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Contents

CHAPTER 1

General introduction

Congenital anomalies

The prevalence of major congenital anomalies (CA) is 2-3% of all births [1]. A CA can be a structural or functional anomaly: structural implies that an organ or body part is missing or incorrectly developed, for example a transposition of the great arteries. An example of a functional anomaly is pyloric stenosis, in which the physical function is present, but not optimal. There are diverse types of CA, varying from the presence of an extra finger (polydactyly) to very severe types of neural tube defects that are not compatible with life. CA can arise during embryonic or fetal developmental [2-4]. A CA detected early in pregnancy can be a reason to terminate a pregnancy. In Europe, in approximately one out of five fetuses in which there is a CA, the pregnancy is terminated after diagnosis of a fetal anomaly [1].

Many abnormal embryos are lost in the very early stage of embryonic development. This 'self-selection process' often results in a spontaneous abortion, mostly without the mother even being aware she has conceived [2]. The organogenesis and further development mostly proceeds smoothly, although in some cases CA may occur. CA are caused by genetic (25%), environmental (10%) or multifactorial (65%) factors. Genetic factors consist of chromosomal anomalies and single gene defects. Environmental factors cover infections (intrauterine and other), maternal metabolic disorders, chemicals, radiation, nutrition, stress and recreational drugs and medications; multifactorial causes of CA are due to more than one factor, including environmental and genetic factors [2,5].

Maternal medication use during pregnancy is considered to be responsible for a small proportion of all CA [4]. However, since there many different medicines, all with different properties, and some have very severe teratogenic effects (see below), it is relevant to investigate possible relations between CA and maternal medication exposure during pregnancy in order to avoid or minimalize the risks of CA in the future.

In this thesis, the focus is on the relation between congenital anomalies and maternal medication exposure during pregnancy and certain aspects of the methods used to study this relationship.

Medication use during pregnancy

The thalidomide tragedy revealed that medication use during pregnancy can cause very severe CA. Thalidomide first came on the market in Germany in 1957 [6]. Besides its effects as a sedative, thalidomide was found to be effective in the treatment of morning sickness in pregnant women [7]. However, a few years later, the physician Lenz noted the increasing number of children being born with reduced limbs (phocomelia) [8]. He thought there might be a relation between the maternal use of thalidomide during pregnancy and the affected children and reported his observations in 1961 [9,10]. Because similar observations were also made in other countries [11,12], thalidomide was withdrawn from the market. However, since thalidomide was marketed in many countries for a few years, it has been estimated that more than 10,000 embryos were –unnecessarily– affected [13]. Its teratogenicity in humans was not anticipated, since it had been found to be non-toxic in rats and mice [14]. This tragedy highlighted an important lesson: that results from animal studies cannot always be extrapolated to humans [15-17], and, since pregnant women are excluded from clinical trials for ethical reasons [18], the possible teratogenic effects of new medicines are often unknown and should be monitored.

Despite uncertainties regarding the teratogenicity of many drugs, approximately 80% of all women use at least one medicine during pregnancy [19]. There are several classification systems for the safety of medication during pregnancy, for example the classification of the Australian Drug Evaluation Committee (ADEC) [20], the Swedish classification system, and that of the Food and Drug Administration (FDA), USA [21]. In Europe, the Australian and Swedish classification systems were most commonly used. However, due to practical perspectives (like how to interpret their coding in practice), these encodings have been abandoned for assessing medication use during pregnancy [4]. For this, manuals like "*Drugs during Pregnancy and Lactation*" by Schaefer et al. can be used [22,23].

Sometimes a woman has the choice of taking a medicine, for instance in the case of headache and using a pain killer. However, in the case of chronic diseases, like epilepsy medication use is unavoidable. Not treating epilepsy during pregnancy is disadvantageous from the standpoint of seizure control [24], although the use of antiepileptic medicines is associated with an increased risk of CA [25,26]. The prescribing physician and patient have to make an informed choice based on the information available (manuals, current literature, etc.) and balance the benefits against the potential risks.

Even with proven high teratogenicity of a medicine, maternal exposure will not always result in a CA. This can be illustrated with the example of isotretinoin. This vitamin A derivative is prescribed for severe types of acne in patients who are resistant to other treatments, but it has also been associated with cardiac, craniofacial and thymic anomalies and anomalies of the central nervous system in offspring when taken in pregnancy [27]. In 1988 it was decided to implement a Pregnancy Prevention Program (PPP), which advised that women of fertile age should use at least one, or preferably two, contraceptive measures up to one month after stopping use of isotretinoin [28]. Despite the PPP, a recent study showed that 2.5 per 10,000 pregnancies were still being exposed to isotretinoin [29]. In another study, 79 women who had been treated with isotretinoin before or during their pregnancy were identified. Eleven of them had a spontaneous abortion, 21 underwent an elective abortion, 2 were lost to follow-up, and 1 was found to be pregnant with a child with a CA (ventral wall defect, bladder outlet obstruction, distal open neural tube defect, and deformities of the spine and lower extremities) and underwent an abortion. However, since the mother had only been exposed 4 months before conception to two 10-mg tablets for two days, the investigators consider her case as "*not related to the maternal exposure to Isotretinoin*". Of the 79 exposed mothers, 44 gave birth to a healthy, full-term baby. Of these 44 women, 19 were exposed to isotretinoin in the period from 1 month before conception or during pregnancy [30]. This study shows that even the use of a strong teratogen like isotretinoin may not affect human embryonic development. Thus, strong teratogens may increase the risk of having a child with a CA, but do not always result in an affected child. There are probably more factors in addition to medication use (for instance, genetic factors) that are involved in the development of CA.

It has sometimes taken many years for the association between a specific CA and a specific medication to be discovered. For instance, although the antiepileptic medicine valproic acid came on the market in 1968 [31], it was thirteen year later, in 1981, that its possible teratogenicity was first suggested [32]. The hope is that modern registers of CA, like European Concerted Action on Congenital Anomalies and Twins (EUROCAT), will alert the medical world at a much earlier stage to any teratogenic effects of new medications.

It is clear that continuous vigilance on medication use and its potential teratogenicity is necessary [33]. Since animal studies cannot be used to predict effects in humans, and since pregnant women are excluded from clinical trials, the safety of using new medicines during

pregnancy can only be established by careful monitoring after they have been released on the market. This is called post-marketing surveillance.

Post-marketing surveillance

Monitoring the safety of medication can be performed in both descriptive and analytical study designs. Relevant designs for both types of study are described more in detail below.

Clinical Trials

Prior to the performance of analytical studies, descriptive studies like *case reports* and *case series* can lead to further research. In a case report or a case series, situations concerning a rare congenital anomaly and specific maternal medication are reported. For example, a case report was published in *The Lancet* of a woman who had taken the contraceptive 'Ovral' during the first trimester of pregnancy and given birth to a girl suffering from tracheo-esophageal fistula [34]. An example of a case series were the observations of the physician Lenz, who reported on the unusually high number of children with phocomelia and the maternal use of thalidomide [9,10]. It is also possible to describe the medication use among pregnant women, as done in *drug utilization studies*: these are a useful tool to provide insight into which medicines are being prescribed during pregnancy and how frequently.

Cohort studies

In *follow-up studies* two groups are followed over time to determine the outcome. One group is exposed to a medication {the index group}, while the other is not {the reference group}. Their outcomes for CA are then monitored. The aim of follow-up studies is to determine the effect of using medicine compared to no exposure. Follow-up studies can be performed prospectively or retrospectively. Prospective studies can be both observational and experimental, while retrospective studies are only observational [35]. In experimental research, an intervention is implemented and the effect is measured over time. By contrast, no interventions are made in observational studies, but the effect of the exposure is measured over time.

Experimental follow-up studies, like *Randomized Clinical Trials (RCT),* cannot be used to study the relation between CA and maternal medication exposure during pregnancy due to practical and ethical issues [18]. However, observational studies can be performed in research

into the relation between CA and maternal medication exposure during pregnancy. *Cohorts* are used in observational studies. In cohorts the index and reference groups are based on the current situation. If a participant is exposed to a medication, she belongs to the index group and if she has had no exposure, she belongs to the reference group. In cohorts there is no randomization involved, which means that the groups are not necessarily equally distributed, but it is possible to select the reference group so that the characteristics between the exposed and the non-exposed groups are the same [35-37]. Cohorts can play a part in studies on maternal medication use in relation to CA, but other pregnancy outcomes, like miscarriages or birth weight, can also be taken into account. For example, women suffering from fertility problems were followed over time. Some of them had no treatment and some were given clomiphene citrate (prescribed as first line treatment) or letrozole (prescribed as second line treatment) before they became pregnant. After pregnancy, the incidence of children with a CA was studied [38].

Case-control studies

In a *case-control study,* cases and controls are defined based on the outcome of interest. The cases have a specific outcome, such as a specific CA, while the controls do not have that outcome. The exposure to medication use is determined for both groups. The medication use can be recorded prospectively (medical files) or collected retrospectively (by maternal interview, for instance) [39,40]. An example is a recent study on valproic acid and the risk of CA. 14 CA found in the literature (signals) were tested in a case-control study data from EUROCAT registries. Cases were defined as fetuses and children with at least one of the 14 identified malformations, which included spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis. Two control groups were used: 1) fetuses and children with a CA not previously linked to valproic acid, and 2) fetuses and children with a chromosomal anomaly. Whether the mother had used valproic acid during the first trimester of pregnancy was examined for all the cases and controls [25].

In case-control studies the odds ratio (OR) can be calculated; this gives a specific ratio between the cases and controls, which can be used to estimate the strength of the association between the exposure and outcome [37].

The combination of a specific CA with a specific medication use is quite rare. To continue with the example of valproic acid and spina bifida: approximately 0.06% of all children

born in the Netherlands suffer from spina bifida [41] and valproic acid is prescribed to approximately 0.2% of all women of child-bearing age [42]. Therefore, thousands of exposed women need to be followed to detect an association of a specific CA to a specific medication. Prospective studies and even retrospective cohort studies focusing on women who used certain medications in pregnancy are therefore not easy to perform. Case-control studies are the most suitable – for example compared to cohort studies – and most common study design used to investigate possible associations between maternal medication use and CA [33].

Data sources in post-marketing surveillance

To perform high quality case-control studies on the relation between CA and maternal medication use during pregnancy, specific data sources are needed on exposure and outcome. Many registries have been set up worldwide since the thalidomide tragedy to monitor the occurrence of CA. These CA registries are united in several networks, such as the EUROCAT, a population-based network of registers for epidemiological surveillance of CA that covers more than one million births per year [43,44]. The US National Birth Defects Prevention Network (NBDPN) is based on CA surveillance systems in eight states [45], and the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) is a worldwide network of CA registries [46]. The primary aim of all these registries is to monitor the incidence of CA, but not all of them collect information on maternal medication use during pregnancy. The quality of the information recorded on maternal medication varies and depends on the sources used. The information is usually derived from two types of sources: self-reports (interviews and questionnaires) and 'medical' records (information extracted from medical files, or pharmacy- or health insurance records).

For the work described in this thesis, we used four different types of databases, including congenital anomaly registries and prescription databases. These sources are described in boxes 1-4.

Box 1. EUROCAT

The concept of EUROCAT was developed in the 1970s in the wake of the thalidomide tragedy [43]. EUROCAT is an European network of approximately 40 population-based registers of congenital anomalies (CA). It covers approximately a third of all births in the European Union, representing more than 1.7 million births per year. EUROCAT focuses on the prevalence, primary prevention and

prenatal diagnosis of CA. In general, all types of births (live births, stillbirths, spontaneous abortions and terminations of pregnancy for fetal anomaly (TOPFA)) are registered [44]. However, TOPFAs are not legally allowed in all regions and they are therefore not recorded by all the registers [47].

CA are coded according to the 9th and 10th versions of the International Classification of Diseases (ICD) coding system [48]. In addition to CA, the registers also record the parents' socio-demographic characteristics, prenatal screening methods and the diagnostic tests performed, and exposure to risk factors (such as maternal medication use in the first trimester, classified according to the Anatomical Therapeutic Chemical (ATC) classification system [49]) [44]. However, the determinants recorded and the quality of information on them varies per registry [47].

EUROCAT Northern Netherlands (NNL)

One of the regional EUROCAT registries is EUROCAT Northern Netherlands (NNL). This registry was started in 1981 and is funded by the Dutch Ministry of Health, Welfare, and Sports. It covers the three northern provinces – Friesland, Groningen and Drenthe – which together represent 10% of all births in the Netherlands [47]. In the last few years, the birth rate in the Netherlands has been around 180,000 per annum [50], so approximately 18,000 children are born per year in the EUROCAT NNL region. Since 2-3% of them have a CA, some 500 cases are added to EUROCAT NNL's register each year [41]. The participation rate of cases has stabilized over the years at 80% [51].

All types of births are registered, and children can now be registered until they reach the age of ten years. In the past the upper age limit at diagnosis was set at 16 years. There is no lower limit for the gestational age at which the CA is detected. Registry staff are involved in active case ascertainment and use multiple sources to identify cases, such as obstetric records, hospital administration data, and pathology records. From 1997 onwards, the parents have been asked to fill out a questionnaire on their sociodemographic characteristics, prenatal screening methods and diagnostic tests, and exposure to risk factors. The response rate to the questionnaire is 80%. Furthermore, if the mother gives permission, her pharmacy data are retrieved for the period of 3 months prior to conception up to delivery. EUROCAT NNL staff conduct telephone interviews to verify whether the medication dispensed was indeed taken and whether any other medication, like over-the-counter (OTC) medication, was also taken during this specific period [47].

Box 2. EUROmediCAT

EUROmediCAT is a database that builds further on the EUROCAT network and pays special attention to maternal medication taken during pregnancy [52-54]. Its aim is "*to build a European system for*

reproductive safety evaluation, which enables us to identify systematically and comprehensively the possible adverse effects in pregnancy of a drug in humans at the earliest stage post marketing, and enables us to monitor and evaluate safety measures undertaken in Europe" [52,53].

For EUROmediCAT, the data from several CA registries are combined with healthcare databases. The system was tested for effectiveness and relevance by studying four selected medication groups: anti-epileptic drugs, insulin analogues, selective serotonin reuptake inhibitors (SSRIs), and anti-asthmatics [55]. These groups were selected since they are medicines used for long periods and are prescribed relatively frequently.

Prescription data linkage

The central EUROCAT database holds information available on maternal medication use in pregnancy, but since this information is mostly retrieved from medical files, it is often incomplete and the quality of data varies widely among registries. To obtain good qualitative data on maternal medication use in pregnancy, the data from primary care and prescription databases could be linked to CA registries. This has been done in EUROmediCAT, where the records from primary care and prescription databases were linked to five CA registries, and the linkage process and linkage rates were evaluated [56-58].

Box 3. IADB

The IADB, previously known as the InterAction DataBase, is a Dutch, population-based, drug prescription database, which was started in 1998 as collaboration between the Unit of PharmacoEpidemiology and PharmacoEconomics (University of Groningen) and community pharmacies in the northern Netherlands. Nowadays, IADB contains prescriptions from 54 community pharmacies located in different parts of the Netherlands and covering a population of 500,000. The IADB is considered to be representative for the Dutch situation [59]. The following factors are recorded for each patient: "*a unique IADB patient number; gender; date of birth, and optionally, a four-digit postal code*"; and for each prescription: "*prescription date (date the drug was dispensed to patient), IADB patient number, amount of medication delivered or number of units (i.e. tablets or inhalers), dosage (number of units prescribed per day), IADB physician number of the prescriber (general practitioner or specialist), IADB pharmacy number, and the ATC Classification [49] (defined daily dose index information, drug number (to link with Z-Index)"* [59]. IADB data are used in pharmacoepidemiological, drug utilization and pharmacoeconomic studies [59].

To study drug use during reproduction, a special pregnancy database was created from the

entire IADB database. Pregnancies were identified by assuming that a woman with the same 'address registration number' and 15–50 years older than a child was the mother The child's date of birth meant the pregnancy period could be calculated. This method was validated and led to 65% of the mothers being identified [60].

Box 4. HAVEN

The HAVEN study, a Dutch acronym for the study of heart anomalies and the role of genetic and nutritional factors, is a population-based case-control study which was set up to investigate the influence of genetic and nutritional determinants on the prevention and pathogenesis of heart anomalies. The study was started in June 2003 in the western part of the Netherlands. In the period up to January 2005, a total of 151 case-children and their parents, and 183 control-children and their parents were included. At the moment of inclusion, the children (cases and controls) were aged 11-18 months [61].

The diagnosis of the cases was confirmed by echocardiography, and/or cardiac catheterization, and/or surgery. Controls were only included if they did not have a major congenital anomaly or a chromosomal disorder. The cases and controls were not related to each other. For all the children and their mothers, biochemical and questionnaire data were collected at the time of inclusion in the study [61]. For the biochemical data, it was assumed that metabolism and nutritional habits were fairly uniform or possibly even more pronounced during pregnancy [62-64]. The questionnaires were based on two periods: the moment of inclusion and the periconceptional period, which was defined as the period of 3 months before conception and up to 10 weeks thereafter. The questionnaire asked for information on maternal age, body mass index (BMI), educational level, ethnicity, cigarette smoking, use of alcohol, use of oral contraceptives and medication, and the age and gender of the child [61].

Objectives of the thesis

Despite uncertainties about the teratogenicity of some medications, approximately 80% of all women use at least one medicine during pregnancy. This means that continuous vigilance (post-marketing surveillance) is required on medication use and its possible teratogenic effects. In this thesis, the focus was on two important aspects of this work: (1) the quality of data used in post-marketing surveillance on maternal medication use in pregnancy, and (2) the methods for monitoring maternal medication use in pregnancy in relation to CA and for assessing risks.

The objectives for studying the data quality were:

1. to evaluate the quality of the current data sources used in congenital anomaly registries
2. to investigate whether the quality of data could be improved by linking prescription data to current data sources.

The objectives for studying the monitoring and risk assessment were:

3. to explore the usefulness of a new method of signal detection using data from a congenital anomaly registry and a prescription database
4. to investigate a possible association between a group of medications and specific birth defects, using data from a case-control study and a congenital anomaly registry.

Outline of the thesis

Part I Data quality

In **chapter 2** we describe the sources used by 19 EUROCAT registries to record maternal medication use in pregnancy and their respective strengths and weaknesses. In **chapter 3** we report how data from primary care or prescription databases were linked to CA registries to obtain more accurate information on maternal medication use in pregnancy. Subsequently, the linkage process and linkage rate were evaluated. In **chapter 4** we evaluate how far prescription data reflect the actual use of medications during pregnancy.

Part II Monitoring and risk assessment

In **chapter 5** we report the prescription patterns for antibiotics before, during and after pregnancy over a 16-year period. In **chapter 6** we compare the drug use rates from EUROCAT NNL to the prescription rates recorded by the IADB, to determine whether this method can be used to detect signals of teratogenic risks from certain medicines. In **chapter 7** we describe a study into whether there is an association between the use of antihistamines in early pregnancy and congenital heart defects. This case-control study was conducted with data from the HAVEN study and from EUROCAT NNL.

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DATA QUALITY

PART I

Chapter 2
EUROCAT special report: sources of information on medication use in pregnancy

Chapter 3
Improving information on maternal medication use by linking prescription data to congenital anomaly registers: a EUROmediCAT study

Chapter 4
Actual use of medications prescribed during pregnancy: a cross-sectional study using data from a population-based congenital anomaly registry

CHAPTER 2

EUROCAT special report: sources of information on medication use in pregnancy

de Jonge L, Bakker MK

http://www.eurocatnetwork.eu/content/Special-Report-Medication-Use-In-Pregnancy.pdf

Introduction

With 43 registries in 23 different countries, EUROCAT surveys over 1.7 million births per year. This is now equal to 29% of the European birth population in any one year. Since most registries collect data on maternal drug use during the first trimester, EUROCAT is highly valuable as a database for pharmacovigilance studies. However, the various registries have different methods of data collection and processing. And since the quality of the data may differ between the registries, it is not always possible to pool data from them for broader studies.

In this report we describe the sources of information on maternal medication use employed by the registries which contributed medication data to the EUROCAT central database for congenital anomaly cases born between 2004-2010.

Methods

The sources of information on maternal medication use, as recorded by the registries that contributed medication data to the central database, were collected on the basis of a questionnaire filled in by the following 19 registries:

- Belgium, Antwerp
- Belgium, Hainaut-Namur
- Croatia, Zagreb
- Denmark, Odense
- France, Paris
- Germany, Mainz
- Germany, Saxony-Anhalt
- Ireland, Cork & Kerry
- Italy, Emilia Romagna
- Italy, Tuscany
- Malta
- Netherlands, Northern Netherlands
- Norway
- Poland
- Poland, Wielkopolska
- Spain, Basque country
- Switzerland, Vaud
- UK, Wales
- Ukraine

The questionnaire is attached in appendix 1a. It focused on the different sources of information for maternal medication use that were used by the registries and how the registries defined ‘unknown medication use’ and ‘no medication use‘ in the EUROCAT Data Management

Program (EDMP). The EDMP is the software program used to upload data from the registries' own software programs; it performs quality checks before the data is added to the EUROCAT central database.

Sources of medication use

We defined two major sources of information on medication use in pregnancy: 'medical files' and 'registry- based data collection methods'. Medical files can be categorized into: medical files from maternal healthcare providers in relation to pregnancy; medical files from healthcare providers of the child, and medical files from maternal healthcare providers not in relation to pregnancy. The healthcare providers have recorded the data on maternal medication use in their medical files. Registry-based data collection methods can be categorized into: interviews by the registry staff and questionnaires (sent out by the registry). In these circumstances the information is provided directly by the mother and not via a healthcare provider. A scheme of the information sources is shown in the figure 2.1.

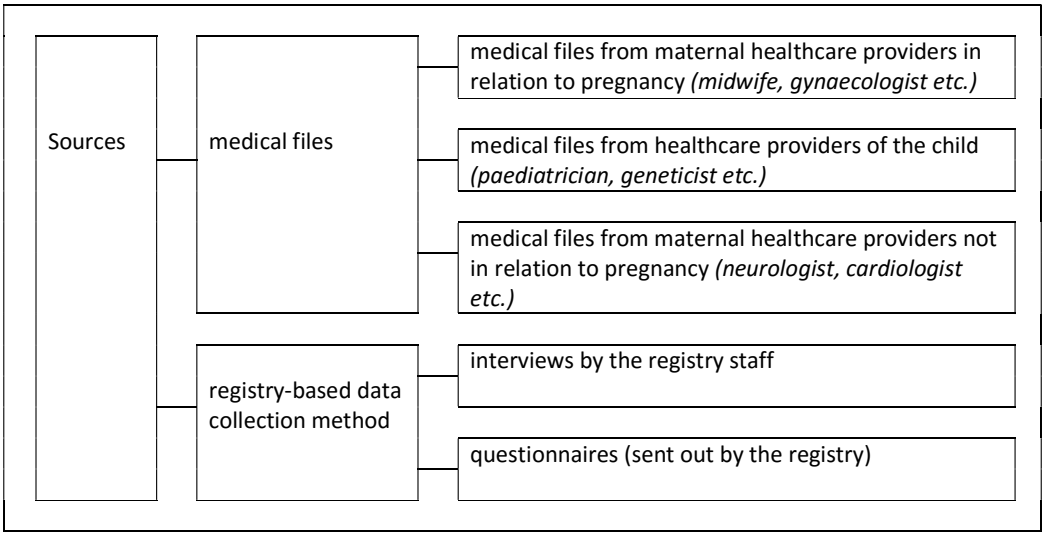

Figure 2.1 Scheme of sources of information

For each of the five sources we asked what type of medication was usually recorded (chronic medication/ medication for short time use/ pregnancy-related medication/ Over The Counter drugs [OTC]), and with what frequency records were made (standard/sometimes/never recorded). In addition, we asked whether the records were based on prescriptions or actual use

as confirmed by the mother; whether the information was based on specific questions or 'open' input from the mother; how the data collection took place, and for what kind of birth types this source was available.

We further asked in which situations the registry recorded maternal medication use as 'unknown', 'no drugs taken' or when the registry left the medication variable empty on the basis of multiple choice options.

Results

We collected information on the sources that provided information on maternal medication use to 19 registries, which then contribute the medication data to the central EUROCAT database.

Table 2.1 shows that all registries, except Tuscany, used at least one type of 'medical file' as a source and 16% (3/19) of the registries used at least one type of 'registry-based data collection method'. 21% (4/19) of the registries only used one source. Paris, Cork & Kerry and Norway only used medical files from maternal healthcare providers in relation to pregnancy as a source. Tuscany only used a questionnaire as a source. 58% (11/19) of the registries used two sources and 21% (4/19) of the registries used three or more sources. Of the registries using three or more sources, Emilia Romagna used medical files from maternal healthcare providers in relation to pregnancy, medical files from health care providers of the child, and medical files from maternal healthcare providers not in relation to pregnancy. Hainaut-Namur used medical files from maternal healthcare providers in relation to pregnancy, medical files from health care providers of the child, and questionnaires sent out by the registry. Mainz used medical files from maternal healthcare providers in relation to pregnancy, medical files from health care providers of the child and medical files from maternal healthcare providers not in relation to pregnancy. Northern Netherlands used medical files from maternal healthcare providers in relation to pregnancy, medical files from health care providers of the child, medical files from maternal healthcare providers not in relation to pregnancy, interviews by the registry staff and questionnaires sent out by the registry.

Table 2.1 Sources of information on maternal medication use

	Medical files			**Registry based data collection method**	
	from maternal healthcare providers in relation to pregnancy [1]	*from health care providers of the child* [2]	*from maternal healthcare providers not in relation to pregnancy*	*interviews by the registry staff*	*questionnaires (sent out by the registry)*
Belgium, Antwerp	X	X	-	-	-
Belgium, Hainaut-Namur	X	X	-	-	X
Croatia, Zagreb	X	X	-	-	-
Denmark, Odense	X	X	-	-	-
France, Paris	X	-	-	-	-
Germany, Mainz	X	X	X	-	-
Germany, Saxony-Anhalt	X	X	-	-	-
Ireland, Cork & Kerry	X	-	-	-	-
Italy, Emilia Romagna	X	X	X[3]	-	-
Italy, Tuscany	-	-	-	-	X
Malta	X	X	-	-	-
Netherlands, Northern Netherlands	X	X	X[4]	X	X[5]
Norway	X	-	-	-	-
Poland	X	X	-	-	-
Poland, Wielkopolska	X	X	-	-	-
Spain, Basque country	X	X	-	-	-
Switzerland, Vaud	X	X	-	-	-
UK, Wales	X	X	-	-	-
Ukraine	X	X	-	-	-
Number of registries in total: **19**	18	15	3	1	3

[1] includes midwife, obstetrician, gynaecologist, delivery units, General Practitioner [GP], pregnancy pass
[2] includes paediatrician, neonatologist, geneticist, paediatric cardiologist, paediatric neurologist, paediatric surgeon
[3] Emilia Romagna Prescription Database, in which prescriptions are recorded irrespective of pregnancy status
[4] pharmacy data, which are recorded irrespective of pregnancy status
[5] maternal medication use of specific drugs (folic acid, multivitamins, vaccinations anaesthetics, insulins, other medication in relation to Diabetes Mellitus) is a standard item in the questionnaire

Medical files from maternal healthcare providers in relation to pregnancy were the most commonly used sources 95% (18/19); this was followed by medical files from health care providers of the child: 79%(15/19). 79% (15/19) of the registries used at least medical files from at least two sources- maternal healthcare providers in relation to pregnancy and medical files from health care providers of the child.

Medical files from maternal healthcare providers in relation to pregnancy

18 registries used medical files from maternal healthcare providers in relation to pregnancy as a source. 83% (15/18) of the registries indicate that chronic medications were usually recorded. For pregnancy-related medications, medications for short term use and OTC medications the rates were 78% (14/18), 50% (9/18) and 44% (8/18), respectively.

For 67% (12/18) of the registries using these sources, they indicated that they were aware whether actually used medications, prescribed medications or a combination of both were recorded in the medical file; whether the recording was based on specific questions of the health care provider, open input from the mother or a combination of both.

Half the registries, 42% (5/12), recorded prescribed and actually used medication based on this source. The others recorded only prescribed medication or only actually used medication: 8% (1/12) and 50% (6/12), respectively.

A majority, 56% (10/18), of sources contained prospective information, but retrospective information or a combination was also possible: 17% (3/18) and 28% (5/18), respectively. All the sources were available for live births and still births. The sources used by the registries of Emilia Romagna, Poland and Wielkopolska (17% (3/18)) were only available for live births and still births. The sources used by the registries of Saxony-Anhalt, Cork & Kerry[1], Malta[2] and Norway (22% (4/18)) were available for live births, still births and fetal deaths. The sources used by the registries of Antwerp, Hainaut-Namur, Zagreb, Odense, Paris, Mainz, Northern Netherlands, Basque country, Vaud, Wales and Ukraine (61% (11/18)) contained information on live births, still births, fetal deaths and Terminations of Pregnancy for Fetal Anomaly (TOPFAs).

[1] TOPFA is illegal in Ireland
[2] TOPFA is illegal in Malta

Medical files from health care providers of the child

15 registries used *medical files from health care providers of the child* as a source. 67% (10/15) of the registries indicate that chronic medications were usually recorded. For pregnancy-related medications, medications for short term use and OTC medications the rates were 40% (6/15), 33% (5/15) and 27% (4/15), respectively.

For 67% (10/15) of the sources, it was known how the health care provider obtained the information on medication. 'Knowing how the health care provider obtained information' means that the registry knows whether the record was for actually used medications, prescribed medications or a combination of both; whether the record was based on specific questions by the health care provider, open input from the mother or a combination of both.

A majority of registries, 70% (7/10), recorded actually used medication based on this source: the others recorded prescribed and actually used medication: 30% (3/10). All information in these sources 100% (15/15) was retrospectively recorded

Medical files from maternal healthcare providers not in relation to pregnancy

Three registries used *medical files from maternal healthcare providers not in relation to pregnancy* as a source: Emilia Romagna, Mainz and Northern Netherlands. Emilia Romagna used the Emilia Romagna Prescription Database, which contained information on dispensed medications prescribed by General Practitioners. OTC and other medications prescribed in private clinics or dispensed by the hospital were not available. Mainz used several sources of information, like hospital data, which contain information on prescribed an actually used medication, Northern Netherlands asked the mother's permission to obtain their pharmacy records from their community pharmacy. These records contained information on all prescribed medications, except those prescribed in private clinics. OTC medication was sometimes recorded. The actual use was verified in a telephone interview with the mother (see interviews by the registry staff).

All sources recorded data prospectively and the data was available for all types of births. However, since for Emilia Romagna the data on women who appear in the certificate of assistance at birth were only retrieved, it was only possible to link live births and still births and not fetal deaths and TOPFAs.

Interviews by the registry staff

Only the Northern Netherlands used interviews by the registry staff as a source of information. During the interview, unclear answers in the questionnaire (see *Questionnaires (sent out by the registry))* could be clarified, the actual use of prescribed medication according to the pharmacy record was verified and , in addition, there was a list of physical complaints to verify the mother's use of OTC during pregnancy. The interview always took place after the birth and was carried out for all types of births.

Questionnaires (sent out by the registry)

Three registries used questionnaires (sent out by the registry) as a source of information: Hainaut-Namur, Tuscany and Northern Netherlands.

For Hainaut-Namur, the use of chronic medication and pregnancy-related medication was usually recorded. The use of medication for short term use was sometimes recorded, but the use of OTC drugs was never recorded. For Tuscany, the use of chronic medication, medication for short term use, pregnancy-related medication and OTC drugs was usually recorded. The questions asked were open questions. For the Northern Netherlands, only the use of specific medications (folic acid, multivitamins, vaccinations anaesthetics, insulins, other medication in relation to diabetes) was a standard item in their questionnaire.

For Hainaut-Namur and the Northern Netherlands the questionnaires were sent out after birth and this was done for all types of birth. For Tuscany the questionnaire was not sent out by the registry, but the mother answered after birth or termination to the single questions in presence of medical professional who completed the questionnaire at that moment. Since the questionnaire was set up with the aim of data collection for the registry, it was classified as registry-based data collection method.

Discrepancies among sources

If more than one source was used, discrepancies concerning the prescription or use of medication were sometimes found, which needed to be resolved. The registries had different solutions to this problem: some made a distinction between the sources in accuracy (differences in prioritizing of the sources); some verified the information (for example, by contacting the sources), and some chose the most likely option.

Information on medication use sent to Central Registry

The information on medication use is sent to the Central Registry in Ulster, where all the information is collected. Table 2.2 shows that 68.4% (13/19) of the registries sent information on medication use only based on the first trimester, whereas 31.6% (6/19) of the registries sent information based on the whole pregnancy.

Table 2.2 Information on medication use sent to Central Registry

	Only based on first trimester	**Based on whole pregnancy**
Belgium, Antwerp	X[1]	
Belgium, Hainaut-Namur		X
Croatia, Zagreb		X
Denmark, Odense	X	
France, Paris	X	
Germany, Mainz	X	
Germany, Saxony-Anhalt	X	
Ireland, Cork & Kerry	X	
Italy, Emilia Romagna		X
Italy, Tuscany	X	
Malta	X	
Netherlands, Northern Netherlands	X	
Norway		X
Poland		X
Poland, Wielkopolska		X
Spain, Basque country	X	
Switzerland, Vaud	X	
UK, Wales	X	
Ukraine	X	
Total:19	13	6

[1] *If a drug wasn't taken in the first trimester but the onset was later we mention the drug in the "general remarks" field*

Definitions of values used in EDMP for 'blank', 'drug use not known', and 'no drugs taken'

In EDMP up to five items can be notified regarding medication use. 'Drugs1' is the first item regarding drug use in EDMP which can be filled. The EUROCAT coding guide specifies that the ATC code for the drug used should be entered in this field. Where no drug is used a "*0*" (zero) is entered in the field; where drug use is not known, a "*9*" is entered. For some EUROCAT case records, the field is not filled in at all and remains 'blank'.

Table 2.3 shows the proportion (%) of cases in EDMP for Drugs1 with respect to 'drug taken', 'blank', 'drug use not known', and 'no drugs taken' for the years 2004-2010. From this table it is clear that registries do not always follow the instructions. Therefore in table 2.4 the details of the definitions of values used in EDMP for Drugs1 with respect to 'blank', 'drug use not known', and 'no drugs taken' are represented as used by the registries.

Table 2.3 Details of the average proportion (%) of cases in EDMP for Drugs1 with respect to 'drug taken', 'blank', 'drug use not known' and 'no drugs taken' for the years 2004-2010

	Drug taken (inclusive a single letter, or a one or two number code and vitamins and minerals) (%)	No drugs taken "0"(%)	Unknown "9" (%)	Blank (%)
Belgium, Antwerp	6.0	8.3	40.5	45.3
Belgium, Hainaut-Namur	*1.7	*0.2	*0.0	*98.1
Croatia, Zagreb	13.2	0.1	2.4	84.3
Denmark, Odense	17.7	68.2	2.0	12.1
France, Paris	10.3	83.5	6.3	0.0
Germany, Mainz	70.4	0.0	0.0	29.6
Germany, Saxony-Anhalt	14.3	5.4	59.3	21.0
Ireland, Cork & Kerry	19.9	54.2	11.1	14.8
Italy, Emilia Romagna	33.8	23.4	42.8	0.0
Italy, Tuscany	13.2	4.1	14.0	68.8
Malta	23.0	73.8	2.3	0.9
Netherlands, Northern Netherlands	46.8	41.4	9.4	2.4
Norway	22.4	59.5	18.0	0.0
Poland	51.8	17.9	19.1	11.2
Poland, Wielkopolska	43.3	19.7	34.6	2.3
Spain, Basque country	7.7	45.1	2.4	44.8
Switzerland, Vaud	14.4	59.8	25.5	0.2
UK, Wales	15.6	37.3	47.0	0.0
Ukraine	3.8	14.5	1.2	80.4
average	31.9	32.0	23.5	12.8

** based on the years 2004-2005*

Table 2.4 Details of the definitions of values used in EDMP for 'blank', 'drug use not known' and 'no drugs taken'

	Definition of 'blank'					**Definition of 'drug use not known'**			**Definition of 'no drugs taken'**	
	Not enough sources of drug use for the mother can be found	*The sources are found, but no mention of a drug having been taken in the first trimester can be found*	*Mention of a drug but the information is illegible or non-specific*	*"Drugs1" is never left blank*	*No drugs taken*	*Not enough sources of drug use for the mother can be found*	*The sources have been found, but no mention of a drug having been taken in the first trimester can be found*	*Mention of a drug but the information is illegible or non-specific*	*Record found that states the woman took no drug in the first trimester*	*No mention of any drug in the sources consulted can be found*
Belgium, Antwerp	X		X			X		X	X	
Belgium, Hainaut-Namur	X	X	X			X			X	X
Croatia, Zagreb	X					X			X	
Denmark, Odense		X				X	X		X	
France, Paris				X		X	X	X		X
Germany, Mainz		X			X					
Germany, Saxony-Anhalt				X		X	X	X	X	X
Ireland, Cork & Kerry				X		X	X	X	X	
Italy, Emilia Romagna		X					X		X	
Italy, Tuscany	X						X		X	
Malta	X					X				X
Northern Netherlands				X		X	X		X	X
Norway		X					X		X	
Poland				X		X	X	X	X	
Poland, Wielkopolska				X		X	X	X	X	
Spain, Basque country				X		X		X	X	X
Switzerland, Vaud				X			X		X	
UK, Wales				X		X		X	X	X
Ukraine	X						X		X	
Total:**19**	6	5	2	9	1	13	13	8	17	8

From table 2.4 it is clear that there were large differences between the 19 registries. These should be kept in mind when compiling and analyzing data.

Most of the registries never left Drugs1 blank. When left blank, it usually meant that it was unknown if a medication was taken because not enough sources were found or the sources did not mention any drugs taken. Mainz defined blank as 'no drugs taken'.

For the definition of 'drug use not known' half of the registries applied more than one definition. More than half of the registries applied '*Not enough sources of drug use for the mother can be found*'. More than half of the registries applied '*The sources have been found, but no mention of a drug having been taken in the first trimester can be found*'. Less than half of the registries applied '*Mention of a drug but the information is illegible or non-specific'*.

For the definition of 'no drugs taken' about three-quarters of the registries applied one definition. For most registries '*Record found that states the woman took no drug in the first trimester' wa*s applicable. The table shows that 'No mention of any drug taken in the sources consulted' is interpreted differently between registries as either 'no drugs taken' or 'unknown drug use'.

Discussion

All registries, except Tuscany, used at least one type of 'medical file' as a source, whereas just three registries used a 'registry-based data collection method' as a source to collect data on maternal medication use. Most registries used one or two sources, while four registries used three or more sources. Medical files from maternal healthcare providers in relation to pregnancy, such as midwives and gynaecologists, were most commonly used as a source, followed by medical files from health care providers of the child. More than half of the registries used both sources. According to the registries, chronic and pregnancy-related medication use were usually recorded, although medication for short term use and OTC medication were less well recorded. Other recording aspects varied among the sources and the registries and they also have different ways of resolving discrepancies among their sources.

Medical files were most commonly used to collect information on maternal medication use. These files were readily available for most registries and the information on maternal medication use was frequently prospectively recorded. However, it was not always clear from these files if all the information on medication use was complete.

The registry-based data collection methods, such as interviews conducted by the registry staff and questionnaires (sent out by the registry), provided information on actually used medication. However, the information could be subject to bias; recall bias due to the time between the birth and the interview or questionnaire; bias due to respondents providing the socially desirable answer; and bias due to a poor response rate. Furthermore, these methods are time-consuming and higher costs are involved.

The completeness of registrations regarding medication use and the kind of medication recorded differed per registry and source of information. Some registries provided information on all kinds of medications, including OTC drugs, while others only had information on chronic medication use and medication used during pregnancy. Another important aspect is that some registries recorded the actual use, while others only recorded the prescribed use. The time of data collection and the types of births for which they took record also play a role in the information their database holds. When using EUROCAT information for further studies, researchers must keep in mind how the registries obtained their information and should take this into account in their analyses and in drawing conclusions.

Conclusion

Most registries used one or two sources to obtain information on maternal medication use. The medical files from maternal health care providers in relation to pregnancy were most commonly used. There were differences between the registries and the sources of information they used to compile their records. When performing further studies, it is important for researchers to keep in mind how the registries obtained their information and to take this into account.

CHAPTER 3

Improving information on maternal medication use by linking prescription data to congenital anomaly registers: a EUROmediCAT study

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Abstract

Introduction: Research on associations between medication use during pregnancy and congenital anomalies is significative for assessing the safe use of a medicine in pregnancy. Congenital anomaly registries do not have optimal information on medicine exposure, in contrast to prescription databases. Linkage of prescription databases to the congenital anomaly registries is a potentially effective method of obtaining accurate information on medicine use in pregnancies and the risk of congenital anomalies.

Methods: We linked data from primary care and prescription databases to five EUROCAT congenital anomaly registries. The linkage was evaluated looking at linkage rate, characteristics of linked and non-linked cases, first trimester exposure rates for six groups of medicines according to the prescription data and information on medication use registered in the congenital anomaly databases and agreement of exposure.

Results: Of the 52,619 cases registered in the congenital anomaly databases, 26,552 cases could be linked. The linkage rate varied between registries over time and by type of birth. The first trimester exposure rates and the agreements between the databases varied for the different medicine groups. Information on anti-epileptic drugs, and insulins and analogue medicine use recorded by congenital anomaly registries was of good quality. For SSRIs, anti-asthmatics, antibacterials for systemic use, and gonadotropins and other ovulation stimulants, the recorded information was less complete.

Conclusion: Linkage of primary care or prescription databases to congenital anomaly registries improved the quality of information on maternal use of medicines in pregnancy, especially for medicine groups which are less fully registered in congenital anomaly registries.

Introduction

Medicines are commonly used during pregnancy: approximately 80% of all women use at least one medicine during pregnancy [1]. Although the use of some medicines is unavoidable for serious or chronic conditions, fetal exposure may increase the risk of a congenital anomaly (CA). One example is the anti-epileptic medication valproic acid, which increases the risk of having a child with spina bifida if taken in the first trimester of pregnancy [2]. However, little is known regarding the teratogenic effects of many medicines. Research on possible associations between medicine use during pregnancy and CA is of great importance for assessing the safe use of a medicine in pregnancy. Since CA are rare outcomes, and medicine needs to be analysed in specific groups or as specific drugs, we need to study large datasets with accurate and detailed information on the type and timing of medicine exposure in pregnancy and the type of a possibly related CA.

The European Surveillance of Congenital Anomalies (EUROCAT) network consists of 43 population-based registries set up for the epidemiological surveillance of CA; the network covers 29% of all births in Europe [3-5]. These registries hold information on fetuses and children with CA, and associated factors such as maternal medicine use in pregnancy. Most of the registries retrieve information on first trimester maternal medicine use from medical files, which may be limited and incomplete [6].

Prescription databases, which are increasingly being used to explore associations between medicine use in pregnancy and CA [7-10], contain more complete information on medicine use than CA registries, and prescribing information is prospectively collected. Given the quality of information on medicine exposure that is recorded in both CA registries and prescription databases, linking prescription databases to the EUROCAT CA registries is a potentially effective method of obtaining accurate information on medicine use in pregnancies that were complicated by fetal CA.

In this study we linked administrative prescription databases with five CA registries. We present the results for six selected groups of medicines: anti-epileptic medicines *(Anatomical Therapeutic Chemical (ATC) code [11] N03A)*, insulins and analogues *(A10A)*, SSRIs *(N06AB)*, anti-asthmatics *(R03),* antibacterials for systemic use *(J01),* and gonadotropins and other ovulation stimulants *(G03G)*.

This research was embedded in the EUROmediCAT project [12], which stimulates the collaboration of health care databases and EUROCAT registries. It was a Seventh Framework Programme study funded by the European Union.

Methods

In this study, prescription/ primary care databases were linked to five EUROCAT CA registries:

- **Wales** - the general practitioner data in the Secure Anonymised Information Linkage (SAIL) Databank [13,14] was linked to the Welsh congenital anomaly registry (CARIS);
- **Norway** - Reseptregisteret (Norwegian Prescription Database, NorPD) was linked to the Medical Birth Registry from Norway (MBRN) [15,16];
- **Denmark, Odense** - Lægemiddelstatistikregisteret (Danish National Prescription Registry) [17] was linked to the congenital anomaly registry of Odense, Denmark;
- **Italy, Emilia Romagna** - Emilia Romagna Prescription Database (ERPD) [18] was linked to Emilia Romagna congenital anomaly registry (IMER), Italy;
- **Italy, Tuscany** - Assistenza Farmaceutica Territoriale (AFT, Pharmaceutical Territorial Assistance) and Farmaci a Erogazione Diretta (FED, Medicine Directly Dispensed by the Health System) [19] were linked to the congenital anomaly registry of Tuscany, Italy (RTDC).

The CA registries collect data on fetuses and infants with CA, including live births (LB), fetal deaths (FD) ≥ 20 weeks of gestational age (including stillbirths), and terminations of pregnancy for fetal anomaly (TOPFA). Information on date of birth, gestational age at birth, maternal age, long-term diseases, maternal medicines and disease exposures during pregnancy are also collected. The first trimester of pregnancy is defined according to the EUROCAT Guide [20] as the period from the first day of Last Menstrual Period (LMP) up to 12 completed weeks of gestation [day 0 to day 83].

The primary care or prescription databases involved in our linkage effort are population-based administrative databases that contain data on medicines prescribed and/or dispensed. In the linked prescription data, the first trimester was defined as the period from the first day of LMP as recorded in the CA database up to 14 completed weeks of gestation [day 0 to day 97]. If the LMP was unknown, it was calculated as the date of birth of the child minus the gestational age at birth as recorded in the CA database. If the gestational age at birth was unknown, a

standardized length of 280 days (40 weeks) for live births and 224 days (32 weeks) for still births was used. If the gestational age was unknown for a TOPFA case, the average age for TOPFA's for the respective registry across the whole of the included time period was used. Characteristics of the primary care/prescription databases and the CA registries have been described in detail elsewhere [4,6,21,22]. Table 3.1 summarizes the birth years, the number of CA cases registered in the study period, the registry sources for maternal medicine use, whether the medicine recorded in the CA data was based on the first trimester only or for the whole pregnancy and the proportion of cases with at least one medicine recorded in the CA database.

We applied a distributed database model, in which the linkage was performed locally for all registries and the linked datasets were kept locally [23]. The linkage was performed by matching identification numbers and/or maternal characteristics in both the primary care/prescription and the CA databases. For CA cases identified in the primary care/prescription databases, the information held on medicine use was added to the information in the CA registry. Details of the linkage process have been described elsewhere [24].

An Access-based software module, the Linkage Data Management Program (LDMP), was developed for this project and used to ensure validated datasets. The LDMP was used to import and export data, validate data, and generate tables for evaluation and analyses. The use of the LDMP ensured the compatibility of anomaly subgroups and medicine groups among the participating registries and allowed tables to be generated in a uniform way. To evaluate the linkage effort, the participating registries provided tables generated by LDMP. Since the Danish regulations do not allow external software to be used on their server, Odense, Denmark was not able to import their data via the LDMP. They generated the aggregated tables locally and generated the tables manually, using the same selection criteria and definitions as in the LDMP.

In the analyses cases that met the EUROCAT case definition were included: cases with major CA defined by the Q-chapter of the International Classification of Diseases 10th revision (ICD10), or in the range 740-759 of ICD9, and a very limited set of conditions not included in the Q chapter [20]. Cases with isolated minor anomalies were excluded from the EUROCAT case definition.

Table 3.1 Summary of birth years, number of cases, and the sources of information on maternal medicine use per registry

	Wales (CARIS)	Norway (MBRN)	Odense, Denmark	Emilia Romagna (IMER)	Tuscany (RTDC)
Birth years included in the linkage	1998-2010	2004-2010	1998-2010	2004-2010	2003-2010
Number of cases registered in study period	17,244	21,136	2,006	6,410	5,823
Sources for maternal use of medicines used by the congenital anomalies registry [6]	Medical files from - health care providers in relation to pregnancy	Medical files from - health care providers in relation to pregnancy - health care providers of the child	Medical files from - health care providers in relation to pregnancy - health care providers of the child	Medical files from - health care providers in relation to pregnancy - health care providers of the child - health care providers not in relation to pregnancy (prescription data)	- Questionnaire
Period of medicine use recorded in congenital anomalies data [6]	1st trimester	whole pregnancy	1st trimester	whole pregnancy	1st trimester
Proportion of cases with at least one medication, including vitamins and minerals, recorded for the years 2004-2010 [6]	15.6%	22.4%	17.7%	33.8%	13.2%

Using the LDMP, each registry evaluated the linkage on the following aspects:

- *Linkage success*, defined as the proportion of cases in the CA database that could be linked to the primary care/prescription data.
- *Comparison of the linked and non-linked cases*: since not all the cases could be linked, we considered it relevant to compare both groups on year of birth and type of birth. A Chi^2 test was performed for both factors to determine the statistical significance. If 20% of the cells in the contingency table had less than five observations, a Fisher Exact test was performed instead of the Chi^2 test. The statistical tests were performed in PASWStatistics 22 (SPSS Inc., IBM, Chicago, IL, USA).
- *Comparison of data on first trimester medicine use*: the 'first trimester exposures rates' and the 'agreement of exposure' were calculated as described in figure 3.1 to compare the data.

		Prescription database		
		+	–	Total
CA database	+	**A**	**B**	A+B
	–	**C**	**D**	C+D
	Total	A+C	B+D	A+B+C+D

First trimester exposure rate according to CA registry data
% of women exposed to medicine in the first trimester according to the CA registry
*(A+B)/(A+B+C+D) *100%*

First trimester exposure rate according to prescription data
% of women exposed to medicine in the first trimester according to the prescription database
*(A+C)/(A+B+C+D) *100%*

Agreement of exposure according to the primary care/prescription data
Number of women using medicine according to both CA registry and prescription database divided by the total number of women with medicine prescribed in the prescription database
*A/(A+C) *100%*

Agreement of exposure according to the CA data
Number of women using medicine according to both CA registry and prescription database divided by the total number of women with medicine prescribed in the CA registry
*A/(A+B) *100%*

- The numbers per registry for each medicine are available on –
http://www.euromedicat.eu/content/WP3%20Deliverable%2011%20Report.pdf -

Figure 3.1 Data in the primary care/prescription databases and the CA databases

These factors were calculated for six groups of medicines: anti-epileptic medicines, insulins and analogues, SSRIs, anti-asthmatics, antibacterials for systemic use, and gonadotropins and other ovulation stimulants. The agreement according to the primary care/prescription data may be influenced by the definition of first trimester exposure (date of prescription in period 0-97 days), therefore we also calculated the agreement using a broader 1st trimester definition (-31 to +97 days after LMP).

Results

The five CA databases included 52,619 cases in total, of which 65.7% (n=34,547) could be linked. The proportion of cases that could be linked ranged from 31.7% in Wales (where 40% of the primary care practices contribute prescription data to the voluntary SAIL database) to 100% in Odense, Denmark. Of the 34,547 registered cases that were linked to prescription databases, 26,552 (76.9%) met the EUROCAT case definition as described in the Methods section (Table 3.2a).

The linked and non-linked EUROCAT cases were compared for year of birth and type of birth for the registries with less than 100% linkage success (Table 3.2b). There was a significant difference between the linked and non-linked cases for all registries in year of birth. For Wales, Emilia-Romagna and Tuscany, the rate of linked cases increased over time, while the number of linked cases decreased over time in Norway. For type of birth, there were no differences between linked and non-linked cases for Wales and Norway. For Emilia Romagna, TOPFA cases were only seen in the non-linked group while, for Tuscany, there were fewer live births (74.0% vs. 86.2%), but more TOPFA cases (25.1% vs. 12.6%) in the linked group.

The first trimester exposure rates according to the CA data and the primary care/prescription database are shown in table 3.3. For the anti-epileptic medicines and the insulins and analogues, there were small, but potentially clinically important differences between the first trimester exposure rates based on the CA registries and the primary care or prescription database. The first trimester exposure rates for anti-asthmatics also revealed small differences between those recorded in the CA registries and in the primary care or prescription database per registry, except for Tuscany. For Tuscany, the first trimester exposure rate recorded in the prescription database was more than six times higher than the rate recorded in the CA registry. For the SSRIs the first trimester exposure rates recorded in the primary care or prescription database were 2-3 times higher than the rates recorded in the CA registries for

Table 3.2a Linkage results per registry

Registry	Wales (CARIS)		Norway (MBRN)		Odense, Denmark		Emilia Romagna (IMER)		Tuscany (RTDC)	
Years of inclusion	1998-2010		2004-2010		1998-2010		2004-2010		2003-2010	
	n	%	n	%	n	%	n	%	n	%
Total number of cases in CA registry	**17244**	**100**	**21136**	**100**	**2006**	**100**	**6410**	**100**	**5823**	**100**
Linked to prescription/primary care database	5472	31.7	20874	98.8	2006	100	3172	49.5	3023	51.9
Total number of EUROCAT cases* linked to prescription database (% calculated on linked cases)	5322	97.3	13474	64.5	2006	100	3034	95.6	2716	89.8

**A EUROCAT case is defined as a child with major CA defined by the Q-chapter of ICD10, or in the range 740-759 of ICD9, and a very limited set of conditions not included in the Q chapter [22]. Cases with only minor anomalies were excluded from the EUROCAT case definition.*

Table 3.2b Description of linked and non-linked EUROCAT cases according to type of birth and year of birth

Registry	Wales (CARIS)		Norway		Odense, Denmark**	Emilia Romagna		Tuscany	
	Linked 5322 (%)	Non linked 11472 (%)	Linked 13474 (%)	Non-Linked 185 (%)	Linked 2006 (%)	Linked 3034 (%)	Non linked 2427 (%)	Linked 2716 (%)	Non linked 2370 (%)
Type of birth							*		*
LB	4502 (84.6)	9685 (84.4)	11848 (87.9)	154 (83.2)	1644 (82.0)	3024 (99.7)	1163 (47.9)	2010 (74.0)	2043 (86.2)
FD	107 (2.0)	224 (1.9)	147 (1.1)	1 (0.5)	47 (2.3)	10 (0.3)	19 (0.8)	23 (0.8)	28 (1.2)
TOPFA	713 (13.4)	1563 (13.6)	1479 (11.0)	30 (16.2)	315 (15.7)	0	1245 (51.3)	683 (25.1)	299 (12.6)

LB: Live births, FD: Fetal death ≥ 20 weeks gestation (including stillbirths); TOPFA: Terminations of pregnancy for fetal anomalies
** P<0.01*
*** all EUROCAT cases from the Danish registry could be linked to the prescription database*

Table 3.2b Description of linked and non-linked EUROCAT cases according to type of birth and year of birth (continued)

Registry	Wales (CARIS)		Norway		Odense, Denmark**	Emilia Romagna		Tuscany	
	Linked 5322 (%)	Non linked 11472 (%)	Linked 13474 (%)	Non-Linked 185 (%)	Linked 2006 (%)	Linked 3034 (%)	Non linked 2427 (%)	Linked 2716 (%)	Non linked 2370 (%)
Year of birth		*		*			*		*
1998	344 (6.5)	1145 (10.0)			143 (7.1)				
1999	326 (6.1)	1026 (8.9)			144 (7.2)				
2000	366 (6.9)	1019 (8.9)			154 (7.7)				
2001	383 (7.2)	872 (7.6)			150 (7.5)				
2002	426 (8.0)	844 (7.4)			155 (7.7)				
2003	437 (8.2	831 (7.2)			131 (6.5)			344 (12.7)	344 (14.5)
2004	493 (9.3)	762 (6.6)	2652 (19.7)	33 (17.8)	136(6.8)	255 (8.4)	385 (15.9)	318 (11.7)	362 (15.3)
2005	442 (8.3)	831 (7.2)	2014 (14.9)	19 (10.3)	161 (8.0)	359 (11.8)	347 (14.3)	279 (10.3)	238 (10.0)
2006	445 (8.4)	869 7.6)	1996 (14.8)	18 (9.7)	192 (9.6)	344 (11.3)	340 (14.0)	317 (11.7)	320 (13.5)
2007	463 (8.7)	879 (7.7)	1777 (13.2)	14 (7.6)	163 (8.1)	359 (11.8)	353 (14.5)	301 (11.1)	252 (10.6)
2008	424 (8.0)	866 (7.5)	1693 (12.6)	27 (14.6)	180 (9.0)	478 (15.8)	352 (14.5)	334 (12.3)	264 (11.1)
2009	421 (7.9)	779 (6.8)	1631 (12.1)	29 (15.7)	155 (7.7)	535 (17.6)	358 (14.8)	361 (13.3)	276 (11.6)
2010	352 (6.6)	749 (6.5)	1711 (12.7)	45 (24.3)	142 (7.1)	704 (23.2)	292 (12.0)	462 (17.0)	314 (13.2)

** P<0.01*

*** all EUROCAT cases from the Danish registry could be linked to the prescription database*

Table 3.3 First trimester exposure rates for CA data and the primary care/prescription data for Wales, Norway, Odense, Denmark, Emilia Romagna, and Tuscany (%)

Medicine subgroup (EUROmediCAT)	**ATC code starting with**	**Wales-CA**	**Wales-PrX**	**Norway-CA**	**Norway-PrX**	**Odense, Denmark-CA**	**Odense, Denmark-PrX**	**Emilia Romagna-CA**	**Emilia Romagna-PrX**	**Tuscany-CA**	**Tuscany-PrX**
Years of inclusion Number of cases		1998-2010 N= 5322		2004-2010 N= 13474		1998-2010 N= 2006		2004-2010 N= 3034		2003-2010 N= 2716	
Anti-epileptics	N03A	0.77	0.66	0.46	0.50	0.55	0.60	0.26	0.33	0.59	0.52
Insulins and analogues	A10A	1.01	0.70	1.25	0.91	0.65	0.70	0.43	0.36	0.70	0.37
Anti-asthmatics	R03	4.47	5.58	1.74	1.89	3.14	3.24	2.11	2.74	0.37	2.39
SSRIs	N06AB	1.05	3.44	0.62	0.79	1.65	1.74	0.33	0.69	0.41	1.44
Antibacterials for systemic use	J01	2.87	12.78	6.43	9.84	-	-	10.12	15.52	1.84	12.96
Gonadotropins and other ovulation stimulants	G03G	1.16	0.34	0.10	3.03	-	-	0.69	1.05	0.07	1.58

CA= Congenital anomaly registry; PrX= prescription or primary care database.
'-' means data were not retrieved

Wales, Emilia Romagna and Tuscany. For antibacterials for systemic use, the first trimester exposure rates recorded in the primary care or prescription databases was much higher than the rates in the CA registries. Furthermore, there was a wide variation over the registries: for the CA registries, the rates ranged from 1.84% (Tuscany) to 10.12% (Emilia Romagna) while for the primary care or prescription databases the rates ranged from 9.84% (Norway) to 15.52% (Emilia Romagna). The first trimester exposure rates for the gonadotropins and other ovulation stimulants were also higher in the prescription databases, except for Wales.

The agreement according to the primary care/prescription data and the agreement according to the CA data for the first trimester is shown in table 3.4a. For the anti-epileptic medicines and insulins and analogues, which are both used for long-term conditions, the agreement between both databases was generally relatively high. The SSRIs and anti-asthmatics, which are also used in long-term conditions, showed a lower agreement between the two databases. Medicines for occasional use, such as antibacterials for systemic use, and gonadotropins and other ovulation stimulants, showed a relatively low agreement between the databases. Extending the time period by including the month before the first trimester did not affect the findings on anti-epileptic medicines and insulins and analogues to a large extent, but the agreement according to the CA data was increased for SSRIs and anti-asthmatics for some of the registries (Table 3.4b).

Discussion

We linked administrative databases to five CA registries and evaluated the results of the linkage for six types of common medicines. The linkage success varied between registries over time and, for the Italian registries, by type of birth. The first trimester exposure rates and the agreements between the databases varied for the different medicine groups. In general, information on anti-epileptic medicines, and insulins and analogue medicine use recorded by CA registries was of good quality. For SSRIs, anti-asthmatics, antibacterials for systemic use, and gonadotropins and other ovulation stimulants, the recorded information was less complete.

A major challenge in using prescription data is linking it to all the cases of CA, irrespective of pregnancy outcome. For Norway and Odense, Denmark, linkage was possible for most cases, as the linkage used personal ID numbers, while the linkage success was lower for the other registries. In Wales, general practitioners (GPs) contribute to SAIL on a voluntary basis, currently 40% of the GPs contribute and although this percentage is increasing, it reduces

Table 3.4a Comparison of parameters based on the first trimester [day 0 to day 97]

		Agreement according to the prescription/ primary care data in %					Agreement according to the CA data in %				
Medicine subgroup (EUROmediCAT)	**ATC code starting with**	**Wales**	**Norway**	**Odense, Denmark**	**Emilia Romagna**	**Tuscany**	**Wales**	**Norway**	**Odense, Denmark**	**Emilia Romagna**	**Tuscany**
Anti-epileptics	N03A	77.1	63.2	91.7	40.0	71.4	65.9	69.4	100.0	50.0	62.5
Insulins and analogues	A10A	81.1	71.5	71.4	63.6	60.0	55.6	52.4	76.9	53.8	31.6
Anti-asthmatics	R03	33.3	33.5	58.5	19.3	6.2	41.6	36.3	60.3	25.0	40.0
SSRIs	N06AB	22.4	38.3	74.3	19.0	17.9	73.2	48.8	78.8	40.0	63.6
Antibacterials for systemic use	J01	7.8	16.4	-	27.8	6.3	34.6	25.2	-	42.7	44.0
Gonadotropins and other ovulation stimulants	G03G	27.8	1.5	-	21.9	2.3	8.1	42.9	-	33.3	50.0

'-' means data were not retrieved

Table 3.4b Comparison of parameters based on the broad definition of the first trimester [day -31 to day 97]

		Agreement according to the prescription/ primary care data in %					Agreement according to the CA data in %				
Medicine subgroup (EUROmediCAT)	**ATC code starting with**	**Wales**	**Norway**	**Odense, Denmark**	**Emilia Romagna**	**Tuscany**	**Wales**	**Norway**	**Odense, Denmark**	**Emilia Romagna**	**Tuscany**
Anti-epileptics	N03A	76.9	58.2	91.7	30.8	62.5	73.2	74.2	100	50	62.5
Insulins and analogues	A10A	82.1	72.3	71.4	63.6	63.6	59.3	56.0	76.9	53.8	36.8
Anti-asthmatics	R03	33.8	30.7	58.9	22.6	5.0	47.9	40.6	68.3	40.6	40.0
SSRIs	N06AB	18.2	35.3	73.0	19.4	16.3	76.8	58.3	81.8	60.0	72.7
Antibacterials for systemic use	J01	7.5	15.1	-	26.7	5.1	42.5	28.8	-	52.4	46
Gonadotropins and other ovulation stimulants	G03G	36.1	1.7	-	22.4	2.6	21.0	64.3	-	71.4	100

'-' means data were not retrieved

the number of Welsh cases that could be linked. For Emilia Romagna, the TOPFA cases could not be included in the linkage, because the CA registry does not have ID numbers for the TOPFA cases or their mothers due to privacy regulations. As a result, the linked cases are biased towards the less severe cases there. In Tuscany, an ID number for the mother was only available for 52% of the TOPFA cases. Therefore, one should be aware that if not all cases can be linked, there may be some bias in the results reported or the linked dataset may not be suitable to analyse a possible association between medication use and severe anomalies that result frequently in terminations of pregnancy.

Medicines prescribed or dispensed before the first trimester were not included in the first trimester definition of the primary care or prescription databases. It is possible that these medicines, although prescribed earlier, were also taken in the first trimester and therefore registered in the CA registry. Technically there is a difference in the definition of the first trimester between the primary care or prescription databases and the CA registries. However, we expect the influence on the first trimester exposure rates to be minimal, since the CA registries collect information on medicine use mainly from medical files (except Tuscany) in which medicine use is recorded as 'used in the first trimester' rather than on a specific date. In addition, the Norwegian CA registry and Emilia Romagna includes information on medicine used during any time in pregnancy, not specifically during the first trimester. Therefore, misclassification of exposure cannot be ruled out; in particular for medicines prescribed or taken at the start or towards the end of the first trimester there may be disagreement between the information recorded in the CA data and the prescription data.

For Emilia Romagna, relatively low rates of agreement were found for medicines taken for long-term conditions. The registry has now changed their data sources for medicine exposures and has added prescription information as a data source.

In general, per registry, the anti-epileptic medicines and insulins and analogues showed small differences between the first trimester exposure rates recorded in the CA registries and the rates in the primary care or prescription databases. In addition, the agreements between the primary care/prescription databases and the CA registries were, in general, relatively high. This was expected, since these medicines are prescribed for long-term conditions and used on a regular, daily basis; they are therefore well recorded in both medical files and prescription databases. However, we noted 98 cases in which insulin (54) and anti-epileptics (44) were prescribed in primary care or prescription database, but not recorded in or abstracted from the

medical files, which are the main data source for the CA registries. Such omissions from the medical records could have serious clinical consequences, unless more accurate histories were taken on admission for delivery.

For the anti-asthmatics, small differences were found between the first trimester exposure rates recorded in the CA registries and the primary care or prescription database per registry. However, the agreements between the primary care/prescription databases and the CA registries were, in general, relatively low. The most plausible explanation for this is that some anti-asthmatics are often taken 'as necessary'. It is possible that they were dispensed before the first trimester, and were therefore not present in the prescription database as a first trimester prescription, but that they were indeed used in the first trimester and therefore recorded in the CA registry. Extending the relevant period with the month before pregnancy, increased the agreement for anti-asthmatics and SSRIs. This emphasizes that the time frame used in the definition of the first trimester may differ for medicines depending on prescribing characteristics. Other explanations for low agreement could be that the prescribed medicines were not taken (non-compliance) or that the medicines were taken, but their use was not recorded. Medicines may not be recorded in medical files for several reasons: women may forget; the midwife may not ask the woman about medicine use when taking the initial medical history, or the question may be asked in a perfunctory manner, so that the woman does not realise the importance of an accurate medical history; women may be uncertain of the starting date of their first trimester; medication use may be mentioned but not recorded in the medical file; or the medicine was prescribed after the first antenatal visit and therefore not recorded in the medical file. Some CA registry records did not give the full name of the medicines taken, so no ATC code could be matched to the prescription database: for example, if the woman cannot name her specific medicine, just 'taking antidepressant' may be recorded. When no information is found in medical records on maternal medication use, registries may either interpret this as 'no medication taken' or 'medication use unknown'. The use of administrative data may overcome this problem.

For the SSRIs, the first trimester exposure rates recorded in the primary or prescription database were 2-3 times higher than the rates recorded in some CA registries. Furthermore, SSRIs had a relatively low agreement according to the primary care/prescription data. The high rate of non-reporting of antidepressants suggests that records might be biased by the stigma surrounding mental illness. This may lead to either non-adherence with prescribed regimens or

non-reporting. Reporting of antiepileptic prescriptions (often for mental illness) may have been similarly affected.

For the antibacterials for systemic use, the rates found in the primary care or prescription databases were much higher than the rates in CA registries and there were differences between the registries. The agreements according to both the primary care/prescription databases and the CA registries were, in general, relatively low. It is likely that, by the time of their interviews with the midwife, some women had forgotten having a short course of antibacterial agents. The differences over the registries can be explained by differences in the prescribing behaviour seen between the regions.

For gonadotropins and other ovulation stimulants, rates in the primary care or prescription databases were generally higher than the rates in CA registries, whereas the agreements according to both the primary care/prescription database and the CA registries were, in general, relatively low. Since these medicines are used in fertility treatments and the prevention of miscarriages, non-compliance is a less plausible explanation. The medicines were presumably used, but not recorded. For gonadotropins and other ovulation stimulants, it is also possible that the woman did not mention their use because she did not consider them as medicines, or she was concerned about possible stigmatisation.

In conclusion, we found that information on anti-epileptics, and insulins and analogues, was fairly complete in the CA registries, whereas for SSRIs, anti-asthmatics, antibacterials for systemic use, and gonadotropins and other ovulation stimulants, the information was less complete. Therefore, the linkage held more added value for SSRIs, anti-asthmatics, antibacterials for systemic use, and gonadotropins and other ovulation stimulants.

In our project, the linkage was performed locally for all registries and the linked datasets were kept locally, according to the distributed database model. This was necessary to comply with confidentiality regulations in Odense, Denmark, Norway and Wales, where linked data may not be sent outside the server. However, since large datasets are needed to study the safety of medicine use in pregnancy, the separate local datasets need to be combined for further studies on the risk of medicines in pregnancy; the ideal situation would be to collect and analyse such linked data in a central unit.

For this project we used data from prescription databases. In principle, prescription data contain the complete, prospectively recorded, medication history, except for Over-The-Counter (OTC) medication and medications dispensed in hospitals and private clinics. However, in

Norway, the prescription database includes medicines dispensed to an individual (out-patient) who collects them at a hospital pharmacy, but it does not include medicines given to individuals who are in hospital (in-patients). Furthermore, the quality of prescription data is not affected by the woman's recall or the accuracy of health care professionals who record medication use in medical files.

Nonetheless, this does not necessarily mean that medicines prescribed or dispensed are actually taken [25]. However, we know from a Dutch cross-sectional study that prescription data will most likely overestimate the exposure, but this overestimation seems to be minimal, which makes prescription records a reliable source for research into associations between medication use in pregnancy and CA [26].

The information on amount and dosage prescribed was not available in a standard way (DDD) in our databases. Therefore, we could not include the duration of the prescription in our definition of exposure [21]. To improve the use of prescription data, information on the amount prescribed and the daily dose should be included in the administrative databases. In addition, more uniformity concerning data definitions (ATC codes, medication grouping, first trimester definition) should also be taken into account to prevent bias.

In a previous Norwegian study, data of the NorPD and MBRN, which were also included in this study, were linked and compared by calculating the sensitivity, the specificity and the positive predictive value (PPV) of recorded medicine in the MBRN for the period 2004-2007, using NorPD as the "*gold standard*" [15]. It was possible to compare the Norwegian study's 'sensitivity values' to our values of agreement according to the prescription database, and to compare the 'PPV values' to our values of agreement according to the CA registry. However, the Norwegian study did not provide data on gonadotropins and other ovulation stimulants specifically, while they did provide data on selective beta-2-adrenoreceptor agonists (ATC code R03AC) and glucocorticoids (ATC code R03BA) instead of anti-asthmatics in general (ATC code R03). We found the values of sensitivity and the agreement according to the prescription data for Norway to be comparable. However, the values of the PPV were higher in the Norwegian study than the values we calculated for the agreement according to the CA registry for Norway. This difference may be related to the fact that the Norwegian study included all deliveries, while we only included deliveries with a CA in the offspring.

In another study, administrative data relating to all pregnancy events (which were classified as a birth, an ectopic pregnancy, or a termination of pregnancy) in Western Australia

were linked to a national database of dispensed medicines for the period 2002-2005. This study had a high linkage rate of health and other data due to very few missed links (0.11%) and low permanent migration (2.7%), and the researchers found that a medicine had been dispensed to 28.0% of women who had a pregnancy event [27,28].

Conclusion

We have described the linkage of primary care or prescription databases to CA registries and shown that this improves the quality of information on maternal use of medicines in pregnancy, especially for some medicine groups which are less fully registered in CA registries, like SSRIs, anti-asthmatics, antibacterials for systemic use, and gonadotropins and other ovulation stimulants. However, if the prescribed medicine is not actually taken, the use of prescription data may lead to an overestimation of exposure. Possible selection bias towards specific types of CA in the linked cases needs further attention.

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CHAPTER 4

Actual use of medications prescribed during pregnancy: a cross-sectional study using data from a population-based congenital anomaly

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Abstract

Introduction and Aim: Data from prescription databases are increasingly being used to study associations between maternal medications used in pregnancy and congenital anomalies. We therefore investigated the extent to which prescriptions reflect the actual use of medication during pregnancy, and whether medicines used during pregnancy are taken according to the prescribed dosage and duration.

Methods: We performed a cross-sectional study in a population-based congenital anomaly register (EUROCAT Northern Netherlands). We included 202 women who had at least one prescription during their pregnancy and who gave birth between 2009 and 2011. Compliance with the prescribed medication was verified by telephone interview. We calculated the compliance rates for several medication groups by dividing the number of mothers who confirmed they had taken the medication by the total number to whom it had been prescribed. Compliance was positive if the mother confirmed she took the medication, even if she only took one of several prescriptions from the same medication group. For each prescription taken, we also determined whether her use conformed to the prescribed dosage and duration.

Results: During the first trimester, the compliance rates ranged from 0.84 (for chronic diseases) to 0.92 (for pregnancy-related symptoms). Most of the medications actually taken were used at the prescribed dosage or lower. More than half of the medications actually taken were used for the duration prescribed or shorter.

Conclusion: Prescription records are generally a relatively reliable source of data for research into associations between medication use in pregnancy and congenital anomalies compared with other data sources. Pharmacy records of medication use in pregnancy might represent an overestimation, which should be taken into account. However, our results show that, except for 'corticosteroids, dermatological preparations'; 'ear, eye, nose and throat preparations'; and 'anxiolytics, hypnotics and sedatives', this overestimation generally seems minimal.

Introduction

Approximately 80% of all women use one or more medications during pregnancy [1]. However, whether new medicines have any teratogenic effects is largely unknown, since data obtained from animal studies cannot always be translated to humans, and pregnant women are excluded from clinical trials for ethical reasons [2]. For chronic illnesses, the use of medication during pregnancy is often unavoidable. The use of some specific medications might result in a higher risk of specific congenital anomalies, such as the anti-epileptic medication valproic acid, which results in an increased risk of spina bifida if used in the first trimester of pregnancy [3]. Given that certain medications are unavoidable during pregnancy and the severity of some congenital anomalies, research into associations between them is highly relevant.

Two types of information are frequently used in studies on medication use in pregnancy: self-reports (interviews and questionnaires) and 'medical' records (information extracted from medical files, or pharmacy or health insurance records). The use of pharmacy databases, which hold data on prescriptions to individuals, is relatively easy. Furthermore, the data are registered prospectively. However, one cannot assume the patient actually takes the medication prescribed [4]. Non-compliance can result in misclassification of exposure and lead to bias in study outcomes [5,6]. Since data from pharmacy databases are increasingly being used for research into associations between medication use in pregnancy and congenital anomalies [7, 8], it is important to verify patients' compliance with the prescribed medication.

The aim of this study is to investigate the extent to which prescriptions reflect the actual use of medication during pregnancy, and whether medicines used during pregnancy are taken according to the prescribed dosage and duration.

Methods

Setting

We conducted a cross-sectional study in which we investigated how accurately prescriptions reflect the actual use of medications during pregnancy by verifying their use and dosage and the duration for which they were taken. We used data from women who had had a child with a congenital anomaly in 2009–2011 and who participated in a population-based congenital anomaly register in the northern Netherlands (EUROCAT NNL). This region has approximately 17,000 births per year [9], which is approximately 10% of all births in the Netherlands [10]. All pregnancy outcomes involving a congenital anomaly are registered,

including live births, stillbirths (a fetus of '24 weeks' gestation that died in the uterus or during birth [11]), spontaneous abortions (a fetus of '24 weeks' gestation that died naturally), and terminations of pregnancy for a fetal anomaly (TOPFA) [11]. For the live births, the age limit for inclusion in the registry is 10 years.

Parental informed consent was required for registration, and the parents were sent a questionnaire enquiring about their socio-demographic characteristics and potential risk factors, including use of medicines. The questionnaire also asked for permission for the mother's pharmacy records for the period from 3 months before conception up to delivery to be requested. After the completed questionnaire and pharmacy information was received, one of our research assistants interviewed the mother by telephone. The research assistant asked about each prescription and checked whether the mother actually took it and whether she followed the prescribed dose and duration [12].

For this study, we included data from mothers who gave birth or had a termination of pregnancy between 2009 and 2011, who received at least one prescription medication during their pregnancy, and who were interviewed between 1 January 2011 and 1 February 2012.

Medication

In our analyses, we only included prescribed medication dispensed by community pharmacies. We had no information on medication dispensed during hospitalization or medication that was bought over the counter (OTC). In vitro fertilization (IVF) medication and contraceptives were excluded since the intake of these medicines is cycle dependent, which makes the exact use difficult to determine. Homeopathic medicines, herbals, allergens, antiparasitic products, insecticides, and repellents were also excluded, because they are available OTC and are rarely prescribed.

For each medication, we extracted the following information: brand or generic name, Anatomical Therapeutic Chemical (ATC) code [13], formulation (oral, inhalation, dermal), date of prescription, total amount prescribed, and daily dosage. Medicines were categorized into three main groups (medication for chronic conditions, medication for occasional and short-term use, and medication for pregnancy-related problems) and several subgroups among these main groups adapted from the scheme used by Bakker et al. [1] and shown in table 4.1.

Table 4.1 Classification of the main groups and subgroups of medications prescribed during pregnancy

Medicines for chronic diseases	**(part of) ATC code***
• Antihypertensives, vasoprotectives, beta blocking agents, calcium channel blockers	C02, C05, C07, C08
• Corticosteroids, dermatological preparations	D07
• Medicines for obstructive airway diseases	R03
Medicines for short-term or occasional use	
• Medicines for functional gastrointestinal disorders, for peptic ulcers and gastro-esophageal reflux disease (GORD)	A02B, A03, excl A03FA01
• Dermatologicals excluding anti-psoriatics and corticosteroids, dermatological preparations	D excl D05 and D07 (D01,D02,D06,D08,D10,D11)
• Antifungals for dermatological use	D01
• Emollients and protectives	D02
• Antibacterials for systemic use	J01
• Anxiolytics, hypnotics and sedatives	N05B, N05C
• Ear, eye, nose and throat preparations	R01, R02A, R05, S01, S02, S03
Medicines for pregnancy-related symptoms	
• Antacids	A02A
• Anti-emetics	A03FA01, A04A, N05AB04, R06AD, R06AE
• Laxatives	A06
• Multivitamins containing folic acid or folic acid and its derivatives	A11BA, B03B
• Iron preparations	B03A
• Gynecological anti-infectives and antiseptics	G01

** Anatomical Therapeutical Classification (ATC) code [13]*

Compliance

The women were sent a list of their prescribed medication before the telephone interview. In the telephone interview, compliance with each prescription was verified on the basis of standard questions (appendix 1b). Within the interview, it was emphasized that the questions on medication use were asked in order to collect data to perform research on congenital anomalies and not to suggest a possible association with the condition of the child.

If a mother confirmed that she had taken her prescribed medication, we defined her as a compliant user for that medication, irrespective of whether she had used the medication exactly as prescribed (correct dosage and correct duration). If a medication was prescribed more than once and the mother had taken just one prescription, she was still counted as a compliant user for that medication.

As this broad definition of compliance might overestimate actual compliance, we also applied a stricter definition of compliance to investigate the effect of any overestimation. In the

strict definition, a mother was counted as a 'compliant user' only if all of the prescriptions of a specific medication were actually taken. If a medication was prescribed more than once but not all the prescriptions had been taken, she was not counted as a 'compliant user'.

We also focused on compliance by grouping the prescriptions according to the different modes of application: oral, dermatological, inhalation, vaginal, rectal, ear, eye, and nasal preparations, and injections. Compliance for each of these groups was calculated according to the broad definition.

The compliance rate for a medication or medication subgroup was calculated by dividing the number of compliant users by the total number of mothers who had been prescribed that medication according to their pharmacy records:

$$\frac{\textit{number of compliant users}}{\textit{total number of mothers given a prescription}}$$

For the compliance rate, the 95% confidence intervals (95% CI) were calculated using the Wald-formula [14]:

$$\text{Compliance} \pm 1.96 * \sqrt{\frac{p.(1-p)}{n}}$$

The Wald-formula can be applied when n*p>5 AND n*(1-p)>5. If this condition was not met, we applied the Wilson-formula to calculate the 95%CI:

$$\frac{K+\frac{1}{2}z^2}{n+z^2} \pm \frac{z*\sqrt{\frac{K.(n-K)}{n}+\frac{z^2}{4}}}{n+z^2}$$

in case of a 95%CI, z=1.96 [14].

The compliance rate was calculated for the first trimester and for the entire pregnancy. The first day of the last menstruation was defined as 'day 0'. The first trimester was defined as the period between day 0 and day 98, whereas the entire pregnancy was defined as period between day 0 and date of birth. The date of prescription determined whether the medication was counted as 'first trimester' or 'entire pregnancy', even if the medication was prescribed in the first trimester, but also used in the second or third trimester.

To minimize the influence of coincidental findings, the compliance rate was only calculated if at least 10 mothers had been prescribed a specific medication subgroup. This

means that the total number of prescriptions and mothers in the three main groups is not necessarily the sum of the subgroups.

Prescriptions per mother, and prescribed dosage and duration

In addition to the compliance, for each medication we calculated the proportion that was actually taken according to the dosage and duration prescribed. We also counted the number of mothers who had one or more prescriptions for each medication group and subgroup. We used PASW Statistics 22 and Excel 2007 for the calculations.

Results

During the data collection period from 1 January 2011 to 1 February 2012, a total of 735 congenital anomaly cases were fully registered, and we received pharmacy records for 420 of the pregnancies. After selecting for pharmacy records that covered the period of 3 months before conception up to delivery, covering mothers who gave birth between 2009 and 2011, and that contained complete information on medications prescribed, date of prescription, and amount and dose prescribed, we had 202 pregnancies to study (Figure 4.1). The time period between date of telephone interview and date of birth ranged from 2 to 35 months with a median of 13 months (interquartile range [IQR] 7.75–18).

Characteristics of the Cases

A total of 29% (59/202) cases were born in 2009; 50% (101/202) in 2010; and 21 % (42/202) in 2011. Most (80%, 162/202) were live births; 6% (12/202) were stillbirths or spontaneous abortions, and 12% (24/202) were TOPFAs. Nine pregnancies ended before the end of the first trimester (before day 98): eight of these were TOPFAs and one was a spontaneous abortion.

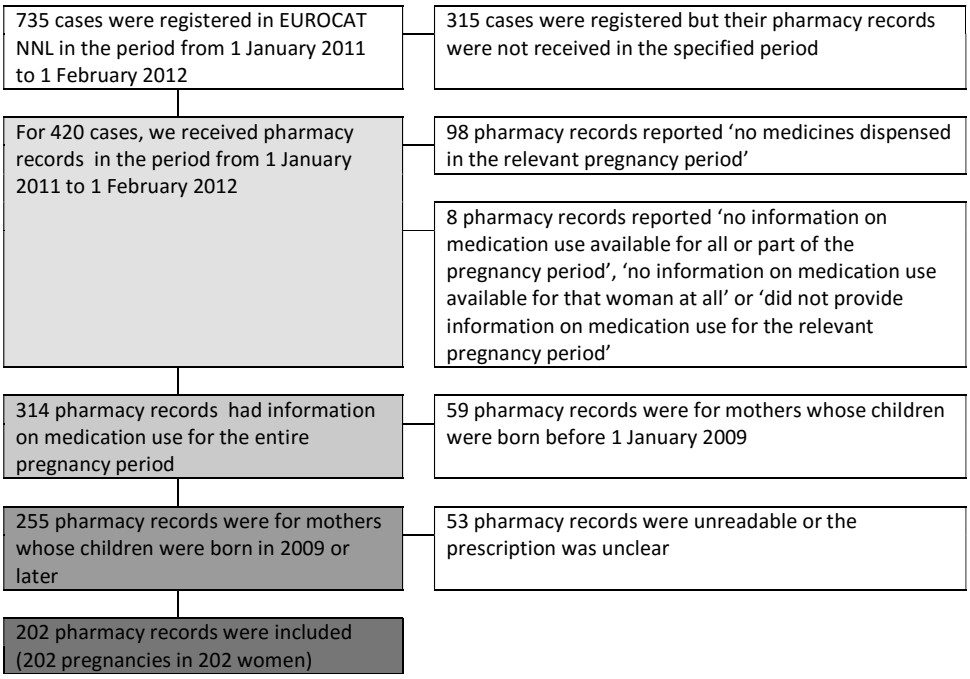

Figure 4.1 Case selection flowchart

Prescriptions

During pregnancy, 38% (77/202) of the mothers were prescribed at least one medication for a chronic disease, and 64% (49/77) of these had more than one prescription for a medication in that specific group. A total of 63% (128/202) of the mothers were prescribed at least one medication for short-term or occasional use, and 58% (74/ 128) of these had more than one prescription for medicines in that specific group. A total of 55% (112/202) of the mothers were prescribed at least one medicine for pregnancy- related symptoms, and 58% (65/112) of these had more than one prescription in that specific group; see Table 4.2

In the group of 202 mothers, a total of 817 prescriptions were prescribed for 142 different medicines during pregnancy. The number of prescriptions per mother during pregnancy varied between 1 and 29 (median 3). During the entire pregnancy, miconazole (gyno), meclozine combinations (Emesafene), amoxicillin, nitrofurantoin, and ferrous fumarate were most commonly prescribed. With the exception of nitrofurantoin and ferrous fumarate, these medications were also most frequently prescribed in the first trimester.

Table 4.2 Overview of the numbers of prescriptions, the women to whom they were prescribed and their compliance rate for the first trimester and the entire pregnancy

	A		B				
Medication	**prx (n)**	**Maximum n of prx per pregnancy**	**Women who were given a prx at least once (n)**	**Women with > 1 prx (n)**	**%**	**Women who confirmed the use of at least one prx (n)**	**Compliance rate (95% CI)**
First trimester							
All medicines together	314	19	129	75	58	117	0.91 (0.86-0.96)^
Medicines for chronic diseases together	85	5	45	24	53	38	0.84 (0.74-0.95)^
• Antihypertensives, vasoprotectives, beta blocking agents, calcium channel blockers	8	3	*	*	*	*	*
• Corticosteroids, dermatological preparations	15	2	13	2	15	9	0.69 (0.42-0.87)#
• Medicines for obstructive airway diseases	21	5	10	6	60	9	0.90 (0.60-0.98)#
Medicines for short-term and occasional use together	113	6	70	24	34	60	0.86 (0.78-0.94)^
• Medicines for functional gastrointestinal disorders and medicines for peptic ulcer and gastro-esophageal reflux disease (GORD)	18	3	12	4	33	11	0.92 (0.65-0.99)#
• Dermatologicals exclusive anti-psoriatics and corticosteroids, dermatological preparations	27	4	20	4	20	18	0.90 (0.70-0.97)#
• Antifungals for dermatological use	7	1	*	*	*	*	*
• Emollients and protectives	8	3	*	*	*	*	*
• Antibacterials for systemic use	31	2	28	3	10	23	0.82 (0.64-0.92)#
• Anxiolytics, hypnotics and sedatives	3	1	*	*	*	*	*
• Ear, eye, nose and throat preparations	17	2	13	4	30	9	0.69 (0.42-0.87)#
Medicines for pregnancy-related symptoms	116	8	60	27	45	55	0.92 (0.82-0.96)#
• Antacids	1	1	*	*	*	*	*
• Anti-emetics	47	7	26	9	35	21	0.81 (0.62-0.91)#
• Laxatives	11	2	*	*	*	*	*
• Multivitamins containing folic acid or folic acid and its derivatives	19	3	14	4	29	14	1.00 (0.78-1.00)#
• Iron preparations	11	3	*	*	*	*	*
• Gynecological anti-infective and antiseptics	27	2	23	4	17	23	1.00 (0.86-1.00)#

A → these columns focus on the prescriptions and the distribution
B → these columns focus on the number of women to whom prescriptions were given, whether they receive one or more prescriptions and their compliance rates
prx = prescription; ^ Wald-method was applied; # Wilson-method was applied

Table 4.2 Overview of the numbers of prescriptions, the women to whom they were prescribed and their compliance rate for the first trimester and the entire pregnancy (continued)

	A		B				
Medication	**prx (n)**	**Maximum n of prx per pregnancy**	**Women who were given a prx at least once (n)**	**Women with > 1 prx (n)**	**%**	**Women who confirmed the use of at least one prx (n)**	**Compliance rate (95% CI)**
Entire pregnancy							
All medicines together	817	29	202	140	69	193	0.96 (0.93-0.98)^
Medicines for chronic diseases together	212	10	77	49	64	71	0.92 (0.86-0.98)^
• Antihypertensives, vasoprotectives, beta blocking agents, calcium channel blockers	45	10	20	10	50	20	1.00 (0.84-1.00)#
• Corticosteroids, dermatological preparations	43	9	24	7	29	18	0.75 (0.58-0.92)^
• Medicines for obstructive airway diseases	47	7	17	9	53	16	0.94 (0.73-0.99)#
Medicines for short-term and occasional use together	317	12	128	74	58	115	0.90 (0.85-0.95)^
• Medicines for functional gastrointestinal disorders … (GORD)	37	6	17	7	41	16	0.94 (0.73-0.99)#
• Dermatologicals exclusive anti-psoriatics and corticosteroids, dermatological preparations	65	5	38	14	37	34	0.89 (0.76-0.96)#
• Antifungals for dermatological use	21	3	16	3	19	14	0.88 (0.64-0.97)#
• Emollients and protectives	28	4	14	7	50	13	0.93 (0.69-0.99)#
• Antibacterials for systemic use	107	6	67	24	36	57	0.85 (0.77-0.94)^
• Anxiolytics, hypnotics and sedatives	13	2	11	2	18	8	0.73 (0.43-0.90)#
• Ear, eye, nose and throat preparations	54	6	31	14	45	26	0.84 (0.67-0.93)#
Medicines for pregnancy-related symptoms	288	19	112	65	58	106	0.95 (0.90-0.99)^
• Antacids	25	4	14	5	36	13	0.93 (0.69-0.99)#
• Anti-emetics	71	19	30	11	37	24	0.80 (0.66-0.94)^
• Laxatives	33	4	22	7	32	18	0.82 (0.61-0.93)#
• Multivitamins containing folic acid or folic acid and its derivatives	34	4	16	8	50	16	1.00 (0.81-1.00)#
• Iron preparations	42	4	22	11	50	19	0.86 (0.67-0.95)#
• Gynecological anti-infective and antiseptics	83	5	52	22	42	51	0.98 (0.90-1.00)#

Compliance

During the first trimester, the compliance rates between the three main groups ranged from 0.84 to 0.92. The highest compliance rate, 0.92 (95% confidence interval [CI] 0.82–0.96), was seen for medicines for pregnancy-related symptoms, while rates for medicines for chronic diseases and for short-term or occasional use were comparable: 0.84 (95% CI 0.74–0.95) and 0.86 (95% CI 0.78–0.94), respectively. For the entire pregnancy, the compliance rates between the three main groups ranged from 0.90 to 0.95. The highest compliance rate, 0.95 (95% CI 0.90–0.99), was seen for medicines for pregnancy-related symptoms, while rates for chronic diseases and for short-term or occasional use were 0.92 (95% CI 0.86–0.98) and 0.90 (95% CI 0.85–0.95), respectively. See Table 4.2.

When we calculated the compliance rates for a selected group that included only the live births and stillbirths, or when we applied the strict definition of compliance, we found the rates were comparable (see appendix 1c). Looking at the medication subgroups, relatively low compliance rates (0.69–0.82) for the first trimester were found for corticosteroids, dermatological preparations; antibacterials for systemic use; ear, eye, nose, and throat preparations; and anti-emetics. High compliance rates (1.00) for the first trimester were found for multivitamins containing folic acid, or folic acid and its derivatives, and for gynecological anti-infectives and antiseptics.

Relatively low compliance rates (0.73–0.88) for the entire pregnancy were found for corticosteroids, dermatological preparations; dermatologicals excluding anti-psoriatics and corticosteroids; antifungals for dermatological use; antibacterials for systemic use; anxiolytics, hypnotics and sedatives; ear, eye, nose, and throat preparations; antiemetics; and laxatives. High compliance rates (0.98–1.00) for the entire pregnancy were found for anti-hypertensives, vasoprotectives, beta blockers, calcium channel blockers; multivitamins containing folic acid, or folic acid and its derivatives; and gynecological anti-infective and antiseptics (Table 4.2).

Focusing on the administration forms, for the first trimester, the compliance rates ranged from 0.69 (ear, eye, nose preparations) to 1.00 (vaginal preparations). For the entire pregnancy, the compliance rates ranged from 0.78 (ear, eye, nose preparations) to 0.98 (vaginal preparations).

We examined whether the time period between date of telephone interview and date of birth influenced the results. We divided the group into women with a short time between the date of telephone interview and date of birth (7.75 months [first quartile]) and a long time

between the date of telephone interview and date of birth (18 months [fourth quartile]). For all medicines together, the compliance was slightly higher in the 'short time' group (n = 50) (0.98 [95% CI 0.90–1.00]) than in the 'long time' group (n = 56) (0.93 [95% CI 0.83–0.97]), but this was not statistically significant (Fisher's exact test p = 0.367).

Dosage and Duration Conform to Prescription

For the medication that was actually taken, we determined whether each prescription was taken as prescribed in terms of the dosage and duration. Of the medication used during the first trimester, the dosage taken was according to that prescribed for 68% (95% CI 58–79) of the medicines for chronic use and up to 88% (95% CI 82–94) of the medicines for pregnancy-related symptoms. Where the dosage used was not according to that prescribed, it was lower than prescribed for 93% (95% CI 69–99) of the medicines for chronic use and those for short-term or occasional use and up to 100% (95% CI 68–100) of the medicines for pregnancy-related symptoms.

The duration was according to that prescribed for 55% (95% CI 44–66) (medicines for chronic use) and up to 66% (95% CI 57–75) (medicines for pregnancy-related symptoms).Where the duration of use was not according to that prescribed, it was shorter than prescribed for medicines for chronic use (54% [95% CI 34–74]) and for pregnancy-related symptoms (77% [95% CI 61–93]), but it was longer for short-term or occasional use (0.56 [95% CI 37–74]).

Of the medicines used during the entire pregnancy, the dosage taken conformed to that prescribed for 75% (95% CI 69–81) (medicines for chronic use) and up to 87% (95% CI 82–91) (for pregnancy-related symptoms). Where the dosage taken was not according to that prescribed, it was lower: 97% (95% CI 84–99) (medicines for chronic use) and up to 100% (95% CI 85–100) (for pregnancy-related symptoms).

The duration conformed to the prescription for 63% (95% CI 57–68) (medicines for short-term or occasional use) and up to 69% (95% CI 63–74) (for pregnancy-related symptoms). Where the duration was not according to that prescribed, it was shorter for medicines for short-term or occasional use (56% [95% CI 45–66]) and for pregnancy-related symptoms (71% [95% CI 60–82]). See Table 4.3a and 4.3b.

Table 4.3a Use of medication conform the prescribed dosage

medication	prx actually taken (n, 100%)	conform prx (n)	% (95% CI)	not been remembered (n)	% (95% CI)	not conform prx (n)	% (95% CI)	Lower dose among those not conform prx (n)	% (95% CI)
First trimester									
all together	277	218	78.7 (73.9-83.5)^	23	8.3 (5.1—11.6)^	36	13.0 (9.0-17.0) ^	34	94.4 (81.9-98.5)#
for chronic diseases together	76	52	68.4 (58.0-78.9) ^	9	11.8 (4.6-19.1) ^	14	18.4 (9.7-27.1) ^	13	92.9 (68.5-98.7) #
for short-term and occasional use together	94	71	75.5 (66.8-84.2) ^	9	9.6 (3.6-15.5)^	14	14.9 (7.7-22.1)^	13	92.9 (68.5-98.7)#
for pregnancy-related symptoms	107	94	87.9 (81.7-94.0)^	5	4.7 (0.7-8.7) ^	8	7.5 (2.5-12.5) ^	8	100.0 (67.6-100)#
Entire pregnancy									
all together	736	589	80.0 (77.1-82.9)^	56	7.6 (5.7-9.5) ^	91	12.4 (10.0-14.7) ^	89	97.8 (92.3-99.4)#
for chronic diseases together	197	147	74.6 (68.5-80.7)^	19	9.6 (5.5-13.8)^	31	15.7 (10.7-20.8)^	30	96.8 (83.8-99.4)#
for short-term and occasional use together	273	212	77.7 (72.7-82.6)^	22	8.1 (4.8-11.3) ^	39	14.3 (10.1-18.4) ^	38	97.4 (86.8-99.5)#
for pregnancy-related symptoms	266	230	86.5 (82.4-90.6)^	15	5.6 (2.9-8.4)^	21	7.9 (4.7-11.1) ^	21	100.0 (84.5-100)#

prx = prescription
^ Wald-method was applied
 # Wilson-method was applied

Table 4.3b Use of medication conform the prescribed duration

medication	prx actually taken (n, 100%)	conform prx (n)	% (95% CI)	not been remembered (n)	% (95% CI)	not conform prx (n)	% (95% CI)	Lower dose among those not conform prx (n)	% (95% CI)
First trimester									
all together	277	168	60.6 (54.9-66.4)^	32	11.6 (7.8-15.3) ^	77	27.8 (22.5-33.1) ^	45	58.4 (47.4-69.4) ^
for chronic diseases together	76	42	55.3 (44.1-66.4) ^	10	13.2 (5.6-20.8) ^	24	31.6 (21.1-42.0) ^	13	54.2 (34.2-74.1) ^
for short-term and occasional use together	94	55	58.5 (48.6-68.5) ^	12	12.8 (6.0-19.5) ^	27	28.7 (19.6-37.9) ^	12	44.4 (25.7-63.2) ^
for pregnancy-related symptoms	107	71	66.4 (57.4-75.3) ^	10	9.3 (3.8-14.9) ^	26	24.3 (16.2-32.4) ^	20	76.9 (60.7-93.1) ^
Entire pregnancy									
all together	736	482	65.5 (62.1-68.9) ^	58	7.9 (5.9-9.8) ^	196	26.6 (23.4-29.8) ^	116	59.2 (52.3-66.1) ^
for chronic diseases together	197	128	65.0 (58.3-71.6) ^	20	10.2 (5.9-14.4)^	49	24.9 (18.8-30.9) ^	24	49.0 (35.0-63.0) ^
for short-term and occasional use together	273	171	62.6 (56.9-68.4) ^	21	7.7 (4.5-10.9) ^	81	29.7 (24.3-35.1) ^	45	55.6 (44.7-66.4) ^
for pregnancy-related symptoms	266	183	68.8 (63.2-74.4) ^	17	6.4 (3.5-9.3) ^	66	24.8 (19.6-30.0) ^	47	71.2 (60.3-82.1) ^

prx = prescription
^ Wald-method was applied
 # Wilson-method was applied

Discussion

We investigated the actual use of medication prescribed during pregnancy, based on 817 prescriptions prescribed to 202 mothers of children with congenital anomalies. The reported compliance for any medication prescribed ranged from 0.84 (medicines for chronic diseases) to 0.92 (for pregnancy-related symptoms) in the first trimester, with the lowest values for 'corticosteroids, dermatological preparations' and 'ear, eye, nose and throat preparations' [0.69] and the highest values for 'multivitamins containing folic acid or folic acid and its derivatives' and 'gynecological anti-infectives and antiseptics' [1.00]. For the entire pregnancy, the reported compliance for any medication prescribed ranged from 0.90 (medicines for short-term or occasional use) to 0.95 (for pregnancy-related symptoms), with the lowest values for 'anxiolytics, hypnotics and sedatives' [0.73] and the highest values for 'multivitamins containing folic acid or folic acid and its derivatives' and 'antihypertensives, vasoprotectives, beta blocking agents, calcium channel blockers' [1.00]. Most of the medicines actually taken were reported as having been taken according to the dosage prescribed and, if not, the dosage taken was lower. More than half of the medicines actually taken were used for the duration prescribed and, if not, the duration was mostly shorter.

Reports in the literature show a wide range in compliance rates for different medicines in general [15,16]. One study showed that, in the general population, the compliance rates for medicines for chronic use were between 40 and 50%, and the compliance rates for medicines for short-term use were between 70 and 80% [17].

Comparison with Other Studies

In a Dutch study in 1990, interviews regarding medication use during pregnancy were performed within 2 weeks after birth, and the results were compared with pharmacy records. The study found that interviews were preferable to pharmacy records in the case of OTC medicines used. However, pharmacy records were found to provide more reliable information for longer recall periods and where mothers used multiple and/or repeated medicines [18]. In a Danish study, researchers compared data in the North Jutland Prescription Database (NJPD) with data from interviews in the Danish National Birth Cohort (DNBC) and calculated the compliance rates. In this study, the researchers defined compliance as the probability of mothers reporting the use of medicines in the DNBC after a prescription had been dispensed, so in fact the mothers' recall was investigated. The study reported a 'compliance' of 70–100% for medicines for chronic use and of 12–59% for medicines for short-term use [5]. In another study, in the EUROCAT NNL, the maternal recall of prescribed medication during pregnancy was investigated by

comparing the results of a paper questionnaire using indication oriented questions with the medication registered in the EUROCAT NNL database based on information from the pharmacy. The sensitivity was calculated as the proportion of women who reported prescription medication use in the questionnaire among those who had been exposed to that medication according to the registry data. A woman was recorded as having been exposed when she confirmed (in a telephone interview) that she had taken the medication prescribed or when she mentioned using OTC medicines. For medication for chronic use, a sensitivity of 0.47 (95% CI 0.40–0.55) was found, i.e., the use of medicines for chronic use was reported in the questionnaire by 47% of the mothers who had received a prescription for a medication for chronic use. For medication for occasional or short-term use, and for pregnancy-related symptoms, the sensitivity was 0.34 (0.29–0.40) and 0.51 (0.43–0.58), respectively [19].

With respect to medication for chronic use, our results are in line with those of the Danish study. However, for medicines for short-term use, the compliance in our study was higher, although the Danish study investigated the recall [5]. Compared with the results from the EUROCAT NNL study, which investigated maternal recall, the reported compliance in our study is higher for all groups [19]. This can be explained by the self-reporting based on interviews and questionnaires, like the Danish and EUROCAT NNL studies, being affected by several aspects influencing accurate recall [20,21], such as language barriers, time pressure, or the woman's circumstances, like perception, expectation, experience, and education [22–24]. One would therefore expect to see under-reporting of medication use in pregnancy when using interviews or questionnaires without the support of pharmacy records [19,25].

The compliance rates for selected groups (excluding spontaneous abortions and TOPFAs and applying a strict definition of 'compliance') were similar to those reported here (see appendix 1c). Although the dosage of a medication and duration of exposure are considered relevant factors in affecting pregnancy outcomes [26], the quality of these parameters in studies using routinely collected administrative data has not been thoroughly examined [27]. Nevertheless, it is important to look at specific medicines or groups of medicines to investigate whether the dosage or duration changes during pregnancy. For example, one study showed that 39% of women who used anti-asthmatics during pregnancy actually discontinued or reduced their medicines [28].

Strengths and Limitations

To our knowledge, this is the first study in which compliance has been investigated by verifying pharmacy records in a structured telephone interview with each mother. Although the women were sent a list of their prescribed medication before the interview, the question still arises as to how accurately they can recall the actual use of a prescribed medication retrospectively. The period between date of telephone interview and date of birth ranged from 2 to 35 months. The compliance rate did not differ significantly among the 'short time' and the 'long time' group; however, regardless of time between the telephone interview and the date of birth, correct recall of the use of a certain medication (particular, that for short-term use) may be difficult. It is possible that women give positive answers to please the interviewer or deny the use of a medication if they feel guilty about their child's condition.

In addition, we only measured compliance in a selected group of women who gave birth to a child with a congenital anomaly. Therefore, by definition, the results are not applicable to the general pregnant population. If women who gave birth to a child with a congenital anomaly recall events during pregnancy better than women with a healthy child (for instance, because they try to find an explanation for their child's congenital anomaly), recall bias has to be taken into account in studies using unaffected controls [29]. Further research is recommended to investigate compliance in the general pregnant population.

Our broad definition of compliance might lead to an overestimation of the compliance rate, although we found that applying a strict definition of compliance did not affect the compliance rates.

Finally, we could only investigate compliance for certain common medication groups, since we did not have enough power to calculate compliance for specific medicines.

Conclusion

Prescription records are generally a relatively reliable source of data for research into associations between medication use in pregnancy and congenital anomalies compared with other data sources. The medication use in pregnancy based on pharmacy records might represent an overestimation, which should be taken into account. However, our results show that, except for 'Corticosteroids, dermatological preparations'; 'Ear, eye, nose, and throat preparations', and 'Anxiolytics, hypnotics and sedatives', this overestimation seems generally minimal.

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MONITORING AND RISK ASSESSMENT

PART II

Chapter 5
Antibiotics prescribed before, during and after pregnancy in the Netherlands: a drug utilization study

Chapter 6
Identifying associations between maternal medication use and birth defects using a case-population approach: an exploratory study on signal detection

Chapter 7
Early pregnancy exposure to antihistamines and risk of congenital heart defects: results of two case-control studies

CHAPTER 5

Antibiotics prescribed before, during and after pregnancy in the Netherlands: a drug utilization study

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Abstract

Purpose: To describe the prescription of antibiotics before, during and after pregnancy, and the trends over a 16-year period in the Netherlands, and to determine whether they were prescribed according to national guidelines.

Methods: The IADB (http://iadb.nl) contains prescriptions dispensed by community pharmacies in the Netherlands. We extracted information on 18,873 pregnancies for 14,969 women between 1994 and 2009, focusing on antibiotics dispensed in the four trimesters before conception to two trimesters after birth (nine trimesters in total). We calculated trends in prescription rates during pregnancy and over time, and also compared the prescription of antibiotics in the Netherlands with safety category based on the Australian Drug Evaluation Committee (ADEC).

Results: During pregnancy 20.8% of the women were prescribed at least one antibiotic. The 'beta-lactam antibacterials/penicillins' group and the specific antibiotic amoxicillin were most commonly prescribed in the nine trimesters covered. The prescription rate of the 'other antibacterials' group during pregnancy increased over the years, in contrast to that of the 'sulphonamides/trimethoprim' group, which decreased. In total, 2.0% of pregnancies were exposed to a 'potentially harmful' antibiotic and 0.8% to a 'harmful' antibiotic. Compared with the period before conception, 'safe' antibiotics were prescribed more often during pregnancy than the other groups.

Conclusions: One in five women was prescribed at least one antibiotic during pregnancy in the Netherlands, which is comparable with rates in other European countries. Our results suggest that antibiotics appear to be prescribed to pregnant women generally in accordance with national recommendations.

Introduction

Many women suffer from bacterial infections during pregnancy, which, if untreated, could lead to maternal and neonatal morbidity and mortality [1-3]. Antibiotics are therefore among the drugs most commonly prescribed to pregnant women [4-12]. The use of antibiotics during pregnancy varies between 19.7% in Germany to 40.8% in the USA [4,8,13]. However, the use of antibiotics during pregnancy also has disadvantages, for example, causing a disbalance of the flora, and an increased risk for certain birth defects caused by specific antibiotics [3,4,5,13-20]. For instance, the folic acid antagonist, trimethoprim, is associated with an increased risk of cardiovascular defects and oral clefts [16,19] and tetracyclines can cause inhibition of growth of the bone and discoloration of fetal teeth [16,20]. The choice of an antibiotic in pregnancy must therefore be well considered.

Although several studies have described the use of anti-infectives or antibiotics, only a few have addressed the different pharmacological subgroups, the trends in use over time, and appropriate prescribing practice.

We describe the different antibiotic subgroups prescribed before, during and after pregnancy in the Netherlands, and the trends over a 16-year period up to 2009. We also investigated whether antibiotics were prescribed in a manner consistent with national guidelines for pregnant women.

Methods

We conducted a drug utilization study among women who gave birth between January 1, 1994 and December 31, 2009, using data from the IADB (http://iadb.nl) [21], a database containing prescriptions dispensed by community pharmacies in the Netherlands. However, drugs which can be bought 'over the counter', i.e. purchased without prescription, or those given during hospitalization are not included in the IADB [22]. The concept of the IADB has been described by Tobi et al. [23] In the Netherlands it is common practice for an individual to register with only one community pharmacy, which makes it possible to record an almost complete overview of the prescriptions dispensed to an individual [21,22,24]. Because registration with a community pharmacy is irrespective of health insurance, the pharmacy population is a good reflection of the general population and the data of the IADB can therefore be considered as population-based [22,25].

For each dispensed prescription, the IADB records: the Anatomical Therapeutical Chemical classification code (ATC code, 2010 version; accessible via http://www.whocc.no/atcddd [26]*);* the dispensing date; the dispensed quantity; the prescribed daily doses; the Defined Daily Dose (DDD, defined as: "*assumed average maintenance dose per day for a drug used for its main indication in*

adults") [27], the number of prescribed days, and the prescribing physician. But the indication for the prescription is not recorded. The IADB also has information about gender, date of birth, and the 'address registration number' of the patient [22,25]. The 'address registration number' is not equivalent to an unique ID number, since different persons with different ID numbers can have the same address registration number. When a person moves, he/she gets a new address registration number or is lost to follow up.

For each child in the IADB, the woman with the same 'address registration number' and 15-50 years older than the child was assumed to be the mother. Schirm et al. validated this method and found that it identified 64.9% of the mothers with high accuracy [25]. The pregnancy period was standardized at 39 weeks and the start of the pregnancy was defined as the date of birth minus 273 days (i.e. 7*39 weeks or 3 trimesters of 13 weeks each).

Between January 1, 1994 and December 31, 2009, 34,698 pregnancies were identified. We included only pregnancies for which information was available for the complete study period of at least four trimesters before conception, three trimesters in pregnancy, and two trimesters after delivery. A period of four trimesters before conception was chosen to provide good reference values for this period before conception and to ensure a good comparison with the period during pregnancy. To investigate whether the values returned to normal, a period of two trimesters after delivery was chosen.

The trimester selection criteria led to 8,972 pregnancies being excluded. To avoid distortion of the results in the 'before' and 'after' periods for each pregnancy, we only included different pregnancies for one mother if there were at least 819 days (9 trimesters of 13 weeks) between one delivery and the next. Otherwise, there could have been some overlap between the 'after' period of the first pregnancy and the 'before' period of the second. If a mother had three pregnancies between 1995 and 2009 and there were more than 819 days (nine trimesters) between pregnancies 1 and 3, but not between pregnancies 1 and 2, or 2 and 3, all three pregnancies were excluded. We also excluded multiple birth pregnancies, because the gestational age of these children is likely to be shorter than those of singleton pregnancies. After all the exclusions, 18,873 pregnancies in 14,969 women were included in our study (Figure 5.1).

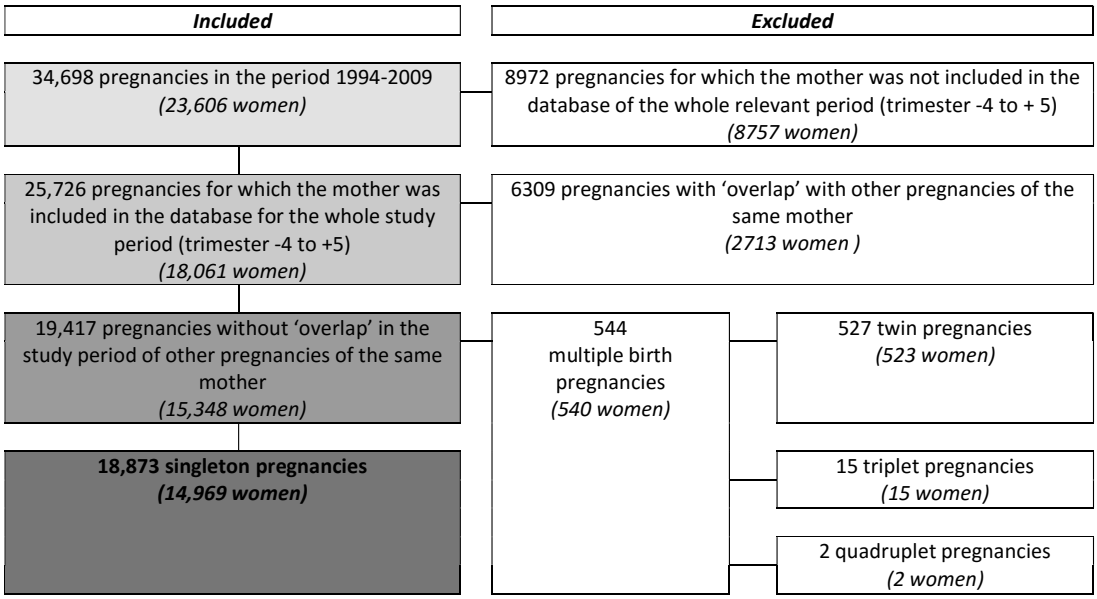

Figure 5.1 Selection of study population

In this population we investigated the prescriptions of antibacterials for systemic use (ATC code starting with J01). The classification of the specific antibiotic subgroups is based on the third level of the ATC classification (pharmacological properties). There were no prescriptions of the 'amphenicols' (J01B) group (for example, J01BA01 chloramphenicol) [26] or the 'combinations of antibacterials' (J01R) group (for example, J01RA01 penicillins, combinations with other antibacterials) [26] dispensed to our population. Because there were just three prescriptions for the 'aminoglycoside antibacterials' (J01G) group (for example, J01GA01 streptomycin) [26] in the study period, we decided to include these prescriptions only in the main group of antibacterials (J01), but not as a specific group. The other groups were: 'tetracyclines' (J01A) (for example, J01AA02 doxycycline) [26]; 'beta-lactam antibacterials/penicillins' (J01C) (for example, J01CA04 amoxicillin) [26]; 'other beta-lactam antibacterials' (J01D) (for example, J01DB04 cefazolin) [26]; 'sulphonamides/trimethoprim' (J01E) (for example, J01EA01 trimethoprim) [26]; 'macrolides/lincosamides/streptogramins' (J01F) (for example, J01FA01 arythromycin) [26]; 'quinolone antibacterials' (J01M) (for example, J01MA02 ciprofloxacin) [26] and 'other antibacterials' (J01X) (for example, J01XE01 nitrofurantoin) [26]. For all these, we calculated trends for three different periods (before, during and after pregnancy) and over time (over the years).

We used the Australian Drug Evaluation Committee's (ADEC) [28] risk classification for pregnancy to classify the safety of the prescribed antibiotics (five classes), because this is most frequently used in

the Netherlands. According to ADEC, class A drugs are considered 'safe', B 'unknown', C 'potentially harmful', D 'harmful' and X ' high risk harmful' [28]. If a drug was not listed in ADEC's risk groups, it was classified as B, 'unknown'. We provide an overview of the dispensed antibiotics in this study and their classifications in appendix 1d.

The prescription rate was calculated as the number of pregnancies per 100 pregnancies, in which at least one prescription from an antibiotic group was dispensed in a specific period. The prescription rate and 95% confidence intervals were calculated for antibiotics in general (J01), for antibiotic subgroups, and for specific antibiotics in a particular period (i.e. the whole study period, the period before, during or after pregnancy, or specific trimesters). Prescriptions for longer than one period were counted only in the period in which they were first dispensed. When we focused on the pattern over time, we merged 3-year periods, starting with years from 1996 to 2007 to avoid distortion, because our study design meant fewer pregnancies were included before 1996 and after 2007.

We calculated the proportion of specific antibiotics before, during and after pregnancy and of the A, B, C, D and X prescriptions as the number of prescriptions for a specific antibiotic or subgroup divided by the total number of prescriptions in a particular period. Prescription rates and time trends were tested in PASW Statistics 18 (SPSS Inc.) using the chi-square test for trend. 95% confidence intervals and p values were calculated for the prescription rates of antibiotic subgroups in the period during pregnancy per 3-year periods. We considered statistical significance for $p < 0.050$. To calculate the 95% confidence interval we used the formula:

$$\hat{p} \pm z_{\alpha/2} \cdot \sqrt{\frac{\hat{p}.(1-\hat{p})}{n}}$$

Results

General

In the 18,873 pregnancies studied, 19,577 prescriptions for 39 different antibiotics were dispensed over the nine trimesters. At least one antibiotic was prescribed during pregnancy in 20.8% of them (n = 3,916). The prescription rate for any antibiotic in the four trimesters before conception was 28.0% (n = 5,285) and in the two trimesters after pregnancy it was 19.6% (n = 3,705).

Use of antibiotic subgroups before, during and after pregnancy

The 'beta-lactam antibacterials/penicillins' group was the most dispensed antibiotic in the period before, during and after pregnancy. Before conception, the prescription rate per trimester remained

constant (3.8%), but it increased in pregnancy. The highest prescription rate was seen in the first trimester after delivery (10.0%). For the 'tetracyclines', 'sulphonamides/trimethoprim', 'macrolides/lincosamides/streptogramins' and 'quinolone antibacterials' groups, the prescription rate per trimester decreased during pregnancy, but increased again after delivery. The 'other beta-lactam antibacterials' group was least prescribed before, during and after pregnancy, with a prescription rate of less than 1%, but there was increased prescribing seen in the third trimester of pregnancy and the first trimester after delivery. The rate of the 'other antibacterials' group remained constant, but with a slight increase seen in the second trimester in pregnancy (Figure 5.2). Data for figures 5.2, 5.3 and 5.4 are given in appendix 1e.

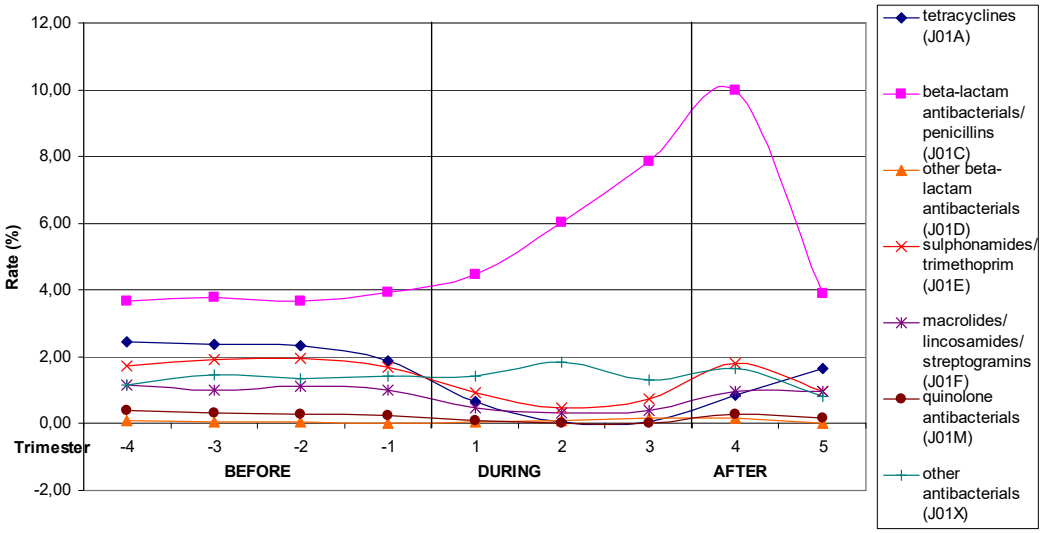

Figure 5.2. Prescription rates of antibiotic subgroups per trimester

Looking at the prescription proportions for specific antibiotics, we found that amoxicillin was the most frequently prescribed antibiotic before, during and after pregnancy. Before conception, the four most frequently prescribed antibiotics were: amoxicillin (J01CA04) 20.2% (n = 1,749); doxycycline (J01AA02) 19.1% (n = 1,650); trimethoprim (J01EA01) 14.7% (n = 1,276) and nitrofurantoin (J01XE01) 12.7% (n = 1,098) of the antibiotic prescriptions. During pregnancy, amoxicillin comprised 59.1% (n = 3,374) of the antibiotic prescriptions. After birth, amoxicillin still comprised 33.4% (n = 1,738) of the antibiotic prescriptions, but other antibiotics were also prescribed more frequently: flucloxacillin (J01CF05) 10.8% (n = 564); amoxicillin and enzyme inhibitor (J01CR02) 10.1% (n = 525); nitrofurantoin 9.8% (n = 509); trimethoprim 9.2% (n = 478) and doxycycline 9.0% (n = 467). A top-10 list of the most

frequently prescribed antibiotics before, during and after pregnancy, and a specification of the pregnancy period, are given in appendix 1f.

Trend over the years

In Figures 5.3a and 5.3b, the prescription rates in the period during pregnancy are shown for the specific antibiotic groups averaged over 3-year periods. For the 'beta-lactam antibacterials/penicillins' group, the rate decreased till 2002-2004, but later increased ($p < 0.001$). The rate of the 'other antibacterials' group increased over the years ($p < 0.001$), unlike the rate of the 'sulphonamides/trimethoprim' group, which decreased over the years ($p = 0.005$). The rates for the 'tetracyclines', 'macrolides/lincosamides/streptogramins' and 'quinolone antibacterials' groups prescribed during pregnancy were constant over time ($p = 0.340$; 0.716; 0.223, respectively). For the 'other beta-lactam antibacterials' group, the highest prescription rate was found in 1999-2001 ($p = 0.001$).

Safety

For all the pregnancies studied, we found 2.0% (n = 375) had been exposed to a 'potentially harmful' antibiotic (category C) and 0.8% (n = 144) to a 'harmful' antibiotic (category D) during the actual pregnancy. No X category (high risk harmful) antibiotics were prescribed in our study. The prescription of 'potentially harmful' antibiotics in pregnancy declined from 2.3% in 1996-1998 to 1.6% in 2005-2007 ($p = 0.007$). For category D, the exposure remained constant in this period ($p = 0.337$).

Figure 5.4 shows that in trimesters -4 and -3 (from 12 to 6 months before conception), 21.9% (n = 967) of all the antibiotic prescriptions were from category D, but this proportion decreased to 0.6% (n = 14) in the third trimester of pregnancy ($p < 0.001$). The proportions of categories B and C antibiotics decreased from 26.4% (n = 1,164) and 17.1% (n = 754), respectively, in trimesters -4 and -3, to 7.1% (n = 129) and 5.3% (n = 91), respectively, in the second trimester of pregnancy. They then increased slightly in the third trimester. This pattern was exactly the opposite to that seen for category A antibiotics, with the highest proportion recorded in the second trimester 86.8% (n = 1,585). For all categories, the changes over the course of the pregnancy were statistically significant ($p < 0.001$).

Of all the antibiotics prescribed during pregnancy in the study period, 10.3% (n = 586) belonged to the categories of 'potentially harmful' and 'harmful' antibiotics (C and D). Of these, trimethoprim and doxycycline were the most prescribed, at 7.0% (n = 400) and 2.4% (n = 136) respectively.

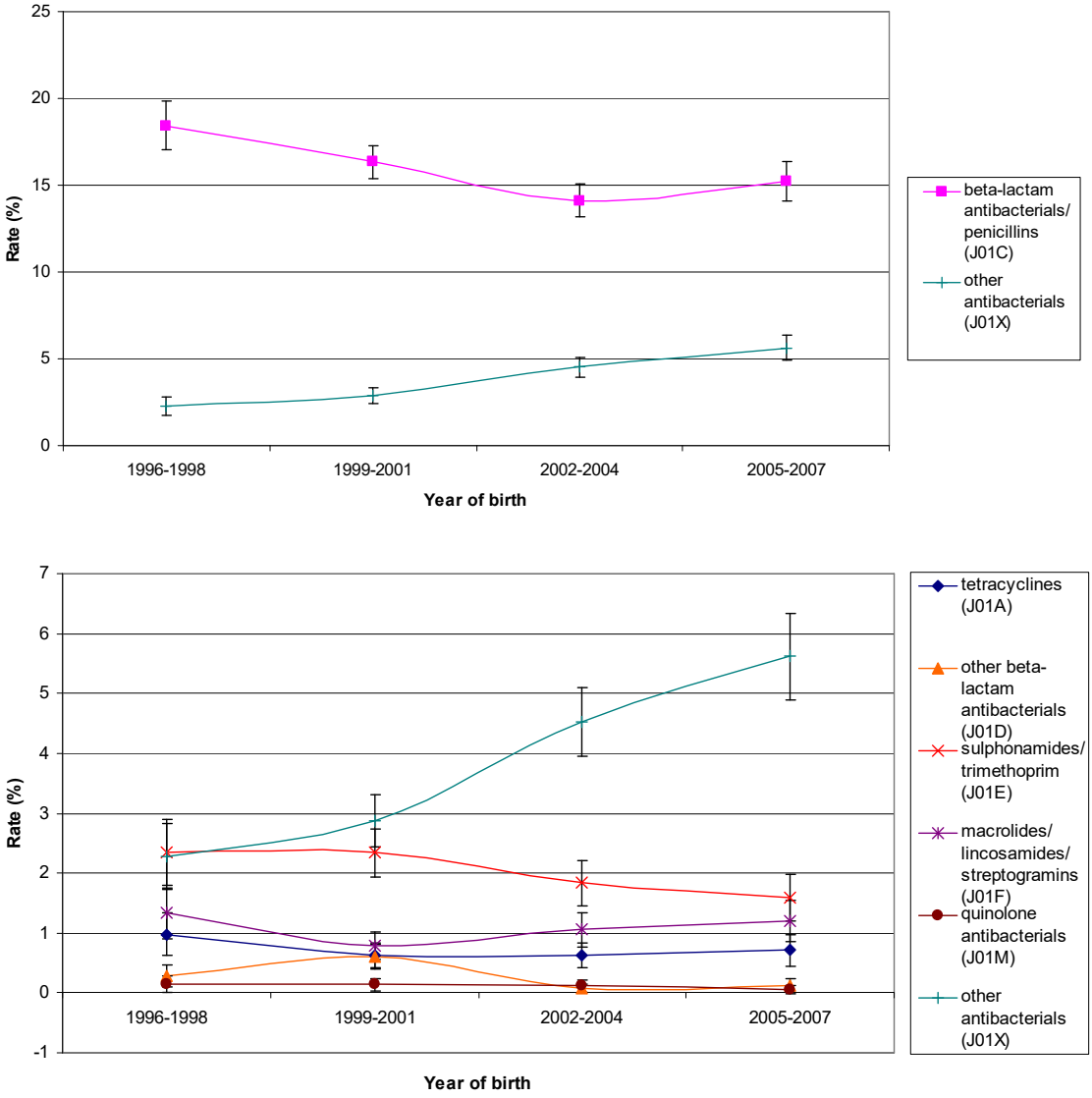

Figure 5.3. Prescription rates of antibiotic subgroups during pregnancy per 3-year periods.
Because of the axis scale, the figure is split into two parts (A and B), with the 'other antibiotics' curve given as reference

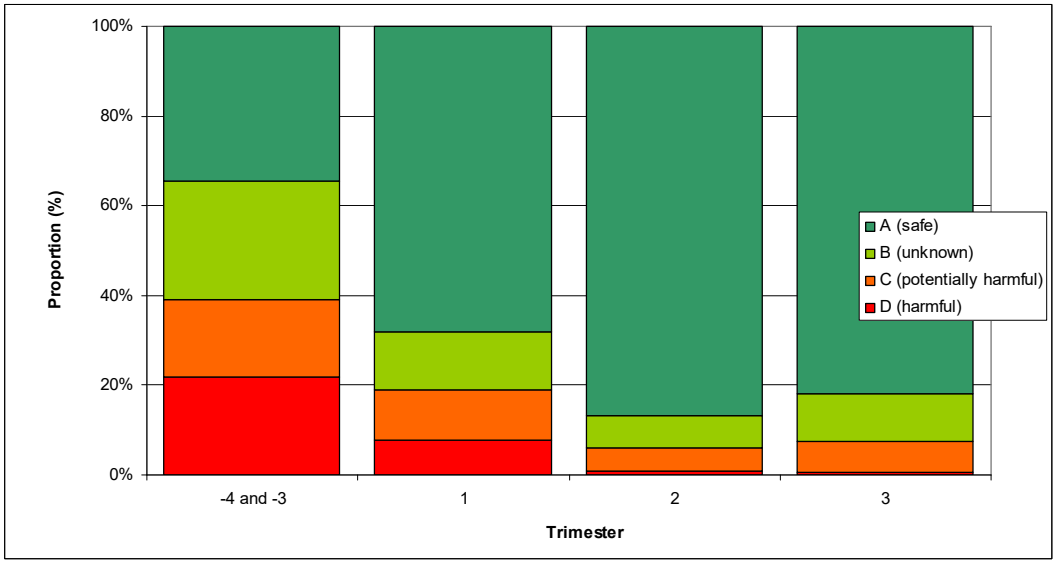

Figure 5.4. The proportion of all prescriptions according to the Australian Drug Evaluation Committee's risk classifications for pregnancy

Discussion

Our study of a population-based cohort of 18,873 pregnancies found that the woman was prescribed at least one antibiotic during pregnancy in 20.8% of cases. The 'beta-lactam antibacterials/penicillins' group were the most frequently prescribed before, during and after pregnancy. Of the specific antibiotics, amoxicillin was most prescribed. The rate for the 'other antibacterials' group prescribed during pregnancy, increased over time and this was statistically significant, whereas the prescription rate for the 'sulphonamides/trimethoprim' group showed a decrease, which was also statistically significant. Compared to the period before conception, the proportion of antibiotics prescribed during pregnancy and classified as A (safe) increased, whereas the proportions of antibiotics classified as B (unknown), C (potentially harmful) and D (harmful) decreased [28].

General

The prescription rate of 20.8% during pregnancy is comparable with data from Germany [13], but is lower than rates reported for the UK [4] and US [2]. The differences can be explained by the national prescribing policies and the different study designs and data sources [29,30].

Use of antibiotic subgroups before, during and after pregnancy

The highest prescription rates before, during and after pregnancy were found for the 'beta-lactam antibacterials/penicillins', which includes amoxicillin. This is in line with results from other studies [4-6,8,10,13,31,32]. Much experience has been acquired with these drugs and most of them belong to category A and are considered to be safe. The decrease in the prescription rates for the 'tetracyclines' and 'sulphonamides/trimethoprim' during pregnancy was also described by Amann et al. [13] Given that the 'tetracyclines' belong to category D (because of their inhibition of bone growth and discoloration of fetal teeth later on in pregnancy [16,20]), and the 'sulphonamides/trimethoprim' to category C (because of the folic acid antagonist properties of trimethoprim, relevant in the beginning of pregnancy [16,19] and the potential risk of sulphonamides on kernicterus or hyperbilirubinaemia [16,18]), the decrease of both groups during pregnancy was expected and is according to prescription guidelines.

The decreased use of the 'macrolides/lincosamides/streptogramins' and 'quinolone antibacterials' was also seen by Amann et al. [13] This can be explained because some of the 'macrolides/lincosamides/streptogramins' group and all of the 'quinolone antibacterials' belong to category B (unknown). Where there is a 'safe' alternative, this should be prescribed first.

Around delivery, the increase of the 'other beta-lactam antibacterials' was also seen by Amann et al. [13] In the Netherlands this group is on the 'reserve list', i.e. they should be prescribed only when other antibiotics are not working or when there is resistance [33]. The increased prescription rate could be explained by the development of resistance. Another explanation could be that the period just before and after delivery is a vulnerable one [34,35] and when other antibiotics are not working, a switch must be made to another type of antibiotic.

According to Amann et al. [13], the prescription rate of the 'other antibacterials' before, during and after pregnancy also remained constant. In this group, nitrofurantoin was the most prescribed; it is only used as an effective treatment and prophylaxis for urinary tract infections. According to the Dutch guidelines, nitrofurantoin is the first choice for urinary treatment in general, but also during pregnancy [36]. However, Crider et al. found periconceptional exposure of nitrofurantoin to be associated with anophthalmia or microphtalmos, hypoplastic left heart syndrome, atrial septal defects, and cleft lip with cleft palate [5]. Furthermore, in late pregnancy, nitrofurantoin should be prescribed with caution because of the possibility of hemolysis in neonates with glucose-6-phosphate dehydrogenase deficiency [17].

Trend over the years

We found a decreasing trend in the prescription rates during pregnancy for the 'sulphonamides/trimethoprim' and 'beta-lactam antibacterials/penicillins'. The decrease in the 'sulphonamides /trimethoprim' might be attributable to a study by Hernandez-Diaz et al. (2000), which found an increased risk of spina bifida and heart defects related to first trimester exposure to the folic acid antagonist trimethoprim [19], although we could not find any change in the Dutch prescription guidelines related to this paper.

Our results for the 'beta-lactam antibacterials/penicillins' show a decrease till 2002-2004 and then a slight increase, and confirmed those of Petersen et al. [4]. We also found an increased rate for the 'other beta-lactam antibacterials' in the period 1999-2001. The reason for this increased rate is difficult to determine, since the total number of such prescriptions in our study was small, at only 69 prescriptions during the 3 trimesters of pregnancy. It is possible that the increase in the prescription rate of 'other antibacterials' might be explained by resistance to other antibacterial groups or by changing trends in therapy. Since we do not have any extra information on resistance, we suggest this increase warrants further attention.

Safety

Despite the limitation that we had no information on the indications for prescription, we can state that the decrease in prescriptions of category D antibiotics in pregnancy was in accordance with the Dutch guidelines: if there is a safer alternative, a known 'harmful' antibiotic is undesirable. A decrease was also seen for categories B and C antibiotics in the first and second trimester of pregnancy, but after the second trimester there was a slight increase. This is difficult to explain, because of the 'potentially harmful' and 'unknown' properties of categories B and C antibiotics; a 'safe' antibiotic is always preferable. However, in the last trimester, there may be problems that cannot be treated with 'safe' antibiotics and then a decision can be taken to choose a category B or C antibiotic. As expected, the proportion of category A antibiotics increased, with the highest proportion reached in the second trimester. One explanation for this could be that not all women are aware of their pregnancy in the first trimester, whereas, by the second trimester, most pregnancies have been recognized and are taken into consideration when a drug is prescribed.

Strengths and weaknesses

Our study reflects the prescribing practices in the Netherlands for antibiotics before, during and after pregnancy, based on prescriptions and the date of dispensing.

One strength of our study is that ATC codes allowed us to study subgroups of antibiotics and even specific drugs. As far as we know, only two studies have been published about the use of antibiotics in pregnancy that reported on the different subgroups [4,13]. Amann et al. described the pattern over trimesters, but not over time [13]. Petersen et al. described the pattern over trimesters and over time [4]; however, they did not use subgroups based on the ATC classifications, which makes it difficult to compare their results to other studies.

The first limitation of our study is that, for practical reasons, it was based on dispensed prescriptions and the date of dispensing, rather than on actual use and the exposure period, so that our data reflect the prescribing practices in the Netherlands.

Second, our way of identifying pregnancies in the IADB also had some limitations: linkage of children to mothers was possible in 64.9% of the mothers. However, we do not expect any selection bias due to mothers with 'children without any prescription'. The main reasons for not being able to link the mother to their child/children were technical, such as having another address registration number than the child, being registered at a different pharmacy to the child, and not living at the same address as the child [25].

Third, pregnancies that ended in a spontaneous abortion or stillbirth will not be identified by linking mothers to their children. However, since our aim was to describe the prescription rates of the various antibiotic categories and their proportions, and to evaluate the adequacy of prescribing, we think this bias should be minimal.

Fourth, the pregnancy period was standardized at 39 weeks because the true gestation was unknown. This standardization is applied in other studies using IADB pregnancy data [37,38]. According to the Perinatal Registration in the Netherlands (PRN) the average gestational age at birth is 39 weeks and 4 days for the period of 1999-2008, while the rate of preterm born children, born before the gestational age of 37 weeks, is 7.7% for the same period [39]. Misclassification of exposure, -when a mother was considered exposed in the second trimester based on the standardized pregnancy period, while the drug was actually prescribed in the first trimester, or vice versa-, cannot be ruled out, but based on the numbers above we find this within acceptable range.

Fifth, there was no information available on the indication for prescribing the drug. We therefore based the accuracy of prescribing on the proportion of the safety categories and the prescriptions for 'reserve antibiotics'.

Finally, we did not distinguish the developmental periods during pregnancy when a drug may be associated with an increased risk for different pregnancy outcomes. For instance, a drug might be harmful during organogenesis, whereas it could be considered safe at the end of pregnancy or *vice versa*. We classified the antibiotics for safety according to the ADEC classification. Although this is commonly used, one should keep in mind that the severity of the ADEC score might apply to the drug's effects in a specific period of the pregnancy.

In conclusion, one in five women in the Netherlands was prescribed at least one antibiotic during pregnancy, which is comparable with rates in other European countries. Our results suggest that antibiotics generally appear to be prescribed to pregnant women in the Netherlands in accordance with national recommendations.

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CHAPTER 6

Identifying associations between maternal medication use and birth defects using a case-population approach: an exploratory study on signal detection

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Abstract

Background: The effects of many drugs on the unborn child are unknown. In a case-population design, drug exposure of cases is compared to that of a source population. This kind of study can be useful for generating signals.

Objective: To see whether a comparison of drug use rates from the birth defect registry EUROCAT NNL (cases) with prescription rates from a population-based prescription database, the IADB, (population), could be used to detect signals of teratogenic risk of drugs.

Methods: We defined 3212 cases from the EUROCAT NNL database, a population-based birth defect registry in the Northern Netherlands and 29,223 population controls from the IADB, a prescription database with data from community pharmacies in the same geographical area, born between 1998 and 2008. We classified the malformations of the 3212 cases into several malformation groups according to organ system (based on the ICD codes and the EUROCAT guidelines). If a child had multiple malformations in several organ systems (n=253, 7.9%), it was counted in all the categories represented. For several groups of malformations we calculated rate ratios (RR) and 95% confidence intervals (CI) for drugs acting on the nervous system and drugs considered to be safe for use in pregnancy. The RRs were based on first trimester drug utilization rates from the cases in the EUROCAT NNL database and prescription rates from the population controls in the IADB.

Results: For drugs acting on the nervous system we found significantly increased RRs for the anti-epileptic drug valproic acid and for some SSRIs. Of drugs considered to be safe, only the anti-hypertensive methyldopa showed significantly increased RRs.

Conclusion: We show that a case-population study is a suitable method for detecting signals of possible teratogenicity, provided that the teratogenic effects and drugs under study are as specific as possible and the drugs are widely used.

Background

The first trimester of pregnancy is the critical period for the developing embryo, since the organogenesis takes place during these first weeks [1]. Many pregnant women use at least one drug on prescription during this first trimester with estimations varying between 22-54% [1-4]. However, for many drugs on the market, the effects on the unborn child still have to be established. Since results from animal studies do not always predict teratogenicity in humans and pregnant women are excluded from pre-marketing trials for ethical reasons, post-marketing surveillance is necessary [5-7].

When a drug enters the market, it takes some time before enough pregnant women are exposed to it and a proper cohort or case-control study can be performed. At first, mainly case reports or case series will be found in the literature. Several pharmaco-epidemiological approaches have been established for rapidly identifying any adverse drug effects, like the case-population and case-cohort designs [8-11]. The case-population or population-based case-cohort approach compares past exposure to a given risk factor in subjects presenting a given disease or symptom (cases) with the exposure rate to this factor in the source population or in the whole cohort [11]. This design can detect rare but serious adverse drug reactions not discovered by clinical trials and has predominantly been used in post-marketing surveillance of adverse drug effects [8-11]. Conditional on having a representative source population, case-population studies are relatively rapid and inexpensive. For the estimation of exposure to the drug under study in the population the cases come from, general consumption data are used [10]. The main limitation of this approach is that general consumption data are often not available.

In this study we explored whether a case-population design can be used to detect signals of teratogenicity as well, by comparing cases from a population-based birth defect registry, with controls derived from a population-based prescription database.

Methods

Cases

Cases were selected from EUROCAT NNL, a population-based birth defect registry in the northern part of the Netherlands, covering approximately 10% of all births in the country. A child can be registered in the database up to the age of 16, there is no lower age limit. All types of births are included in the registry: live births, stillbirths, spontaneous abortions and terminations of pregnancy [12].

Parental informed consent is required for registration. Approximately 80% of the parents agree with inclusion of their child in the registry. Parents are asked to complete a questionnaire with questions about socio-demographic characteristics, prenatal screening methods and diagnostic tests, and exposure to possible risk factors (chemicals, recreational drugs, etc.).

Maternal permission is asked to obtain the mother's pharmacy records for the period of 3 months before conception until delivery. Actual use of the prescribed medication is verified in a telephone interview and only the actually used medication is registered [12].

Information on congenital malformations is obtained from the medical files, including pathology reports and coded afterwards, according to the International Statistical Classification of Diseases and Related Health Problems (ICD) coding system (until 2001: ICD-9; from 2002: ICD-10) by trained registry staff. Drugs that were taken by the mother are coded according to the Anatomical Therapeutic Chemical (ATC) classification system [1,13,14].

From the EUROCAT NNL database we selected all fetuses and children (live births, stillbirths, spontaneous abortions and terminations of pregnancy) born between 1998 and 2008 (n=6025). We excluded cases without complete pharmacy records and without complete information regarding medication use (n=1606; 26.7%). Since genetic and chromosomal disorders are not thought to be related to maternal medication use [15], cases with a genetic or chromosomal disorder (n=1207; 20.0%) were also excluded. Our final dataset consisted of 3212 cases. The cases were classified into different groups of malformations based on the ICD codes and the EUROCAT guidelines [16]. Table 6.1 shows the number of cases classified into the different malformation groups. Appendix 1g gives a list of all the malformations that are coded within the different malformation groups studied. If a child had multiple malformations, it was counted in all the categories represented (n=253, 7.9%), therefore numbers do not add up to 3212. However, a child with several different cardiac malformations is only counted as one case within the groups of heart defects.

Table 6.1 Number of cases classified into the different malformation groups

Malformation group	Cases (n (% of 3212))
Malformations of the central nervous system	208 (6.4)
Cardiac malformations	873 (27.2)
Clefts	294 (9.2)
Malformations of the respiratory tract	55 (1.7)
Malformations of the digestive system	362 (11.2)
Genital malformations	314 (9.8)
Malformations of the urinary tract	309 (9.6)
Malformations of the musculo-skeletal system	668 (20.8)
Malformations of the limbs	184 (5.7)

Percentages do not add up to 100% since children may have more than one malformation and therefore are counted in more than one malformation group.

Population

From the IADB, a population-based prescription database, which contains prescription data from approximately 55 community pharmacies in the Netherlands we selected the population controls. The IADB covers an estimated population of 500,000 individuals, which is considered representative of the general population. Because most Dutch patients only use one pharmacy, an almost complete medication history of each individual is registered in the database. Prescribed drugs are recorded by their ATC code [14]. Data on date of dispensing, amount dispensed, dose regimen and the prescriber are also available. Each patient has a unique, anonymous identifier and their date of birth and gender are known. No information about medication prescribed during hospitalization or over-the-counter (OTC) drugs is available.

For the IADB pregnancy database, pregnancies are identified by connecting a child in the IADB to the female aged 15-50 years with the same address code as the child, providing there were no other females of this age with the same address code. This method allows 64.9% of the mothers to be identified. Validation of this method has been described elsewhere [17]. The theoretical pregnancy period is defined by taking the date of birth of the child minus 273 days (3 trimesters of 91 days). All 29,223 children, born from 28,528 pregnancies, with a date of birth between 1998 and 2008 were included in this study, including 1320 twins and 56 multiple births.

Drugs

Because malformations develop in the first trimester of pregnancy [1], we focused on drug use and prescription during this period. We defined the first trimester as the first 13 weeks of pregnancy. A case was defined to be exposed to one of the drugs under study when the drug was registered to be used during the first 13 weeks after the first day of the last menstrual period (LMP). For the population the exposure definition was based on the date of prescription: if the mother received a prescription in the first 13 weeks of pregnancy, the child was considered exposed. We selected two drug groups for our case-population study.

The first group consisted of all drugs acting on the nervous system (drugs with an ATC code starting with N). These types of drugs have been studied frequently and certain teratogenic effects have been identified, especially with the anti-epileptics [5,18-24]. A suitable method to detect signals of teratology should be able to detect known teratogenic effects.

The second group consisted of all drugs considered to be safe, classified as A ("*drugs that have been taken by a large number of pregnant women and women of child-bearing age without an increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed*") according to the Australian Drug Evaluation Committee (ADEC) [25], except drugs for fertility treatment. We did not expect any teratogenic effects to be found in this group. The ATC classification is based on the organ system that a drug acts on and subsequently on its therapeutic and chemical characteristics, while the ADEC classification aims to classify risks associated with taking particular medicines in pregnancy based on the available evidence [13,25]. The two drug groups under investigation were therefore composed differently. Because the IADB does not contain information on the use of OTC medication, only prescribed drugs were included.

Analyses

For the cases and population, mean maternal age and the distribution of the birth years over the study period were calculated and compared using the t-test and the Mann Whitney U test, respectively. From the EUROCAT NNL data, we calculated first trimester user rates among malformation groups as the percentage of cases exposed to a specific drug. To reduce the risk of chance findings, we calculated user rates only for drug groups and for specific drugs with at least three exposed cases in the first trimester. From the IADB data, we calculated prescription rates as the percentage of infants exposed in utero. Because a drug usually acts on a certain organ system and causes specific birth defects, we did not compare the user rate among all malformations

together with the IADB prescription rates. By taking all malformations together, any teratogenic effect would have been diluted and signals could have been missed. The drug use rates among the malformation groups were compared with the IADB prescription rates by calculating rate ratios (RR) and 95% confidence intervals (CI). Analyses were performed using PASW Statistics (IBM, Chicago, IL, USA, Version 18).

Results

Table 6.2 shows the distribution of the birth years of the cases and our population per study year. The number of births per year decreased over time for the population, because it can take some time before a pregnancy is identified in the IADB. A Mann Whitney U test showed no significant difference (p=0.412) between the distribution of the years of birth of the cases and of the IADB population in the study period. The mean age of the case mothers at birth was 30.4 years. The mean age of the population mothers at birth was 30.0 years. A t-test showed a significant difference ($p < 0.001$). Table 6.3 shows the user rates (cases) and prescription rates (population) for the drugs investigated according to malformation group. (Our criterion of at least three exposed cases led to) Based on our criterion of at least three exposed cases, seven specific drugs acting on the nervous system and seven specific drugs considered to be safe were included in our analyses.

Table 6.2 Distribution of the birth years of the cases and general population per study year

	cases: EUROCAT NNL (n_{total} = 3212)		**general population: IADB (n_{total} = 29223)**	
Study year	n	%	N	%
1998	294	9.2	3136	10.7
1999	303	9.4	3353	11.5
2000	286	8.9	3256	11.1
2001	273	8.5	3105	10.6
2002	280	8.7	3043	10.4
2003	320	10.0	2887	9.9
2004	307	9.6	2763	9.5
2005	305	9.5	2419	8.3
2006	316	9.8	2006	6.9
2007	260	8.1	1740	6.0
2008	268	8.3	1515	5.2

Table 6.3 User rates (cases) and prescription rates (general population) for the drugs investigated

	CASES - malformation categories [1] (n=3212)									POPULATION (n=29223)
	central nervous system (n=208)	*heart (n=873)*	*clefts (n=294)*	*respira-tory tract (n=55)*	*digestive system (n=362)*	*genitals (n=314)*	*urinary tract (n=309)*	*muscular -skeletal (n=668)*	*limbs (n=184)*	
Drugs acting on nervous system (ATC code: N)										
• sumatriptan (n(%])	0	4 (0.46)	0	0	0	0	<3[2]	0	0	58 (0.20)
• valproic acid (n[%])	3 (0.01)	5 (0.57)	<3[2]	0	<3[2]	0	<3[2]	<3[2]	0	28 (0.09)
• diazepam (n[%])	<3[2]	3 (0.34)	<3[2]	<3[2]	0	<3[2]	<3[2]	<3[2]	<3[2]	86 (0.29)
• oxazepam (n[%])	<3[2]	3 (0.34)	<3[2]	<3[2]	3 (0.96)	<3[2]	<3[2]	3 (0.45)	0	161 (0.55)
• fluoxetine (n[%])	<3[2]	3 (0.34)	<3[2]	0	3 (0.96)	0	0	<3[2]	0	65 (0.22)
• citalopram (n[%])	0	0	0	0	<3[2]	0	0	3 (0.45)	0	35 (0.12)
• paroxetine (n[%])	0	11 (1.26)	<3[1]	0	<3[2]	<3[2]	4 (1.29)	4 (0.60)	0	181 (0.62)
Drugs considered to be safe (ADEC classification: A)										
• metoclopramide (n[%])	<3[2]	5 (0.57)	<3[2]	0	<3[2]	<3[2]	<3[2]	<3[2]	<3[2]	155 (0.53)
• methyldopa (n[%])	0	0	0	0	3 (0.83)	3 (0.96)	3 (0.97)	<3[2]	0	52 (0.18)
• thyroxine (n[%])	<3[2]	10 (1.15)	3 (1.02)	0	4 (1.10)	<3[2]	<3[2]	6 (0.90)	3 (1.63)	299 (1.02)
• amoxicillin (n[%])	11 (5.29)	28 (3.21)	13 (4.42)	4 (7.27)	19 (5.25)	14 (4.46)	13 (4.21)	21 (3.14)	7 (3.80)	994 (3.40)
• nitrofurantoin (n[%])	<3[2]	10 (1.15)	3 (1.02)	<3[2]	3 (0.83)	<3[2]	4 (1.29)	9 (1.35)	3 (1.63)	388 (1.33)
• salbutamol (n[%])	5 (2.40)	8 (0.92)	3 (1.02)	<3[2]	7 (1.93)	8 (2.55)	6 (1.94)	13 (1.95)	5 (2.72)	426 (1.46)
• budesonide (n[%])	0	5 (0.57)	<3[2]	<3[2]	<3[2]	<3[2]	<3[2]	<3[2]	<3[2]	83 (0.28)

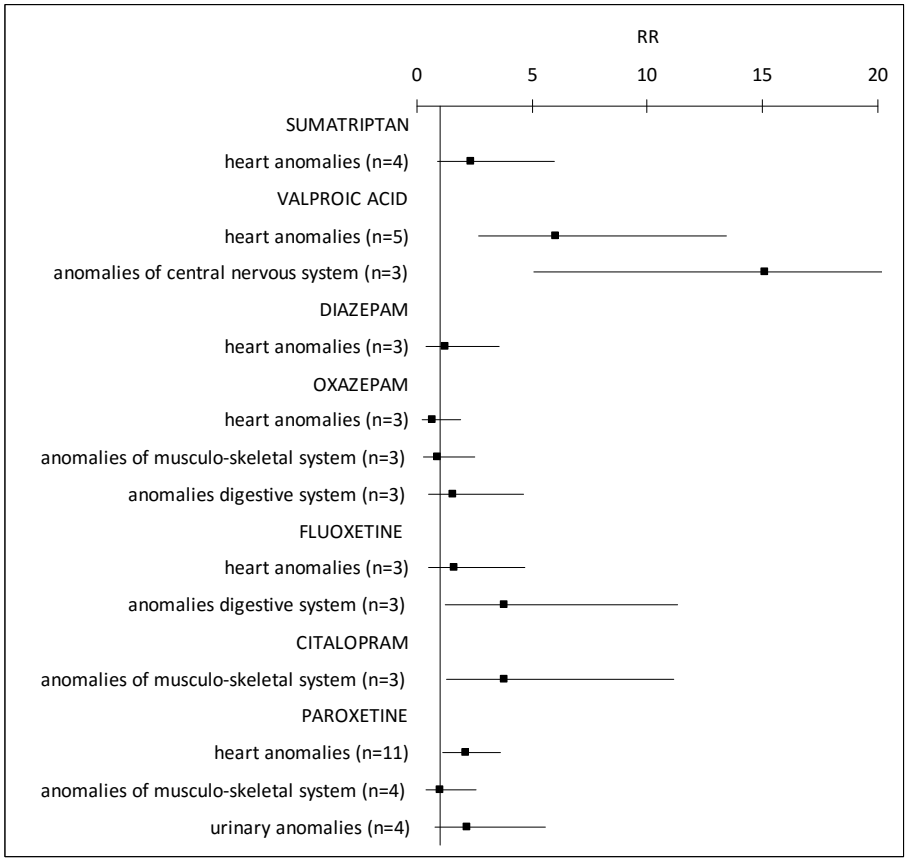
ATC = Anatomical Therapeutic Chemical; ADEC = Australian Drug Evaluation Committee;

[1] Children with multiple malformations were counted in multiple categories (n=253, 7.9%);

[2] unequal to 0, but numbers too low to calculate a reliable RR

Drugs acting on the nervous system

Figure 6.1 shows the RRs for the drugs acting on the nervous system that could be calculated for the malformation groups. The anti-epileptic drug valproic acid showed a significantly increased RR for heart anomalies of 5.98 (2.66-13.44) and for anomalies of the central nervous system of 15.05 (5.09-44.51). For some selective serotonin re-uptake inhibitors (SSRIs), we found certain significantly increased RRs: fluoxetine and anomalies of the digestive system: 3.73 (1.23-11.32); citalopram and anomalies of the musculo-skeletal system: 3.75 (1.26-11.14) and paroxetine and heart anomalies: 2.03 (1.14-3.62). The malformations observed can be found in appendix 1h.



** valproic acid – anomalies of central nervous system (n=3) 15.05 (5.09-44.51)*

Figure 6.1 Rate ratios (RR) calculated for drugs acting on the nervous system for the different malformation groups

We found no significantly increased RR for the anti-migraine drug sumatriptan, nor for the benzodiazepines, diazepam and oxazepam.

Drugs considered to be safe

The RRs for specific drugs in the group of 'safe' drugs are shown in figure 6.2. The anti-hypertensive methyldopa showed significantly increased RRs for anomalies of the digestive system: 4.66 (1.54-14.06) *genital* anomalies: 5.37 (1.78-16.22) and urinary anomalies: 5.46 (1.81-16.49). The malformations observed can be found in appendix 1h. We found no significantly increased RR for metoclopramide, thyroxine, amoxicillin, nitrofurantoin, salbutamol or budesonide.

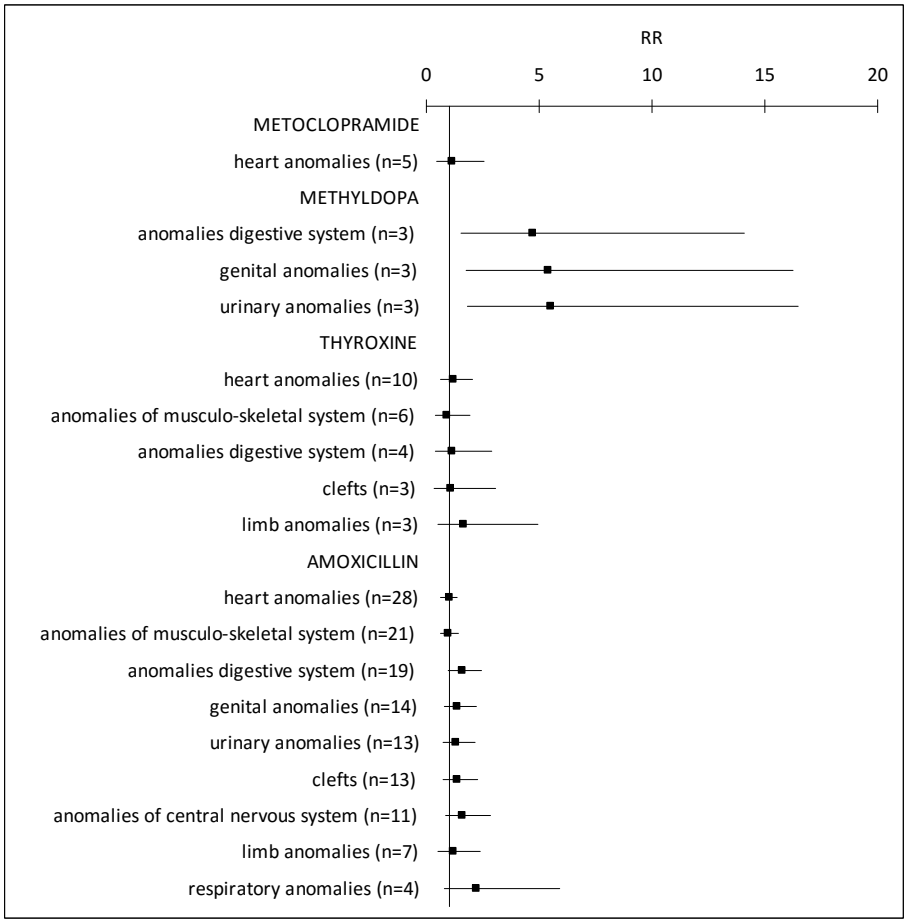


Figure 6.2 Rate ratios (RR) calculated for drugs considered to be safe for the different malformation groups

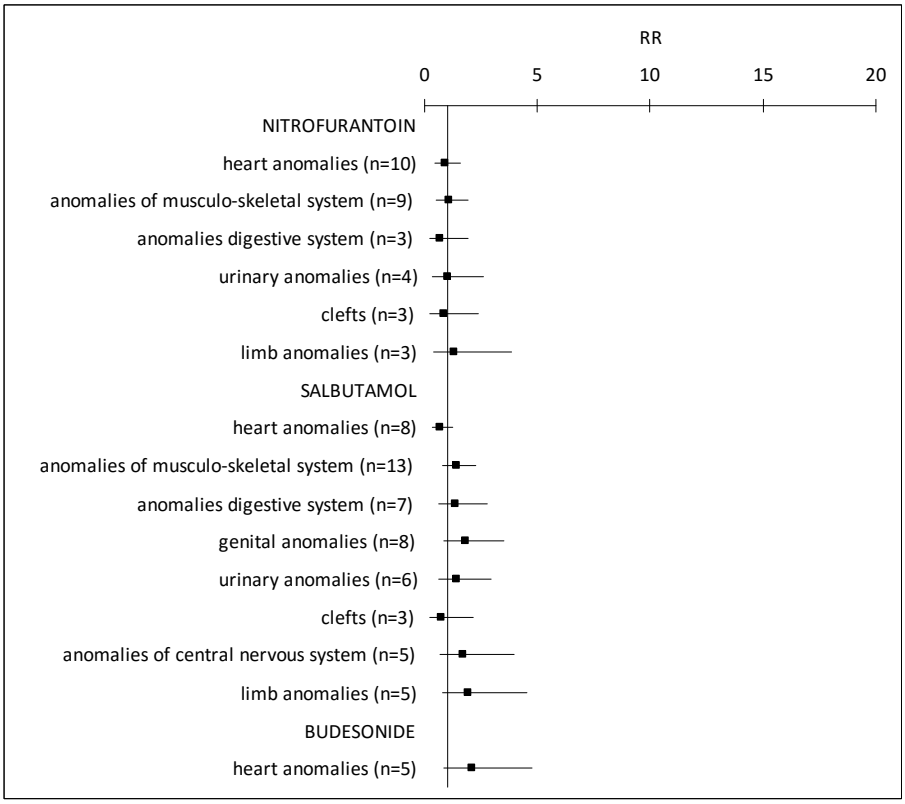


Figure 6.2 Rate ratios (RR) calculated for drugs considered to be safe for the different malformation groups (continued)

Discussion

In this case-population study, we investigated whether comparing drug use rates from a population-based birth defects registry with prescription rates from a population-based prescription database could be used as a suitable detection method for the teratogenic risk of drugs. For drugs acting on the nervous system, we found significantly increased RRs for the anti-epileptic drug valproic acid and for some SSRIs. Of the drugs considered to be safe, only the anti-hypertensive methyldopa showed significantly increased RRs.

A suitable method for the detection of possible teratogenicity should be able to detect known teratogenic effects but should not detect any effects if a drug is considered to be safe. Based on the Bradford Hill criteria on causality [26], Meyboom et al. stated seven basic criteria for determining a signal [27,28]. Of these criteria "*quantitative*

strength of the association, consistency of the data, biological plausibility and experimental findings" can be applied to our study. A method to detect signals must pick up signals quickly and easily, and should therefore be easily applicable and relatively inexpensive. Although they have limitations, like needing to control for potential confounders and quantifying the strength of the association found, case-population studies are considered to be useful for generating signals and testing hypotheses [11].

For the anti-epileptic drug valproic acid we found increased RRs for heart anomalies and for anomalies of the central nervous system. These results are in line with previous results [18,19,21,22,29]. The association between fluoxetine and anomalies of the digestive system was previously reported by Bakker et al. [30] using the same data from EUROCAT NNL. This association was confirmed by Colvin et al. [31].

Citalopram has been associated in the literature with neural tube defects [32] and septal heart defects [33] but we found no report of an association with musculo-skeletal malformations. The association we found was based on three cases: two of them were affected by singular dysplasia of the hip, while the third case had a dysplasia and luxation of the hip. The broad confidence interval around the RR of 3.75 (1.26-11.14) indicates that this estimate is not very precise. As far as we know, this is the first report of such an association. There is no evidence of biological plausibility for the association of citalopram with hip anomalies. It should be noted that hip malformations are common in the Northern Netherlands, with an etiology that showed to be multifactorial [34] and is unlikely to be drug-induced. Our finding therefore needs further investigation in other datasets.

We found an increased RR for paroxetine and heart anomalies in general. The association between paroxetine and cardiac malformations, especially right ventricle outflow tract obstructions, has been reported by several other studies [33,35,36]. Using data from the same birth defect registry, EUROCAT NNL, a recent case-control study on first trimester use of paroxetine and congenital heart defects found a significantly increased risk for atrium septum defects but not for heart anomalies in general [37]. The association between paroxetine and cardiovascular malformation is still point of discussion though. In his study of three meta-analyses on this topic, Scialli states that by applying the Bradford Hill criteria of causality noted before, 'scientific evidence does not support for the conclusion that paroxetine causes cardiovascular defects' [38].

As expected, the RRs we found for the drugs considered to be safe were generally around one. However, significantly increased RRs were found for methyldopa and anomalies of the digestive system, genital anomalies and urinary anomalies. One child contributed to all of these malformation groups. Due to low numbers this had a substantial effect on the RRs calculated possibly leading to a false-positive signal. Furthermore, methyldopa is the most extensively used anti-hypertensive in pregnancy, because it is considered to be safe and efficient [39]. A number of studies have shown little difference in teratogenic risk between several anti-hypertensive medications and untreated hypertension, suggesting that the underlying hypertension itself might increase the risk for congenital malformations [40-43]. Additional studies are needed to elaborate on these findings.

Strengths and limitations

Comparing data from EUROCAT NNL and IADB offers the opportunity to compare first trimester drug exposure based on pharmacy data in two different databases, covering approximately the same geographical area and the same period. Since the data are available, the method is relatively easy and inexpensive. The IADB is a population-based, non-selected database, including a large number of pregnancies [17]. Almost complete records of prescription data are available because Dutch normally only use one local pharmacy. For EUROCAT NNL, information about drug use is based on pharmacy records and verified in telephone interviews. The complementary use of pharmacy records and interview data provides the most complete medication history possible [44].

When using data from a prescription database, it is unknown whether the drug was actually taken, possibly leading to an overestimation of drug use. Olesen et al. [45] studied pregnant women's compliance in using prescribed drugs and found that it was high for drugs used to treat chronic diseases (70-100%) but lower for short-term treatments. Another limitation is that since we only focused on the prescription date and not on the duration of the prescription, we will have missed drugs prescribed before the pregnancy, but used during pregnancy. The IADB only contains live births and has no information about congenital malformations, but since it is a population-based record, we expect about 3% of the children to have a congenital anomaly [46]. These low numbers will only cause a minimal bias.

The actual gestational period of the pregnancies in the IADB is not known. Taking the theoretical gestation to determine first trimester exposure may have led to some misclassifications. For more than one third of all children registered with the IADB a mother cannot be identified, possibly leading to selection bias. However criteria for linking a child to a parent are very strict to avoid mismatching. Schirm et al demonstrate that more than 99% of the coupled children were coupled to the right mother [17]. For EUROCAT NNL, approximately 80% of the parents agree with inclusion of their child in the registry. Women who agree with registration might differ from women who do not agree with regard to type of anomaly or demographic factors, therefore selection bias can not be excluded.

Only cases with complete pharmacy records and medication use were included. The cases excluded from the study population contained more miscarriages, terminated pregnancies and stillbirths than the cases with complete records and were relatively more earlier in our study period. Malformations amongst stillbirths and terminations differ from malformations amongst live born, often being more serious and not compatible with life. Medications used might be different for these groups as well. Some bias may have occurred, which could have led to underestimation of medication use among cases and not detecting some signals. However, this selection criterion was necessary to ensure the quality of our data.

We found a significant difference among the mean ages of the case and population mothers. In absolute terms, the difference is only of a small order, i.e. 0.4 years. Ideally, the results should be adjusted for age. However, due to small numbers adjustment was not possible.

Due to the nature of the population data used, we were not able to adjust for potential confounding factors. Since we wanted to test a method for detecting signals quickly and easily, further studies designed to confirm or reject the signals we found should address the issue of confounders.

We could not detect associations described in the literature for several drugs acting on the nervous system. Some of these associations, like the increased risk of clefts with exposure to diazepam, are controversial and literature reports are often inconsistent. We could only calculate RRs for a limited association between drugs and malformations groups because of small case groups and the incidental use of several drugs. Sample size

calculations show that for the detection of a small risk (RR=2) and an exposure of 0.2% in the pregnant population, like for some of the medication from the drugs acting on the nervous system we studied, approximately 7100 cases would be needed. For a relatively common birth defect like a heart defect (prevalence 0.7%), this would cover about 1 million births. Larger databases are necessary to detect potential teratogenic effects of drugs not commonly used, from a large registration area with population data and also information on drug use. This could probably be realized by adding other congenital anomaly registries with detailed information about drug use and the availability of population data.

Conclusion

This study was conducted to test the case-population approach for detecting signals, by comparing exposure rates between cases (from a birth defect register, EUROCAT NNL) and the general population (represented by a pharmacy database, IADB). We show how this method was able to detect known teratogenic risks for several widely used drugs acting on the nervous system. It did not detect any teratogenic effects for most drugs that are considered to be safe, assuming there were enough cases for a particularly anomaly. We can therefore assume that this is a suitable method for detecting signals of possible teratogenicity, providing that the teratogenic effects and drugs studied are as specific as possible, and the drugs are widely used.

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CHAPTER 7

Early pregnancy exposure to antihistamines and risk of congenital heart defects: results of two case-control studies

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Abstract

Objective: We aimed to study the association between use of antihistamines in early pregnancy and congenital heart defects (CHD) in the offspring.

Design: Two case–control studies.

Setting: HAVEN study, Erasmus MC, University Medical Centre, Rotterdam, and EUROCAT Northern Netherlands (NNL), University Medical Center Groningen, Groningen, the Netherlands. We studied 361 children with CHD and 410 controls without congenital malformations from the HAVEN study and replicated the analyses in 445 children with CHD and 530 controls from the EUROCAT NNL registry. Information about antihistamine use in early pregnancy and potential confounders was obtained from questionnaires postpartum. We calculated the association between antihistamines and CHD risk by multivariable logistic regression analysis.

Main outcome measures: Odds ratios (OR) with 95% confidence intervals (CI). In the HAVEN study, 25 of 771 mothers used antihistamines that were associated with an increased CHD risk (OR 3.0, 95% CI 1.2–7.3), particularly atrioventricular septal defects (AVSD) (OR 5.1, 95% CI 1.3–20.5) and perimembranous ventricular septal defects (pVSD) (OR 5.1, 95% CI 1.8–14.4). Mothers with severe nausea who did not use antihistamines had a reduced risk (OR 0.7, 95% CI 0.5–0.98), whereas nauseous mothers using antihistamines showed an almost fivefold increased risk of pVSD (OR 4.8, 95% CI 1.1–21.8). The association between antihistamines and AVSD was confirmed in the EUROCAT cohort (OR 3.5, 95% CI 1.4–8.7), but we could not replicate the association with overall CHD risk. We found a positive association between antihistamine use in early pregnancy and CHD risk, particularly AVSD, which seemed to be independent of nausea/vomiting.

Introduction

Congenital heart defects (CHD) affect 7.2 per 1,000 live births and occur substantially more often among stillbirths and miscarriages [1,2]. Due to a high infant morbidity and mortality, CHD also impose a considerable burden of personal suffering and societal costs [3]. Over the past 10 years, epidemiological studies have made major breakthroughs in understanding both the inherited and noninherited causes of CHD [4–6]. However, so far, only around 15% of CHD can be attributed to a known cause; the majority are thought to result from complex interactions between largely unknown subtle genetic variations and periconceptional exposures [7, 8].

The thalidomide tragedy of the late 1950s and early 1960s made us aware that medication use in early pregnancy poses serious risks to the fetus [9]. At present, several medicines have been shown to be teratogens for heart development, such as retinoids and anticonvulsants [5]. Since the removal of Bendectin (doxylamine/pyridoxine) from the American market in 1983 because of claims of teratogenicity and litigation, pharmacotherapeutic interventions for pregnancy-related nausea/vomiting have been viewed with great suspicion [10]. Nausea/vomiting affect a mean rate of 70% of pregnant women and the symptoms usually appear during between the 4th and 14th week [11]. Antihistamines for treating pregnancy-related nausea/vomiting are among the most frequently prescribed medications during pregnancy [12]. In pregnant rats, exposure to antihistamines has been shown to increase the frequency of congenital malformations [13, 14], although evidence from human studies during pregnancy is inconsistent [15–18]. Nonetheless, antihistamines are still popular and widely prescribed during early pregnancy. In Germany, 14% of pregnant women received anti-emetic prescriptions [19]. CHD is one of the most prevalent congenital malformations developing in the same period that nausea/vomiting presents.

We used data from the HAVEN study and from a population selected from the EUROCAT Northern Netherlands (NNL) registry to investigate the relationship between maternal use of antihistamines, prescribed for both pregnancy-related nausea/vomiting and other indications, and the risk of specific CHDs.

Methods

Study populations

HAVEN study

The HAVEN study is a population-based, case–control family study to investigate lifestyles, environmental and genetic determinants in the pathogenesis and prevention of CHD [20]. HAVEN is a Dutch acronym for Heart Defects, Vascular status, Genetic factors and Nutrients. 361 eligible cases were identified at the age of around 16 months from the registries of four tertiary referral hospitals in Amsterdam, Leiden and Rotterdam, in the western part of the Netherlands. Two pediatric cardiologists trained at the same hospital diagnosed all the CHD phenotypes after birth by echocardiography and/or cardiac catheterization and/or surgery. We assume that the different CHD phenotypes may be due to comparable exposures, but that they develop differently depending on genetic background and timeframe of the exposure. The phenotypes we included were: Tetralogy of Fallot (n = 44), complete atrioventricular septal defects (AVSD) (n = 37), perimembranous ventricular septal defect (pVSD) (n = 98), aortic valve stenosis (n = 8), pulmonary valve stenosis (n = 60), coarctation of the aorta (n = 32), transposition of the great vessels (n = 50), hypoplastic left heart syndrome (n = 17), and miscellaneous types (n = 15) consisting of univentricular heart, aorta interruption, mitral valve atresia, tricuspid valve atresia, and corrected transposition of the great arteries. A genetic disorder or syndrome was present in 58/361 of the cases (16.0%). 410 controls were randomly selected from the registries of the public child healthcare centers covering the source population of the cases. The Dutch healthcare system includes a regular checkup of all newborns for health, growth and development by pediatric physicians in such a center. The controls did not have any major malformations or chromosomal defects according to the medical records obtained at 16 months of age. They were invited to participate at the same age as the cases, at around 16 months. None of the children in the study population had been adopted. Participating families were not related to each other and were able to speak, read and write the Dutch language. We had 74.5% response from the case families and 61.4% from the control families. The main reasons not to participate were giving no permission to take a blood sample from their child for research purposes and the expected time effort. The study design has been described in more detail previously [20]. The Central Committee of Research in Humans and the Medical Ethical Committees of the participating hospitals approved the protocol and written consent from the parents was obtained prior to their participation.

For the analyses, we included 361 cases with CHD and 410 controls between October 2003 and February 2007. Mothers with diabetes (n = 6), hyperhomocysteinaemia (n = 1), epilepsy (n = 6), hypertension (n = 6) and rheumatoid arthritis (n = 2) were excluded as these conditions could confound the associations we were investigating.

We chose to study the mother–child pairs at 16 months after birth; this time of investigation was standardized and minimizes recall bias and differential effects between the recall by case and control mothers regarding their periconceptional medication use, nausea/vomiting, and lifestyle behaviors. In addition, the study moment at more than 1 year after birth was chosen because most CHD are detected within the first year of life, thereby minimizing misclassification of control children. The mothers completed a questionnaire on demographics, illnesses, lifestyle behaviors and medication use at the study moment and during their periconceptional period, defined as 3 months prior to conception and up to 10 weeks after conception. The questionnaires were filled in at home and checked for completeness and consistency by the researcher during the participant's visit to our clinic.

The history of prescribed and over the counter antihistamine use during the first 10 weeks of pregnancy was obtained from the questionnaire and coded according to the internationally accepted Anatomical Therapeutic Chemical (ATC) classification (controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology) [21]. Medicines were coded based on their pharmacological and chemical properties. Anti-emetics were meclozine, meclozine/pyridoxine combination and cyclizine (piperazines), other antihistamines were cetirizine and levoceterizine (piperazines), amino-alkyl ethers and phenothiazines. We defined a child as having been exposed to the medicine during the first 10 weeks of pregnancy if the mother had taken the medicine during this 10-week period. In addition, the history of pregnancy-related nausea/vomiting was evaluated. Information on nausea/vomiting in the first 10 weeks of pregnancy was categorized as no nausea or vomiting, mild nausea with or without incidental vomiting, and severe nausea/vomiting. The last category was characterized by daily nausea with vomiting or with a serious influence on dietary intake.

Mothers who reported any use of alcohol or cigarettes were considered as alcohol users and smokers. Periconceptional vitamin use was defined as daily intake during the whole periconceptional period, defined as starting 3 months prior to conception and up to 10 weeks after conception. Educational level was classified according to the definitions of Statistics Netherlands into low (primary/lower, vocational/intermediate, secondary), intermediate

(intermediate, vocational/higher, secondary) and high education (higher vocational/university) [22]. Ethnicity was categorized as Western (both parents were born in the Netherlands, or in a European country or non-Western (one of the parents was of non-European origin) [22]. Standardized maternal measurements of weight (weighing scale, SECA, Germany, accurate to 0.5kg) and height (anthropometric rod, SECA, Germany, accurate to 0.1cm) were also performed during the clinic visit at 16 months after delivery. Body mass index (BMI) after birth was defined as weight in kilograms divided by the height in meters squared.

EUROCAT Northern Netherlands (NNL)

EUROCAT NNL is a population-based birth defect registry in the northern part of the Netherlands (the three Northern provinces Friesland, Groningen and Drenthe); it covers approximately 10% of all Dutch births. A child can be registered with a defect up to the age of 16, there is no lower age limit. All types of births are included in the registry: live births, stillbirths, spontaneous abortions and terminations.

Parental informed consent is required to register a child and parents are asked to fill in a questionnaire on sociodemographic characteristics, prenatal screening methods and diagnostic tests, and prenatal exposure to possible risk factors (chemicals, drugs, etc.). With consent of the mother information on prescribed medications from the period 3 months before conception up to delivery are obtained from her pharmacy. The actual use of the prescribed medication and use of over the counter medication is later verified in a telephone interview.

Birth defects are coded according to the ICD coding system. For births up to 2001, ICD-9 is used, while for births from 2002 onwards, ICD-10 is used [21]. Medication taken by the mother is coded according to the ATC classification system.

From the EUROCAT NNL database, 445 cases and 530 controls were selected. All the children were born in a 12-year period between 1st January 1997 and 31st December 2008. To comply with the HAVEN study, only live births were included. Of the 445 cases, 58 were diagnosed with Tetralogy of Fallot, 58 with complete AVSD, 121 pVSD, 14 with aortic valve stenosis, 39 with pulmonary valve stenosis, 51 with coarctation of the aorta, 66 with transposition of the great vessels and 38 with hypoplastic left heart syndrome. In total, 74/445 of the EUROCAT cases (16.6%) also had a genetic disorder. Since EUROCAT NNL only includes children and fetuses with a birth defect, children with isolated hip dysplasia and/or luxation were selected as controls. The use of antihistamines has not been associated with these

disorders. We excluded mothers with diabetes, hyperhomocysteinaemia, epilepsy, hypertension and rheumatoid arthritis because these conditions could confound the associations we were investigating.

Anti-emetics were meclozine, meclozine/pyridoxine combination and cyclizine (piperazines), other antihistamines were cetirizine and levoceterizine (piperazines), amino-alkyl ethers and phenothiazines. Exposure to an antihistamine was defined as any antihistamine use during the first 14 weeks of pregnancy, calculated from the first day of the last menstrual period. No information was available on nausea/vomiting.

Mothers who reported any periconceptional use of alcohol and/or cigarettes were considered as alcohol users and/or smokers. Periconceptional use of folic acid or multivitamins containing folic acid was defined as any use of these during the 3 months before conception up to the end of the first trimester. To record educational level, we used the definitions set by Statistics Netherlands.

Ethnicity was categorized as 'Western' if the mother was born in Europe, North America, Australia, New Zealand or Indonesia, and 'non-Western' if the mother was born in any another country. Maternal weight and height were based on the situation before pregnancy and were self-reported.

Statistical analyses

HAVEN study

In the HAVEN analyses, normality of continuous variables was tested by the one-sample Kolmogorov–Smirnov Test. BMI showed a positively skewed distribution even after logarithmic transformation. Continuous variables of the maternal characteristics were therefore presented as medians with interquartile ranges, and differences between cases and controls were tested by the Mann–Whitney U test.

Categorical variables were tested between cases and controls by the Chi squared test. We used a forward, stepwise, multivariable regression model to study associations between use of antihistamines during early pregnancy, stratified for anti-emetics and other antihistamines, and the risk of both overall CHD and the separate CHD phenotypes. The risk estimates were adjusted for the variables that were either significantly different between cases and controls or that had a $P<0.1$ in the logistic model (maternal age, educational level, ethnicity, parity, sex of the child and any medication except antihistamines). Crude and adjusted odds ratios (ORs) and

95% confidence intervals (CIs) were calculated for use of antihistamines during early pregnancy if at least two cases had been exposed. In the HAVEN data, we then performed a combined analysis of anti-emetic use in early pregnancy and nausea/vomiting, with no antihistamine use and no nausea/ no vomiting as a reference, and separately presented the results for complete AVSD and pVSD defects, as these were found to be associated with antihistamine use. Trends across severity of nausea/vomiting towards CHD risk were evaluated by the linear-by-linear association test. Statistical analyses were performed with SPSS for Windows software (version 20.0; SPSS Inc, Chicago, IL, USA).

EUROCAT NNL

The normality of continuous variables, maternal age and BMI was tested by the one-sample Kolmogorov–Smirnov Test. Maternal age was normally distributed for the EUROCAT population. These characteristics were therefore presented as mean and standard deviation, and the differences between cases and controls were tested by the independent t test. Since BMI was not normally distributed, these characteristics were presented as medians with interquartile ranges and the differences between cases and controls were tested by the Mann–Whitney U test.

Categorical variables were tested between cases and controls by the Chi squared test. We used a logistic regression model to study associations between early pregnancy use of antihistamine, stratified for anti-emetics and other antihistamines, and the risk of both overall CHD and the separate CHD phenotypes. The risk estimates were adjusted for the same potential confounders or effect modifiers as in the HAVEN study. Crude and adjusted ORs and 95% CIs were calculated if at least two cases had been exposed.

Results

Socio-demographic and lifestyle characteristics of case mothers of a child with CHD and controls are presented in table 7.1. HAVEN study case mothers showed a slightly higher age than controls, but ethnicity, educational level, BMI, parity, child gender and periconceptional exposures were not different except for a higher medication use in case mothers (27%) than in healthy controls (19%).

For the EUROCAT population case mothers were also slightly older than control mothers. The large majority of cases and controls were of Western origin, however the cases

were slightly more often of non-Western origin (3% [15/445] vs. 1% [5/530]). Furthermore, we found a statistically significant difference in educational level and parity between cases and controls. There were more girls among the controls, since hip dysplasia is more common among girls.

Table 7.1 Characteristics of mothers of a child with congenital heart defects and of controls

	HAVEN		EUROCAT	
	CHD	**Controls**	**CHD**	**Controls**
	(n = 361)	(n = 410)	(n = 445)	(n = 530)
Maternal age (years)	32.9 (29.8-36.2)*	32.7 (28.8-35.1)	31.4 (4,543)^	30.0 (4,032)
BMI (kg/m^2)	24.4 (22.0-28.0)	24.4 (22.1-28.0)	23.5 (21.4-26.6)	23.5 (21.4-25.9)
Ethnicity:				
Western	300 (83)	318 (78)	422 (97)#	518 (99)
Non-Western	61 (17)	92 (22)	15 (3)	5 (1)
Educational Level:				
Low	90 (25)	96 (24)	91 (21)*	75 (16)
Intermediate	161 (45)	199 (48)	211 (49)	280 (59)
High	110 (30)	115 (28)	126 (29)	124 (26)
Parity (first child)	152 (42)	200 (49)	147 (34)^	249 (48)
Sex of the child (male)	205 (57)	229 (56)	256 (58)^	78 (15)
Periconceptional use of:				
Alcohol yes	138 (38)	132 (32)	88 (21)	86 (17)
Cigarettes, yes	63 (18)	89 (22)	114 (26)	108 (21)
B-vitamins, yes	182 (50)	206 (50)	300 (67)	367 (69)
Any medication, yes	98 (27)#	78 (19)	191 (43)	203 (38)
Antihistamines, yes	18 (5) #	7 (2)	22 (5)	20 (4)

CHD, congenital heart defect
HAVEN controls are healthy children without congenital malformation.
EUROCAT controls are children with an isolated hip disorder (dysplasia or dislocation).
Data are median (interquartile range), mean (standard deviation) or n (%), compared by Mann–Whitney U Test or Chi squared test
** P value B 0.05,*
 # P value B 0.01,
^ P value B 0.001

In the HAVEN study, antihistamine use was reported in 3.2% of case and control mothers, of which 5.0% in case mothers (18 of 361) and 1.7% in control mothers (7 of 410) (Table 7.2). The use of antihistamines was associated with a threefold increased risk of CHD (crude OR 3.0, 95% CI 1.2–7.3). Because of the small number of exposed cases, adjustment for potential confounders might not be useful. However, for completeness we added the adjusted ORs to Table 7.2. After stratification for anti-emetics, i.e., meclizine and the

Table 7.2 Early pregnancy exposure to antihistamines, stratified for anti-emetics and other antihistamines, and the risk of congenital heart defects

	Total antihistamines			Anti-emetics			Other antihistamines		
	Cases/ Controls	OR (95% CI)	OR (95%CI)*	Cases/ Controls	OR (95% CI)	OR(95%CI)*	Cases/ Controls	OR (95% CI)	OR (95%CI)*
HAVEN database n = 361/410									
Total CHD, n = 361	18 / 7	3.0 (1.2-7.3)	2.6 (1.02-6.7)	10 / 4	2.9 (0.9-9.3)	2.2 (0.6-7.2)	8 / 3	3.1 (0.8-11.7)	2.8 (0.7-11.2)
Tetralogy of Fallot, n = 44	2 / 7	2.7 (0.6-13.6)	3.4 (0.6-19.9)	0 / 4	NE	NE	2 / 3	6.5 (1.05-39.8)	8.5 (1.2-63.2)
Transposition of the great vessels, n=50	2 / 7	2.4 (0.5-11.9)	2.4 (0.4-14.2)	1 / 4	NE	NE	1 / 3	NE	NE
Complete AVSD, n = 37	3 / 7	5.1 (1.3-20.5)	9.0 (1.6-50.8)	2 / 4	5.8 (1.03-32.8)	6.8 (0.9-50.7)	1 / 3	NE	NE
Perimembranous VSD, n = 98	8 / 7	5.1 (1.8-14.4)	5.2 (1.6 - 16.7)	5 / 4	5.5 (1.4-20.7)	4.5 (1.1-18.8)	3 / 3	4.3 (0.9-21.6)	4.3 (0.8-23.7)
EUROCAT database, n = 445/530									
Total CHD, n = 445	22/20	1.3 (0.7-2.5)	1.2 (0.6-2.5)	20/18	1.3 (0.7-2.6)	1.2 (0.5-2.6)	2/2	1.2 (0.2-8.6)	1.2 (0.1-10.1)
Tetralogy of Fallot, n = 58	2/20	0.9 (0.2-4.1)	0.4 (0.1-2.8)	2/18	1.0 (0.2-4.5)	0.5 (0.1-3.8)	0/2	NE	NE
Transposition of the great vessels, n=66	3/20	1.2 (0.4-4.2)	0.9 (0.2-3.9)	3/18	1.3 (0.4-4.7)	1.3 (0.3-5.4)	0/2	NE	NE
Complete AVSD, n = 58	7/20	3.5 (1.4-8.7)	3.6 (1.3-9.9)	5/18	2.8 (1.0-7.8)	2.8 (0.9-9.0)	2/2	10,0 (1.4-72.4)	9.4 (1.0-85.2)
Perimembranous VSD, n = 121	4/20	0.9 (0.3-2.6)	0.7 (0.2-2.3)	4/18	1.0 (0.3-2.9)	0.8 (0.2-2.8)	0/2	NE	NE

*AVSD, atrioventricular septal defect. VSD, ventricular septal defect. CHD, congenital heart defect. OR, odds ratio. CI, confidence interval. NE, not estimated from logistic regression model. * Odds ratios adjusted to maternal age, and educational level, ethnicity, parity, sex of the child and periconceptional use of any medication except antihistamines. Anti-emetics are meclozine, meclozine/pyridoxine combination and cyclizine (piperazines). Other antihistamines are cetirizine and levoceterizine (piperazines), amino-alkyl ethers and phenothiazide.*

meclozine/pyridoxine combination as well as other antihistamines, the risk estimates were comparable although significance was lost due to small numbers. Stratification per CHD phenotype in the HAVEN study revealed that antihistamine use, particularly antiemetic medication, was associated with the occurrence of complete AVSD (crude OR 5.8, 95% CI 1.03–32.8) and pVSD (crude OR 5.5, 95% CI 1.4–20.7). Furthermore, other antihistamines were associated with an increased risk of Tetralogy of Fallot (crude OR 6.5, 95% CI 1.05–39.8). Risk estimates for coarctation of the aorta, aortic valve stenosis, pulmonary valve stenosis, hypoplastic left heart syndrome, and the miscellaneous subgroup were not calculated as fewer than two cases in each category were exposed.

In the EUROCAT population, antihistamine use was reported in 4.3% of case and control mothers, of which 4.9% in case mothers (22/445) and 3.8% in control mothers (20/530). The positive association between periconceptional use of antihistamine medication and complete AVSD was confirmed (OR 3.5, 95% CI 1.4–8.7) in the EUROCAT population. However, the association between periconceptional use of antihistamine medication and the total group of CHDs, pVSD and Tetralogy of Fallot was not confirmed: respectively we found OR 1.3, 95% CI 0.7–2.5; OR 0.9, 95% CI 0.3–2.6 and OR 0.9, 95% CI 0.2–4.1.

In the HAVEN study, in a subgroup analysis after excluding cases with a known genetic factor, the observed associations remained between antihistamine use and overall CHD risk (OR 3.2, 95% CI 1.3–8.0), AVSD (OR 11.5, 95% CI 1.2–111) and pVSD (OR 6.0, 95% CI 2.0–17.7). In the EUROCAT population, the association between antihistamines other than anti-emetics and AVSD also remained after excluding cases with a known genetic factor (OR 15.9, 95% CI 1.4–184), but the association between overall antihistamine use and AVSD (OR 3.0, 95% CI 0.7–14.0) attenuated to non-significant. In the HAVEN study, 52% of case mothers and 59% of control mothers reported nausea/vomiting. We demonstrated a significant trend towards a reduced overall CHD risk by increasing severity of nausea/vomiting, P = 0.020. Severe nausea and vomiting without the use of anti-emetic medication seemed to be associated with a reduced risk of CHD (OR 0.7, 95% CI 0.5–0.98) (Table 7.3). However, mothers with severe nausea/vomiting who used anti-emetic medication tended to have an increased risk of overall CHD offspring, albeit non-significant. Remarkably, the reduced risk in the group of mothers with severe nausea/vomiting changed into an almost fivefold increased risk for particularly pVSD (OR 4.8, 95% CI 1.1–21.8). These analyses could not be replicated as this information was not available for the EUROCAT population.

Table 7.3 Maternal use of anti-emetics in combination with nausea and vomiting during early pregnancy in association with risk of congenital heart defect, HAVEN study results

Anti-emetic use	Nausea/ vomiting	Total CHD			Complete AVSD			Perimembranous VSD		
		Cases / Controls	OR (95% CI)	OR (95% CI)*	Cases / Controls	OR (95% CI)	OR (95% CI)*	Cases / Controls	OR (95% CI)	OR (95% CI)*
		(n = 353/407)			(n = 36/407)			(n = 95/407)		
-	no	167/168	reference	reference	16/168	reference	reference	39/168	reference	reference
-	mild	96/118	0.8 (0.6-1.2)	0.8(0.6-1.1)	10/118	0.9 (0.4-2.0)	1.0 (0.4-2.3)	28/118	1.0 (0.6-1.8)	1.0 (0.6-1.8)
-	severe	80/117	0.7 (0.5-0.98)	0.7(0.5-1.01)	8/117	0.7 (0.3-1.7)	0.9 (0.3-2.2)	23/117	0.8 (0.5-1.5)	1.0 (0.5-1.7)
+	no	0/0	NE	NE	0/0	NE	NE	0/0	NE	NE
+	mild	0/0	NE	NE	0/0	NE	NE	0/0	NE	NE
+	severe	10/4	2.5 (0.8-8.2)	1.8 (0.5-6.1)	2/4	5.2 (0.9-30.1)	6.8 (0.9-53.2)	5/4	5.4 (1.4-21.0)	4.8 (1.1-21.6)

*AVSD, atrioventricular septal defect. VSD, ventricular septal defect. CHD, congenital heart defect. OR, odds ratio. CI, confidence interval. NE, not estimated from logistic regression model. * Odds ratios adjusted to maternal age, and educational level, ethnicity, parity, sex of the child, periconceptional use of any medication except antihistamines. The reference group comprised all mothers not exposed to antihistamine medication and who had no complaints of nausea and vomiting. We excluded 8 cases and 3 controls using antihistamines other than anti-emetics for this analysis.*

Discussion

Main findings

The HAVEN study showed that antihistamine use was associated with a threefold increased overall CHD risk and a fivefold increased risk of pVSD and AVSD. In addition, a positive association was found with Tetralogy of Fallot for antihistamines other than anti-emetics. These associations were independent of the mother's nausea/vomiting. In the EUROCAT population we confirmed the association between the mother's antihistamine use and the increased risk of having a child with AVSD, but we could not confirm the other associations.

Strengths and limitations

One of the strong points of our study is that we replicated the association with AVSD in two large, independent populations with good information about medication use during pregnancy. In the HAVEN study, results from a standardized questionnaire were verified in a personal interview, while in the EUROCAT registry, information on medication use is based on pharmacy records and verified in telephone interviews. Another strength of our study is the accuracy of the diagnoses of the specific CHD phenotypes: for the HAVEN study, two pediatric cardiologists diagnosed all the CHD cases, while for EUROCAT, a medical doctor and clinical geneticist specializing in heart anomalies classified the cases and controls.

One weakness of our study is that there could have been selection bias since only live births were included. CHD can be part of a chromosomal or genetic disorder and such pregnancies are terminated relatively more often or result in early fetal loss. Another type of bias that always has to be considered in case–control studies is recall bias [23]. In the HAVEN study we therefore standardized the data collection shortly after pregnancy. In EUROCAT, the pharmacy data was for prescriptions dispensed shortly before and during pregnancy, and their use was verified with the mother. Use of anti-emetics was 5.0 and 5.4% in the HAVEN and EUROCAT populations, respectively, which agrees with the 5.8% reported in a study on drug prescription patterns in the Netherlands [12]. Frequencies of use by controls were, however, lower at 1.7 and 3.9%. No other medicines or maternal illnesses could explain the difference in overall medication use between cases and controls. If, in the control group, under-reporting is an issue, differential recall bias cannot be excluded in the HAVEN study. However, if there was selective recall bias, we would have expected mothers of a CHD child to recall more nausea/vomiting for which they used medication than the controls. The mothers were not

aware of our specific questions on associations between medication use and CHD. In the HAVEN study, a fixed 2 year time interval was chosen between first trimester of pregnancy and the interview, which was similar between cases and controls. The distance between the region of EUROCAT NNL and the Western part of the Netherlands where the HAVEN study cases were recruited is significant. Therefore, there is only a very small risk of overlap in patients between the two databases. Finally, we are aware that our observed associations are based on a small number of antihistamine exposures, leading to imprecise risk estimates with large confidence intervals.

Interpretation

Our findings are in line with the results reported by Queißer-Luft et al. [15] who showed that early pregnancy use of anti-allergics, mainly antihistamines, was associated with a seven- to nine-fold increased risk of CHD and musculoskeletal anomalies. Our results might underestimate the true risk if antihistamines are also associated with cases of isolated hip dysplasia, which were used as controls in the EUROCAT analyses. Recent data from the National Birth Defect Prevention Study also revealed positive associations between doxylamine, which is the major compound of Bendectin, and spina bifida, cleft lip, left ventricular outflow tract obstruction defects, and hypoplastic left heart syndrome [24]. Associations were also demonstrated between meclozine use and orofacial clefts, and between antihistamine use and pVSDs.

In a prospective cohort study among 16,536 women exposed to meclozine and 540,660 unexposed women, there was no difference in the occurrence of congenital malformations. Although this was a large cohort, the data may be distorted by confounding by indication, since their results were not adjusted for nausea/vomiting [16]. In a second prospective cohort study, investigating frequencies of congenital malformations in 196 women with first trimester exposure to cetirizine and 1,686 controls, no increased risk was found for any congenital malformation, but the study might have been underpowered and medication among control mothers was not specified [17]. Furthermore, the number of exposed cases is too limited to detect only a modest teratogenic effect of antihistamine use. A meta-analysis revealed that antihistamine use in early pregnancy protected against all types of major congenital malformations [18]. However, by pooling all types of malformations, a differential effect for a specific birth defect would be considerably diluted. Moreover, they did not investigate confounding by indication. A meta-analysis of 16 cohort and 11 case–control studies on the

association with Bendectin, which is pharmacologically closely related to meclozine, showed no difference in risk [25].

It is conceivable that the presence of nausea/vomiting indicates the adaptation of the maternal endocrine and metabolic system to pregnancy, and as such may protect the embryo from harmful or teratogenic exposures [26]. However, severe nausea/vomiting has been associated with orofacial clefting, renal dysgenesia and urinary tract defects [27]. The absence of nausea/vomiting in pregnant women may also reflect a reduced production of placental human chorionic gonadotrophin and thyroxin, resulting in impaired placental growth and subsequently slower fetal growth and development [28].

Our results suggest that antihistamine medication might be a cardiac teratogen. An alternative hypothesis is that it is not the medication, but rather the resulting reduction in nausea/vomiting that increases CHD risk. A reduction in nausea/vomiting during early pregnancy might result in increased fetal exposure to harmful agents or unknown teratogens that stimulate the mother's vomiting.

The underlying mechanisms for a potential teratogenic effect from antihistamines are unknown and we can therefore only speculate. In adults, blockage of H1-receptors, expressed in several tissues such as heart, placenta, and endothelium, can lead to reflex tachycardia, ventricular arrhythmias and hemodynamic changes in the heart [29]. H1-receptors play an important role in embryonic development [30]. If we hypothesize that the H1-receptors are also expressed in the fetal heart, its inhibition might lead to hemodynamic changes and subsequent CHD.

AVSD is strongly correlated with Down syndrome [31]. In the HAVEN study, in total 21 of 33 cases with AVSD, and 2 of 3 exposed AVSD cases, also had Down syndrome. Down syndrome was not correlated with antihistamine use nor with complaints of nausea in the first trimester. In the EUROCAT population, 35 of 58 cases with AVSD, and 4 of 7 exposed AVSD cases, had Down syndrome. We did not exclude cases with a genetic abnormality from our analyses, as this is clearly not the only factor determining risk for CHD. In this group, environmental exposures are also important modifiers. Furthermore, in our study population, there may be more cases with an underlying genetic factor, but they cannot be excluded because most of the genetic causes of CHD are not yet known. However, excluding cases with a known genetic factor did not substantially change the results.

Conclusion

We found a positive association between maternal antihistamine use and risk of CHD, in particular pVSD and AVSD, in the HAVEN study. It appears that it is not the pregnancy-related nausea/vomiting, but rather the exposure to antihistamines that seems to increase the risk of CHD. The EUROCAT data confirmed the association between antihistamine use and AVSD, but not with overall CHD risk; nor could we investigate the association with nausea/vomiting. Our findings therefore warrant further investigation, which should take into account the need for a high number of exposed cases with a specific CHD phenotype.

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CHAPTER 8

Discussion

Congenital Anomaly (CA) registries play an important role in the monitoring of CA. In particular, the monitoring of CA in relation to maternal medication use in pregnancy is a specific function of these registries that makes certain demands on their data quality and on their methods of monitoring and risk assessment. In this chapter I discuss several aspects of data quality and the methods of risk assessment important for using CA registries to monitor the role of maternal medication use and make recommendations for future research.

Data quality

Information on maternal medication use during pregnancy in CA registries can originate from different sources. As described in chapter 2 of this thesis, these sources can be roughly categorized into 'medical files' *(medical files from maternal health care providers in relation to the pregnancy; medical files from health care providers to the child, and medical files from maternal health care providers not in relation to the pregnancy)* and 'registry-based data collection methods' (*interviews by the registry staff and questionnaires that are sent out by the registry*). In general, medical files from maternal health care providers are the most common data sources. However, the information in these files is often incomplete with respect to maternal medication use during pregnancy because not all maternal health care providers record all the medications used during pregnancy. For example, some maternal health care providers record all medications, including short-term use and pregnancy-related medications, while other providers only record information on medications for chronic conditions. Furthermore, the time of data collection by health care providers (prospective or retrospective) and the types of births that they include in their records also play a role [1].

A method to obtain more complete information on maternal medication use during pregnancy is by linkage to different data sources on medication use. Linkage of 'prescription data' to CA registries, for example, improved the quality of information on maternal use of medicines in pregnancy, particularly with respect to selective serotonin reuptake inhibitors (SSRIs), anti-asthmatics, antibacterials for systemic use and gonadotropins and other ovulation stimulants [2]. This 'prescription data' can be derived from pharmacy records, general practitioner (GP) data and insurance data. There are, however, differences between the different types of prescription data that should be considered. For instance, GP data is mainly based on what is prescribed, while pharmacy data is mainly based on what is dispensed [3]. Prescription data are increasingly used for research on maternal medication use in pregnancy in

relation to CA [3,4]. Prescription data are prospectively collected, are reasonably complete in comparison to information available from other kinds of medical files, and are relatively easy and inexpensive to acquire. Furthermore, because the dispensing date is recorded, prescription data allow the researcher to define the period of medication exposure more precisely. This is relevant because the potentially sensitive period of gestation may depend on the organ system of interest in a given study on the role of maternal medication use in pregnancy in relation to a specific CA.

Despite the usefulness of prescription data in general, in our study on prescription data linkage (chapter 3), we found that linkage was not possible in all CA cases. In the Emilia Romagna (Italy) registry, women with a termination of pregnancy for fetal anomaly (TOPFA) could not be linked to the prescription database. This was a consequence of Emilia Romagna's patient registration method: mothers with a terminated pregnancy did not receive an identification number that would have allowed linkage to their prescription data. Since severe CA lead more frequently to TOPFA, the more severe CA are underrepresented in the linked Emilia Romagna group. It is therefore important to realize that these differences can bias the study outcome and they need to be taken into account when analyzing the results.

Although prescription data are more complete than medical files, they often omit prescriptions issued in secondary care and private practice [3], and over the counter (OTC) medications are often missing. It is also unclear whether prescribed medicines were actually used and if so, whether they were used exactly as prescribed. The issue of non-compliance has been addressed in several other studies using health care databases [5-7]. Assuming that prescribed medicines were taken, even if they were not, can result in biased outcomes. In our study on the actual use of prescribed medications (chapter 4), we found that the compliance rate for prescribed medications was high in general, but differed between different groups of medications. The highest compliance rates were found for medication for chronic conditions and for pregnancy-related complaints. Thus, for most medication groups, prescription records are a relatively reliable source of data for research into associations between medication use in pregnancy and congenital anomalies, at least compared to other data sources.

While linkage with multiple sources makes information on maternal medication use during pregnancy more complete, the existing information in the CA registries (which is mostly derived from medical files) and the new prescription data also complement each other. For instance, some medications (such as certain anti-asthmatics) can be prescribed long before they

are actually used, and the use of these medications may be recorded in the CA registry but not in the prescription database covering the first trimester. More frequently, however, medication is recorded in the prescription database, but not recorded in the CA registry. Missing information on maternal medication use in the CA registry can occur for several reasons: maternal medication use may not be correctly recorded in the medical files, e.g. if the mother did not mention her medication use, or if the health care provider did not ask or record this information correctly, or if the registry staff has not retrieved the information from the medical files correctly. In addition, it is also possible that the prescribed medication may not be used at all (non-compliance).

In general, we found that the linkage of prescription data to the CA registries improved the quality of data [2] and that the prescription data reflect the actual use of prescribed medications [8]. Therefore, the highest quality of information on maternal medication use would be a combination of information obtained from medical files and supplemented with prescription data. Medical files alone do not provide complete information on maternal medication use, but can supply information on actual medication use (i.e. which medications the mother actually took). Prescription data are more complete, but do not provide information on actual medication use. Depending on the type of medication being studied, researchers should carefully consider which source is preferable. For example, in the case of a study on anti-asthmatics, which are often used 'if necessary', medical files would probably provide more correct information. In contrast, in the case of a study on SSRI use, which is often stigmatized and therefore under-reported to health care providers, prescription data probably supply more correct information. Another option is to define exposure when the medication is recorded in at least one of the data sources, or when a more strict definition is preferable, when the exposure is recorded in both data sources [9].

Risk assessment

To perform research on maternal medication use during pregnancy in relation to CA, good qualitative data is needed. In the previous paragraphs, data quality was discussed. In the next section of my discussion, I focus on assessing the risks of teratogenicity through detection and verification of signals of potentially teratogenic medicines.

Signal detection

Signal detection methods offer the opportunity to detect signals of the potential teratogenicity of medicines. Although case reports and case series can be used for signal detection, data from CA registries can also be used to investigate, in a hypothesis-free and systematic way, if there is an unexpectedly high exposure rate to a specific medication among cases with a specific type of CA.

There are several pharmaco-epidemiological approaches that can be used as signal detection methods. One example is the method often applied within the National Birth Defect Prevention Study (NBDPS), a multi-center case-control study that covers births in 10 American states. Among cases with a specific CA, the first trimester exposure of women to a specific medicine is examined. These first trimester exposure rates are compared to the first trimester exposure rates of healthy controls [10,11]. Within the EUROmediCAT project, a different methodology was applied in a dataset of 14,950 registrants of non-chromosomal CA with first trimester drug exposure for birth years between 1995-2011 from 15 EUROCAT registries. This dataset was systematically screened for associations between 59 specific non-chromosomal CA and 836 specific medications and medication groups, based on the teratogenic mechanism of action using a case-malformed control analysis. Since many tests were performed, which can result in false-positive associations, the analysis was controlled for multiple testing [12].

In chapter 6 we applied another methodology, the 'case-population design'. Within this design, maternal exposure to a specific medication or medication group in subjects with a specific CA (cases) is compared with the exposure rate to the medication in the source population (general pregnant population). We explored whether a case-population design can be used to detect signals of teratogenicity by comparing exposure rates in cases from the population-based birth defect registry EUROCAT NNL (northern Netherlands), with exposure rates in a reference pregnant population derived from the population-based prescription database IADB, previously known as the InterAction DataBase. By comparing prescription rates from a population-based prescription database with user rates from a population-based CA registry, we were able to confirm known teratogenic risks for several medicines acting on the central nervous system, such as valproic acid, and we did not detect teratogenic effects for most medicines considered to be safe, with the exception of methyldopa. The method applied in this thesis of comparing the prescription rates in the general pregnant population to the user rates in a CA registry therefore seems to be a suitable method to detect signals of possible

teratogenicity. However, data on the general pregnant population are not always available. Furthermore, the manner of data collection in the general pregnant population and the CA registry may differ, which could bias results. Within the method applied by the EUROmediCAT project, the procedure of data collection is the same for cases and controls, but the controls are children with a different CA for which the origin of the CA is often unknown, thus there is also a chance of biased results. However, in general, this potential bias will be reduced by heterogeneity of different CA in the control group. Within the method applied by the NBDPS, a comparison is made between cases and healthy controls. The manner of data collection is the same for both cases and controls, which may result in less biased results. However, a difference in recall between both groups may also result in recall bias.

Signal verification

Signal verification is most often performed in case-control studies and should be performed in a dataset other than the dataset used to generate the signal. Furthermore, the use of case-control studies introduces new issues that need to be addressed. One of these is the selection of an *appropriate control group*. To avoid selection bias, the control group should be recruited from the same population as that from which the cases where derived, and no unusual or unequal relation between exposure and outcome should be present [13]. Ideally, healthy non-malformed controls should be chosen, but this is not always possible when a case-control study is performed with data from a CA registry like EUROCAT. In that situation, malformed controls, with malformations that are not related to the exposure under study, are used [14-16].

Confounding factors are related to both the exposure and the outcome and may bias the results if the analyses are not adjusted for these factors [17]. Therefore it was important to identify possible confounding factors such as maternal age when studying the association between fertility treatment and trisomy 21 [18]. In studies of medication use, a specific type of confounding should be emphasized: 'confounding by indication'. This confounder occurs because patients with a more severe type of disorder are more likely to be prescribed a specific medicine. As a result, a 'worse outcome' could be attributed to the severity of the disease instead of the medicine [19]. In addition, it can be unclear whether the disease or the medication prescribed is related to the outcome. Options that allow the researcher to adjust for confounding are, for example, stratification and the application of multivariable regression models.

A second issue, *sample size,* should also be taken into account. Since the combination of a specific medicine and a specific CA is quite rare, case-control studies are the most suitable study design, especially in comparison to cohort studies. However, the power of these studies to identify small to moderate risks is low. There are several ways to increase the power of the signal detection. One way is to choose another control group or to increase the size of the control group, but in practice the maximum ratio of case and control chosen is 1:4 [20]. Other options to include more cases are by increasing the research region (but this is very costly) and by combining data from several CA registries. The latter is also done within the EUROmediCAT project and has been shown to add value [18]. Verification of a signal in two or more databases to determine whether the results are replicable (chapter 7) adds value because replicated results strengthen the study outcomes. And the gold standard of any scientific study is its replicability.

Conclusions

Maternal medication use during pregnancy is very common despite uncertainties about the teratogenicity of many medicines. Post-marketing surveillance is crucial for investigating the possible teratogenic effects of medicines. However, as discussed above, the combination of a specific CA with a specific medication is quite rare. CA registries, which facilitate case-control studies, are highly valuable in studies of medications as the possible causes of congenital anomalies. However, it is challenging to properly analyze these and the other available data.

There are also several data sources on maternal medication use in pregnancy available and used, but the quality of the information recorded is variable and none of the sources provide complete information. To obtain more complete information the linkage of prescription data to CA registries, will add value, and can be applied in future research. Moreover, given the rarity of the combination of a specific CA and a specific medication, the signal power to perform this kind of research might be too low within a single CA registry. A greater investigative signal power could then be achieved via collaboration between several CA registries. The EUROmediCAT project, in which data from several CA registries are combined and enriched with data from health care databases, is a good example of an international collaboration monitoring maternal medication use in pregnancy with the aim of increasing signal detection and verification, and the design applied within the EUROmediCAT project can serve as a basis for future research.

The post-marketing surveillance of maternal medication use in pregnancy related to CA started after the thalidomide tragedy of the early 1960s as discussed in the Introduction to this thesis. Fortunately, and partly due to strict post-marketing surveillance, we have been spared a comparable disaster to date, but continuous vigilance remains of utmost importance. Due to new technical developments, such as new methods to detect signals of teratogenicity and linkage of data sources, post-marketing surveillance may get easier and more accurate. However, despite these positive developments, research on the teratogenicity of medications combining professional expertise and data from several health care databases will always be needed.

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CHAPTER 9

Summary
Samenvatting (Dutch)

Summary

Maternal medication use during pregnancy is very common, despite uncertainties about the teratogenicity of many medicines. Continuous vigilance (post-marketing surveillance) is therefore crucial for investigating any possible teratogenic effects of medicines on the fetus. Two important aspects of this surveillance are studied in this thesis: the quality of data that is used in the post-marketing surveillance of maternal medication taken during pregnancy, and the methods used for monitoring maternal medication in pregnancy in relation to congenital anomalies (CA) and for assessing the potential risks of CA.

EUROCAT is a European network of population-based CA registers and includes EUROCAT Northern Netherlands (NNL). EUROCAT covers approximately one-third of all births in Europe (including live births, still births, spontaneous abortions, and terminations due to fetal anomalies (TOPFAs)). The main objective of the EUROCAT network is to monitor the prevalence of congenital anomalies in Europe and provide epidemiologic information on them. Since most registries collect data on maternal medication use, EUROCAT is also highly valuable in post-marketing surveillance. However, the various registries use different methods to collect their data and consequently the quality of data may vary between the registries.

Data quality

In **chapter 2** we describe the sources used to derive information on maternal medication use by 19 CA registries. We defined two major sources of information on medication use in pregnancy: 'medical files' and 'registry-based data collection methods'. Medical files were categorized into: 1) medical files from maternal healthcare providers in relation to pregnancy (such as midwives, obstetricians and gynaecologists); 2) medical files from healthcare providers of the child (such as paediatricians, neonatologists and geneticists); and 3) medical files from maternal healthcare providers not in relation to pregnancy (such as pharmacy data). Registry-based data collection methods were categorized into: 1) interviews conducted by the registry staff and 2) questionnaires (sent out to parents by the registry). Except for one registry, all the registries used medical files as their main source (mostly 'medical files from maternal healthcare providers in relation to pregnancy'), and just three registries used registry-based data collection methods' as an additional source. Most registries used more than one source. However, the completeness of the information on maternal medication use differed per registry. Some

registries record all kinds of medications, including OTC drugs, while others only had information on chronic medication use and pregnancy-related medication use. The quality of what is recorded also varied over the medication groups (since not all registries record all the kinds of medication) and sometimes also over medication groups per registry (for instance, when a registry *always* records chronic and pregnancy-related medications, *sometimes* records medications for short-term use, but *never* records OTC medications). Since there were major differences between the registries, with respect to their sources and completeness of information used to compile their records, it is important for researchers to keep this in mind when performing studies on the possible risks associated with maternal medication use.

Since prescription databases contain more complete information on medication use than CA registries, we linked prescription data to data from five EUROCAT registries (described in **chapter 3**). In our evaluation of the linkage, we focused on six medication groups: anti-epileptic drugs, insulins and analogues, SSRIs, anti-asthmatics, antibacterials for systemic use, and gonadotropins and other ovulation stimulants. Here we also found that the first trimester exposure rates and agreement between the data sources varied for the different medication groups. However, in general, we can state that information on anti-epileptic drugs, and insulins and analogue medicine, as recorded by the five EUROCAT registries, was of good quality, since it was recorded in both the EUROCAT registries as well as the prescription databases. In contrast, the information on SSRIs, anti-asthmatics, antibacterials for systemic use, and gonadotropins and other ovulation stimulants was less complete, which means that for these medication groups, there was extra value in linking the prescription databases to the EUROCAT registries.

As shown in chapter 3, the linkage to prescription data can add useful information to CA registries and make the records on medication use in pregnancy more complete. However, it should not be assumed that the mother always takes the medication prescribed or dispensed to her. We therefore investigated how far prescriptions reflect the actual use of medication during pregnancy by retrospectively verifying the compliance of prescribed medication in a telephone interview with mothers of children with CA (**chapter 4)**. We looked at three medication groups: 1) medicines for chronic diseases; 2) medicines for short-term or occasional use, and 3) medicines for pregnancy-related symptoms, and calculated the compliance rate by dividing the number of compliant users by the total number of mothers who had been prescribed that medication according to their pharmacy records. We found that during the first trimester, the

reported compliance rates ranged from 0.84 (for chronic diseases) to 0.92 (for pregnancy-related symptoms). For the entire pregnancy, the reported compliance rate ranged from 0.90 (medicines for short-term or occasional use) to 0.95 (for pregnancy-related symptoms). Furthermore, we found that most of the medications actually reported as taken were used at the prescribed dosage or lower, and more than half of the medications actually taken were used for the duration prescribed or for a shorter period. Using pharmacy records might therefore overestimate maternal medication use in pregnancy, which should be taken into account. However, since this overestimation seems to be minimal, prescription records can still be used as a reliable source of data for research into medication use in pregnancy.

Monitoring and risk assessment

Since we have shown prescription records are a reliable source, we used data from the IADB prescription database to determine whether antibiotics were prescribed according to national guidelines, by investigating the prescription patterns of antibiotics before, during and after pregnancy for a 16-year period (described in **chapter 5**). We found that one out of five women was prescribed at least one antibiotic during pregnancy. The 'beta-lactam antibacterials/ penicillins' subgroup, to which amoxicillin belongs, was most commonly prescribed. Compared with the period before conception, 'safe' antibiotics were prescribed more often during pregnancy than the other groups of antibiotics, in accordance with national guidelines.

We explored whether comparing prescription rates from a population-based prescription database, the IADB, with user rates from a population-based CA registry, EUROCAT NNL, could be used as a suitable detection method for possible teratogenic risk of a medication (**chapter 6)**. Such a method should be able to detect known teratogenic effects but should not detect any effects if a drug is considered to be safe. We therefore focused on two medication groups: 1) medicines acting on the central nervous system (drugs with an ATC code starting with N), of which certain teratogenic effects have been identified for AEDs and SSRIs among others, and 2) medicines considered to be safe, classified as A according to the Australian Drug Evaluation Committee (ADEC). For medicines acting on the central nervous system, we indeed found significantly increased rate ratios (RRs) for valproic acid, an anti-epileptic medicine, and for some SSRIs. For medicines considered to be safe, only methyldopa, to treat hypertension, showed significantly increased RRs for anomalies of the digestive system, genitals and urinary

tract. However, these increased RRs were determined from low numbers of cases, so they may lead to a false-positive signal. Based on these two groups, we concluded that comparing prescription rates seems a suitable method for detecting signals of possible teratogenicity, providing the teratogenic effects and medicines studied are as specific as possible, and the medicines are widely used.

In **chapter 7** we performed two case-control studies using two study databases (EUROCAT NNL and the HAVEN study) to investigate whether the results from them were similar. In both databases we investigated the relationship between maternal use of antihistamines, prescribed as anti-emetics, and the risk of specific congenital heart anomalies (CHD). In the HAVEN study we found an increased risk of CHDs in general (OR 3.0, 95% CI 1.2–7.3), and particularly of atrioventricular septal defects (AVSD) (OR 5.1, 95% CI 1.3–20.5) and perimembranous ventricular septal defects (pVSD) (OR 5.1, 95% CI 1.8–14.4). However, the data in EUROCAT NNL could only confirm the risk of AVSD (OR 3.5, 95% CI 1.4–8.7); we could not replicate the other associations found. These findings warrant further investigation in larger datasets.

To conclude, many women use medicines during pregnancy, despite uncertainties about their teratogenicity. This means post-marketing surveillance is required to detect possible teratogenic effects of medicines, although the combination of a specific CA with a specific medication is quite rare. CA registries, which facilitate case-control studies, are valuable in studies of medications as the possible causes of CA. However, it is challenging to analyse these and the other available data properly. There are several data sources on maternal medication use in pregnancy, but the quality of the information recorded is variable and none of the sources provide complete information. To obtain more complete information, we support the linkage of prescription data to CA registries, which will add value for future research. Moreover, given the rarity of the combination of a specific CA and a specific medication, the signal power to perform this kind of research might well be too low within a single CA registry. A greater signal power can be achieved via collaborations between several CA registries. The EUROmediCAT project, in which data from several CA registries are combined and enriched with data from health care databases, is a good example of an international collaboration for monitoring maternal medication use in pregnancy. The project aims to increase signal detection

and provide verification, and the design used in EUROmediCAT can serve as a basis for future research.

To date, partly due to strict post-marketing surveillance, we have been spared a disaster comparable to the thalidomide tragedy, but continuous vigilance remains of utmost importance. Due to technical developments, such as new methods to detect signals of teratogenicity and to link data sources, post-marketing surveillance may become easier and more accurate. However, despite these developments, we will continue to need research on the teratogenicity of medications combining professional expertise and data from several health care databases.

Samenvatting (Dutch)

Veel vrouwen gebruiken medicijnen tijdens hun zwangerschap, terwijl van verschillende geneesmiddelen het niet duidelijk is of deze schadelijk zijn voor het ongeboren kind. Om mogelijke teratogene effecten van medicijnen te onderzoeken, is continue waakzaamheid door middel van post-marketing surveillance cruciaal. In dit proefschrift ligt de focus op twee hoofdaspecten:

1) *de kwaliteit van data gebruikt in post-marketing surveillance naar medicijngebruik bij vrouwen tijdens de zwangerschap* en

2) *methoden om medicatiegebruik bij vrouwen tijdens de zwangerschap in relatie tot aangeboren afwijkingen te monitoren en mogelijke risico's met betrekking tot aangeboren afwijkingen te beoordelen*.

EUROCAT is een Europees netwerk van registraties (waaronder EUROCAT Noord Nederland) die aangeboren afwijkingen registreren. Dit netwerk dekt ongeveer een derde van alle 'geboorten' (levend geboren, dood geboren, spontane zwangerschapsbeëindigingen en geïnduceerde zwangerschapsbeëindigingen vanwege een aangeboren afwijking), wat neerkomt op ongeveer 1,7 miljoen geboortes per jaar. Het belangrijkste doel van het EUROCAT-netwerk is het monitoren van de prevalentie van en het verschaffen van epidemiologische data over aangeboren afwijkingen in Europa. Omdat de meeste EUROCAT-registraties informatie over medicatiegebruik bij vrouwen tijdens de zwangerschap verzamelen, is EUROCAT van grote waarde in post-marketing surveillance. Echter, de registraties hebben verschillende manieren om data te verzamelen, waardoor de kwaliteit ervan verschilt over de registraties.

Datakwaliteit

In **hoofdstuk 2** beschrijven we voor 19 EUROCAT-registraties welke bronnen ze gebruiken om informatie over medicijngebruik bij vrouwen tijdens de zwangerschap te verzamelen. We hebben hierbij onderscheid gemaakt tussen twee categorieën: 'medische dossiers' en 'data collectie methoden geïnitieerd door de registratie'. 'Medische dossiers' kan worden onderverdeeld in 1) 'medische dossiers van zorgverleners die betrekking hebben op de moeder gedurende de zwangerschap (zoals verloskundigen en gynaecologen)'; 2) 'medische dossiers van zorgverleners die betrekking hebben op het kind (zoals kinderartsen, neonatologen en genetici)' en 3) 'medische dossiers van zorgverleners die betrekking hebben op de moeder in

het algemeen, dus niet specifiek gedurende de zwangerschap (zoals prescriptiegegevens uit de apotheek)'. 'Data collectie methoden geïnitieerd door de registratie' worden onderverdeeld in 1) 'interviews die zijn uitgevoerd door iemand van de registratie ' en 2) 'vragenlijsten die zijn verstuurd door de registratie'. Op één centrum na, gebruiken alle registraties 'medische dossiers' als bron (veelal 'medische dossiers van zorgverleners die betrekking hebben op de moeder gedurende de zwangerschap'). 'Data collectie methoden geïnitieerd door de registratie' worden door slechts drie registraties gebruikt. De meeste registraties gebruiken meer dan één bron. Echter, de volledigheid van de informatie over medicatiegebruik bij vrouwen tijdens de zwangerschap verschilt per registratie. Sommige registraties leggen alle soorten medicijnen vast, inclusief medicatie die zonder recept verkrijgbaar is (Over The Counter (OTC)), terwijl andere registraties alleen informatie over chronische medicatie en aan zwangerschap gerelateerde medicatie vastleggen. De kwaliteit van wat wordt vastgelegd, verschilt over de medicatiegroepen (omdat niet alle registraties alle soorten medicijnen vastleggen) en soms ook over de medicatiegroepen per registratie (bijvoorbeeld een registratie kan chronische medicatie en aan zwangerschapsgerelateerde medicatie *altijd*; medicatie gebruik voor kortdurend gebruik *soms* en OTC-medicatie *nooit* vastleggen etc.).

Omdat de data die beschikbaar is in prescriptiedatabases completer is dan de data die is vastgelegd in de aangeboren afwijkingen registraties, hebben we data over prescripties gelinkt aan data van vijf EUROCAT-registraties, zoals beschreven wordt in **hoofdstuk 3**. Het resultaat van het linken van de databases hebben we geëvalueerd aan de hand van zes groepen van geneesmiddelen: anti-epileptica; insuline en analogen; selectieve serotonine heropname remmers (SSRI's); antiastmatica; antibiotica voor systemisch gebruik en gonadotrofinen en andere ovulatie stimulerende middelen. In het algemeen kunnen we stellen dat de data afkomstig van de EUROCAT-registraties met betrekking tot anti-epileptica en insuline en analogen van goede kwaliteit is, aangezien de overeenstemming tussen deze beide databases (EUROCAT en prescriptiedatabases) voor wat betreft de blootstelling in het eerste trimester en tijdens de zwangerschap groot was. De EUROCAT-data betreffende selectieve serotonine heropname remmers (SSRI's); antiastmatica; antibiotica voor systemisch gebruik en gonadotrofinen en andere ovulatie stimulerende middelen was minder compleet, waardoor het koppelen van de prescriptiedatabases aan de EUROCAT-data van toegevoegde waarde is.

Zoals bleek uit hoofdstuk 3 kan het linken van een prescriptiedatabase aan data van aangeboren afwijkingen, registraties betreffende medicatiegebruik bij vrouwen tijdens de zwangerschap completer maken. Er kan echter niet altijd aangenomen worden dat de moeder de medicatie die voorgeschreven of verstrekt is, ook daadwerkelijk heeft ingenomen. Daarom onderzochten we in hoeverre prescripties een goede afspiegeling zijn van het daadwerkelijke medicatiegebruik tijdens zwangerschap. Dit hebben we onderzocht door retrospectief in een telefooninterview met moeders van kinderen met een aangeboren afwijking het gebruik van voorgeschreven medicatie (therapietrouw) te verifiëren (**hoofdstuk 4**). We hebben de medicijnen ingedeeld in drie groepen: 1) medicijnen voor chronische ziekten; 2) medicijnen voor kortdurend gebruik en 3) medicijnen voor zwangerschapsgerelateerde symptomen. De therapietrouw is berekend door het aantal vrouwen dat daadwerkelijk medicatie heeft ingenomen te delen door het aantal vrouwen dat medicatie kreeg voorgeschreven. In het eerste trimester vonden we dat de therapietrouw varieerde van 0,84 (medicijnen voor chronische ziekten) tot 0,92 (medicijnen voor zwangerschapsgerelateerde symptomen). Gedurende de hele zwangerschap, varieerde de gerapporteerde therapietrouw van 0,90 (medicijnen voor kortdurend gebruik) tot 0,95 (medicijnen voor zwangerschapsgerelateerde symptomen). Daarnaast vonden we dat de meeste medicijnen die daadwerkelijk werden ingenomen, werden gebruikt conform de voorgeschreven dosering of in lagere doses. Verder werd meer dan de helft van de medicijnen die daadwerkelijk ingenomen werden, gebruikt conform de voorgeschreven duur of voor een kortere periode. Door dit onderzoek kunnen we stellen dat data over prescripties het medicatiegebruik bij vrouwen tijdens zwangerschap overschatten. Dit zou potentieel leiden tot een onderschatting van het teratogene effect van deze middelen. Echter, de overschatting lijkt minimaal, waardoor data over prescripties gebruikt kunnen worden als betrouwbare bron bij het onderzoek naar medicijngebruik tijdens de zwangerschap.

Monitoren en risicobeoordeling

Aangezien data over prescripties als betrouwbare bron kunnen worden gezien, hebben we in **hoofdstuk 5** met data van een prescriptiedatabase, de IADB, bepaald of antibiotica worden voorgeschreven conform de nationale richtlijnen over een periode van 16 jaar. We vonden dat één op de vijf vrouwen tenminste één antibioticum gebruikt tijdens een zwangerschap. De subgroep 'beta-lactam antibiotica/ penicillines', waar amoxicilline tot behoort, werd het meest frequent voorgeschreven. In vergelijking met de periode voor

conceptie worden 'veilige' antibiotica vaker voorgeschreven tijdens zwangerschap dan andere antibiotica. Dit is conform de nationale richtlijnen.

In **hoofdstuk 6** hebben we onderzocht of het mogelijk is om mogelijke teratogene effecten van medicijnen te detecteren door de blootstelling aan bepaalde medicatie te vergelijken tussen de IADB (op basis van prescripties) en EUROCAT NNL (op basis van geregistreerd gebruik). Een goede signaaldetectiemethode voor teratogeniciteit zou in staat moeten zijn om bekende teratogene effecten te detecteren, maar zou geen effect moeten vinden wanneer een geneesmiddel veilig is. Daarom selecteerden we twee groepen: 1) medicijnen die werken op het centrale zenuwstelsel (de ATC code begint met de letter 'N'), waarvan bepaalde teratogene effecten zijn gevonden voor anti-epileptica en SSRI's en 2) medicijnen waarvan aangenomen wordt dat ze veilig zijn (geclassificeerd als 'A' door het Australische Medicatie Evaluatie Comité (ADEC). Voor medicijnen die werken op het centrale zenuwstelsel vonden we inderdaad significant verhoogde percentage blootgestelden voor het anti-epilepticum valproïnezuur en voor sommige SSRI's in de aangeboren afwijkingen registratie (EUROCAT). Voor medicijnen waarvan aangenomen wordt dat ze veilig zijn, liet alleen het antihypertensivum methyldopa een significant verhoogd percentage blootgestelden zien bij afwijkingen aan het maagdarmstelsel, de genitaliën en de urinewegen. Omdat dit verhoogde percentage blootgestelden is gebaseerd op kleine aantallen, hebben we hier mogelijk te maken met een vals-positief signaal. Op grond van de twee gekozen groepen kunnen we dus stellen dat deze methode geschikt lijkt om signalen van mogelijke teratogeniciteit te detecteren, onder voorwaarde dat zowel de medicijnen als de aangeboren afwijkingen zo specifiek mogelijk beschreven zijn en de medicijnen veelvuldig gebruikt worden.

In **hoofdstuk 7** hebben we twee case-controle studies uitgevoerd met twee verschillende databases (de HAVEN-studie en EUROCAT NNL). Eerst werd er met data uit de HAVEN-studie een case-controle studie gedaan om de relatie tussen gebruik van antihistaminica bij zwangere vrouwen, voorgeschreven als anti-emetica, en specifieke aangeboren hartafwijkingen (CHD) te onderzoeken. Vervolgens hebben we binnen de database van EUROCAT Noord Nederland gekeken of we de in de HAVEN-studie gevonden bevindingen konden repliceren. In de HAVEN-data werd een verhoogd risico gevonden voor CHD's in het algemeen (OR 3.0, 95% CI 1.2–7.3); atrioventriculair septum defecten (AVSD) (OR 5.1, 95% CI

1.3–20.5) en perimembraneuze ventriculaire septum defecten (pVSD) (OR 5.1, 95% CI 1.8–14.4). Met behulp van de EUROCAT-data kon alleen een verhoogd risico op een AVSD bevestigd worden (OR 3.5, 95% CI 1.4–8.7). De relatie tussen antihistaminica en CHD's zal verder onderzocht moeten worden.

Veel vrouwen gebruiken geneesmiddelen tijdens zwangerschap, ondanks dat niet van alle geneesmiddelen bekend is of ze teratogeen zijn. Post-marketing surveillance is noodzakelijk om de teratogene effecten van medicijnen te onderzoeken. Echter, de combinatie van een specifieke aangeboren afwijking met een specifiek medicijn is zeldzaam. Registraties voor aangeboren afwijkingen, die gebruikt kunnen worden om case-controle studies uit te voeren, zijn van toegevoegde waarde in onderzoek naar medicijngebruik en mogelijke oorzaken van aangeboren afwijkingen. Het goed analyseren van data blijft een uitdaging. Zo zijn er verschillende bronnen beschikbaar met gegevens over medicatiegebruik, maar de kwaliteit van de vastgelegde informatie is variabel en geen van de bronnen is compleet. Completere informatie over medicatiegebruik kan verkregen worden door prescriptiedata aan registraties van aangeboren afwijkingen te linken. Gezien de zeldzaamheid van een specifieke aangeboren afwijking en specifieke medicatie, heeft een enkele registratie van aangeboren afwijkingen te weinig power. De power kan vergroot worden door registraties van aangeboren afwijkingen te laten samenwerken. Het EUROmediCAT-project, waarin data van verschillende registraties van aangeboren afwijkingen gecombineerd en verrijkt worden met data uit databases van zorgverleners, is een goed voorbeeld van een internationale samenwerking om maternaal medicatiegebruik tijdens de zwangerschap te monitoren om signalen van teratogeniciteit te detecteren en verifiëren. Het design dat wordt toegepast in het EUROmediCAT-project kan als basis dienen voor verder onderzoek.

Mede door strikte post-marketing surveillance, heeft zich niet weer een ramp voorgedaan zoals de thalidomide tragedie, maar continue waakzaamheid blijft van cruciaal belang. Door nieuwe technische ontwikkelingen, zoals nieuwe signaaldetectiemethoden en het linken van databronnen, wordt deze post-marketing surveillance makkelijker en meer accuraat. Door deze positieve ontwikkelingen kan het onderzoek naar teratogene effecten goedkoper, grootschaliger en ook sneller worden, dit alles ten behoeve van de zwangere en haar kind.

APPENDIX 1

1a: Appendix belonging to Chapter 2

1b: Appendix belonging to Chapter 4

1c: Appendix belonging to Chapter 4

1d: Appendix belonging to Chapter 5

1e: Appendix belonging to Chapter 5

1f: Appendix belonging to Chapter 5

1g: Appendix belonging to Chapter 6

1h: Appendix belonging to Chapter 6

Appendix 1a: appendix belonging to chapter 2 'EUROCAT special report: sources of information on medication use in pregnancy' - Questionnaire

For EUROmediCAT WP3 and JOINT ACTION WP9 we are working on an overview of used sources for maternal medication use in pregnancy. We would like to map which sources are used and what kind of information these sources provide.

For the sources we distinguish 'Medical files as source for maternal medication use in pregnancy' and 'Specific data collection methods by registry'.
Medical files can be made by maternal care givers (think of midwife/obstetric/ gynecologist etc.), but also by care givers of the child (think of pediatrician, clinical geneticist etc.).
Specific data collection methods can be interviews by a registry employee, questionnaires sent out by the registry etc.
For different kind of medication (Chronic medication/ medication for short time use/ pregnancy related medication/ OTC) we would like to know whether medication use is standard/ sometimes/ never recorded. Besides, we would like to know whether the records are based on prescriptions or actual use; whether the information is based on questions or 'open' input by the mother; in which way the data collection takes place and for what kind of birth types this source is available.
In addition, we would like to map the definitions of values filled in in EDMP for 'blank', 'drug use not known' and 'no drugs taken'.

In the past, Janneke Jentink interviewed some registry leaders about data collection methods; Anthony Wemakor sent out questionnaires and during the EUROCAT *meeting in Budapest Marian Bakker and Hao Wang asked the present registry leaders to complete a questionnaire as well. Our idea is to combine and verify this information and to complement, where necessary.*

Therefore, we designed a questionnaire and filled it out, as far as possible. Our question to you is whether you can verify the entered questions and complete where necessary.

If you are unsure which box applies best to your situation, please don't tick a box, but mention it in the comment/ explanation section underneath.

Medical files as source for maternal medication use in pregnancy

- **Medical files from obstetric care giver (midwife/obstetric/ gynecologist)**
- **Medical files from caregivers of the child (for instance pediatrician, clinical geneticist etc.)**
- **Other sources (specified..)**

Specific data collection methods by registry

- **Interview with mother by registry**
- **Questionnaire by registry**
- **Other sources (specified..)**

Definitions of values filled in in EDMP

Medical files as source for maternal medication use in pregnancy

- **Medical files from obstetric care giver (midwife/obstetric/ gynecologist)**

☐ Applicable, please continue with the questions on this source
☐ Not applicable, please continue with the next source

Please specify which care giver:

The first questions are on the types of medication which could be recorded.

1. *Chronic medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of *chronic drugs*, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. *BJOG* 2006; 113: 559-5

2. *Medication for short time use** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of medication for short time use, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. BJOG 2006; 113: 559-5

3. *Pregnancy related medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of *pregnancy related medication*, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. *BJOG* 2006; 113: 559-5

4. *OTC medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* *OTC medication* is medication which is available Over the Counter, so without prescription.

The next questions are on the procedures on obtaining information on medication.

5. Do you know how the caregiver obtains information on medication use in pregnancy?

☐ yes, please go to question 6
☐ no, please go to question 10

Comments:

6. Prescriptions of medication can be recorded, but the actually use of medication can be registered as well. How does this information source handle this?

☐ Only prescribed medication is
☐ Only actually used medication is
☐ Prescribed and actually used medication are
recorded.

Comments:

7. The recorded medication is in response to

☐ specific questions asked by the care giver, please go to question 8
☐ 'open' input by the mother, please go to question 10
☐ specific questions asked by the care giver and 'open' input by the mother, please go to question 8

Comments:

8. The questions asked by the care giver are

☐ open
☐ closed
☐ open and closed.

Comments:

9. The care giver asks for

(please tick all those which apply)

☐ specific drug groups
☐ specific drugs
☐ variable/ not clear

Comments:

Medication use can be recorded during one moment in or the whole pregnancy (prospective) and after pregnancy (retrospective). How does this information source handle this?

10. Data collection takes place in a

☐ retrospective (recorded after pregnancy)
☐ prospective (recorded during pregnancy)
☐ retrospective and prospective

Comments:

Does this information source contain information on medication use for all types of birth?

11. This source is available for

(please tick all those which apply)

☐ live births
☐ still births
☐ fetal death
☐ TOPFAs

Comments:

12. Did this reporting method change over time?

☐ yes, please specify
☐ no

Comments:

- **Medical files from caregivers of the child (for instance pediatrician, clinical geneticist etc.)**

☐ Applicable, please continue with the questions on this source
☐ Not applicable, please continue with the next source

Please specify which care giver:

The first questions are on the types of medication which could be recorded.

1. *Chronic medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of *chronic drugs*, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. *BJOG* 2006; 113: 559-5

2. *Medication for short time use** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of medication for short time use, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. BJOG 2006; 113: 559-5

3. *Pregnancy related medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of *pregnancy related medication*, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. *BJOG* 2006; 113: 559-5

4. *OTC medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* *OTC medication* is medication which is available Over the Counter, so without prescription.

The next questions are on the procedures on obtaining information on medication.

5. Do you know how the caregiver obtains information on medication use in pregnancy?

☐ yes, please go to question 6
☐ no, please go to question 10

Comments:

6. Prescriptions of medication can be recorded, but the actually use of medication can be registered as well. How does this information source handle this?

☐ Only prescribed medication is
☐ Only actually used medication is
☐ Prescribed and actually used medication are
recorded.

Comments:

7. The recorded medication is in response to

☐ specific questions asked by the care giver, please go to question 8
☐ 'open' input by the mother, please go to question 10
☐ specific questions asked by the care giver and 'open' input by the mother, please go to question 8

Comments:

8. The questions asked by the care giver are

☐ open
☐ closed
☐ open and closed.

Comments:

9. The care giver asks for

(please tick all those which apply)

☐ specific drug groups
☐ specific drugs
☐ variable/ not clear

Comments:

Medication use can be recorded during one moment in or the whole pregnancy (prospective) and after pregnancy (retrospective). How does this information source handle this?

10. Data collection takes place in a

☐ retrospective (recorded after pregnancy)
☐ prospective (recorded during pregnancy)
☐ retrospective and prospective

Comments:

Does this information source contain information on medication use for all types of birth?

11. This source is available for

(please tick all those which apply)

☐ live births
☐ still births
☐ fetal death
☐ TOPFAs

Comments:

12. Did this reporting method change over time?

☐ yes, please specify
☐ no

Comments:

- **Other sources (specified..)**

☐ Applicable, please continue with the questions on this source
☐ Not applicable, please continue with the next source

Please specify which care giver:

The first questions are on the types of medication which could be recorded.

1. *Chronic medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of *chronic drugs*, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. *BJOG* 2006; 113: 559-5

2. *Medication for short time use** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of medication for short time use, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. BJOG 2006; 113: 559-5

3. *Pregnancy related medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of *pregnancy related medication*, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. *BJOG* 2006; 113: 559-5

4. *OTC medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* *OTC medication* is medication which is available Over the Counter, so without prescription.

The next questions are on the procedures on obtaining information on medication.

5. Do you know how the caregiver obtains information on medication use in pregnancy?

☐ yes, please go to question 6
☐ no, please go to question 10

Comments:

6. Prescriptions of medication can be recorded, but the actually use of medication can be registered as well. How does this information source handle this?

☐ Only prescribed medication is
☐ Only actually used medication is
☐ Prescribed and actually used medication are
recorded.

Comments:

7. The recorded medication is in response to

☐ specific questions asked by the care giver, please go to question 8
☐ 'open' input by the mother, please go to question 10
☐ specific questions asked by the care giver and 'open' input by the mother, please go to question 8

Comments:

8. The questions asked by the care giver are

☐ open
☐ closed
☐ open and closed.

Comments:

9. The care giver asks for
(please tick all those which apply)
☐ specific drug groups
☐ specific drugs
☐ variable/ not clear

Comments:

Medication use can be recorded during one moment in or the whole pregnancy (prospective) and after pregnancy (retrospective). How does this information source handle this?

10. Data collection takes place in a
☐ retrospective (recorded after pregnancy)
☐ prospective (recorded during pregnancy)
☐ retrospective and prospective

Comments:

Does this information source contain information on medication use for all types of birth?

11. This source is available for
(please tick all those which apply)
☐ live births
☐ still births
☐ fetal death
☐ TOPFAs

Comments:

12. Did this reporting method change over time?
☐ yes, please specify
☐ no

Comments:

Specific data collection methods by registry

- **Interview with mother by registry**

☐ Applicable, please continue with the questions on this source
☐ Not applicable, please continue with the next source

The first questions are on the types of medication which could be recorded.

1. *Chronic medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of *chronic drugs*, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. *BJOG* 2006; 113: 559-5

2. *Medication for short time use** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of medication for short time use, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. BJOG 2006; 113: 559-5

3. *Pregnancy related medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of *pregnancy related medication*, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. *BJOG* 2006; 113: 559-5

4. *OTC medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* *OTC medication* is medication which is available Over the Counter, so without prescription.

The next questions are on the procedures on obtaining information on medication.

5. Prescriptions of medication can be recorded, but the actually use of medication can be registered as well. How does this information source handle this?

☐ Only prescribed medication is
☐ Only actually used medication is
☐ Prescribed and actually used medication are
recorded.

Comments:

6. The recorded medication is in response to

☐ specific questions asked by the registry employee, please go to question 7
☐ 'open' input by the mother please go to question 9
☐ specific questions asked by the registry employee and 'open' input by the mother, please go to question 7

Comments:

7. The questions asked by the registry employee are

☐ open
☐ closed
☐ open and closed.

Comments:

8. The registry employee asks for

(please tick all those which apply)

☐ specific drug groups
☐ specific drugs
☐ variable/ not clear

Comments:

Medication use can be recorded during one moment in or the whole pregnancy (prospective) and after pregnancy (retrospective). How does this information source handle this?

9. Data collection takes place in a

☐ retrospective (recorded after pregnancy)
☐ prospective (recorded during pregnancy)
☐ retrospective and prospective

Comments:

Does this information source contain information on medication use for all types of birth?

10. This source is available for

(please tick all those which apply)

☐ live births
☐ still births
☐ fetal death
☐ TOPFAs

Comments:

11. Did this reporting method change over time?

☐ yes, please specify
☐ no

Comments:

- **Questionnaire by registry**

☐ Applicable, please continue with the questions on this source
☐ Not applicable, please continue with the next source

The first questions are on the types of medication which could be recorded.

1. *Chronic medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of *chronic drugs*, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. *BJOG* 2006; 113: 559-5

2. *Medication for short time use** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of medication for short time use, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. BJOG 2006; 113: 559-5

3. *Pregnancy related medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of *pregnancy related medication*, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. *BJOG* 2006; 113: 559-5

4. *OTC medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* *OTC medication* is medication which is available Over the Counter, so without prescription.

The next questions are on the procedures on obtaining information on medication.

5. Prescriptions of medication can be recorded, but the actually use of medication can be registered as well. How does this information source handle this?

☐ Only prescribed medication is
☐ Only actually used medication is
☐ Prescribed and actually used medication are
recorded.

Comments:

6. The recorded medication is in response to

☐ specific questions asked in the questionnaire, please go to question 7
☐ 'open' input by the mother please go to question 9
☐ specific questions asked in the questionnaire and 'open' input by the mother. please go to question 7

Comments:

7. The questions asked in the questionnaire are

☐ open
☐ closed
☐ open and closed.

Comments:

8. In the questionnaire is asked for

(please tick all those which apply)

☐ specific drug groups
☐ specific drugs
☐ variable/ not clear

Comments:

Medication use can be recorded during one moment in or the whole pregnancy (prospective) and after pregnancy (retrospective). How does this information source handle this?

9. Data collection takes place in a

☐ retrospective (recorded after pregnancy)
☐ prospective (recorded during pregnancy)
☐ retrospective and prospective

Comments:

Does this information source contain information on medication use for all types of birth?

10. This source is available for

(please tick all those which apply)

☐ live births
☐ still births
☐ fetal death
☐ TOPFAs

Comments:

11. Did this reporting method change over time?

☐ yes, please specify
☐ no

Comments:

- **Other sources (specified..)**

☐ Applicable, please continue with the questions on this source
☐ Not applicable, please continue with the next source

Please describe the source

The first questions are on the types of medication which could be recorded.

1. *Chronic medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of *chronic drugs*, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. *BJOG* 2006; 113: 559-5

2. *Medication for short time use** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of medication for short time use, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. BJOG 2006; 113: 559-5

3. *Pregnancy related medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* For examples of *pregnancy related medication*, please check Table 1 of Bakker M, Jentink J, Vroom F et al. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. *BJOG* 2006; 113: 559-5

4. *OTC medication** is

☐ standard
☐ sometimes
☐ never
recorded.

Comments:

* *OTC medication* is medication which is available Over the Counter, so without prescription.

The next questions are on the procedures on obtaining information on medication.

5. Prescriptions of medication can be recorded, but the actually use of medication can be registered as well. How does this information source handle this?

☐ Only prescribed medication is recorded.
☐ Only actually used medication is recorded.
☐ Prescribed and actually used medication are recorded.

Comments:

6. The recorded medication is in response to

☐ specific questions asked in the source, please go to question 7
☐ 'open' input by the mother please go to question 9
☐ specific questions asked in the source and 'open' input by the mother, please go to question 7

Comments:

7. The questions asked in the source are

☐ open
☐ closed
☐ open and closed.

Comments:

8. In the source is asked for

(please tick all those which apply)

☐ specific drug groups
☐ specific drugs
☐ variable/ not clear

Comments:

Medication use can be recorded during one moment in or the whole pregnancy (prospective) and after pregnancy (retrospective). How does this information source handle this?

9. Data collection takes place in a

☐ retrospective (recorded after pregnancy)
☐ prospective (recorded during pregnancy)
☐ retrospective and prospective

Comments:

Does this information source contain information on medication use for all types of birth?

10. This source is available for

(please tick all those which apply)

☐ live births
☐ still births
☐ fetal death
☐ TOPFAs

Comments:

11. Did this reporting method change over time?

☐ yes, please specify
☐ no

Comments:

General:

If more than one source of information used, how does the registry solve the discrepancies?

The information on medication use, sent to the Central Registry in Ulster, where all the information is collected, is based on

☐ the first trimester
☐ the whole pregnancy

Definitions of values filled in in EDMP

The last part of the questionnaire is on the definitions you handle of values filled in in EDMP, namely: 'blank'; 'drug use not known' and 'no drugs taken'.

Could you please specify which applies/ apply to your registry?
(please tick all those which apply)

Definition of 'blank'	☐ *When I cannot find enough of the sources of drug use for the mother* ☐ *When I have found the sources but I cannot find any mention of a drug having been taken in the first trimester* ☐ *When there is mention of a drug but the information is illegible or non-specific* ☐ *Other, specify* ☐ *I never leave "Drugs1" blank*
Definition of 'drug use not known'	☐ *When I cannot find enough of the sources of drug use for the mother* ☐ *When I have found the sources but I cannot find any mention of a drug having been taken in the first trimester* ☐ *When there is mention of a drug but the information is illegible or non-specific* ☐ *Other, specify*
Definition of 'no drugs taken'	☐ *When I find a record that states the woman took no drug in the first trimester* ☐ *When I find no mention of any drug in the sources that I consult* ☐ *Never because we cannot be sure of our sources* ☐ *Other, specify*

Comments:

Appendix 1b: appendix belonging to chapter 4 'Actual use of medications prescribed during pregnancy: a cross-sectional study using data from a population-based congenital anomaly registry - Questionnaire

For each prescription the following aspects were verified:

- Did you actually use the medication prescribed?
  - No
  - Yes
  - Do not remember

- Did you start with the medication direct after the date of prescription?
  - No, … days/weeks/months later
  - Yes
  - Do not remember

- Was the daily dose used conform prescription?
  - No, the daily dose used was higher/ lower than prescribed
  - Yes
  - Do not remember

- Was the duration conform prescription?
  - No, the medication was used shorter/longer than prescribed
  - Yes
  - Do not remember

- Did you stop the use of the medication for a while and continued later on in pregnancy?
  - No
  - Yes
    - When?
    - For how long?
  - Do not remember

Appendix 1c: appendix belonging to chapter 4 'Actual use of medications prescribed during pregnancy: a cross-sectional study using data from a population-based congenital anomaly registry - Compliance rates calculated according to the standard definition, in a selected population including only live births and still births and according to the strict compliance definition

	"standard" ~ definition of compliance	**Compliance rate among LB and SB population, excluding SA and TOPFAs**	**Strict* 'compliance' definition**
First trimester			
Total number of women	129	107	129
medications for chronic use	0.84 (0.74-0.95)^	0,83 (0,71-0,96)^	0,82 (0,71-0,93)^
medications for short-term and occasional use	0.86 (0.78-0.94)^	0,85 (0,76-0,94)^	0,84 (0,76-0,93)^
medications for pregnancy related symptoms	0.92 (0.82-0.96)#	0,92 (0,81-0,97)#	0,88 (0,80-0,96)^
Entire pregnancy			
Total number of women	202	172	202
medications for chronic use	0.92 (0.86-0.98)^	0,92 (0,84-0,97)#	0,91 (0,84-0,97)^
medications for short-term and occasional use	0.90 (0.85-0.95)^	0,89 (0,83-0,95) ^	0,89 (0,84-0,94)^
medications for pregnancy related symptoms	0.95 (0.90-0.99)^	0,96 (0,90-0,98) #	0,92 (0,87-0,97)^

~ standard definition of compliance: If a mother confirmed that she had taken **at least one** of the prescriptions of a specific medication. If a medication was prescribed more than once and the mother had taken just one prescription, she was still counted as a compliant user for that medication.

* strict definition of compliance: if a mother confirmed that she had taken **all** of the prescriptions of a specific medication. If a medication was prescribed more than once but not all the prescriptions had been taken, she was not counted as a 'compliant user'.

^ Wald-method was applied

Wilson-method was applied

Appendix 1d: appendix belonging to chapter 5 'Antibiotics prescribed before, during and after pregnancy in the Netherlands: a drug utilization study' - Classification of the dispensed antibiotics according to Australian Drug Evaluation Committee's risk classifications for pregnancy*

Category A		Category B		Category C		Category D	
Generic name	**ATC code**	**Generic name**	**ATC code**	**Generic name**	**ATC code**	**Generic name**	**ATC code**
amoxicillin	J01CA04	pheneticillin	J01CE05	trimethoprim	J01EA01	doxycycline	J01AA02
phenoxymethylpenicillin	J01CE02	combinations	J01CE30	sulphamethizole	J01EB02	tetracycline	J01AA07
benzathine benzylpenicillin	J01CE08	flucloxacillin	J01CF05	sulphamethoxazole and trimethoprim	J01EE01	minocycline	J01AA08
cefalexin	J01DB01	amoxicillin and enzyme inhibitor	J01CR02			gentamicin	J01GB03
erythromycin	J01FA01	cefradine	J01DB09			neomycin	J01GB05
clindamycin	J01FF01	cefuroxime	J01DC02				
nitrofurantoin	J01XE01	cefaclor	J01DC04				
		loracarbef	J01DC08				
		ceftriaxone	J01DD04				
		cefixime	J01DD08				
		ceftibuten	J01DD14				
		roxithromycin	J01FA06				
		clarithromycin	J01FA09				
		azithromycin	J01FA10				
		ofloxacin	J01MA01				
		ciprofloxacin	J01MA02				
		norfloxacin	J01MA06				
		levofloxacin	J01MA12				
		moxifloxacin	J01MA14				
		pipemidic acid	J01MB04				
		polymyxin B	J01XB02				
		metronidazole	J01XD01				
		fosfomycin	J01XX01				
		methenamine	J01XX05				

** There were no dispensed antibiotics in 'Category X'*

Appendix 1e: appendix belonging to chapter 5 'Antibiotics prescribed before, during and after pregnancy in the Netherlands: a drug utilization study' – prescription rates and proportions belonging to figures 5.2-5.4

Data belonging to figure 5.2 Prescription rates per trimester for antibiotic subgroups

	Time period								
	before				during			after	
Antibiotic subgroup	**-4**	**-3**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**
tetracyclines (J01A)	2.44	2.38	2.33	1.87	0.66	0.07	0.05	0.87	1.65
beta-lactam antibacterials/ penicillins (J01C)	3.68	3.77	3.66	3.93	4.48	6.01	7.84	10.00	3.90
other beta-lactam antibacterials (J01D)	0.08	0.05	0.04	0.03	0.05	0.10	0.18	0.18	0.02
sulphonamides/ trimethoprim (J01E)	1.74	1.90	1.95	1.70	0.91	0.48	0.73	1.79	0.95
macrolides/lincosamides/streptogramins (J01F)	1.14	1.02	1.10	1.02	0.48	0.30	0.39	0.98	0.98
quinolone antibacterials (J01M)	0.38	0.30	0.30	0.25	0.10	0.01	0.01	0.29	0.17
other antibacterials (J01X)	1.17	1.47	1.33	1.43	1.44	1.85	1.32	1.65	0.81

Data belonging to figure 5.3 Prescription rates of antibiotic subgroups during pregnancy per 3-year periods

	Time period			
Antibiotic subgroup	**1996-1998**	**1999-2001**	**2002-2004**	**2005-2007**
tetracyclines (J01A)	0.98	0.62	0.62	0.72
beta-lactam antibacterials/ penicillins (J01C)	18.43	16.34	14.13	15.22
other beta-lactam antibacterials (J01D)	0.28	0.60	0.08	0.13
sulphonamides/ trimethoprim (J01E)	2.34	2.34	1.83	1.59
macrolides/ lincosamides/ streptogramins (J01F)	1.33	0.78	1.05	1.21
quinolone antibacterials (J01M)	0.14	0.14	0.12	0.05
other antibacterials (J01X)	2.27	2.87	4.52	5.62

*Data belonging to figure 5.4 The proportion of all prescriptions according to the Australian Drug Evaluation Committee's risk classification for pregnancy**

	Time period			
	Before conception	**During pregnancy**		
ADEC subgroups	**-4 and -3**	**1**	**2**	**3**
A	34.62	68.00	86.84	81.75
B	26.39	13.18	7.07	10.87
C	17.07	11.05	5.26	6.75
D	21.92	7.77	0.82	0.63

** There were no dispensed antibiotics in 'Category X'*

Appendix 1f: appendix belonging to chapter 5 'Antibiotics prescribed before, during and after pregnancy in the Netherlands: a drug utilization study' – Top 10 most-dispensed antibiotics

Top 10 most-dispensed antibiotics: before, during and after pregnancy

	BEFORE (1 year before conception up to conception) *8,662 antibiotic receipts in total*				**DURING (conception to delivery)** *5,708 antibiotic receipts in total*				**AFTER (from delivery to 6 months after delivery)** *5,207 antibiotic receipts in total*			
	ATC-code	**antibiotic**	**No. of receipts**	**%**	**ATC-code**	**antibiotic**	**No. of receipts**	**%**	**ATC-code**	**antibiotic**	**No. of receipts**	**%**
1	J01CA04	amoxicillin	1749	20.19	J01CA04	amoxicillin	3374	59.1	J01CA04	amoxicillin	1738	33.38
2	J01AA02	doxycycline	1650	19.05	J01XE01	nitrofurantoin	952	16.7	J01CF05	flucloxacillin	564	10.83
3	J01EA01	trimethoprim	1276	14.73	J01EA01	trimethoprim	400	7.0	J01CR02	amoxicillin and enzyme inhibitor	525	10.08
4	J01XE01	nitrofurantoin	1098	12.68	J01CR02	amoxicillin and enzyme inhibitor	259	4.5	J01XE01	nitrofurantoin	509	9.78
5	J01CE05	pheneticillin	615	7.10	J01FA01	erythromycin	161	2.8	J01EA01	trimethoprim	478	9.18
6	J01CR02	amoxicillin and enzyme inhibitor	445	5.14	J01AA02	doxycycline	136	2.4	J01AA02	doxycycline	467	8.97
7	J01FA09	clarithromycin	354	4.09	J01CE05	pheneticillin	119	2.1	J01CE05	pheneticillin	234	4.49
8	J01FA10	azithromycin	275	3.17	J01CF05	flucloxacillin	56	1.0	J01FA09	clarithromycin	139	2.67
9	J01EE01	sulfamethoxazole and trimethoprim	221	2.55	J01DB09	cefradine	34	0.6	J01FA01	erythromycin	128	2.46
10	J01CF05	flucloxacillin	191	2.21	J01FA10	azithromycin	34	0.6	J01FA10	azithromycin	107	2.05

Appendix 1f: appendix belonging to chapter 5 'Antibiotics prescribed before, during and after pregnancy in the Netherlands: a drug utilization study' – Top 10 most-dispensed antibiotics (continued)

Top 10 most-dispensed antibiotics: during pregnancy, better specified

	1ST TRIMESTER *1,647 antibiotic receipts in total*				**2ND TRIMESTER** *1,825 antibiotic receipts in total*				**3RD TRIMESTER** *2,236 antibiotic receipts in total*			
	ATC-code	**antibiotic**	**No. of receipts**	**%**	**ATC-code**	**antibiotic**	**No. of receipts**	**%**	**ATC-code**	**antibiotic**	**No. of receipts**	**%**
1	J01CA04	amoxicillin	767	46.6	J01CA04	amoxicillin	1128	61.8	J01CA04	amoxicillin	1479	66.1
2	J01XE01	nitrofurantoin	293	17.8	J01XE01	nitrofurantoin	388	21.3	J01XE01	nitrofurantoin	271	12.1
3	J01EA01	trimethoprim	165	10.0	J01EA01	trimethoprim	91	5.0	J01CR02	amoxicillin and enzyme inhibitor	144	6.4
4	J01AA02	doxycycline	114	6.9	J01CR02	amoxicillin and enzyme inhibitor	57	3.1	J01EA01	trimethoprim	144	6.4
5	J01CE05	pheneticillin	61	3.7	J01FA01	erythromycin	57	3.1	J01FA01	erythromycin	63	2.8
6	J01CR02	amoxicillin and enzyme inhibitor	58	3.5	J01CE05	pheneticillin	33	1.8	J01CE05	pheneticillin	25	1.1
7	J01FA01	erythromycin	41	2.5	J01DB09	cefradine	14	0.8	J01CF05	flucloxacillin	20	0.9
8	J01FA10	azithromycin	25	1.5	J01CF05	flucloxacillin	13	0.7	J01DC02	cefuroxime	17	0.8
9	J01CF05	flucloxacillin	23	1.4	J01AA02	doxycycline	11	0.6	J01DB09	cefradine	15	0.7
10	J01FA09	clarithromycin	17	1.0	J01CE02	phenoxymethylpenicillin	6	0.3	J01AA02	doxycycline	11	0.5

Appendix 1g: appendix belonging to chapter 6 'Identifying associations between maternal medication use and birth defects using a case population approach: an exploratory study on signal detection'- malformations that are coded within the malformation groups studied*

Malformations of the nervous system

- Anencephalus and similar
- Encephalocele, but exclude if associated with anenephalus
- Spina Bifida
- Hydrocephalus, but exclude hydranencephaly or associated with NTD
- Microcephaly, but exclude if associated with NTD
- Arhinencephaly / holoprosencephaly

Congenital heart defects

Exclude isolated PDA with GA<37weeks

- Common arterial truncus
- Transposition of great vessels
- Single ventricle
- Tetralogy of Fallot
- VSD
- ASD
- AVSD
- Triscuspid atresia and stenosis
- Ebstein's anomaly
- Pulmonary valve stenosis
- Pulmonary valve atresia
- Aortic valve atresia/stenosis
- Hypoplastic left heart
- Hypolastic right heart
- Coarctation of aorta
- Total anomalous pulm venous return
- PDA as **only** CHD in term infants (GA +37 weeks); Livebirths only

Oro-facial clefts

Exclude if associated with holoprosencephaly or anencephaly subgroups

- Cleft lip with or without cleft palate
- Cleft palate

Respiratory malformations

- Choanal atresia
- Cystic adenomatous malformation of lung

Malformations of the digestive system

- Oesophageal atresia with or without trachea-oesophageal fistula
- Duodenal atresia or stenosis but exclude if also annular pancreas
- Atresia or stenosis of other parts of small intestine
- Ano-rectal atresia and stenosis
- Hirschsprung's disease
- Atresia of bile ducts
- Annular pancreas
- Diaphragmatic hernia

Genital malformations

- Hypospadia
- Indeterminate sex

Malformations of the urinary tract

- *Bilateral* renal agenesis including Potter syndrome
- Renal Dysplasia
- Congenital hydronephrosis
- Bladder exstrophy and / or epispadia
- Posterior urethral valve and / or prune belly

Malformations of the musculo-skeletal system

- Hip dislocation and / or dyspasia

Malformations of the limbs

- Limb reduction
- Upper limb reduction
- Lower limb reduction
- Complete absence of a limb
- Club foot – talipes equinovarus
- Polydactyly
- Syndactyly

** According to the EUROCAT guidelines: http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3-Chapter-3.3-Jan13.pdf*

Appendix 1h: appendix belonging to chapter 6 'Identifying associations between maternal medication use and birth defects using a case population approach: an exploratory study on signal detection'- Malformations observed within cases exposed to the different drugs studied

valproic acid

heart anomalies RR 5.98 (2.66-13.44)

observed malformations:

- VSD [2x]
- VSD + aortic pulmonary window [1x]
- Fallot's [1x]
- tetralogy [1x]
- coarctation of aorta [1x]

anomalies of the central nervous system RR 15.05 (5.09-44.51)

observed malformations:

- spina bifida [2x]
- hydrops fetalis+ mental retardation+ epilepsia+ congenital cataract [1x]

fluoxetine

anomalies of the digestive system RR 3.73 (1.23-11.32)

observed malformations:

- hypertrophic pyloric stenosis [3x]

citalopram

*anomalies of the musculo-skeletal system RR 3.75 (1.26-11.14**)***

observed malformations:

- congenital deformities of the hip [2x]
- congenital deformities of the hip + unbalanced translocation [1x]

paroxetine

heart anomalies RR 2.03 (1.14-3.62)

observed malformations:

- VSD [4x]
- ASD [1x]
- coarcatation of aorta [2x]
- bicuspid aortic valve [1x]
- congenital pulmonary valve stenosis + cafe au lait spots [1x]
- VSD + clubfeet [1x]
- transposition + AVSD + dextroposition of the heart [1x]

methyldopa

anomalies of the digestive system RR 4.66 (1.54-14.06)

observed malformations:

- cloacal dysgenesia sequence [1x]
- hypertrophic pyloric stenosis [1x]
- atresia of oesophagus with tracheo-oesophageal fistula [1x]

genital anomalies RR 5.37 (1.78-16.22)

observed malformations:

- cloacal dysgenesia sequence [1x]
- hypospadias [2x]

urinary anomalies RR 5.46 (1.81-16.49)

observed malformations:

- cloacal dysgenesia [1x]
- vesico uretral reflux [2x]

APPENDIX 2

List of co-authors and affiliations

Dankwoord

Curriculum Vitae

Courses attended during PhD project

List of publications

List of recent SHARE theses

List of co-authors and affiliations

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Dankwoord

Cliché, maar waar: een proefschrift schrijf je niet alleen. Daarom zou ik graag de volgende mensen willen bedanken.

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Curriculum Vitae

Linda de Jonge was born in Hoogeveen on July 6, 1986. After finishing high school in 2004, she studied Pharmacy at the University of Groningen. Linda became interested in research and epidemiology by performing her Master's thesis titled "*Foliumzuurinterventie op Curaçao een onderzoek naar aanleiding van de foliumzuurinterventie anno 2005*" (under supervision of prof. dr. L.T.W. de Jong-van den Berg and drs. A.N.G. Tjin-A-Tsoi) and a local internship on Bonaire (under supervision of prof. dr. A.J.M. Loonen and drs. J.G. Ensing). She graduated in the summer of 2010 and after that she started her PhD project, which resulted in this thesis, at EUROCAT Northern Netherlands. During her PhD project she finished her training and obtained an official registration as epidemiologist by the Netherlands Epidemiological Society (VVE).

Courses attended during PhD project

2015 - Publishing using Word (RuG, Centre for Information technology (CIT))

2014 - Basics in Medicine (UMCG, Clinical and Psychosocial Epidemiology [CPE], Research Master)

2014 - Multivariate Analyses: How to handle three variables (UMCG, Graduate School of Medical Sciences [GSMS], PhD level)

2014 - Medical Statistics (UMCG, GSMS, epidemiology, PhD level)

2013 - Critical appraisal of literature for SHARE students (UMCG, GSMS, PhD level)

2013 - Clinical Relevance versus Statistical Significance (UMCG, GSMS, PhD level)

2013 - Publishing in English (UMCG, GSMS, PhD level)

2012 - Clinical Epidemiology (UMCG, CPE, Research Master)

2012 - Public Health Epidemiology (UMCG, CPE, Research Master)

2012 - Good Research Practices: GLP/GCP (UMCG, GSMS, PhD level)

2012 - Presentation skills (UMCG, GSMS, PhD level)

2012 - International Meyler Course in Pharmacovigilance (RuG)

2011 - Study Design in Clinical Epidemiology (UMCG, CPE, Research Master)

2011 - Science writing (UMCG, GSMS, PhD level)

2011 - Project management (UMCG, GSMS, PhD level)

2011 - Pharmacoepidemiology and drug Safety (Erasmus university, Netherlands Institute for Health Sciences [NIHES], Erasmus Winter Programme)

2010 - SPSS-cursus (RuG, CIT)

List of publications

- Arts MHL, Michielsen PJS, Petrykiv S, **de Jonge L**, Oude Voshaar RC. Treatment of Charles Bonnet syndrome with continuous positive airway pressure in an older adult. Eur Psychiatry 2016 [in press].
- Arts MHL, Buis J, **de Jonge L**. Misdiagnosis of anterior cutaneous nerve entrapment syndrome as a somatization disorder. Eur Psychiatry 2016 [in press].
- Petrykiv S, Arts MHL, **de Jonge L**. Between scylla and charybdis: Where does the treatment of Addison's disease in late-life depression go first? Eur Psychiatry 2016 [in press].
- Petrykiv S, **de Jonge L**, Michielsen PJS, Arts MHL. Electroconvulsive therapy in depressed older adults with unrepaired abdominal aortic aneurysm: safety first! Eur Psychiatry 2016 [in press].
- Arts MHL, Michielsen PJS, Petrykiv S, **de Jonge L**. A tribute to Johann Gottlieb Burckhardt-Heussler (1836-1907), the pioneer of psychosurgery. Eur Psychiatry 2016 [in press].
- Petrykiv S, **de Jonge L**, Arts MHL. Case-report and review of selective serotonin reuptake inhibitor-induced delirium in older adults. Eur Psychiatry 2016 [in press].
- Petrykiv S, **de Jonge L**, Michielsen PJS, Arts MHL. Case-report of autointoxication with nutmeg committed by a suicide attempter. Eur Psychiatry 2016 [in press].
- **de Jonge L**, Jordan S, Tucker D, Thayer D, Pierini A, Gini R, Garne E, Hansen AV, Neville AJ, Puccini A, Bakker MK. Linkage of prescription data to congenital anomaly registers to improve Information on maternal medication use: a EUROmediCAT study. Pharmacoepidemiol Drug Saf. 2015;24:33-34.
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- **de Jonge L**, de Walle HEK, de Jong-van Den Berg LTW, van Langen IM, Bakker MK. Actual use of medications prescribed during pregnancy: a cross-sectional study using data from a population-based congenital anomaly registry. Drug Safety 2015;38:737-747. **

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- **de Jonge L**, Bakker MK. EUROCAT special report: sources of information on medication use in pregnancy. 2014. http://www.eurocat-network.eu/content/Special-Report-Medication-Use-In-Pregnancy.pdf **
- Smedts HP, **de Jonge L**, Bandola SJ, Baardman ME, Bakker MK, Stricker BH, Steegers-Theunissen RP. Early pregnancy exposure to antihistamines and risk of congenital heart defects: results of two case-control studies. Eur J Epidemiol. 2014;29:653-661.**
- **de Jonge L**, Bos HJ, van Langen IM, de Jong-van den Berg LT, Bakker MK. Antibiotics prescribed before, during and after pregnancy in the Netherlands: a drug utilization study. Pharmacoepidemiol Drug Saf. 2014;23:60-68.**
- **de Jonge L**, Zetstra-van der Woude PA, Bos HJ, de Jong-van den Berg LT, Bakker MK. Identifying associations between maternal medication use and birth defects using a case-population approach: an exploratory study on signal detection. Drug Saf. 2013;36:1069-1078.**
- **de Jonge L**, Langenburg AMA, Ensing JG, Boek CM, Pras N, Loonen AJM. Psychofarmacaverstrekkingen op Bonaire. Tijdschrift voor psychiatrie 2012;54:81-87.

*** published in this thesis*

List of recent SHARE theses

This thesis is published within the **Research Institute SHARE** (Science in Healthy Ageing and healthcaRE) of the University Medical Center Groningen / University of Groningen. Further information regarding the institute and its research can be obtained from our internetsite: http://www.share.umcg.nl/

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Tuuk K van der
Who's at risk? Prediction in term pregnancies complicated by hypertensive disorders
(prof PP van den Berg, prof BWJ Mol, dr MG van Pampus, dr H Groen))

Vitkova M
Poor sleep quality and other symptoms affecting quality of life in patients with multiple sclerosis
(prof SA Reijneveld, prof Z Gdovinova, dr JP van Dijk, dr J Rosenberger)

Sudzinova A
Roma ethnicity and outcomes of coronary artery disease
(prof SA Reijneveld, dr JP van Dijk, dr J Rosenberger)

Otten E
Introducing eHealth and other innovative options into clinical genetic patient care in view of increase efficiency and maintenance of quality of care; patients' and providers' perspectives
(prof IM van Langen, prof AV Ranchor, dr E Birnie)

Pouwels K

Self-controlled designs to control confounding

(prof E Hak)

Voerman AE

Living with prostate cancer; psychosocial problems, supportive care needs and social support groups

(prof R Sanderman, prof M Hagedoorn, dr APh Visser)

Janse M

The art of adjustment

(prof AV Ranchor, prof MAG Sprangers, dr J Fleer)

Nigatu YT

Obesity and depression; an intertwined public health challenge

(prof U Bültmann, prof SA Reijneveld)

Aris-Meijer JL

Stormy clouds in seventh heaven; a study on anxiety and depression around childbirth

(prof CLH Bockting, prof RP Stolk, dr H Burger)

Kluitenberg B

The NLstart2run study; running related injuries in novice runners

(prof RL Diercks, dr H van der Worp, dr M van Middelkoop)

Benjaminse A

Motor learning in ACL injury prevention

(Prof E Otten, prof KAPM Lemmink, prof RL Diecks)

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