 multiple choice questions. The questions are based on what you have learned in the previous chapters. You need to answer at least 17 questions correctly to pass the course and receive your certificate. Thisf corresponds to a score of 70% or higher. Don't worry if you don't pass the first time, you can take the exam a maximum of three times. Good luck!
CHAPTER 2		
2	Multiple choice question	Question 1 **What is the definition of a minor malformation:** a. A minor malformation is not life-threatening but can cause lifelong disability b. A minor malformation is not life-threatening but can have limited social or cosmetic consequences for the affected individual

		c. A minor malformation poses no significant health problem in the neonatal period and tends to have limited social or cosmetic consequences for the affected individual d. A minor malformation poses no significant health problem in the neonatal period but tends to have social or cosmetic consequences for the affected individual **Feedback correct:** Well done! The definition of a minor malformation is poses no significant health problem in the neonatal period and tends to have limited social or cosmetic consequences for the affected individual **Feedback incorrect:** No, sorry! The definition of a minor malformation is poses no significant health problem in the neonatal period and tends to have limited social or cosmetic consequences for the affected individual
3	Multiple choice question	Question 2 **An otherwise healthy child is born with camptodactyly, which is a rare condition in which one or more fingers are permanently bent. How would you classify this?** a. Major malformation **b. Minor malformation** c. Camptodactyly is not a congenital malformation **Feedback correct:** Well done! Camptodactyly is considered to be a minor malformation. The condition does not pose a significant health risk to the neonate, surgery is not needed and it has limited consequences. **Feedback incorrect:** No, sorry! Remember the definitions of major and minor malformations. Major malformations can be life-threatening, need surgical intervention or can cause lifelong disability. Minor malformations pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences for the affected individual.
4	Multiple choice question	Question 3 **Fill in the blank in the following statement:** The teratogenic effect of medication should be expressed as …….: a. The absolute risk b. The risk of the medication compared to another medication

		c. An increase of the background risk **Feedback correct:** Well done! In every pregnancy there is a basic risk of having a child with a congenital malformation. Therefore the effect of a teratogen should be expressed as an increase of the basic risk. **Feedback incorrect:** No, sorry! Remember that in every pregnancy there is a background risk of having a child with a congenital malformation, even when there is no exposure to a teratogen.
5	Multiple choice question	Question 4 **Which of these statements is correct?** a. A teratogen has a specific mechanism of action b. The effect of a teratogen is usually the result of a multifactorial process c. Environmental factors can be an important factor in teratogenicity **d. All statements are correct** **Feedback correct:** Well done! All statements are true. Teratogens have a specific mechanism of action, although the specific mechanism is unknown for many of them. It is often a multifactorial process. Effects can result from interactions between environmental and genetic factors. **Feedback incorrect:** No, sorry! All statements are true. Teratogens have a specific mechanism of action, although the specific mechanism is unknown for many of them. It is often a multifactorial process. Effects can result from interactions between environmental and genetic factors.
6	Multiple choice question	Question 5 **Which drug is known for its embryopathy?** a. Paracetamol **b. Isotretinoin** c. Gabapentin d. Omeprazole **Feedback correct:**

		Well done! An embryopathy is a recognizable and distinct pattern of human malformations (with or without associated growth disorders or fetal death) and functional defects. Isotretinoin can cause malformations of the ear, central nervous system, heart and skeleton, miscarriage and developmental defects. **Feedback incorrect:** No, sorry! This drug causes no embryopathy. Remember that an embryopathy is a recognizable and distinct pattern of human malformations (with or without associated growth disorders or fetal death) and functional defects. Isotretinoin can cause malformations of the ear, central nervous system, heart and skeleton, miscarriage and developmental defects.
CHAPTER 3		
7	Multiple choice question	Question 6 Statement 1: drug use in the two weeks after conception is more risky for developing birth defects than drug use in the second month of pregnancy. Statement 2: the predisposition of the central nervous system is sensitive to harmful external influences for a long time. **Select which of these statements are true?** a. Only statement 1 is true **b. Only statement 2 is true** c. Both statements are true d. Both statements are not true **Feedback correct:** Well done! Statement 2 is true. Statement 1 is not true. The first two weeks after conception is also referred to as the all or none period. At this stage, the cells of the embryo can differentiate into any tissue. Loss or damage to these cells will not result in a congenital birth defect. **Feedback incorrect:** No, sorry! Statement 2 is true. Statement 1 is not true. The first two weeks after conception is also referred to as the all or none period. At this stage, the cells of the embryo can differentiate into any tissue. Loss or damage to these cells will not result in a congenital birth defect.
8	Multiple choice question	Question 7 **Which medicines do NOT/are least likely to cross the placenta?**

		a. Lipophilic drugs with low protein binding b. Lipophilic drugs with high protein binding c. Hydrophilic drugs with low protein binding d. **Hydrophilic drugs with high protein binding** **Feedback correct:** Well done! Low protein binding means that the free fraction, able to cross the placenta, is high. **Feedback incorrect:** No, sorry! Low protein binding means that the free fraction, able to cross the placenta, is high.
9	Multiple choice question	Question 8 **Which substance is known to have a threshold value for the development of abnormalities?** a. Paracetamol b. Lamotrigine **c. Valproic Acid** d. Nifedipine **Feedback correct:** Well done! Various pregnancy register studies have shown the dose- dependent teratogenic risk of valproic acid with rates of major congenital malformations (MCMs). Daily doses of valproic acid greater than 1000 mg or 1100 mg of sodium valproate increased the prevalence of congenital malformations compared to lower doses. **Feedback incorrect:** No, sorry! The answer is actually valproic acid. Various pregnancy register studies have shown the dose- dependent teratogenic risk of valproic acid with rates of major congenital malformations (MCMs). Daily doses of valproic acid greater than 1000 mg or 1100 mg of sodium valproate increased the prevalence of congenital malformations compared to lower doses.
10	Multiple choice question	Question 9 In the event of an imminent preterm birth, the mother is treated with a corticosteroid to stimulate lung maturation in the fetus. **If you could choose from one of the following two drugs, prednisone or dexamethasone, which would you choose?**

		a. Prednisone **b. Dexamethasone** **Feedback correct:** Well done! Dexamethasone is not metabolized in the placenta, so it can easily cross the placenta and reach the child unimpeded. Prednisone is largely broken down by the placenta, so that little can reach the child. In order to have an effect, very high doses would have to be taken. **Feedback incorrect:** No, sorry! Dexamethasone is not metabolized in the placenta, so it can easily cross the placenta and reach the child unimpeded. Prednisone is largely broken down by the placenta, so that little can reach the child. In order to have an effect, very high doses would have to be taken.
11	Multiple choice question	Question 10 **When used up to which period does Lithium give a small increased risk of an Ebstein anomaly (a heart defect)?** a. When used until conception b. When used up to 8 weeks of pregnancy c. When used from 12 weeks onwards **Feedback correct:** Well done! Exposure in the first trimester can lead to birth defects. **Feedback incorrect:** No, sorry! Think about in which period does the development of tissues and organs take place. In fact there is only increased risk when Lithium is used up to 8 weeks of pregnancy.
CHAPTER 4		
12	Multiple choice question	Question 11 **Which physiological changes related to pregnancy may alter drugs effects?** a. Hepatic, renal, GI, CV b. Respiratory, hormonal c. Weight gain **d. All of the above**

		Feedback correct: Well done! All of the above answers are correct. **Feedback incorrect:** No, sorry! All of the above are correct.
13	Multiple choice question	Question 12 **Methadone metabolism changes during pregnancy mainly due to…?** a. Protein binding b. Liver metabolism c. Placental metabolism **d. All of the above** **Feedback correct:** Well done! All of the above answers are correct. **Feedback incorrect:** No, sorry! All of the above are correct.
14	Multiple choice question	Question 13 **What is the goal of a PPP?** a. To avoid unwanted pregnancies b. To avoid the birth of twins **c. To minimize the risk of exposure to teratogenic medications during pregnancy** d. To prevent congenital anomalies **Feedback correct:** Well done! The goal of a PPP To minimize the risk of exposure to teratogenic medications during pregnancy to prevent congenital anomalies. **Feedback incorrect:** The goal of a PPP To minimize the risk of exposure to teratogenic medications during pregnancy to prevent congenital anomalies.
15	Multiple choice	Question 14

	question	**When assessing the safe use of a medication during pregnancy, the only needed information is the medication name. Is this statement correct or incorrect?** a. Correct **b. Incorrect** **Feedback correct:** Well done! This statement is indeed not true. Much more information is needed to assess the safe use of a medication during pregnancy. **Feedback incorrect:** No, sorry! This statement is not true. This statement is indeed not true. Much more information is needed to assess the safe use of a medication during pregnancy.
16	Multiple choice question	Question 15 **Which are the stakeholders concerned by ethical issues?** a. Pregnant women b. Partners c. Health practitioners **d. All of the above** **Feedback correct:** Well done! All of the above answers are correct. **Feedback incorrect:** No, sorry! All of the above are correct.
CHAPTER 5		
17	Multiple choice question	Question 16 **After medication transfer from plasma to breast milk, what happens when the plasma concentration in medication decreases?** a. The medication diffuses from the plasma into the breast milk **b. There is a dynamic equilibrium between the breast plasma and the breast milk** c. The medication remains in breast milk as in a reservoir

		d. The medication is metabolised in the breast with time **Feedback correct:** Well done! After medication transfer from plasma to breast milk, there is a dynamic equilibrium between the breast plasma and the breast milk. **Feedback incorrect:** No, sorry! After medication transfer from plasma to breast milk, there is a dynamic equilibrium between the breast plasma and the breast milk.
18	Multiple choice question	Question 17 What do you do when you do <u>not</u> know about the risk of a medication use during breastfeeding? a. You ask key questions to clarify the benefits/risk ratio of the medication use **b. You tell the mother to discontinue the breastfeeding** c. You read LactMed d. You call the reference site of medication and breastfeeding **Feedback correct:** Well done! When you are not sure about the risk of a medication use during breastfeeding, you do not tell the mother to discontinue the breastfeeding. Instead you ask key questions to clarify the benefits/risk ratio of the medication use, you read LactMed and you call the reference site of medication and breastfeeding. **Feedback incorrect:** No, sorry! When you are not sure about the risk of a medication use during breastfeeding, you do not tell the mother to discontinue the breastfeeding. Instead you ask key questions to clarify the benefits/risk ratio of the medication use, you read LactMed and you call the reference site of medication and breastfeeding.
19	Multiple choice question	Question 18 **What elements can contribute to reassure a mother that she can breastfeed her infant even if she takes a medication?** a. The infant is older than six months b. The medication the mother uses is Amiodarone **c. The medication the mother is paracetamol** d. The mother wants to do an innovative therapy

		Feedback correct: Well done! You can reassure the mother that she can breastfeed when she uses paracetamol. In any other case, you cannot reassure her. **Feedback incorrect:** No, sorry! You can reassure the mother that she can breastfeed when she uses paracetamol. In any other case, you cannot reassure her.
20	Multiple choice question	Question 19 A mother on lamotrigine visits you and complains about her newborn who sleeps all the time. She adds that breastfeeding is more and more difficult and her newborn lost 10% of his weight. You suspect an adverse drug reaction to lamotrigine via breast milk. **What is your reaction?** **a. You hospitalize the newborn** b. You determine the concentration of plasma in the mother and the newborn. c. You explain to the mother she needs to change her diet d. You do nothing **Feedback correct:** Well done! If the newborn loses too much weight, you hospitalize the newborn. Other correct answers would be: You report the suspicion of adverse drug reaction to the nearest medication information center even if you are not sure. You also focus on the rehydration and re-nutrition of the newborn. **Feedback incorrect:** No, sorry! If the newborn loses too much weight, you hospitalize the newborn. Other correct answers would be: You report the suspicion of adverse drug reaction to the nearest medication information center even if you are not sure. You also focus on the rehydration and re-nutrition of the newborn.
21	Multiple choice question	Question 20 Adverse drug reaction via breast milk is more frequent with? a. Boys b. Girls **c. Infants of 2 months or less** d. Infants older than 6 months

		Feedback correct: Well done! Adverse drug reaction via breast milk is more frequent with very young infants of 2 months or less. **Feedback incorrect:** No, sorry! Adverse drug reaction via breast milk is more frequent with very young infants of 2 months or less.
CHAPTER 8		
22	Multiple choice question	Question 21 **The four important parameters needed to assess causality between drug administration during pregnancy and the appearance of an adverse effect:** **a. Medication's name, duration, exposure time, maternal & obstetrical history** b. Medication's name, duration, pharmacokinetic data, physician's name c. Exposure time, maternal & obstetrical history, address, duration d. Duration, pharmacokinetics data, physician's name, medication's name **Feedback correct:** Well done! The four important parameters needed to assess causality between drug administration during pregnancy and the appearance of an adverse effect are the medication's name, duration, exposure time, maternal and obstetrical history. **Feedback incorrect:** No, sorry! The four important parameters needed to assess causality between drug administration during pregnancy and the appearance of an adverse effect are the medication's name, duration, exposure time, maternal and obstetrical history.
23	Multiple choice question	Question 22 **Which data storage has criteria for inclusion?** a. TIS b. Database **c. Registry** d. None of the above

		Feedback correct: Well done! The registry has criteria for inclusion. **Feedback incorrect:** No, sorry! The registry has criteria for inclusion.
24	Multiple choice question	Question 23 **Who can report an adverse outcome after exposure during pregnancy to specific medication?** a. A pregnant woman b. Healthcare providers c. QPPV **d. All of the above** **Feedback correct:** Well done! All of the above can report an adverse outcome after exposure during pregnancy to specific medication. **Feedback incorrect:** No, sorry! All of the above can report an adverse outcome after exposure during pregnancy to specific medication.
25	Multiple choice question	Question 24 **In which information source, the maternal compliance to the studied medication is unknown?** **a. Database** b. Registry c. TIS d. None of the above **Feedback correct:** Well done! The right answer is the database. **Feedback incorrect:** No, sorry! The right answer is the database.
26	Multiple choice question	Question 25 Which of the following was the earliest described human teratogen?

		a. Thalidomide **b. Rubella** c. Valproate d. Aminopterin **Feedback correct:** Well done! The earliest described human teratogen was Rubella. **Feedback incorrect:** No, sorry! The earliest described human teratogen was Rubella.
27	Text	**Thank you for your participation!** You have completed the course.