The use of a birth defects case-control monitoring system in studying the safety of medication use in pregnancy

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The use of a birth defects case-control monitoring system in studying the safety of medication use in pregnancy

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Scope

Eurocat Northern Netherlands (NNL) is a population-based birth defects registry. Eurocat is an acronym for European Registration of Congenital Anomalies and Twins. Besides the monitoring of the occurrence of birth defects over time, the main goal is to contribute to the prevention of birth defects by identifying possible risk factors. Therefore, detailed information is collected on possible risk factors, such as life style factors, occupational exposure and medication use in pregnancy. Initially, information on maternal medication use was collected from medical files. This information appeared, however, to be very incomplete. Therefore, routine collection of pharmacy data was introduced in 1997. Since that time, the registry has collected information on maternal medication used in pregnancy on more than 5,000 children and foetuses with birth defects.

Post-marketing surveillance of medication used in pregnancy and their safety for the developing embryo is of great importance because many women use drugs during pregnancy but possible teratogenic effects of drugs are still largely unknown. In this thesis I use data from Eurocat NNL and the Interaction Database, a population-based prescription database, to study possible risks of medication use in pregnancy in the context of a birth defects case-control monitoring system.

Chapter 1 contains a general introduction on the different study designs that are used in the post-marketing surveillance of medication use in pregnancy and the specific objectives of this thesis. Which drugs are used in pregnancy and the pattern of their use throughout pregnancy is described in chapter 2. Because Eurocat NNL does not include non-malformed children, the selection of an appropriate control group is particularly challenging in case-control studies on risks of medication use. Chapter 3 addresses this topic. In order to identify possible new teratogenic effects of drugs, surveillance studies have been performed previously within the Eurocat database, using the incomplete data on maternal medication use. In chapter 4 a signal is described that came up in a new surveillance study, using data on maternal medication use based on the pharmacy data. In chapter 5 a case-control study is presented that was undertaken after several -mostly follow up- studies were published on the possible association between maternal use of selective serotonin reuptake inhibitors (SSRIs) and congenital heart defects. We conducted a specific case-control study on the occurrence of specific heart defects and maternal use of paroxetine, a specific SSRI. Finally, in the last chapter, I discuss the usefulness of the Eurocat database to study possible risks of medication use in pregnancy and give recommendations for improvement.

CHAPTER 1

Introduction

Thalidomide was put on the market as an effective and safe sedative in 1957. Because it was also effective as an anti-emetic, the drug was prescribed to pregnant women. In 1961, a number of reports appeared on children born with severe birth defects, including severe limb reduction defects and eye anomalies. The mothers of these children had used thalidomide in early pregnancy. When these reports were published, thalidomide and other drugs that contained thalidomide were withdrawn from the market. It was estimated that by then over 10,000 embryos had been affected by the drug worldwide.[1]

Because it took relatively long for the clusters of malformed children and the cause to be identified, birth defects registries were set up all over the world to monitor the occurrence of birth defects and to detect possible new teratogens at an early stage.

Also since the thalidomide tragedy, regulations for reproductive toxicity testing in the pre-marketing phase have become much more stringent. Nevertheless, by the time a drug is put on the market, the information on possible teratogenic effects is still limited for several reasons. Firstly, results of animal studies are not always predictive for the human situation. Teratogenic effects that occur in animals, may not occur in humans, and vice versa. There is often a considerable variation in effects among different animal species. In the case of thalidomide, for instance, animal studies were performed in mice, which are insensitive to thalidomide and therefore gave no indication of a teratogenic effect. Thalidomide resistance is based on the capacity of the glutathione-dependent antioxidant defence. Mouse embryonic fibroblasts are found to have higher glutathione levels than those of sensitive species, such as humans and certain rabbit species.[2] Secondly, pre-marketing clinical trials in humans are also unable to detect teratogenic effects, because these trials are mostly too small and pregnant women are excluded from participating in such trials on a standard basis.

Although the safety of many drugs has not been established, the majority of women use drugs in pregnancy; estimations vary from 40-99%, depending on the type of medications included in the study and the sources used.[3-5] Differences in maternal drug use and prescription rates have also been described on an international level[6] and in relation to socio-economic status for instance.[7;8] In certain situations, such as in women with epilepsy, the treatment benefits are greater than possible teratogenic risks. Because it is not realistic to avoid all drug use in pregnancy, it is very important that drug use in pregnancy is subject to systematic post-marketing surveillance and several approaches are used to study the safety of medication use in pregnancy in the post-marketing situation. These study designs can be considered complementary to each other.

STUDY DESIGNS IN POST-MARKETING SURVEILLANCE

Drug utilisation studies

Drug utilisation studies are performed to investigate the types of drugs taken and the prevalence of use in specific time periods before and during pregnancy. Large automated databases, for example from health care insurers or prescription databases, are usually used for these types of studies.[3;9;10] Since these databases do not include information on the use of non-prescription over-the-counter (OTC) medication in pregnancy, this data has to be obtained from birth or birth defects registries, in which the mother is actually asked if she has used OTC drugs in pregnancy[11], or from cohort studies.[12;13] Such drug utilisation studies can reveal whether potentially teratogenic drugs are prescribed in pregnancy and to what extent.[14-18] Furthermore, prescription rates obtained from these studies can serve as a reference value in other analytical studies, in order to determine if the exposure rates among controls are valid (comparable to the general pregnant population).

Case reports and case series

Alert clinicians, who related an unusual pattern of malformations or a very rare birth defect in a child to the use of an unusual drug in the mother's pregnancy, have discovered several teratogenic drugs, such as warfarin and isotretinoin. The underlying principle of this approach is that the random chance that a rare and unusual malformation or pattern of malformations may coincide with a rare exposure is very small. Because of the low specificity, case reports and case series are not suitable for detecting teratogenic effects of relatively commonly used drugs, such as antidepressants, or for detecting relatively common birth defects. Recently Carey et al.[19] proposed stringent guidelines for using this approach in determining human teratogenicity. These guidelines include the identification of three or more cases with a distinct pattern of malformation of multiple defects (two or more malformations) or a particularly rare phenotype that occurs in less than 1 in 1,000 births in combination with an uncommon pregnancy exposure of less than 1 in 1,000 pregnancies. Since case reports do not include denominator data, it is difficult to establish the frequency of the adverse outcome, and since they suffer from reporting bias, the initial observations have to be confirmed by epidemiological analyses to elucidate the possible causal relationship between exposure and effects.

Cohort studies

In cohort or follow-up studies, women who have taken a particular drug in pregnancy are followed to determine the pregnancy outcome and then compared to the pregnancy outcome of women not exposed to that drug. Cohort studies on medication use and birth defects are mostly performed within pregnancy exposure registries, such as EURAP, an

international registry of antiepileptic drugs and pregnancy[20], and within databases from Teratology Information Services (TIS).[21] Some of the strengths of cohort studies include the prospective collection of information on medication use before the outcome of the pregnancy is known and the ability to study several other adverse pregnancy outcomes besides evident birth defects, such as the rate of miscarriage and preterm birth, low birth weight, etc. The weaknesses include selective inclusion of patients (volunteers, self-referral in TIS databases), a reporting bias towards more severe outcomes, and differences in quality and completeness of data (loss to follow-up). Moreover, cohort studies are not very efficient. The occurrence of (specific) birth defects is rare and large numbers of exposed pregnancies are required. They are therefore costly and it takes a lot of time to recruit sufficient participants and collect all the data.[22;23]

Another setting in which cohort studies are performed is within linked automated databases. The linkage of administrative databases can create large cohorts and is more efficient. However, the original purpose of the databases that are linked is not to study teratogenic risks so that concessions have to be made on the quality of the data, such as the use of prescription data instead of information on the actual use of medication, general instead of detailed information on birth defects, and only limited information available on possible confounders. Cohort studies are primarily able to identify high-risk teratogens, because the number of exposed pregnancies is, in general, too small to detect mild to moderate risks or specific for birth defects.

Case-control studies

In case-control studies, cases with a specific birth defect are selected and compared to a control group with reference to the exposure of interest. Case-control studies are frequently performed in the context of a birth defects surveillance system, such as the Metropolitan Atlanta Congenital Defects Program[24] or within a national or international network of birth defects registries, such as the European Concerted Action on Congenital Anomalies and Twins (EUROCAT).[25] In general, case-control studies have more power than cohort studies to identify mild to moderate risks for specific birth defects in relation to relatively commonly used drugs. The information on the condition of the child or foetus is mostly very detailed, and extra information can be obtained on a number of possible risk factors and confounders. Disadvantages include the retrospective nature of data collection (after the pregnancy outcome is known), which may cause recall bias compared to a non-malformed control group. In the absence of a non-malformed control group, malformed controls are used, which may introduce selection bias if the exposure of interest also causes other malformations that are included in the control group. In general, case-control studies are more efficient regarding the cost and effort needed to recruit participants and to collect all the data. Table 1 provides an overview of the purposes,

Table 1. Overview of study designs in post-marketing surveillance of safety of medication use in pregnancy.

	Drug utilisation studies	Case reports and series	Cohort studies	Case-control studies
Descriptive / analytical	Descriptive	Descriptive	Analytical	Analytical
Purpose	To investigate type of drugs used in pregnancy	To report on possible new teratogenic drugs (hypothesis generating)	To study possible risks and safety of medication use in pregnancy	To study possible risks and safety of medication use in pregnancy
Setting	Large automated databases (prescription databases, health insurance databases)	Clinical practice	Pregnancy registries Databases from Teratology Information Services (TIS) and their networks Linked automated databases	Birth defects surveillance systems and networks Specific case-control studies
Advantages	Cost-effective Large numbers can easily be obtained Can serve as reference for analytical studies	Can detect early on any associations between rare birth defects and rare exposures	Prospective data collection Suitable to study: • uncommon exposures (newly marketed drugs). • wide range of adverse birth outcomes besides birth defects Suitable for detecting high-risk teratogens Information available on possible risk factors and confounders (pregnancy and TIS databases)	Suitable to identify mild to moderate risks for specific birth defects in relation to relatively commonly used drugs Suitable to study rare outcomes such as birth defects More efficient in data collection
Disadvantages	No information on the use of OTC medication No information on the actual use of prescribed medication No information on the actual length of gestation	Depends on alert clinicians Not suitable to identify associations for relatively common birth defects or relatively commonly used drugs Signals have to be confirmed in analytical studies, cannot be used for testing	Selective inclusion of patients Sensitive to selective loss-to-follow-up (biased to adverse outcomes) Differences in quality of data Costly Linkage of automated databases: lower data quality	Not suitable to study possible teratogenic risks or safety of rare medications Retrospective data collection Selection of a proper control group

setting, advantages and disadvantages of these four study designs.

CASE-CONTROL MONITORING

A birth defects case-control monitoring system, with ongoing data collection on birth defects and maternal medication use, is a valuable instrument for actively monitoring the safety of drugs used in pregnancy. With a birth defects case-control monitoring system, it is possible to conduct multiple case-control studies on several types of birth defects in association with a wide range of drugs used in pregnancy. In addition, it is possible to study multiple exposures in relation to multiple outcomes, single exposure in relation to multiple outcomes, and single exposure in relation to single outcomes.[26]

There are several birth defects case-control monitoring systems, such as the Slone Birth Defects Study[27] and the National Birth Defects Prevention Study.[28] Both are multi-centre studies, which include cases with selected birth defects and non-malformed controls. Information on maternal medication use and other possible risk factors is collected by telephone interview. In Europe, the Spanish Collaborative Study of Congenital Malformations (ECEMC) also incorporates an ongoing case-control study on birth defects and medication use in pregnancy. The cases are newborn infants with birth defects, detected in the first 3 days of life, while the controls are non-malformed infants, matched on sex, date of birth and hospital where the cases were born. Information on maternal medication use is collected through a personal interview with the mother within 3 days of delivery.[29]

The International Clearinghouse for Birth Defects Surveillance and Research, a world-wide network of birth defects registries, has established a special type of case-control monitoring system on medication use. The Malformation Drug Exposure (MADRE) database compiles information on cases with birth defects with a positive history of first trimester maternal medication use from 12 participating birth defects registries. The case-control analysis is an 'exposed case-only' design, because all the subjects are affected by some birth defect and have been exposed to some medication. The MADRE database is used to perform systematic surveillance of birth defects and maternal medication use in order to detect possible new teratogenic drugs[30] and to perform specific case-control studies on the risks of maternal medication use.[31]

In the Northern Netherlands there are two initiatives that, together, form a birth defects case-control monitoring system: a registry of congenital anomalies, Eurocat Northern Netherlands, and a prescription database, the Interaction Database.

Eurocat Northern Netherlands (Eurocat NNL)

Eurocat NNL is population-based birth defects registry, which was established in 1981.

Initially it covered the province of Groningen and the northern part of Drenthe, but after two expansions, the registry has covered the provinces of Groningen, Friesland and Drenthe since 1989, with approximately 18,000 births per year (10% of all births in the Netherlands). Yearly, approximately 500-600 cases are registered. The main objectives of Eurocat NNL are: (1) to monitor the frequency of congenital anomalies in time, (2) to study the effects of changes in health policies (folic acid supplementation, introduction of prenatal screening), and (3) to study possible risk factors. Eurocat NNL is funded by the Dutch Ministry of Health, Welfare and Sport, and is a member of the 'European Concerted Action on Congenital Anomalies and Twins' network and of the International Clearinghouse for Birth Defects Surveillance and Research.

Children and foetuses with birth defects are eligible for registration if the mother lived in the designated region at the time of the birth. There is no lower age limit (terminations of pregnancy and spontaneous abortions of foetuses with birth defects are also included), but affected children have to be notified to the registry before the age of 16. Notification of children and foetuses with birth defects is voluntary and registry staff are involved in actively searching for eligible cases using multiple sources, such as hospital registration databases, pathology reports, cytogenetic reports, etc. Since 1989, parents have to give consent for the registration. Information on possible risk factors, such as smoking habits and maternal medication, use in pregnancy was originally collected from medical files or requested from the general practitioner. However, this data was often incomplete and in 1997 the methodology of data collection was therefore expanded by the important introduction of a parental questionnaire and the routine collection of pharmacy data. The actual use of prescribed drugs and the use of OTC drugs is verified in a telephone interview. All the drugs that were actually used in the period from three months before pregnancy till delivery are registered with as much detail as possible in the database, including the name of the drug, daily dose, and period it was taken. The drugs are coded using the Anatomical Therapeutic Chemical (ATC) classification system.[32] This methodology serves as an example of good practice for other birth defects registries. Because Eurocat NNL does not collect information on non-malformed children, malformed controls are used in case-control studies.

InterAction DataBase (IADB.nl)

The IADB.nl is a population-based prescription database that includes information from community pharmacies in the north-eastern part of the Netherlands. Since 1999, the IADB.nl contains prescriptions for an estimated population of 500,000 individuals. A pregnancy database has been generated in the IADB.nl. For each child in the IADB.nl, the female person, 15-50 years older than the child and with the same postal/zip code is considered to be the mother, provided there are no other female persons in that age

category at the same postal code. Approximately 65% of the mothers can be identified with this methodology.[33] Because the actual length of the pregnancy is unknown, the length of the pregnancy is standardised at 39 weeks. The prescription data is recorded prospectively and covers prescriptions from different prescribers. Each prescription record contains information on the name of the drug, the date of dispensing, the quantity dispensed, the dose regime, and the prescribing physician. The IADB.nl does not include data on OTC drugs or medication dispensed during hospitalisation. All the drugs are coded according to the ATC classification system.[32]

Objectives

This thesis explores the usefulness of Eurocat NNL and the IADB.nl for a birth defects case-control monitoring system on the safety of drugs used in pregnancy.

The objectives of the thesis are:

1) to investigate the type of drugs women use before and during pregnancy;
2) to asses whether children with a chromosomal or monogenic disorder constitute an appropriate control group with reference to maternal medication use;
3) to identify possible new teratogenic drugs using a surveillance methodology;
4) to study possible teratogenic effects of medication used in pregnancy, using a case-control design.

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CHAPTER 2.1

Drug utilisation studies

Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands

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ABSTRACT

Objective. To compare the prescription of drugs in women over a period from 2 years before until 3 months after pregnancy regarding the type of drugs used and the foetal risk.

Methods. A cohort study was performed with data from the InterAction Database, containing prescription drug dispensing data from community pharmacies. Included were 5,412 women giving birth to a child between 1994-2003 and for which complete pharmacy records were available. Drugs were classified in 3 categories: (I) drugs for chronic conditions, (II) drugs for occasional use and (III) drugs for pregnancy-related symptoms and classified according to the Australian classification system. The prescription rate was calculated as the number of women per 100 who received one or more prescriptions for a given drug within a specified time period.

Results. 79.1% of the women received at least one prescription during pregnancy. The prescription rate for most drugs for chronic diseases and for occasional use decreased during pregnancy, whereas, as expected, the prescription rate for pregnancy-related drugs increased. During the first trimester of pregnancy, 1.7% of all drugs prescribed for chronic conditions were classified as harmful and 2.3% of the occasional drugs

Conclusions. The increase in prescription rate during pregnancy is caused by an increase in prescription rate for drugs for pregnancy-related symptoms. The prescription of harmful drugs is more commonly associated with drugs for occasional use rather than with drugs for chronic conditions. Therefore, a more cautious prescribing of drugs to healthy women in the fertile age is necessary.

INTRODUCTION

Since the teratogenic risk for most drugs is still undetermined, it is important to monitor drug use regularly among pregnant women. Drug utilisation studies reveal that most women use drugs during pregnancy with estimations varying from 44%[1] to 99%.[2] However, comparison is difficult because of differences in study design. Interviews or prescription databases may be used for collecting drug use data and the type of drugs studied may or may not include over-the-counter (OTC) drugs such as vitamins, iron, and analgesics. Most studies find an increasing trend in drug use during pregnancy.[2-7]

Drug use can not always be avoided during pregnancy. For women with certain chronic medical conditions such as epilepsy, diabetes, inflammatory bowel disease and asthma, the use of drugs is essential and benefits for mother and child may well outweigh the teratogenic risk of the drug.[8;9] Other non-chronic diseases, related or unrelated to the pregnancy, may require medical treatment. Most studies do not distinguish between the different reasons for which the drugs are prescribed. Therefore it is not clear to what extent changes in drug use among pregnant women can be explained by chronic, occasional or pregnancy-related drug use.

The aim of this study was to compare the prescription of drugs in pregnant women with respect to the type of drugs and the foetal risk before, during and after pregnancy.

METHODS

This study was performed with the InterAction Database (IADB) which contains data on prescriptions dispensed from community pharmacies in the Netherlands. The IADB includes all prescription drugs from an estimated population of 220,000 from 1994 to 1999 and was expanded to approximately 450,000 since 1999.[10;11] Registration is irrespective of health insurance and is considered representative for the general population. Each prescription record contains information about the drug, date of dispensing, quantity dispensed, dose regimen and the prescribing physician. The indication for the prescription is not known. All drugs are coded according to Anatomical Therapeutic Chemical (ATC) classification.[12] Each patient has a unique (anonymous) identifier; date of birth and gender of patients are known. Due to a high patient-pharmacy commitment in the Netherlands and sophisticated pharmacy software, the medication records for each patient are virtually complete.[13] The IADB does not include OTC drugs and drugs dispensed during hospitalisations.

To identify mothers, all children born between January 1st 1994 and January 1st 2004 were selected in the database. For each child within the IADB, the female person 15-50 years older than the child with the same address code was considered to be the

mother providing there were no other female persons 15-50 years older with the same address code. Using this method 65% of the mothers could be identified. Validation of this method is described in detail by Schirm et al.[14] Because only the child's birth date is known, the theoretical conception date was determined as the date of birth minus 273 days (i.e. 9 months). Between January 1st 1994 and January 1st 2004 10,261 women were identified with a total of 13,894 pregnancies. To rule out the influence of previous pregnancies, we included only the first pregnancy, as registered in the database, for which complete pharmacy records were available in the IADB from 2 years before the theoretical conception date until 3 months after delivery. According to these criteria 5,501 women were included. To avoid misclassification of medication use, we subsequently excluded women who gave birth to twins (N=87) or triplets (N=2), because the gestation period in twin and triplet pregnancies is more likely to be shorter than in singleton pregnancies. Thus, for the final analysis pharmacy data for 5,412 women were used. To allow direct comparisons of prescription rates over time, the whole study period of three years was divided into 12 periods of 13 weeks (trimesters). The 12 trimesters were numbered as can be seen in figure 1.

We ordered drugs that were commonly prescribed into 3 mutually exclusive categories: (I) drugs for chronic conditions, (II) drugs for occasional and short time use and (III) drugs for pregnancy-related symptoms. Drugs and drug groups belonging to these three categories are listed in table 1. Drugs for chronic conditions are not necessarily taken on a chronic basis, but can also be taken during episodes when the disease surfaces. The drugs were also classified based on the Australian risk classification for pregnancy (table 2).[15] Categories D and X were combined, because for both categories the use of drugs during pregnancy is clearly contra-indicated and only one drug was classified as X (isotretinoine, D10BA01). The three B categories were combined for statistical purposes. Drugs that were not classified according to the Australian classification were categorised as B, because their foetal risk was obviously unknown.

Per trimester we counted the number of specific drugs that were prescribed to individual women, excluding contraceptives. If a specific drug was prescribed twice during a trimester, it was counted only once. In addition, prescriptions covering more than one trimester were counted only in the trimester in which they were dispensed. The prescription rate was calculated as the number of women per 100 who received one or more prescriptions for a given drug or drug class within one trimester or otherwise specified time period. Prescription rates were tested in SPSS 12.0.2 for Windows over the 3-year study period and the pregnancy period using the X^2 for trend.

Table 1. Categorisation drugs and drug groups included in this study, according to their ATC-code. The drug categories are mutually exclusive.

Category I	**Drugs for chronic conditions**	**ATC-code**
Drugs used in diabetes		A10
Corticosteroids, dermatological preparations		D07
Corticosteroids for systemic use		H02
Thyroid therapy		H03
Anti-inflammatory and antirheumatic products		M01
Antimigraine medication		N02C
Anti-epileptics		N03A
Antipsychotics		N05A, excl. N05AB04
Antidepressants		N06A
Anti-asthmatics		R03
Category II	**Drugs for occasional and short time use**	**ATC-code**
Antispasmodic and anticholinergic agents and propulsives		A03, excl A03FA01
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents		A07
Antifungals for dermatological use		D01
Emollients and protectives		D02
Antibiotics and chemotherapeutics for dermatological use		D06
Anti-acne preparations		D10
Antibacterials for systemic use		J01
Analgesics and antipyretics		N02B
Anxiolytics		N05B
Hypnotics and sedatives		N05C
Antiparasitic products, insecticides and repellents		P
Antihistamines for systemic use		R06 excl. R06AD and R06AE
Ear, eye, nose and throat preparations		S02,S03, S01, R01, R02A, R05
Category III	**Pregnancy-related drugs**	**ATC-code**
Antacids		A02A
Anti-emetics		A03FA01, A04A, N05AB04, R06AD, R06AE
Laxatives		A06
Iron preparations		B03A
Folic acid and derivates		B03B
Gynaecological anti-infectives and antiseptics		G01
Gonadotropins and other ovulation stimulants		G03G

Table 2. Risk classification based on the Australian risk classification [15] and as used in this study.

Category	Description	Foetal risk classification in this study
A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.	safe
B	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage or have shown evidence of an increased occurrence of foetal damage, of which the significance is considered uncertain in humans.	undetermined
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.	potentially harmful
D / X	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.	harmful

RESULTS

The mean age at birth of the 5,412 mothers included was 29.6 years (range 15-49 years). During the 3-year study period, they received a total of 78,944 drugs, excluding contraceptives, of which 12,407 drugs were dispensed during pregnancy. Overall, 5,236 women (96.7%) received at least one prescription drug during the 3-year study period, and 4,280 women (79.1%) received at least one prescription drug during their pregnancy. Figure 1 presents per trimester the prescription rates for all drugs, excluding contraceptives. In the 2 years before pregnancy the prescription rate was constant, approximately 43 per 100 women. The average number of drugs per trimester among women prescribed drugs was 2.0 (range 1-17). The prescription rate increased from 43.6 per 100 women in the first trimester to 49.3 and 60.8 per 100 women in the 2nd and 3rd trimester of pregnancy. During pregnancy, the mean number of prescription drugs per trimester among women prescribed drugs was approximately the same as before pregnancy (1.9). During the 3-year study period 865 different drugs (based on ATC-code) were prescribed to our study population, while during the pregnancy period 470 different drugs were prescribed. The drugs categorised in table 1 accounted for 57.3% of all the different drugs prescribed and for 81.9% of all prescriptions during the 3-year study period. For the pregnancy period these percentages were 65.7% and 89.1% respectively.

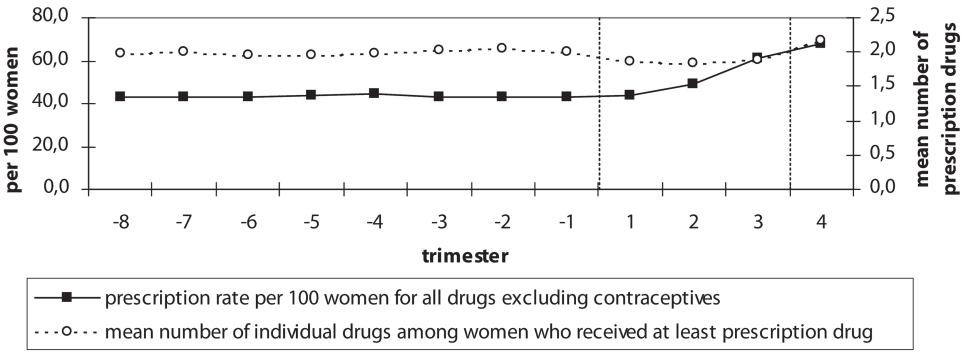

Figure 1. Prescription rate for all prescriptions and the mean number of drugs dispensed among women with at least one prescription.

Trimester –8 - –5 represents the 2nd year before pregnancy, trimester –4 - –1 represents the 1st year before pregnancy. The period between the dotted lines (trimester 1-3) is the pregnancy period and trimester 4 is the period after pregnancy.

A graphical reproduction of the prescription patterns for certain drug groups of the 3 categories is shown in figures 2, 3 and 4.

A clear decrease in prescription rate in pregnancy was seen for antidepressants and antipsychotics (N06A/N05A), antimigraine drugs (N02C; figure 2), anti-inflammatory and antirheumatic drugs (M01). The prescription rates for anti-epileptics (N03A; figure 2), anti-asthmatics (R03) were nearly constant during pregnancy. There seems to be an increase in prescription rate for insulins (A10; figure 2), but this was not statistically significant.

The prescription rates for drugs for occasional use generally showed a decrease during

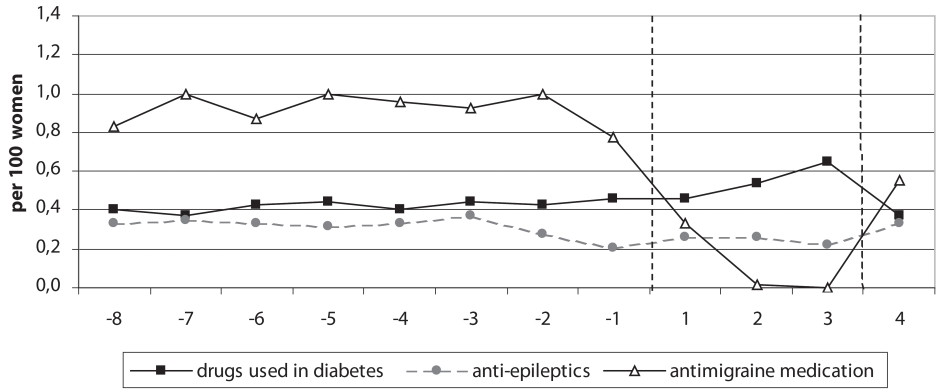

Figure 2. Prescription patterns for certain drugs for chronic conditions in the period from 2 years before pregnancy until 3 months after delivery.

The dots represent the prescription rate per trimester for the specific drug class. The period between dotted lines is the pregnancy period.

Categorisation of drug groups according to table 1: drugs used in diabetes (A10), antimigraine medication (N02C) and anti-epileptics (N03A).

pregnancy followed by an increase after delivery. For antibiotics (J01; figure 3) there was a decrease in prescription rate in the first trimester in pregnancy, but an increasing pattern in the second and third trimester. For antispasmodic and anticholinergic agents (A03) and for antihistamines for systemic use (R06) there was a decrease in prescription rate during pregnancy. For analgesics (N02B, figure 3), hypnotics and anxiolytics (N05C/N05B) and for ear, eye, nose and throat preparations (S02,S03,S01,R01,R02A,R05; figure 3) there was a decreasing trend during the 3-year period, but constant rates during pregnancy.

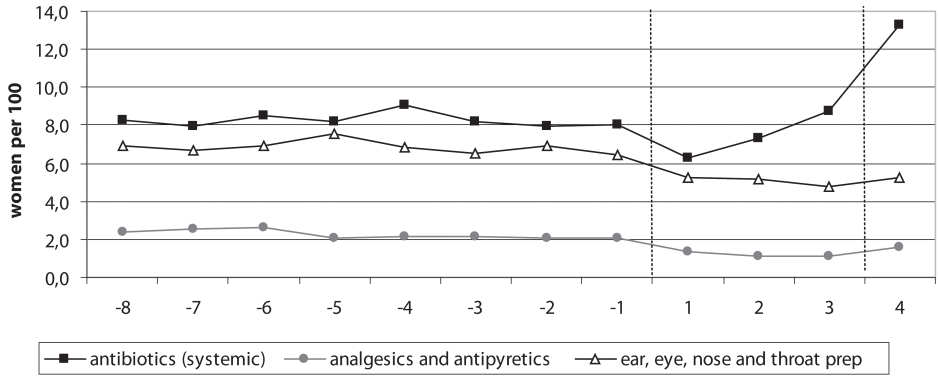

Figure 3. Prescription patterns for certain drugs for occasional and short time use in the period from 2 years before pregnancy until 3 months after delivery.

The dots represent the prescription rate per trimester for the specific drug class. The period between dotted lines is the pregnancy period.

Categorisation of drug groups according to table 1: antibacterials for systemic use (J01), analgesics and antipyretics (N02B) and ear, eye, nose and throat preparations (S02, S03, S01, R01, R02A, R05)

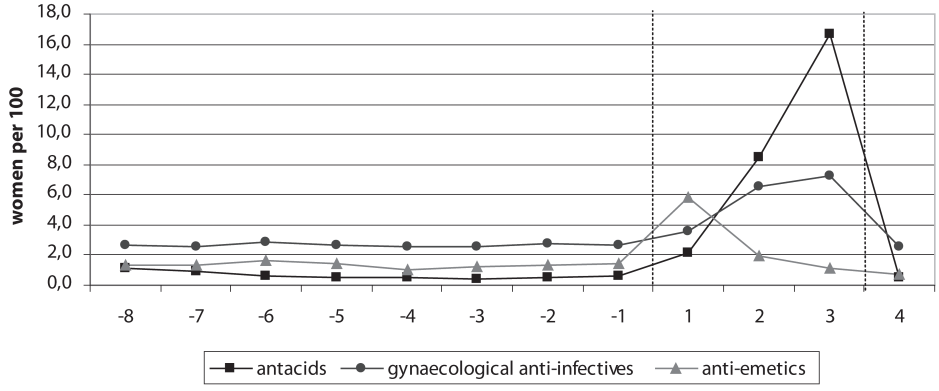

Figure 4. Prescription patterns for certain drugs for pregnancy-related symptoms in the period from 2 years before pregnancy until 3 months after delivery.

The dots represent the prescription rate per trimester for the specific drug class. The period between dotted lines is the pregnancy period.

Categorisation of drug groups according to table 1: antacids (A02A), gynaecological anti-infectives and antiseptics (G01) and anti-emetics (A03FA01, A04A, N05AB04, R06AD and R06AE)

As expected, the prescription patterns for drugs for pregnancy-related symptoms showed an increase during pregnancy. For folic acid and derivates (B03B), and for anti-emetics (A03FA01, A04A, R06AD, R06AE; figure 4) the highest rates can be seen in the first trimester. Iron-preparations (B03A), antacids (A02A; figure 4) and gynaecological anti-infectives (G01; figure 4) were most prescribed in the second and third trimester in pregnancy. The prescription of laxatives (A06) was highest after pregnancy. Ovulation stimulants (G03G) were most prescribed before pregnancy with a prescription rate of 4.2 per 100 women.

Figures 5, 6 and 7 show the distribution of the foetal risk classification of the prescribed drugs. In these figures we included only the drugs that were ordered in the three categories according to table 1. As previously described, there was a clear decrease in the total number of prescribed drugs for chronic conditions (figure 5) and for occasional and short time use (figure 6) during pregnancy. This decrease was in contrast with the number of prescribed drugs for pregnancy-related symptoms, which showed a large increase during pregnancy, as shown in figure 7. When taking all categories together, 81.7% of all drugs prescribed during pregnancy, were classified as A, 10.9% as B, 6.3% as C and 1.1% as D or X. For the drugs prescribed during the first trimester these percentages were 70.9, 16.5, 10.2 and 2.4 respectively. However, when we look at the distribution of the prescribed drugs per category (chronic, occasional or pregnancy-related), large differences are observed.

In the first trimester, only 50.4% of the prescribed drugs for chronic diseases were considered safe (A), 30.8% were potentially harmful (C) and 1.7% were classified as harmful (D or X). During pregnancy the proportion of class A drugs increased to 67% in the third

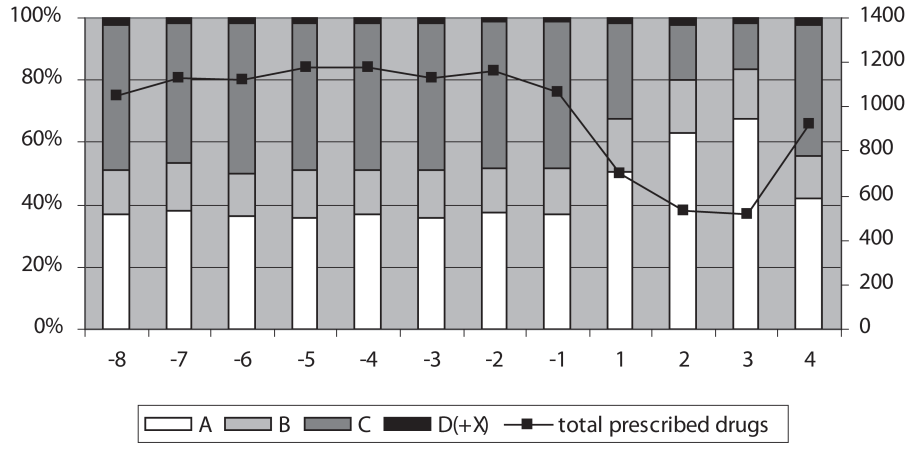

Figure 5. Total number of prescription drugs for chronic conditions* per trimester, and the distribution of these drugs according to the pregnancy risk classification.

* Only the prescribed drugs that were categorised as drugs for chronic conditions, as presented in table 1, were counted.

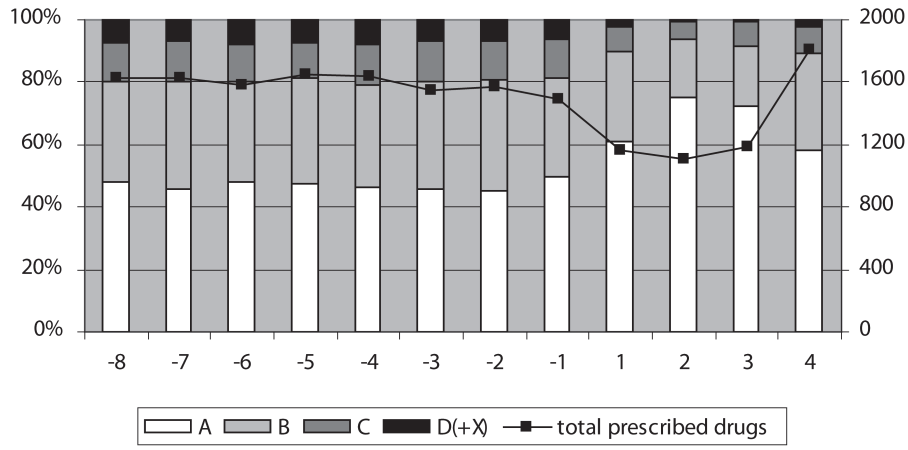

Figure 6. Total number of prescription drugs for occasional and short time use* per trimester, and the distribution of these drugs according to the pregnancy risk classification.

* Only the prescribed drugs that were categorised as drugs for occasional and short time use, as presented in table 1, were counted.

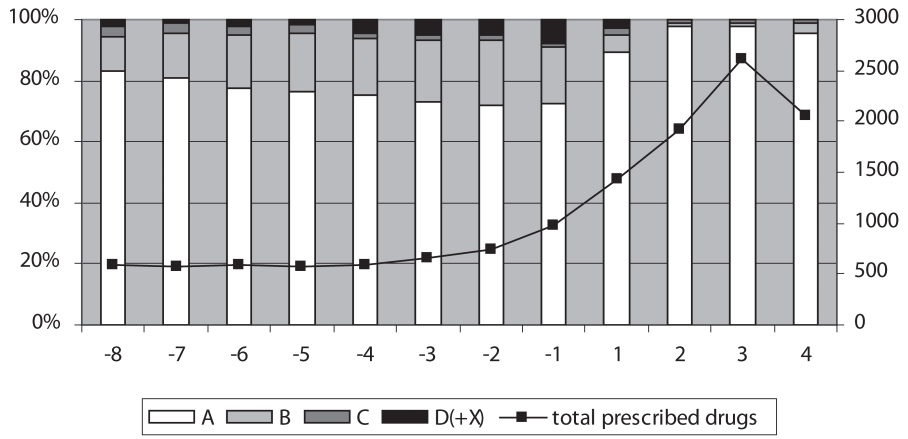

Figure 7. Total number of prescription drugs for pregnancy-related symptoms* per trimester, and the distribution of these drugs according to the pregnancy risk classification.

* Only the prescribed drugs that were categorised as drugs for pregnancy related symptoms, as presented in table 1, were counted.

trimester and the proportion of drugs classified as C decreased to less than 15%. The proportion of harmful drugs was constant (1.9% in the third trimester). After pregnancy, the proportion of potentially harmful and harmful drugs increased to 45%. When we look at the prescribed drugs for occasional and short time use, 60.8% of the drugs in the 1st trimester were classified as safe, 7.8 % as potentially harmful and 2.3% as harmful. During pregnancy the proportion of drugs classified as A increased to over 70% in the second and

third trimester. The proportion of harmful drugs decreased to 0.4% in the third trimester. The majority of the drugs prescribed for pregnancy-related symptoms in the 1st trimester was classified as safe, 2.1% as potentially harmful and 2.9% as harmful. In the second and third trimester of pregnancy, 97.6% of the drugs prescribed for pregnancy-related symptoms were classified as A, 1.0 % as C and 0.2% as D or X.

DISCUSSION

A clear change in drug prescription patterns is visible among pregnant women in the Netherlands. Drugs for chronic conditions and for occasional and short time use were prescribed less during pregnancy, while at the same time an increased prescribing of drugs for pregnancy-related symptoms was seen. For all three categories the proportion of drugs classified as safe increased during pregnancy compared with the period before and after pregnancy.

The prescription rate covering the 3-year study period was very high with 97 per 100 women receiving at least 1 prescription drug. The high prescription rate may reflect the origin of our study population. To be included in the prescription database, a person had to purchase at least one prescription at a participating pharmacy since 1994. In our population, the prescription rate during pregnancy, including vitamins and iron, was 79%. This percentage is somewhat higher than found in a Dutch cohort of women with a low-risk pregnancy (76.5% of the women attending a gynaecologist used medications during pregnancy and 57.4% of the women attending a midwife), but in the latter study iron-supplements were excluded.[16] The prescription rate in this study is high compared to register based studies in Denmark (44.2%, excluding iron and vitamins)[1], Finland (46.2%)[17] and the United states (64% excluding vitamins and minerals).[18] Higher prescription rates during pregnancy were found in the Southwest of France (99%, including iron and vitamins)[2] and in Germany (96.4% including and 85.2% excluding vitamins).[4] Several explanations can be given for the differences in prescription rates. The Danish study used a database which did not include prescribed drugs that were not refunded, such as benzodiazepines, many analgesics and antacids, explaining the lower prescription rates. Cultural prescribing differences might play also a role in these variations.

Except for drugs used in diabetes, most drugs for chronic conditions were prescribed less during pregnancy. In the trimester after pregnancy the prescription rate increased, but not to the pre-pregnancy level. Low prescription rates shortly after pregnancy are most likely a result of breastfeeding. For some drugs, such as antidepressants and antipsychotics and anti-epileptics, the decrease in prescription rate started before pregnancy. This decrease may indicate precautionary measures by women planning pregnancy, as the safety of these drugs is not established. Several studies have associated the use of

antidepressants with adverse pregnancy outcomes such as spontaneous abortions, low birth weight and gestational age.[19;20] From our data it is not possible to infer whether the decreases are physician or woman driven. As the indication for prescription is not known the possible adverse effects of stopping some of these medications is not known. The prescription rate of antimigraine medication decreased in the second and third trimester of pregnancy which might be a consequence of less migraine attacks during pregnancy, or the use of other analgesics such as paracetamol. Anti-inflammatory and antirheumatic drugs were also rarely prescribed in pregnancy: the use of these drugs is contra-indicated in pregnancy and, moreover, rheumatic disease activity improves in most patients during pregnancy.[21]

The prescription of most drugs for occasional and short time use decreased during pregnancy. The increase in the prescriptions for antibiotics in the second and third trimester can be explained by urinary tract infections, a complication in pregnancy for which treatment is recommended. The high prescription rate of antibiotics after pregnancy is most likely caused by infections of the breast and uterus. Because antibiotics are also frequently prescribed outside pregnancy, we decided to categorise antibiotics as drugs for occasional and short time use.

The proportion of class A drugs prescribed during pregnancy is somewhat lower than the proportion found in an other study conducted with the IADB (81.7% vs. 86%).[6] This difference can be explained because we restricted our analysis to the drugs that were ordered into the three categories (65.7% of all drugs). In the previous study of the IADB all drugs were included. The proportion of category A drugs in our study is much higher than found in a Danish study where 40.9% of al prescriptions during pregnancy were classified as safe (A).[22] We found that 2.4 % of all drugs prescribed in the 1st trimester were harmful drugs. The harmful drugs prescribed in the 1st trimester for pregnancy-related symptoms were ovulation-stimulating drugs and for chronic conditions were anti-epileptics. Doxycycline, a tetracycline antibiotic, was responsible for the high percentage of harmful drugs for occasional use in the first trimester. Doxycycline may affect the bone and tooth development of the developing foetus and is therefore contra-indicated in pregnancy.

The strength of our study was that for all women included in this study, complete data was available on drugs prescribed in the period from 2 years before pregnancy until 3 months after delivery. Because we applied a cohort design comparing the prescription rates during pregnancy with the prescription rates before pregnancy in the same population, selection bias is minimised. Some drug utilisation studies compare drug use among pregnant women to drug use among non-pregnant women of comparable age. This might introduce bias, since factors related to pregnancy and drug use might be disproportionately present in the two groups. A Finnish study showed that more non-pregnant women had a chronic disease such as epilepsy, rheumatoid diseases, diabetes,

hypertension, ulcerative colitis and psychotic and mental disorders when compared with pregnant women of comparable age.[17]

By distinguishing drugs based on their indication, we could demonstrate that the increase in prescription rate during pregnancy is caused by an enhanced prescribing of drugs for pregnancy-related symptoms. Most other drug utilisation studies which look into drug use patterns among pregnant women make no distinction between the indications for drug use.

Although our study was conducted with data from a population-based prescription database, only women with a live born child are included. Women with a spontaneous or induced abortion and women whose pregnancy resulted in a still birth or whose child did not survive until the first prescription were not included.

Since we have no information on the actual length of the gestation period, the time of conception was estimated as 273 days (39 weeks) before birth. The use of a standard gestational period, mostly 270 days, is common in studies using administrative data.[4;17;18] A recent study, comparing administrative data and data from a birth registry, showed that gestational age assumptions can result in a small proportion of misclassification. The extent of potential drug exposure misclassification was larger for category X drugs in the first trimester of pregnancy.[23] We believe that administrative datasets with estimated gestational age can be useful in research on prescription of drugs during pregnancy. However, in studies evaluating the risk of drugs on birth outcome, precise timing of drug exposure is essential and then administrative datasets alone are insufficient.

In our study ovulation-inducing drugs were prescribed in the first trimester of pregnancy, an indication that misclassification has occurred. Prescription of other harmful drugs in the first trimester can also be explained by unawareness of the pregnancy. Although almost 80% of the pregnancies in the Netherlands are planned, a woman mostly does not recognise her pregnancy until the third week after conception.

The prescription rate as defined in this study reflects the prescribing behaviour of physicians and can not be translated directly into exposure rates. Drugs prescribed for a longer period of time, can lead to an underestimation of exposure in the subsequent trimesters. Also, particularly in pregnancy, prescribed drugs are not always taken, leading to overestimation of drug exposure. In a Danish study, only 43% of all drugs dispensed to pregnant women were reported to be taken. Compliance was high for drugs used in chronic diseases, but low for drugs used for local or short-time treatment.[24] Furthermore, the prescription database does not include drugs administered in hospitals and OTC drugs. For some drugs underestimation of exposure may be considerable. The prescription rate of analgesics and antipyretics, for instance, is very low with approximately 1.5 per 100 women during pregnancy. The number of women who used analgesics during pregnancy is probably much higher, because analgesics are freely available in the Netherlands. In a

recent study in the United States where data on maternal drug use was evaluated from 2 case-control studies of birth defects, at least 65% of the women took paracetamol at some point during pregnancy.[25] Other pregnancy-related drugs such as antacids, laxatives, folic acid and some anti-emetics are also available as OTC drugs in the Netherlands.

Although not all drugs prescribed to the study population were ordered into the 3 categories, we believe that this study is representative for drugs prescribed to pregnant women. The drugs included in the 3 categories accounted for almost 90% of all prescriptions in the pregnancy-period. Drugs not included in the analyses were rarely prescribed.

The use of population-based prescription databases is an important tool to monitor the use of drugs among pregnant women to identify problems. In addition, this individual-level exposure data can serve as a reference for future risk assessment studies and provide relevant information for education programmes of health professionals as well as for prevention. Although drug use during pregnancy is mostly studied in relation to the occurrence of congenital anomalies at birth, other adverse long-term effects in the offspring, such as developmental delay, may also be associated with maternal drug use in the 2nd and 3rd trimester. In a cohort study in the Southwest of England, frequent paracetamol use in late pregnancy was associated with an increased risk of wheezing in the offspring at 30-42 months.[26] If maternal drug use can be linked to the prescription of drugs to their children, prescription databases may also be used to screen for certain long-term drug effects.

In conclusion, this register-based study shows that the majority of the Dutch women use drugs during pregnancy. The increase in prescription rate during pregnancy is caused by an increase in prescription rate for drugs used for pregnancy-related symptoms whereas the prescription rate for drugs for chronic diseases and for occasional and short time use declines during pregnancy. Also, the prescription of harmful drugs decreases during pregnancy. However, 2.3% of all drugs prescribed for occasional and short time use in the 1st trimester was classified as harmful. Therefore, the results of this study argue in favour for a cautious prescribing of drugs to healthy women in the fertile age, in which the prescription of harmful drugs should be avoided as much as possible.

Acknowledgements

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Appendix

Prescription rate per 100 women per trimester* and the results of the Chi2 test for trend for all drugs and for the drugs ordered into the three categories.

	Trimester												Chi2 test for trend					
													total period			pregnancy		
	-8	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	X2	p	slope	X2	p	slope
All drugs	43.0	43.4	43.3	44.0	44.2	43.0	43.2	43.3	43.6	49.3	60.8	68.0	873.218	0.000	/	320.495	0.000	/
Drugs for chronic diseases																		
Drugs used in diabetes (A10)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.4	2.126	0.145		1.695	0.193	
Corticosteroids, dermatological (D07)	4.7	5.1	4.7	5.1	5.1	4.9	5.2	2.7	3.9	3.6	3.4	4.7	29.701	0.000	\	1.400	0.237	
Corticosteroids, systemic (H02)	0.8	0.7	0.8	0.8	0.8	0.7	0.9	0.7	0.4	0.4	0.4	0.6	14.823	0.000	\	0.000	1.000	
Thyroid therapy (H03)	0.7	0.7	0.7	0.8	0.8	0.8	1.0	0.9	0.9	0.9	0.9	1.0	4.930	0.026	/	0.000	1.000	
Anti-inflammatory and antirheumatic drugs (M01)	6.2	6.4	7.1	7.2	7.4	7.1	7.4	6.7	2.2	0.7	0.3	5.0	407.643	0.000	\	86.643	0.000	\
Antimigraine medication (N02C)	0.8	1.0	0.9	1.0	1.0	0.9	1.0	0.8	0.3	0.0	0.0	0.6	72.332	0.000	\	25.607	0.000	\
Anti-epileptics (N03A)	0.3	0.4	0.3	0.3	0.3	0.4	0.3	0.2	0.3	0.3	0.2	0.3	1.844	0.174		0.150	0.698	
Antipsychotics and antidepressants (N05A, excl. N05AB04; N06A)	3.0	3.0	2.9	3.1	3.0	2.9	3.2	2.6	1.9	1.0	0.9	2.1	107.641	0.000	\	17.374	0.000	\
Anti-asthmatics (R03)	2.4	2.9	2.7	2.9	2.9	2.6	2.6	2.6	2.4	2.4	2.3	2.1	9.788	0.002	\	0.145	0.704	
Drugs for short time and occasional use																		
Antispasmodic and anticholinergic agents and propulsives (A03, excl. A03FA01)	1.6	1.4	1.5	1.5	1.5	1.6	1.3	1.4	0.9	0.3	0.4	0.7	89.387	0.000	\	15.780	0.000	\
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents (A07)	0.6	0.7	0.7	0.7	0.7	0.6	0.7	0.6	0.6	0.5	0.6	1.9	16.933	0.000	/	0.017	0.897	
Antifungals for dermatological use (D01)	2.6	2.3	2.4	2.7	2.1	2.4	2.4	2.1	2.6	2.9	3.2	4.7	44.349	0.000	/	3.579	0.059	
Emollients and protectives (D02)	2.0	2.3	1.9	2.0	2.1	1.6	2.0	1.7	2.1	2.3	2.2	2.7	4.457	0.035	/	0.276	0.599	

	Trimester												Chi2 test for trend					
													total period			pregnancy		
	-8	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	X2	p	slope	X2	p	slope
Antibiotics and chemotherapeutics for dermatological use (D06)	1.3	1.4	1.1	1.1	1.0	1.0	1.0	1.0	0.8	0.7	0.6	1.2	16.963	0.000	\	0.644	0.422	
Anti-acne preparations (D10)	1.3	1.4	1.1	1.1	1.0	1.0	1.0	1.0	0.8	0.7	0.6	1.2	9.940	0.002	\	6.557	0.010	\
Antibacterials for systemic use (J01)	8.2	8.0	8.5	8.2	9.0	8.2	7.9	8.1	6.3	7.3	8.8	13.3	19.427	0.000	/	24.448	0.000	/
Analgesics and antipyretics (N02B)	2.4	2.5	2.7	2.1	2.1	2.1	2.0	2.1	1.4	1.1	1.1	1.6	69.431	0.000	\	1.743	0.187	
Anxiolytics, hypnotics and sedatives (N05B, N05C)	2.7	2.9	2.5	2.9	3.2	3.0	2.9	2.6	1.2	0.9	1.5	2.4	66.673	0.000	\	1.797	0.180	
Antiparasitic products, insecticides and repellents (P)	0.7	0.7	0.6	1.0	0.9	0.8	0.9	0.7	0.2	0.1	0.3	0.7	22.614	0.000	\	1.074	0.300	
Antihistamines for systemic use (R06, excl. R06AD and R06AE)	2.2	2.2	1.7	1.9	1.8	2.3	2.2	1.8	1.0	0.4	0.3	1.2	109.604	0.000	\	20.800	0.000	\
Ear, eye, nose and throat preparations (S02, S03, S01, R01, R02A, R05)	6.9	6.7	6.9	7.6	6.9	6.5	6.9	6.4	5.2	5.2	4.8	5.2	63.942	0.000	\	1.111	0.292	
Drugs for pregnancy related symptoms																		
Antacids (A02A)	1.1	0.9	0.6	0.5	0.5	0.4	0.5	0.6	2.1	8.5	16.7	0.5	1533.455	0.000	/	692.835	0.000	/
Anti-emetics (A03FA01, A04A, N05AB04, R06AD, R06AE)	1.3	1.4	1.6	1.4	1.0	1.3	1.3	1.4	5.8	2.0	1.1	0.8	24.677	0.000	/	208.959	0.000	\
Laxatives (A06)	1.5	1.8	1.3	1.3	1.3	1.5	1.2	1.5	2.4	2.9	2.8	6.9	334.565	0.000	/	2.018	0.155	
Iron preparations (B03A)	3.2	2.4	1.8	1.5	1.2	1.1	1.2	1.3	5.2	21.0	31.5	30.4	6638.584	0.000	/	1208.418	0.000	/
Folic acid and derivates (B03B)	1.2	1.5	1.6	2.0	2.4	3.1	4.1	6.1	8.6	3.5	4.7	5.2	460.647	0.000	/	79.302	0.000	\
Gynaecological anti-infectives and antiseptics (G01)	2.6	2.5	2.8	2.7	2.5	2.5	2.7	2.7	3.6	6.5	7.2	2.6	168.624	0.000	/	67.139	0.000	/
Gonadotropins and other ovulation stimulants (G03G)	0.9	1.0	1.3	1.5	1.9	2.5	2.8	4.2	2.4	0.1	0.1	0.0	25.649	0.000	\	168.553	0.000	\

Trimester -8 till -5 represents the 2nd year before pregnancy, trimester -4 till -1 represents the 1st year before pregnancy.
Trimester 1 - 3 is the pregnancy period and trimester 4 is the period after pregnancy.

Total number of prescription drugs per trimester*, and the distribution of these drugs according to the risk classification
Only the prescribed drugs that were categorised into drugs for chronic conditions, drugs for occasional use and drugs for pregnancy related symptoms were included.

	Trimester											
	-8	-7	-6	-5	-4	-3	-2	-1	1	2	3	4
Drugs for chronic diseases												
Total number of prescription drugs	1052	1133	1120	1174	1174	1131	1162	1062	701	536	520	919
Proportion (%) classified as												
A	36.7	38.0	36.2	35.7	36.8	35.9	37.5	36.7	50.4	62.9	67.5	41.8
B	14.5	15.5	14.0	15.5	14.3	15.5	14.1	15.2	17.1	17.4	16.0	13.7
C	46.7	44.5	48.0	47.1	47.4	46.8	47.0	47.1	30.8	17.5	14.6	42.3
D(+X)	2.1	1.9	1.8	1.7	1.4	1.9	1.4	1.0	1.7	2.2	1.9	2.2
Drugs for short time and occasional use												
Total number of prescription drugs	1632	1628	1587	1651	1636	1553	1573	1497	1166	1109	1186	1805
Proportion (%) classified as												
A	47.9	45.9	48.3	47.6	46.5	45.7	45.5	49.9	60.8	75.1	72.2	58.1
B	32.2	34.3	32.0	33.6	32.4	34.3	35.5	31.5	29.1	18.8	19.4	31.2
C	12.5	13.0	11.8	11.8	12.9	13.1	12.1	12.6	7.8	5.5	8.0	8.6
D(+X)	7.4	6.7	7.9	7.1	8.2	6.9	6.9	5.9	2.3	0.5	0.4	2.1
Drugs for pregnancy related symptoms												
Total number of prescription drugs	593	573	588	570	594	659	748	975	1433	1913	2612	2051
Proportion (%) classified as												
A	83.0	80.6	77.7	76.7	75.1	73.0	72.1	72.4	89.2	97.6	97.6	95.3
B	11.6	14.7	17.3	18.8	18.7	20.3	21.0	18.5	5.9	1.2	1.3	3.7
C	3.4	3.5	2.7	2.6	1.9	1.8	2.1	1.5	2.1	1.0	1.0	1.0
D(+X)	2.0	1.2	2.2	1.9	4.4	4.9	4.8	7.6	2.9	0.2	0.1	0.0

* Trimester -8 till -5 represents the 2nd year before pregnancy, trimester -4 till -1 represents the 1st year before pregnancy.
Trimester 1 - 3 is the pregnancy period and trimester 4 is the period after pregnancy.

CHAPTER 2.2

Drug utilisation studies

Increase in use of Selective Serotonin Re-uptake Inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands

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ABSTRACT

Objectives. Recent case-control studies suggest a relationship between the use of Selective Serotonin Re-uptake Inhibitors (SSRIs) and the occurrence of birth defects and other adverse pregnancy outcomes. We determined the extent of the use of selective serotonin reuptake inhibitors (SSRIs) before and during pregnancy and its trend over the years 1995-2004 in the Netherlands.

Methods. The study was performed with data from a population based prescription database. Within this database, women giving birth to a child between 1995-2004 were identified. The exposure rate and 95% confidence interval (CI) was calculated as the number of pregnancies per 1000 that were exposed to an SSRI in a defined period (per trimester or in the year preceding delivery). Exposure rates were calculated for 2-year periods: 1995/1996, 1997/1998, 1999/2000, 2001/2002 and 2003/2004. Trends in exposure rates were analysed using the X^2-test for trend.

Results. Included were 14,902 pregnancies for which complete pharmacy records were available from 3 months before pregnancy until delivery. A total of 310 pregnancies were exposed to an SSRI in the year preceding delivery. The exposure rate increased from 12.2 (95%CI: 7.0-19.8) in 1995/1996 to 28.5 (95%CI: 23.0-34.9) in 2003/2004.

Conclusion. There is a significant increase in the use of SSRIs among pregnant women in the Netherlands over the last 10 years, parallel with the increase in exposure in women of fertile age. In light of the recent warnings about the use of SSRIs in pregnancy, health care professionals should be careful in prescribing SSRIs to women planning a pregnancy.

INTRODUCTION

Occurrence of significant depressive symptoms and major depressive disorders are not uncommon in pregnant women. Prevalence rates vary between 7%[1] and 20%.[2] Since the introduction of Selective Serotonin Re-uptake Inhibitors (SSRIs) in the 1980s, the prevalent and incident use of SSRIs has increased over the use of tricyclic antidepressants (TCAs).[3] In several -mostly prospective- cohort studies on the use of SSRIs in pregnancy no increased risk was found of general major congenital malformations.[4-6] Other cohort studies found adverse pregnancy outcomes, such as a higher rate of spontaneous abortions[7], lower birth weight and shorter gestation[8] or an increased proportion of children with minor anomalies.[9] The use of SSRIs in pregnancy has also been associated with neonatal withdrawal syndrome[10] and with an increased risk of persistent pulmonary hypertension.[11] The results of recent case-control studies suggest that SSRIs are no major teratogens, but specific SSRIs appear to modestly increase the risk of various specific (cardiac) malformations.[12-17]

Since clear data on the prevalence of SSRI use in pregnancy over the last decade is limited, we wanted to determine the extent of SSRI use in the trimester before pregnancy and during the different trimesters in pregnancy and to analyse the trend of its use over the years 1995-2004 based on data available for the Netherlands.

METHODS

For this study we used data from the Interaction Database (IADB.nl). The IADB.nl is a population-based prescription database which contains data from prescriptions dispensed from community pharmacies. It covers a population in the northern and eastern parts of the Netherlands. The database comprised data on approximately 220,000 people in 1994, and has gradually expanded to data on approximately 500,000 people in 1999. Registration occurs irrespective of health insurance and is considered representative for the general population. Each prescription record contains information on the name of the drug, the date of dispensing, the quantity dispensed, the dose-regimen and the prescribing physician. The indication for prescribing is not known. All the drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system.[18] Each patient has a unique identification-number and date of birth, sex and address-code are known. Since most patients restrict their visits to a single pharmacy, their medication records are virtually complete. The database does not include information on over-the-counter (OTC) medication and medications dispensed during hospitalisations.[19]

Within the IADB.nl a pregnancy database has been generated. To identify mothers, all children born after January 1st 1994 were selected. For each child within the IADB.nl,

the female person, 15-50 years older than the child and with the same address-code is considered to be the mother, providing there are no other female persons in that age-category with the same address-code. Validation of this method is described in detail by Schirm et al.[20] Using this method, for 35% of the children the mother could not be identified, because the mother has a separate address-code, or because the mother is registered with another pharmacy. Since the major reason for not identifying the mother is not the lack of pharmacy registration, selection bias towards drug using families seems to be limited.

Because the actual length of the pregnancy is unknown, the theoretical conception date was determined as the date of birth minus 273 days. The length of the pregnancy is therefore standardised at 39 weeks, which can be divided in 3 trimesters of 13 weeks.

From this pregnancy database we selected all mothers between 15-49 years of age, who gave birth to a child between 1995 and 2004 and for which complete data was available on the year preceding delivery (13 weeks before the theoretical conception date until delivery). The 13 weeks before the conception will be referred to as trimester 0 and the trimesters in pregnancy as trimester 1, 2 and 3.

Prescriptions for SSRIs were identified by ATC-codes starting with N06AB. The theoretical period of use was calculated for each prescription for SSRIs, based on the date of dispensing, the quantity dispensed and the dose regimen. The exposure rate was then calculated as the number of pregnancies per 1000 pregnancies that were in theory exposed to an SSRI in a defined period: women who received a prescription in one trimester which was extended into the next trimester were counted in both trimesters in which they had access to the drug. Exposure rates were calculated for 2-year periods: 1995/1996, 1997/1998, 1999/2000, 2001/2002 and 2003/2004.

To compare the exposure rates in the pregnant population with the exposure rates in the general population of women of fertile age (15-49 years) the age-standardised one-year exposure rates in women of fertile age were also calculated using the 5-year age distribution among the pregnant women. The age-standardised one-year exposure rates were averaged over the 2-year periods. The rate ratio was calculated as the age-standardised one-year exposure rate to the pregnancy exposure rate.

The calculation of exposure rates per trimester does not give insight in the patterns of use for individual women. If drugs are prescribed for short time use, then it is in theory possible that for each trimester the exposed pregnancies occur with new users. To study possible changes in the patterns of use in pregnancy we distinguished the following groups: 1/ women who used SSRIs before pregnancy only, 2/ women who used SSRIs before and continued use in pregnancy and 3/ women who started use of SSRIs in pregnancy. Patterns of SSRI-use were analysed with respect to two time-frames: birth years 1995-1999 and 2000-2004.

The defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults. Between the birth years 1995-1999 and 2000-2004, we compared the total DDDs prescribed in the year preceding delivery, the total number of days of the prescription(s) and the average DDD calculated as the total DDDs prescribed, divided by the total number of days of the prescription(s) and categorized as <= 1 DDD and >1 DDD.

Trends in exposure rates over 2-year periods were analysed in SPSS 12.0 for Windows (Chicago, USA) using the X^2 test for trend. Continuous data were analysed using the T-test for 2 groups and one-way Anova for >2 groups. The total DDDs prescribed and the total number of days of the prescriptions were analysed using the Mann-Whitney U test. Proportions were compared using the X^2 test. The 95% confidence interval (CI) for the exposure rates was calculated using the Score method with continuity correction for small proportions.[21]

RESULTS

Within our population 14,902 pregnancies occurring to 10,897 women could be identified between 1995-2004. For 7,432 women (68%) 1 pregnancy was identified in the period 1995-2004 and for 3,465 women (32%) 2 or more pregnancies. The maximum number of pregnancies of one woman was 6. The mean maternal age at birth was 29.9 (SD: 4.5). The mean maternal age at birth differed significantly between the birth years (p=0.000), from 29.2 (SD: 4.3) in 1995/1996 till 30.1 (SD: 4.6) in 2001/2002.

In the year preceding delivery, 455 out of 14,902 pregnancies (3.1%) were exposed to an antidepressant (ATC-code: N06A). The mean age at birth of the women who used an antidepressant in this period was 30.4 (SD: 5.0) and 29.9 (SD:4.5) for women who did not use an antidepressant before or during pregnancy (p=0.043).

Exposure to an SSRI (N06AB) in trimester 0-3 occurred in 310 pregnancies (2.1%) with 292 women: 274 women with 1 exposed pregnancy and 18 women with 2 exposed pregnancies. In the 10-year period, paroxetine was the most commonly used SSRI (n=180, 58.1%), followed by fluoxetine (n=67, 21.6%) and fluvoxamine (n=39, 12.6%). Citalopram and sertraline were the least used SSRIs with 8.4% (n=26) and 3.5% (n=11). Among the exposed pregnancies, the use of paroxetine increased from 37.5% (6 / 16 pregnancies) in 1995/1996 to 60.4% in 2003/2004 (55 / 91 pregnancies), whereas the use of fluoxetine and fluvoxamine decreased from 37.5% (6 / 16) resp. 31.3% (5 / 16) in 1995/1996 to 19.8% (18 / 91) resp. 5.5% (5 / 91) in 2003/2004. In 13 pregnancies more than 1 type of SSRI was used in trimester 0-3 (subsequently). The 2 most prevalent combinations were paroxetine and fluoxetine (5 pregnancies) and paroxetine and fluvoxamine (4 pregnancies).

In figure 1 exposure rates for SSRIs per trimester are shown per 2-year periods. The

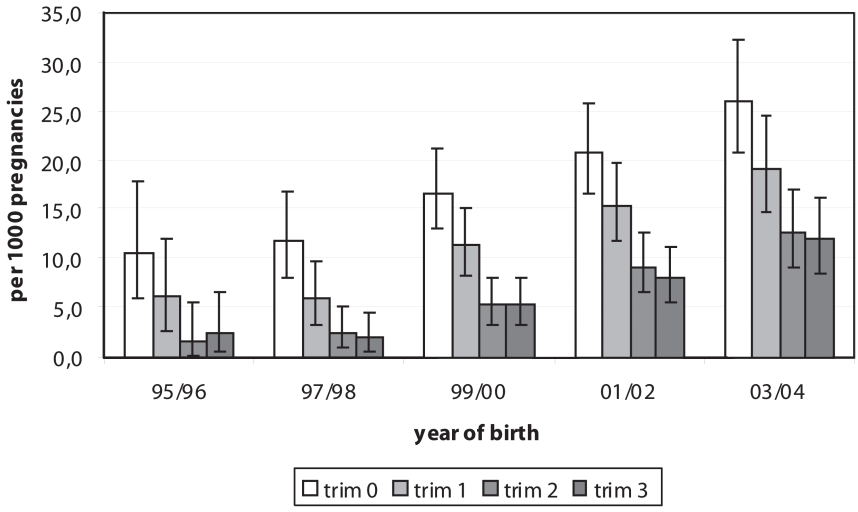

Figure 1. Exposure rate (and 95% confidence interval) for SSRIs per trimester per 1000 pregnancies per 2-year periods in a cohort of 14,902 pregnancies in the Netherlands.

pattern of use within period 0-3 is similar for all 2-year periods. The use of SSRIs is highest in the trimester before the conception, decreases in the first trimester and further in the second trimester. The use of SSRIs in the third trimester is comparable with the use in the second trimester. The decrease in use over period 0-3 is statistically significant for all 2-year periods (1995/1996: X^2 for trend=11.323, p=0.001; 1997/1998: X^2 for trend=25.337, p=0.000; 1999/2000: X^2 for trend=33.368, p=0.000; 2001/2002: X^2 for trend=29.503, p=0.000; 1995/1996: X^2 for trend=21.989, p=0.000). The use of SSRIs showed an significantly increasing trend over time for each of the trimesters (Trimester 0: X^2 for trend=21.936, p=0.000, Trimester 1: X^2 for trend=26.038, p=0.000; Trimester 2: X^2 for trend=30.776, p=0.000; Trimester 3: X^2 for trend=26.186, p=0.000).

In figure 2 the exposure rate for any use of an SSRI in the year preceding delivery per 2-year periods is presented. The exposure rate increased from 12.2 (95% CI: 7.0-19.8) per 1000 pregnancies in 1995/1996 to 28.5 (95% CI: 23.0-34.9) per 1000 pregnancies in 2003/2004. This increase runs parallel with the increase in use in the general population of women between 15 and 49 years of age. The age-standardised one-year exposure rate (averaged over 2-year periods) in this population increased from 36.8 per 1000 in 1995/1996 to 75.7 per 1000 in 2003/2004. The rate ratio was 3.0, 4.0, 3.6, 3.2 and 2.7 for the respective 2-year periods. Between 1995 and 2004, the pregnancy rate in women between 15 and 49 years of age was 13.1 per 1000 person years.

Among the women who used SSRIs in the year preceding delivery (n=310), 90.0% of the pregnancies were exposed to SSRIs only (including combinations of SSRIs). In 10.0%, both SSRIs and other types of antidepressants were used. In table 1 the pattern

Table 1. Pattern of use of SSRIs and average DDD[1] in 1995-1999 and 2000-2004 for pregnancies exposed to an SSRI in period from 3 months before conception until delivery.

	total		1995-1999		2000-2004		p
	N=310	*(100%)*	N=90	*(100%)*	N=220	*(100%)*	
Use before pregnancy	274	*88.4*	81	*90.0*	193	*87.7*	
Use discontinued before theoretical conception date	105	*38.3*	39	*48.1*	66	*34.2*	0.03
Use continued in pregnancy	169	*61.7*	42	*51.9*	127	*65.8*	
Start use in pregnancy	36	*11.6*	9	*10.0*	27	*12.3*	
Average DDD prescribed							
<= 1DDD	229	*73.9*	69	*76.7*	160	*72.7*	0.474
> 1DDD	81	*26.1*	21	*23.3*	60	*27.3*	

[1] SSRI denotes Selective Serotonin Reuptake Inhibitors. DDD denotes Defined Daily Dose. SSRIs include paroxetine (ATC: N06AB05; DDD:20mg), fluoxetine (ATC: N06AB03; DDD: 20mg), fluvoxamine (ATC: N06AB08; DDD: 100mg) citalopram (ATC: N06AB04; DDD: 20mg) and sertraline (ATC: N06AB06; DDD: 50mg).

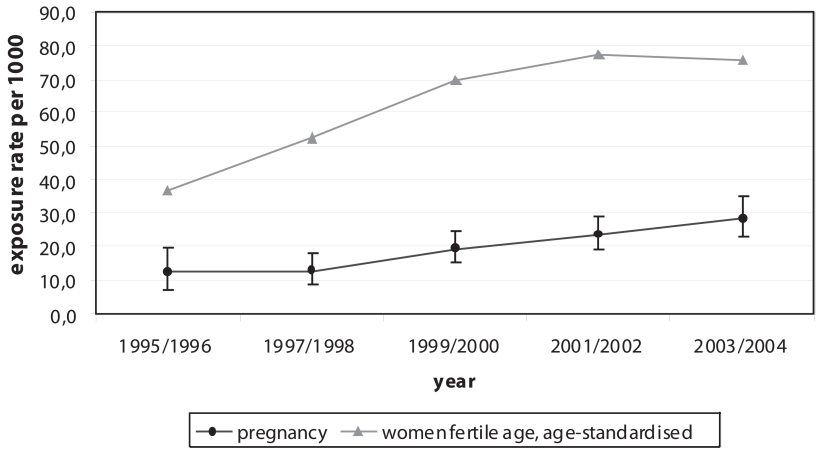

Figure 2. Average exposure rate per 2-year periods for any use of SSRIs in year preceding delivery (including 95% confidence interval), compared to the average age–standardised one-year exposure-rate per 2-year periods for women in the fertile age (15-49 years)

of SSRI-use for pregnancies exposed to SSRIs in the year preceding delivery is presented. Only in 11.6% of the exposed pregnancies the use of SSRIs started in pregnancy. This percentage did not differ between 1995-1999 and 2000-2004. However, when we look at the pregnancies in which an SSRI was already used before pregnancy, we see that in the more recent time period continuation of SSRI use in pregnancy was more prevalent, with 65.8% versus 51.9% in the earlier period (p=0.03). When these analyses were restricted to those pregnancies in which SSRIs were already used before pregnancy and no other types

of antidepressants were used (n=253), the results were comparable (65.9% vs 51.9%).

In 2000-2004 the length of use of SSRIs and the total DDDs prescribed was significant higher than in 1995-1999 (median number of days: 99.5 vs 64, p=0.008; median total DDDs: 111.5 vs 67.5; p=0.009). The average DDD (average daily dose) in the year preceding delivery varied between 0.3 and 4.0 and 191 women (61.6%) received an average DDD of 1. The proportion of women who received an average DDD <= 1 did not differ between 1995-1999 and 2000-2004 with 76.7% and 72.7% respectively (table 2, p=0.474).

DISCUSSION

The results of this observational study show that there is a significant increase in the use of SSRIs during pregnancy in the Netherlands over the last 10 years. The increase in use is present in all trimesters before and during pregnancy and runs parallel with the increase in use of SSRIs in women of fertile age. In addition, in the recent years continued use of SSRIs from before pregnancy into the 1st trimester is more frequent along with an increase in the length of use and the total DDDs prescribed. The average daily dose prescribed did not change. The most commonly prescribed SSRI over the whole study period is paroxetine.

To our knowledge, this study is the first to examine trends in use of SSRIs before and during pregnancy over a 10 year period. The validity of the exposure rates for use of SSRIs in the year preceding delivery is equivalent to the age-standardised one-year exposure rates in women of fertile age, since both data derive from the same source-population. We did not adjust for multiple pregnancies per woman, because we wanted to conduct an observational study in which we considered each pregnancy as an independent event.

The use of a population-based prescription database is an important tool in monitoring the use of drugs among pregnant women. The data is recorded prospectively and covers prescriptions from different prescribers. The IADB.nl was gradually expanded between 1994 and 1999 by including pharmacies from geographical areas that were not covered before. The pharmacies that were added to the IADB.nl were representative for the north-eastern region. When we calculated the average exposure rates per 2 year periods for any use of SSRIs in the year preceding delivery restricted to those pharmacies that participated in the IADB.nl in the first 2 years (1994 and 1995), the results were comparable to the exposure rates found in table 2. The results of this study will therefore not likely be influenced by the expansion of the database.

There are several limitations in using an administrative prescription-database such as the unknown actual use and the standardised length of pregnancy. Since the actual use is unknown, the exposure rates found in this study are an estimation. The use of SSRIs in pregnancy may be an overestimation if women stop taking their medication

when they plan to become pregnant or when they discover they are pregnant. Also, because the length of the pregnancy was standardised at 39 weeks, misclassification of exposure is possible. The use of SSRIs in the 1st trimester could be an overestimation if use in pregnancy is associated with preterm birth. From the literature it is not clear if there is a relation between the use of SSRIs and preterm birth. Some studies have found an association between the use of SSRIs and preterm birth[9;22], whereas others did not.[8;23] However, definitions of exposure and preterm birth differed between these studies.

Also, the methodology used to identify mothers and pregnancies has its limitations. We were able to identify approximately 65% of the mothers for children included in the IADB.nl. Since the validated method has a sensitivity of 99%[20], it is not to be expected that non-pregnant women were misclassified as being pregnant. Failure to identify a pregnancy when the child is known can mostly be attributed to administrative reasons and selection towards drug using families seems therefore limited. The detection rate may be improved using less strict criteria. On the other hand, this would most likely lead to a loss of sensitivity, which we find not desirable. Additionally, pregnancies are not identified if they resulted in a spontaneous or induced abortion, a still birth or an early neonatal death or if the child is not (yet) registered with a pharmacy. A Dutch study on drug use in children, using pharmacy dispensing data from the IADB.nl showed that approximately 80% of the children had used at least one prescription drug (and therefore were registered with a pharmacy) within the first 2 years of life.[24] Since it may take some time for a new born child to be registered with a pharmacy, the number of unidentified pregnancies may be larger in the most recent years than in previous years. This will most likely result in an underestimation of maternal drug use in most recent years.

The prevalence rates per trimester for use of SSRIs followed the same pattern as for antidepressants in general, found in a Dutch cohort of 29,005 women giving birth between January 2000 and July 2003.[25] In this study, the use of antidepressants decreased from 2.9% before pregnancy to 2.1% in the 1st trimester and 1.8% in the 2nd and 3rd trimester. Paroxetine was the most commonly used antidepressant (approximately 47% of all antidepressants used). Reefhuis et al.[26] found an prevalence of SSRI-use of 2.8% among a cohort of 4094 mothers who gave birth to a healthy child between October 1997 and December 2002. The data were obtained from a population-based case-control study of congenital anomalies, conducted in eight states in the USA. Self reported measures were used. That prevalence of use is comparable to the use (2.9%) in a matched control group consisting of mothers of a healthy child found in a study by Chambers et al.[11] and estimates from both studies were somewhat higher than in our study, which is 2.1%. The higher use can be explained by the fact that in general use of antidepressants is higher in the United States.

In the late 1990's a number of prospective cohort studies were published which did

not find an increased overall risk of major congenital malformations after the use of SSRIs in pregnancy.[4;6;9;27] However, most of these cohort studies lacked sufficient power to detect an increased risk of specific congenital malformations. Case-control studies have more statistical power to detect moderately increased risks for specific birth defects than cohort studies. They are more efficient in terms of sample size and time. Case-control studies are also sensitive to selection- and recall bias which can be minimized by the choice of an appropriate control group and the use of prospectively collected (pharmacy) data on prenatal medication use.

Since paroxetine is one the most commonly used SSRIs among pregnant women, sufficient data are now becoming available to detect these moderately increased risks for specific congenital malformations.[11-13] The safety of SSRIs which are less frequently used has not yet been established. It is very important that more data become available on the safety of the newer antidepressants. Case-control birth defects monitoring systems that include information on prenatal medication use might be helpful in providing these safety and risk estimates. As data accumulate, the risk estimates for these drugs will become more precise.[28]

The decision whether to use antidepressants in pregnancy should be taken after careful consideration of the benefits and risks for both mother and child. In some cases the benefits of treatment may well outweigh the teratogenic risks. Untreated depression in pregnancy appears to carry substantial perinatal risks, such as preterm birth, restricted foetal growth, preeclampsia, spontaneous abortions and delayed cognitive and emotional development. These adverse effects may be caused by psychopathological events which have physiological effects on the foetus. Depression may also lead to an unhealthy behaviour that can indirectly affect the outcome of the pregnancy.[29] Also, the results of a recent cohort study found that women who discontinued antidepressant medication close to conception experienced more frequently a relapse of major depression during pregnancy than women who maintained their medication.[30]

Recently, the American College of Obstetricians and Gynaecologists ("ACOG"), recommended that treatment with all SSRIs during pregnancy should be individualized and paroxetine use among pregnant women or women planning on becoming pregnant should be avoided, if possible women of fertile age who take SSRIs should be advised to consult a specialist before they get pregnant to develop a treatment plan regarding their condition and the use of SSRIs in which risks and benefits for mother and child are well-considered.[31] In the Netherlands, where 80% of the pregnancies are planned it should then be possible to avoid the unnecessary use of SSRIs in pregnancy as much as possible.

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CHAPTER 3

Selection of controls in case-control studies on maternal medication use and risk of birth defects

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ABSTRACT

Background. In case-control studies on teratogenic risks of maternal drug use during pregnancy, the use of normal or malformed controls may lead to recall-bias or selection bias. This can be avoided by using controls with a genetic disorder. However, researchers are hesitant to use these as controls because it is unknown whether their selection is independent of exposure status. The aim of this study is to investigate whether first trimester drug use among mothers of children with genetic disorders is representative for the 'general pregnant population'.

Methods. From a birth defects registry 565 mothers of infants with a genetic disorder born between 1998-2004 were selected (the 'genetic population'). The first trimester exposure rate was calculated for prescription-only drugs as the number of exposed women per 100. By calculating the rate ratio (RR) and 95% confidence interval (CI), the exposure rates in the 'genetic population' were compared with those in the 'source population' obtained from a population-based prescription database and consisting of 10,870 mothers who gave birth to a child between 1998-2004.

Results. The mean age at birth was 32.1 for the genetic population and 29.6 for the source population. (p=0.000). In the genetic population, a higher use was found for anti-migraine medication (RR=2.7, 95% CI=1.0-7.8) and for ovulation stimulants (RR=1.6; 95% CI=1.0-2.6). After adjustment for maternal age, the difference in use of ovulation stimulants disappeared.

Conclusions. Except for anti-migraine medication, first trimester drug use among mothers of infants with genetic disorders is representative for the general pregnant population.

INTRODUCTION

One of the major challenges in case-control studies on birth defects and maternal drug use is the choice of an appropriate control group. Cases are identified in a source population and then classified as exposed or not exposed. Principles for the selection of the control-group are: (1) they should be sampled from the same source population from which the cases come; (2) they should be sampled independently of exposure status as the control group is needed to determine the proportions of exposed and unexposed subjects in the source population.[1]

In case-control studies on birth defects and maternal drug use several types of controls are used. In some studies 'healthy' or 'normal' controls are used: infants with no apparent birth defect. The use of non-malformed controls allows for direct comparison between exposure of infants with the birth defect of interest and of non-malformed infants. The odds ratio (OR) gives an estimate of the relative risk. The use of non-malformed controls can lead to recall bias if mothers of infants with birth defects remember the use of drug in pregnancy better than mothers of non-malformed infants do. The OR will then be an overestimation. Recall bias may occur in particular for drugs used for only a short time period.[2]

Because non-malformed controls are not always available and in order to reduce the possibility of recall-bias, a number of studies have used as controls infants with a birth defect other than the malformation under study. A disadvantage of the use of these controls is that, if the relevant exposure also causes other malformations that are present in the controls too, it will cause teratogenicity non-specificity bias, also referred to as selection bias.[3;4] This will lead to an underestimation of the OR.

To avoid selection bias, infants and foetuses with a single gene or chromosomal disorder represent a third type of controls that are being used in case-control studies. This is done under the assumption that genetic conditions are unrelated to maternal drug use, because single gene disorders and chromosomal disorders have their origin before or just after conception. However, since mothers of infants with a genetic disorder represent a selective population, we do not know whether they are sampled from the source population (being all pregnant women in the same geographical area) independent of the exposure status. Therefore, investigators are hesitant to use this type of controls. The aim of the present study is to investigate whether first trimester exposure to prescription-only drugs in mothers of infants with genetic disorders can be considered a good estimate of first trimester exposure in the general pregnant population.

METHODS

For this study two datasets were used: the European Registration of Congenital Anomalies and Twins Northern Netherlands (Eurocat NNL) and the InterAction Database (IADB.nl).

Eurocat NNL

Eurocat NNL is a population-based birth defects registry in the northern part of the Netherlands. It was established in 1981. The registry monitors approximately 20,000 births per year. Children and foetuses with birth defects, including those associated with chromosomal and single gene disorders, are notified to the registry by physicians and midwives on a voluntary basis and after parental consent. Children and foetuses with congenital anomalies diagnosed before or after birth are eligible for registration at the Eurocat registry if the mother lived in the region at the time of birth and the child has not reached the age of 16 at notification. Spontaneous and induced abortions are also included. Since 1997, pharmacy data is routinely collected on drugs that were dispensed 3 months before the start of the pregnancy until delivery. The actual use of the dispensed drugs and of over-the-counter (OTC) drugs is verified in a telephone interview with the mother. The methodology has been described in detail elsewhere.[5] The drugs that were taken by the mother are coded using the Anatomical Therapeutical Chemical (ATC) classification system [6] and entered into the database.

To determine drug use in mothers giving birth to a child with a genetic condition, all infants and foetuses with a chromosomal anomaly or single gene disorder born between 1998 and 2004, were selected from the Eurocat database (reference date: August 1, 2006). Live births, still births, terminations of pregnancy for foetal anomalies and spontaneous abortions (foetal deaths less than 24 weeks of gestation) were included. All anomalies that were present in a foetus or child had to be associated with the chromosomal or single gene disorder. Drug use in pregnancy had to be known. Only the first registered pregnancy in the Eurocat database was included to exclude the influence of maternal disease. The selected population will be referred to as the 'genetic population'. For most cases in the Eurocat database the actual length of gestation is known, so that the start of the pregnancy can be determined as the date of the last menstrual period (LMP). The first trimester was determined as the first 13 weeks after LMP.

IADB.nl

The source population for the Eurocat database is all pregnant women in the northern part of the Netherlands. Drug use in this population can be determined using the IADB.nl, a population-based prescription database which contains data from prescriptions dispensed from a sample of community pharmacies in the same working area as Eurocat

NNL. The database comprised data on approximately 220,000 people in 1994 and has gradually expanded to data on approximately 500,000 people in 1999. Each prescription record contains information on the name of the drug, the ATC-code, the date of dispensing, the quantity dispensed, the dose regimen and the prescribing physician. The database does not have information on OTC-drugs and drugs dispensed during hospitalisations. Each patient has a unique identification number and date of birth, gender and address code are known. Within the IADB.nl a pregnancy database has been generated. For each child in the database, the female individual 15-50 years older than the child and with the same address code is considered to be the mother, provided that there is no other female in that age category with the same address code. With this methodology, 65% of the mothers could be identified. The methodology has been validated and described in detail elsewhere.[7] In the IADB-pregnancy database the length of the pregnancy is standardised at 39 weeks (273 days). The first trimester is determined as the first 13 weeks (91 days) of pregnancy.

From the IADB-pregnancy database we selected all mothers who gave birth between 1998 and 2004. Only the first registered pregnancy in this period was included to exclude the influence of maternal disease. This population will be referred to as the 'source population'.

Calculation of exposure rates

Both the Eurocat database and the IADB.nl use the ATC-classification system in which drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. To compare drugs use between the genetic and the source population, we selected (based on their therapeutic or pharmacological properties) a total of 15 drug groups that consists of prescription-only drugs which are frequently prescribed. Thus, the source of information on drug use was the same for both populations, i.e. pharmacy data. For the selected drug groups the exposure rate was calculated as the number of women per 100 that used a specific drug from the drug group in the first trimester. The 95% confidence interval (CI) for the exposure rates was calculated using the Score method with continuity correction for small proportions.[8] We chose to calculate first trimester exposure rates, because the first trimester is the most critical period for foetal development. Also, although induced and spontaneous abortions were included in the genetic population, the gestation period of most of these pregnancies will be at least 13 weeks.

Statistical analysis

Statistical analyses were performed in SPSS 12.0 for Windows (Chicago, USA). Because maternal age could be a confounding factor, we compared mean maternal age at birth

between the genetic population and the source population (using the T-test). In the source population, we also investigated which drug groups were associated with maternal age, using binary logistic regression. The rate ratio and 95% confidence interval (CI) was calculated as the ratio of the exposure rate among the genetic population compared to the exposure rate among the source population. For those drugs whose use was associated with maternal age, we calculated the rate ratio adjusted for maternal age.

RESULTS

In the Eurocat database, 3057 foetuses and infants born between 1998 and 2004 were registered. From this database, 661 foetuses and infants with a genetic disorder were selected, including 3 twin-pairs and 14 sibling-pairs. Only one pregnancy per mother was included, leaving a total of 644 pregnancies. After exclusion of 79 pregnancies because of missing information on first trimester drug use, the genetic population existed of 565 mothers who gave birth to a child with a genetic condition. Of these, 356 mothers (63.8%) gave birth to a child with a chromosomal disorder, of which trisomy 21 was the most prevalent disorder (n=182, 51.1%), followed by trisomy 18 (n=44, 12.4%), microdeletion syndromes (n=23, 6.5%) and trisomy 13 (n=14, 3.9%). A total of 229 mothers gave birth to a child with a single gene disorder.

Between 1998 and 2004 14,300 pregnancies were identified in 10,870 mothers in the IADB.nl. For each mother with two or more pregnancies in the defined period, the first pregnancy was included.

The mean age at birth was 32.1 (95% CI: 31.6-32.5) for the genetic population and 29.6 (95% CI: 29.5-29.7) for the source population. This age difference is significant (T-test, p=0.000). In the source population, all births are live births per definition. Included in the genetic population were 419 live births (74.2%), 21 spontaneous abortions (3.7%), 92 induced abortions (16.3%) and 33 still births (5.8%). For 5 pregnancies (0.9%) the gestation was less than 13 weeks (9 weeks, 1 pregnancy; 10 weeks, 1 pregnancy; and 12 weeks, 3 pregnancies). For another 4 pregnancies the actual length of gestation was unknown, but these pregnancies all resulted in live births. Therefore the gestation lasted at least 13 weeks.

In Table 1, the exposure rates for the specific drug groups are compared between the genetic population and the source population by calculating the rate ratio and 95% CI. The use of gonadotropins and other ovulation stimulants (G03G) and the use of antimigraine medication (N02C) appears to be higher in the genetic group than in the source population, although the difference is statistically borderline significant. There were no statistically significant differences in use for the other drug groups.

In the pregnancy database generated from the IADB.nl, maternal age was associated

Table 1. Number and first trimester exposure rate (in %) for specific drug groups for the genetic and the source population, 1998-2004.

	Genetic population			Source population				
Drug groups (ATC-code)	**N=565**	**%**	**95% CI**	**N=10870**	**%**	**95% CI**	**Rate Ratio**	**95%CI**
Antibacterials for systemic use (J01)	26	**4.6**	3.0 - 6.7	630	**5.8**	5.4 - 6.3	**0.8**	0.5 – 1.2
Antiemetics (A03FA01, A04A, N05AB04, R06AD, R06AE)	23	**4.1**	2.6 - 6.0	590	**5.4**	5.0 - 5.9	**0.7**	0.5 – 1.1
Gynaecological anti-infectives & antiseptics (G01)	23	**4.1**	2.6 - 6.0	418	**3.8**	3.5 - 4.2	**1.1**	0.7 - 1.6
Gonadotropins & other ovulatution stimulants (G03G)	19	**3.4**	2.0 - 5.2	223	**2.1**	1.8 - 2.3	**1.6**	1.0 - 2.6
Corticosteroids. dermatologic preparations (D07)	18	**3.2**	1.9 - 5.0	369	**3.4**	3.1 - 3.8	**0.9**	0.6 - 1.5
Anti-asmathics (R03)	13	**2.3**	1.2 - 3.9	226	**2.1**	1.8 - 2.4	**1.1**	0.6 - 1.9
Antipsychotics exc. prochlorperazine and antidepressants (N05A. excl. N05AB04; N06A)	12	**2.1**	1.1 - 3.7	171	**1.6**	1.4 - 1.8	**1.4**	0.8 - 2.4
Corticosteroids for systemic use (H02)	4	**0.7**	0.2 - 1.8	50	**0.5**	0.3 - 0.6	**1.5**	0.6 - 4.3
Antimigraine medication (N02C)	4	**0.7**	0.2 - 1.8	28	**0.3**	0.2 - 0.4	**2.7**	1.0 - 7.8
Antidiarrheals. intestinal and anti-inflammatory/anti-infective agents (A07)	4	**0.7**	0.2 - 1.8	56	**0.5**	0.4 - 0.7	**1.4**	0.5 - 3.8
Anxiolytics. hypnotics and sedatives (N05B. N05C)	4	**0.7**	0.2 - 1.8	137	**1.3**	1.1 - 1.5	**0.6**	0.2 - 1.5
Drug used in diabetes (A10)	3	**0.5**	0.1 - 1.5	32	**0.3**	0.2 - 0.4	**1.8**	0.6 - 5.9
Anti-epileptics (N03A)	3	**0.5**	0.1 - 1.5	28	**0.3**	0.2 - 0.4	**2.1**	0.6 - 6.8
Thyroid therapy (H03)	2	**0.4**	0.0 - 1.3	84	**0.8**	0.6 - 1	**0.5**	0.1 - 1.9
Antibiotics & chemotherapeuticals for dermatological use (D06)	1	**0.2**	0.0 - 1.0	82	**0.8**	0.6 - 0.9	**0.2**	0.03 - 1.7

Table 2. Number and first trimester exposure rate (in %) for specific drug groups for the genetic and the source population adjusted for maternal age, 1998-2004.

	<=30				>30					
	Genetic population		Source population		Genetic population		Source population			
Drug groups (ATC-code)	**n=231**	**%**	**n=6247**	**%**	**n=334**	**%**	**n=4623**	**%**	**Adjusted rate ratio**	**95% CI**
Antipsychotics exc. prochlorperazine and antidepressants (N05A. excl. N05AB04; N06A)	3	**1.3**	78	**1.2**	9	**2.7**	93	**2.0**	1.2	0.7 – 2.2
Thyroid therapy (H03)	2	**0.9**	30	**0.5**	0	**0.0**	54	**1.2**	0.4	0.1 – 1.6
Drugs used in diabetes (A10)	0	**0.0**	14	**0.2**	3	**0.9**	18	**0.4**	1.6	0.5 – 5.4
Anxiolytics. hypnotics and sedatives (N05B, N05C)	1	**0.4**	57	**0.9**	3	**0.9**	80	**1.7**	0.5	0.2 - 1.4
Gonadotropins and ovulation stim (G03G)	7	**3.0**	91	**1.5**	12	**3.6**	132	**2.9**	1.5	0.9 – 2.4
Antiemetics (A03FA01. A04A. N05AB04. R06AD. R06AE)	11	**4.8**	372	**6.0**	12	**3.6**	218	**4.7**	0.8	0.5 – 1.2

with the prescription of antipsychotics and antidepressants (N05A excluding N05AB04; N06A) thyroid hormones (H03), drugs used in diabetes (A10), anxiolytics, hypnotics and sedatives(N05B; N05C), gonadotropins and other ovulation stimulants (G03G) and with the prescription of antiemetics (A03FA01, A04A, N05AB04, R06AD, R06AE) (results not shown). Exposure rates for these drugs were compared between the two populations, adjusted for maternal age (Table 2). After adjustment, the difference in use of gonadotropins and other ovulation stimulants between the genetic and the source population disappeared. Results for the other drug groups did not change.

DISCUSSION

We found that in general the use of prescription-only drugs in the first trimester of pregnancy is comparable between mothers of infants with a genetic disorder and the general population of pregnant women. The use of antimigraine medication and gonadotropins and other ovulation stimulants was higher in the genetic population, although statistically borderline significant. The higher use of ovulation stimulants disappeared after adjusting for maternal age.

This study is the first to investigate whether sampling of mothers of infants with a chromosomal anomaly or single gene disorder from a source population of pregnant women is independent from the exposure status. We were able to compare the medication use between these two populations directly because (1) the source of information, pharmacy data, was the same for the two populations and only prescription-only drugs were included; (2) mothers in the genetic population originated directly from the source population, since we used two population-based databases within the same geographical area and time period; (3) the use of the ATC-classification system in both databases enabled us to categorise the drugs in the specific drug groups in the same way for both populations.

However, there are also some differences between the two databases. The IADB.nl includes only information on drug prescriptions, the actual use is unknown, whereas in the Eurocat database only drugs actually taken are registered. In this study we thus compared exposure rates with prescription rates. Nevertheless, we do not expect the drug exposure rates to differ notably from the drug prescription rates, since drugs that are prescribed and dispensed by the pharmacy are mostly initially taken, although not always for the entire prescribed period.

In the Eurocat database, the actual length of gestation is known for almost all pregnancies. The start of the pregnancy could therefore be determined with much certainty. The inclusion of 5 pregnancies with a gestation less than 13 weeks will not likely have influenced the results, because it involved only a small proportion (0.9%) of the

pregnancies.

In the IADB.nl the start of the pregnancy is standardised at 273 days before the date of birth and therefore less certain. This may lead to misclassification of first trimester exposure if the length of the pregnancy deviates from the 39 weeks that is used as standard. In the Netherlands 7.8% of all births of at least 20 weeks gestation were less than 37 weeks gestation and 5.3% were of 42 weeks gestation or more in 2003.[9] However, the extent of misclassification is difficult to establish, because it also depends on the time of drug prescription. Misclassification for drugs prescribed close to the start or end of the estimated first trimester is more likely than for drugs prescribed in the middle of the first trimester.

Although the overall drug exposure rate in the first trimester is approximately 44%[10], the exposure rates for specific drugs are much smaller. Therefore we decided to calculate first trimester exposure rates for drug groups based on their pharmacological or therapeutic properties. Since the genetic group was relatively small we can not entirely exclude the possibility that for certain drug groups differences in use between the two populations exist, but can not be demonstrated because of lack of power. The use of drugs used in diabetes (A10) and anti-epileptics (N03A) was approximately two times higher in the genetic population, although not statistically significant. The difference in use of antimigraine medication was even higher in the genetic population with a rate ratio of 2.7 (95% CI: 1.0-7.8). Nevertheless, we believe that the significantly higher use of antimigraine medication among the mothers of infants with a genetic condition is a chance finding. The overall image is that of a similar medication use in both populations: a rate ratio of 1 was included in all 95% CI and for none of the drug groups an apparent trend in use was seen.

In case-control studies on birth defects and maternal medication use, selection of controls should be well considered. The use of controls with birth defects other than those under interest may cause selection bias or teratogenicity non-specificity bias and lead to an underestimation of the effect. The use of non-malformed controls is preferred above malformed controls, provided the method of data collecting uses a source of prospectively collected data on medication use, such as pharmacy data, and the source is the same for cases and controls.[11] However, in many birth defects registries, non-malformed controls are not available. The use of non-malformed controls obtained from a population-based prescription database is only possible if detailed information is available on the gestational length of the pregnancy and other possible confounding factors.

The advantage of using controls with a chromosomal or single gene disorder over controls with other malformations than the malformation under study is that the exposure is most likely not related to the outcome and, as this study has shown, that they are sampled from the source population independent of the exposure status. However,

the use of controls with a genetic disorder also has its restrictions. Because the cause of the disorder is known, it might be possible that mothers of infants with a genetic disorder do not scrutinize their pregnancy in the same way as mothers of infants with a non-genetic birth defect. Therefore, the use of prospectively collected data on medication use is preferable as applies to the use of non-malformed controls. Also, if the case group includes infants with a birth defect caused by a chromosomal or single gene disorder which is not yet identified, the estimation of the effect will be diluted. Furthermore, the presence of confounding factors, such as maternal age, can not be ruled out. In our study we found that mothers who gave birth to a child with a genetic condition were older than the 'general pregnant population'. This was to be expected since maternal age is a risk factor for chromosomal anomalies. Maternal age is also associated with the use of a few drug groups. However, when we adjusted the analyses for maternal age, the results did not change, except for gonadotropins and other ovulation stimulants for which the difference in use disappeared after stratification for maternal age.

In conclusion, we found that the use of drugs in the first trimester among women who gave birth to a child with a genetic condition is comparable with the first trimester maternal drug use in the general population of pregnant women. Therefore, in case-control studies on maternal drug use and the risk of birth defects, the use of infants and foetuses with a genetic disorder is an appropriate choice. Sampling of these controls is independent of exposure status. The odds ratio is a good estimate of the relative risk. This may not apply to case-control studies on use of antimigraine medication and birth defects, although we believe that the significant higher use of antimigraine medication among mothers giving birth to a child with a genetic disorder can be attributed to chance. As in all case-control studies, an important condition is that the information for both cases and controls on drug use is valid and precise and preferably available from prospectively collected data sources.

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CHAPTER 4

Fluoxetine and infantile hypertrophic pylorus stenosis: a signal from a birth defects – drug exposure surveillance study

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ABSTRACT

Objectives. We report an association found in a surveillance study which systematically evaluated combinations of specific birth defects and drugs used in the first trimester of pregnancy.

Methods. The database of a population-based birth defects registry (birth years 1997-2007) was systematically screened for combinations of drugs and malformations that were disproportionately present compared to the rest of the database. Combinations with at least 3 exposed cases and a $p<0.01$ (Fisher Exact test) were studied to analyse details of the malformation, timing of exposure, and additional case-control analyses were performed.

Results. Among the significant associations found, an association between maternal use of fluoxetine and infantile hypertrophic pyloric stenosis (IHPS) was of particular interest. In total 3/178 (1.7%) of the children with a HPS were exposed to fluoxetine in the first trimester compared to 8/4077 (0.2%) fluoxetine exposures among the children with other malformations ($p=0.009$, OR=8.7, 95% CI=2.3-33.2). The three exposed cases were all isolated and fluoxetine was used in gestational weeks 4–8, 2–8 and -10–19, respectively. In additional case-control analyses, using controls with a genetic disorder and after adjustment for maternal age and smoking in the first trimester of pregnancy, the adjusted odds ratio was 9.8 (95% confidence interval: 1.5–62.0).

Conclusion. Although we cannot rule out the possibility of chance, we believe it is appropriate to consider this association between IHPS and fluoxetine as a signal. We therefore encourage other investigators to study this association in their data.

INTRODUCTION

One of the objectives of a birth defects registry is to detect possible new teratogens at an early stage. Conducting a surveillance study to systematically evaluate combinations of specific birth defects and risk factors is one of the methods to identify possible new risk factors for malformations.[1-4] Here we report on a possible association between the maternal use of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), and infantile hypertrophic pyloric stenosis (IHPS) that was found in a surveillance study performed in a population-based birth defects registry.

METHODS

Eurocat Northern Netherlands (NNL) is a population-based birth defects registry, which covers approximately 18,000-19,000 births per year. All types of birth, including spontaneous abortions and terminations of pregnancy, are included. There is no lower age limit, but affected children have to be reported to the registry before 16 years of age.

Parents have to give consent before the information on malformation and determinants can be registered in the database. Information on malformations of children and foetuses is collected from several sources. For births up to 2001, the malformations were coded using the ICD-9 classification system with BPA extension, for births starting from 2002, ICD-10 was used. The parents are asked to fill in a questionnaire on sociodemographic characteristics, prenatal screening and diagnostic tests, and on possible risk factors. Detailed information on maternal medications is collected from pharmacy data (which is fully registered in the Netherlands) and use of the dispensed medication is verified in a telephone interview with the mother. Medications used were coded using the Anatomical Therapeutical Chemical (ATC) classification system.[5]

On 1 January 2009, the Eurocat database contained 5,528 registrations of children and foetuses born between 1997 and 2007. Good information on maternal medication use, including pharmacy data, was available for 4,255 children and foetuses (77%). Parents withheld permission to obtain pharmacy data in 845 cases (15%). There was no pharmacy data on the patient for the requested period available for the other 396 cases (7%). Of the 4,255 cases with pharmacy data, 2,065 (48.5%) used one or more drugs in the first trimester (excluding folic acid, multivitamins and homeopathic products). These 4,255 cases with good information on maternal medication use were systematically screened for combinations of drugs and malformations that were disproportionately present compared to the rest of the database. The methodology used for the so-called quantitative signal detection is described in Figure 1 and in a previous study.[6]

Because many tests are performed in these quantitative analyses, several associations

Quantitative signal detection
The basic principle of quantitative signal detection is to find combinations of birth defects and specific drugs or drug classes that are more frequently present than expected in the database compared to other birth defects, by calculating cross tabulations between selected birth defects and selected drugs.

Inclusion criteria
Birth defects are included if they present either as isolated defects or in combination with other, but unrelated, defects (without an overall or syndrome diagnosis) . In the latter situation, the defects are analysed as separate defects. Defects associated with a chromosomal or single gene disorder are not included. A birth defect associated with another defect (for instance, a clubfoot associated with a neural tube defect) is only included in the primary birth defect category. Defects as part of a non-genetic syndrome are only included in the syndrome category. Statistical considerations mean that only birth defects occurring in 10 or more affected subjects from the study population are selected.

Only specific drugs and drug classes that are chemically related within the same anatomical and therapeutic setting (first 5 positions of the ATC code) are included if 10 or more subjects from the study population were exposed to them in the first trimester of pregnancy.

If a drug class and an underlying specific drug comprise the same number of exposed subjects for a specific malformation or birth defects category, only the specific drug is included in the analyses. The same applies to the malformations: if the more specific malformation (for instance, spina bifida) comprises the same number of subjects exposed to a specific drug as in the malformation group defined more broadly (for instance, neural tube defects), only the most specific malformation is included in the analyses.

Analysis
If a combination of a specific birth defect and drug or drug class contains at least three cases, the Fisher Exact test is performed to test whether the number of observed cases differs from the number of expected cases. The odds ratio (OR) and the 95% confidence interval (CI) are calculated as a measure for the strength of the signal. The OR is calculated as the ratio of the exposure odds among cases with a specific malformation to the exposure odds among all other registrations with other birth defects. .

Figure 1. Short description of the methodology used for quantitative signal detection in a population-based birth defects registry

will occur just by chance (type I errors or false-positive findings). Therefore, associations between drugs and malformations with a significantly disproportionate number of exposed cases ($p<0.01$) were subjected to a more detailed analysis to see whether they could be considered genuine signals. First, the malformations and timing of exposure was better specified for the exposed cases. If the malformations were homogenous and the timing of exposure occurred before or at the time of the development of the defect, additional case-control analyses were performed. Cases were defined as registrations with the birth defects of interest, either isolated or in combination with other malformations, but not associated with a (genetic) syndrome. Because Eurocat NNL does not collect information on non-malformed controls, the controls consisted of children and foetuses with chromosomal or monogenic disorders, in which the birth defect of interest was not present. Maternal medication use is not related to the genetic disorder and sampling from the source population is done independently of exposure status.[7] Exposure was defined as any use of the specific drug in the first trimester, while 'not exposed' was defined as no use

of the drug or another drug from the same class in pregnancy. Characteristics between cases and controls were compared using the chi square test for categorical variables and the Student T-test for continue variables. Odds ratios were calculated with adjustment for possible confounders using SPSS 16.0 for Windows.
Since this study was conducted within the objectives of the registry and with anonymous data, approval of an ethical board was not necessary.

RESULTS

Among the 11 significant associations found, the association between maternal use of fluoxetine and IHPS was of particular interest. In total there were 178 cases with IHPS, of which the majority had isolated IHPS (n=167, 94%). In total 3 children with IHPS were exposed to fluoxetine in the first trimester (1.7%) compared to 8 fluoxetine exposures among the 4,077 registrations with other malformations (0.2%). This difference is statistically significant (p=0.009, OR=8.7, 95% CI: 2.3-33.2). First trimester exposure to SSRIs in general was not significantly associated with IHPS (4 exposed cases among the

Table 1. Characteristics of the 3 cases with isolated hypertrophic pyloric stenosis that were exposed to fluoxetine in the first trimester

	Case 1	Case 2	Case 3
Year of birth	2003	2005	2006
Boy/girl	boy	girl	boy
Gestational age (weeks)	33	41	41
When discovered (after birth)	6 weeks	within 1 month	6 weeks
Maternal age (years)	37	34	32
Period of fluoxetine use (after last menstrual period)	weeks 4 to 8	weeks 2 to 8	weeks -10 to 19
Smoking in first trimester	no	yes	yes
Additional medication use	paroxetine in part of 2nd and 3rd trimester	vitamin B12 in trimester 1 nitrazepam in trimester 1	omeprazol in trimester 1 miconazol/ hydrocortison in part of 2nd trimester clotrimazol in various periods in pregnancy
Use of folic acid in advised period*	part of period	entire advised period	part of period
Ethnicity	Caucasian	Caucasian	Caucasian
Familial occurrence	yes, paternal grandfather	yes, father	no

* Dutch advised period of use for folic acid: 4 weeks before conception to 8 weeks after

IHPS cases versus 48 among the other malformed cases (p=0.171, OR=1.9; 95% CI: 0.7-5.4). The possible association between fluoxetine and IHPS was further examined.

In Table 1 the characteristics of the three exposed cases are presented. They were all live-born infants with isolated IHPS. Exposure occurred in gestational weeks 4 to 8, 2 to 8 and from 10 weeks before to 19 weeks in pregnancy.

In the additional case-control analyses, controls were defined as children and foetuses with chromosomal or monogenic disorders, not associated with IHPS (n=945). After excluding children with a genetic disorder associated with IHPS and children exposed to fluoxetine in the second or third trimester, or to another SSRI in pregnancy, 177 cases with IHPS and 932 controls remained. The vast majority of the cases (n=166, 94.0%) were isolated cases of hypetrophic pyloric stenosis with no other malformations present. The controls consisted of children and foetuses with chromosomal disorders (n=517, 55.5%) and monogenetic disorders (45.5%). Trisomy 21 was the most prevalent chromosomal disorder (n=252), followed by trisomy 18 (n=74), microdeletion syndromes (n=43) and Turner syndrome (n=24). Te most prevalent monogenetic disorders include neurofibromatosis type I (n=16), postaxial polydactyly (n=16), long QT syndrome (n=14) and cystic fibrosis (n=14). In total 3 cases and 2 controls were exposed to fluoxetine in the first trimester. Table 2 presents characteristics of the cases and controls. The crude OR was 8.0; 95% CI: 1.3-48.3. After adjusting for maternal age and maternal smoking in the first trimester, the OR remained statistically significant (adjusted OR=9.8; 95% CI: 1.5-62.0). Because IHPS showed a familial occurrence in two of the exposed cases, we also performed analyses restricted to cases with familial occurrence of IHPS (n=39). The adjusted OR remained statistically significant (adjusted OR=32.2, 95% CI: 4.2-245.5).

Table 2. Characteristics of cases and controls used in the additional case-control analyses.

		Cases **Infantile hypertrophic pyloric stenosis**		**Controls** **Genetic disorders**		
		n=177	%	n=932	%	p
Year of birth	1997-2001	91	51.4	458	49.1	0.580
	2002-2007	86	48.6	474	50.9	
Sex	boy	153	86.4	510	54.8	0.000
	missing			*1*		
Maternal age	mean (SD)	31.8 (4.9)		29.5 (4.1)		0.000
	missing	*1*				
Smoking in 1st trimester	yes	60	34.1	200	21.7	0.000
	missing	*1*			*12*	
Use of folic acid	yes	121	68.8	622	67.2	0.696
in 1st trimester	*missing*					

DISCUSSION

Use of SSRIs in early pregnancy, in particular paroxetine, has been associated with congenital heart defects,[8] while use in late pregnancy has been associated with peripheral pulmonary hypertension[9] and with poor neonatal adaptation.[10] An increased risk for hypertrophic pyloric stenosis, as found in our study, has not been reported before.

Between 1997 and 2007 in the Northern Netherlands, the prevalence of IHPS, not associated with genetic conditions, was on average 1 per 1,000 births and did not show a significantly increasing or decreasing time trend.[11] IHPS presents typically 3-8 weeks after birth through projectile vomiting but little is known about its pathogenesis. Because the pylorus muscle in IHPS patients showed no hypertrophy at birth, some physicians consider IHPS to be an acquired condition. However, the general consensus is that the condition has a multifactorial aetiology, in which both genetic and environmental factors are involved. Exogenic risk factors include maternal age, smoking in pregnancy, postnatal antibiotic use and possibly the sleeping position of the child. A genetic influence in the condition is supported by the male predominance and familial occurrence, while differences in the prevalence of IHPS in ethnic groups are indicative for both genetic and environmental factors.[12] In our study population, familial occurrence was present in about 20% of the IHPS cases and two of the three exposed cases had an affected family member. Familial occurrence might be the strongest predictor for the development of IHPS, but we still do not know why some infants with a genetic predisposition develop IHPS whereas others do not. When we restricted our case-control analyses to cases with a familial occurrence of IHPS, the OR remained significant but with a large confidence interval. We could not investigate if the association was also present in cases without familiar occurrence due to low numbers.

Although we could not find studies in which the use of selective serotonin reuptake inhibitors was directly related to the development of IHPS, we believe that there may be a biologically plausible pathway. Fluoxetine is an SSRI that increases synaptic serotonin (5-hydroxytryptamine, 5-HT) levels by inhibiting the reuptake of serotonin via the 5-HT transporter. Not only serotonergic neurons, but also epithelial cells of the intestinal mucosa are endowed with this mechanism for terminating the effect of serotonin released by neurons and enterochromaffin cells, respectively.[13] Serotonin plays a stimulatory role in the motility of the gastrointestinal tract.[14] All enteric serotonergic neurons develop early and 5-HT seems to be involved in late developing enteric neurons.[15] Fluoxetine passes through the placenta and may therefore affect the development of the foetal myenteric plexus by increasing the activity of endogenously released 5-HT. However, since we did not find an association between IHPS and SSRIs in general, it cannot be excluded that there are properties of fluoxetine that distinguish it from other SSRIs, like its relatively high

affinity for the 5-HT_{2C} –receptor,[16] or other aspects that play an important role.

It is possible that factors before birth, such as increased levels of serotonin, affect the developing foetus and increase the child's susceptibility for developing IHPS. The actual development of IHPS may then be triggered by factors after birth, such as the ingestion of milk or the sleeping position. Because IHPS usually presents a few weeks after birth and/or is not considered to be congenital, children with IHPS are often not included in birth defects registries, or IHPS may not be registered as an adverse outcome in cohort studies. Thus, a possible association between IHPS and maternal use of fluoxetine may have been missed by earlier studies.

The signal between IHPS and the use of fluoxetine was observed in a systematic surveillance study in which we preformed many statistical tests. Although we set our significance level at 0.01, the association we found could still be a false-positive signal. If the association between IHPS and fluoxetine is due to chance, it is very unlikely that it will re-occur in our next surveillance study when more data has been collected, similar to a signal on the use of loratadine and hypospadias that was found in a large birth registry but which disappeared after further data was gathered.[17] Only one other surveillance study investigating the occurrence of specific birth defects in relation to first trimester use of specific SSRIs reported on the possible association between fluoxetine and pyloric stenosis. They found no significant association (based on 6 exposed cases, OR=0.9; 95%CI=0.4-2.1).[18] Our results show more statistical instability, because of the smaller study population. Nevertheless, we believe that the internal validity of our data is high. Our use of prescription data makes any information bias with regard to maternal medication use very unlikely. Furthermore, since we use active ascertainment for the majority of the cases and multiple sources for information, we do not suspect any bias in the reporting of birth defects with regard to maternal medication use. The methodology used is adequate, since we also identified in our dataset the well-known association between valproic acid and spina bifida (based on 3 exposures among 68 spina bifida cases vs 15 exposures among 4,187 other malformed registrations, p=0.003, OR=12.8, 95% CI=3.6-45.4).

In conclusion, although we cannot rule out the possibility of chance and there are only three exposed cases, we believe it is appropriate to consider the association we found between IHPS and fluoxetine as a signal, given the homogeneity of the cases, the timing of exposure, the consistency in the additional case-control analyses, and a plausible biological explanation. We therefore encourage other investigators to study this association in their data.

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CHAPTER 5

First trimester use of paroxetine and congenital heart defects, a population-based case-control study

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ABSTRACT

Background. There is a need for case-control studies on the effect of paroxetine on the occurrence of specific heart defects.

Methods. We performed a case-control study, with data from a population-based, birth defects registry in the Netherlands. All the children born between 1997-2006 were selected. Cases were defined as foetuses and children with isolated heart defects, while the controls were foetuses and children with a genetic disorder with no heart defect. We excluded children for whom there was no information on maternal medication use and deceased children and foetuses who were not examined post mortem. First trimester exposure to paroxetine was compared between cases and controls by calculating adjusted odds ratios (adjOR).

Results. We included 678 cases with isolated heart defects and 615 controls. The first trimester exposure rate was 1.5% for cases and 1.0% for controls. After excluding mothers who used paroxetine outside the first trimester, or who had used another SSRI, we found no significantly increased risk for heart defects overall (10 exposed cases, adjOR=1.5; 95% CI: 0.5-4.0), but we did find a significantly increased risk for atrium septum defects (ASD) (3 exposed cases, adjOR=5.7; 95% CI: 1.4-23.7).

Conclusions. Our results suggest that the use of paroxetine in early pregnancy is associated with an increased risk of atrium septum defects. The results stress the importance of studying possible teratogenic effects of a drug preferably with respect to well-specified malformations.

Keywords: Congenital heart defects, atrium septum defects, selective serotonin reuptake inhibitors, paroxetine, case-control study

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) are currently the most widely prescribed drugs for depression and depressive symptoms, and since 1995 the use of SSRIs among pregnant women in the Netherlands has increased from 1% to almost 3%.[1] This increase runs parallel with an increase in SSRI use by women of child-bearing age. The use of SSRIs in early pregnancy has recently been associated with an increased risk of congenital anomalies. In 2005 the manufacturer of paroxetine, a frequently used SSRI, issued a warning that preliminary analyses from safety data showed an increased risk of cardiovascular anomalies after use of paroxetine compared to use of other antidepressants.[2] After this warning several cohort studies were published on this association, but the results are inconclusive.[3-7] Together, these cohort studies indicate that SSRIs do not have a major teratogenic effect.

Since case-control studies have more statistical power, these studies are preferred over cohort studies to detect moderately increased risks for specific birth defects. In 2007, two case-control studies were published that used data from two large surveillance studies in the USA.[8,9] They investigated SSRI use in association with various groups of specific birth defects. Some of the results from the study based on National Birth Defects Prevention Study (NBDPS) could not be replicated by the study based on data from the Slone Epidemiology Centre Birth Defects study, but both studies found an increased risk of right ventricular outflow tract obstruction defects after the use of paroxetine. In a third study, designed as a nested case-control study which used data from a 'medication and pregnancy database' in Canada, an increased risk was found for major cardiovascular malformations after a dosage of more than 25 mg paroxetine per day, using a reference group of mothers who took other antidepressants in the first trimester.[10]

Since so far, no case-control study on the use of paroxetine in pregnancy and the risk of specific cardiovascular malformations has been published. We therefore, set out to investigate the possible association between the use of paroxetine in early pregnancy and the occurrence of specific heart defects, using a case-control study design.

METHODS

Setting

The study was designed as a case-control study. Cases and controls were derived from the Eurocat Northern Netherlands (NNL) database, a population-based birth defects registry for the northern part of the Netherlands. The annual number of births covered is approximately 19,000. The registry is notified about infants and foetuses with a congenital malformation by physicians and midwifes on a voluntary basis. Reports are actively

collected from obstetric and paediatric hospital departments, cytogenetic laboratories, and pathology departments. Miscarriages and terminations of pregnancy after prenatal diagnosis are included, but the child has to be notified to the registry before sixteen years of age. Cases are only registered after informed consent has been obtained from the parents. The overall response rate is approximately 80%. Information on malformations is obtained from the medical files and coded by trained research staff. For births up to 2001 the Ninth revision of the International Classification of Diseases with modification from the British Pediatric Association (ICD9-BPA) is used, for births starting from 2002 the ICD10-BPA is used. A clinical geneticist reviews cases with multiple anomalies. Since 1997, parents provide information by filling in a questionnaire on the course of the pregnancy, prenatal screening and diagnostic procedures, exposure to occupational hazards, smoking and drinking habits, and socio-economic background. Information on medications dispensed before and during pregnancy is obtained from pharmacy data, which is fully registered in the Netherlands. The use of the prescribed medications as well as the possible use of over-the-counter medication is verified in a telephone interview with the mother.

Case definition

With a prevalence of approximately 8 per 1,000 births, cardiac anomalies are the most common birth defects.[11,12] They present as isolated defects but also occur frequently in children with genetic or other syndromes. Teratogenic effects will most likely not cause an increase in all birth defects but only in specific birth defects. Therefore we defined our cases as foetuses or children with isolated congenital heart defects, born between 1997 and 2006. Our definition included foetuses or children with simple or complex heart defects only and excluded foetuses or children with associated genetic or other syndromes, or with extra-cardiac malformations. Children with minor heart anomalies, such as a persistent ductus Botalli in those born before 37 weeks of gestation, a single umbilical artery, or a functional or non-specified cardiac murmur were not included. A clinical geneticist (WSKF) reviewed the cases and classified them into phenotypic sub-groups based on embryological origin.

Control definition

Eurocat NNL does not collect information on non-malformed controls. We therefore used foetuses and children with a chromosomal or single gene disorder as controls. The reason for choosing this control group was that medication use was not related to the genetic disorder and sampling from the source population was done independently of exposure status. From a previous study[13], we concluded that the first trimester use of prescription drugs among mothers of children with a genetic condition did not differ significantly from the source population consisting of all pregnant women.

Genetic disorders are frequently associated with a heart defect. The risk of developing a heart defect is greater for children with certain chromosomal or other genetic disorders (for instance, trisomy 21, del 22q11) than for children without such genetic anomalies[14], but it is still not known why some children suffering from such a disorder develop a heart defect while others do not. Since a relationship between drug exposure and development of a heart defect in a child with a genetic disorder cannot be ruled out, we excluded children with an associated heart defect from the control group. Stillbirths, neonatal deaths and terminations of pregnancy without a post mortem examination were also excluded from the controls, to ensure there were no heart defects present in the control group that could lead to misclassification. Because this excluded a relatively large number of controls, we performed chi square or Fisher Exact tests to see whether the excluded controls represented a selection in terms of year of birth or paroxetine use.

Exposure definition

The estimated prevalence of SSRI use in the year before delivery was 2.5%, according to a population-based cohort study using data from a prescription database. Of all SSRIs, paroxetine is most commonly used with approximately 60%.[1] Children were considered to have been exposed if the mother used paroxetine at some point in the period from 4 weeks before conception through the 12th week of her pregnancy. We will refer to this whole period as 'first trimester'. The remaining children were considered not exposed if the mother had not used paroxetine in pregnancy or any other SSRI at any time during the pregnancy. If the mother used paroxetine outside the first trimester, or at an unknown time in the pregnancy, or if the mother used another type of SSRI during the pregnancy, the child was excluded from the case-control analyses.

Analyses

As possible confounders we took into account: year of birth, pregnancy outcome, maternal age, gravidity, mother's educational level, smoking, use of alcohol, body mass index (BMI) calculated as weight before pregnancy divided by height squared, use of folic acid, and pre-existing maternal diabetes or epilepsy. Cases and controls, and exposed and unexposed groups, were described according to these characteristics, and chi square and Fisher Exact tests were used to determine which characteristics differed between the cases and controls and between the exposed and unexposed groups. The mean maternal age was compared using the Student's T-test. We calculated crude and adjusted ORs using logistic regression for all heart defects and for specific heart defects. Analyses were performed using SPSS 16.0 for Windows (Chicago, USA).

RESULTS

On April 1st 2008, the Eurocat database contained 5,125 registrations of children with congenital anomalies born between 1997-2006. Of these, 775 children and foetuses were registered with isolated heart defects and 1,097 children and foetuses with a genetic disorder, including 628 with a chromosomal disorder and 469 with a monogenetic disorder. A total of 97 cases (12.5%) and 149 (13.6%) controls were excluded because information on maternal medication use was missing. These proportions are not significantly different (p=0.50). Thus, the remaining case group consisted of 678 children and foetuses with an isolated heart defect. Among the remaining 948 controls, 158 had a major heart defect (131 associated with a chromosomal disorder and 27 with a monogenetic disorder). For another 175 deceased children and foetuses, it was uncertain whether they had had a heart defect because no post mortem examination had been performed or the information on the post mortem examination was missing. After excluding the children and foetuses with a genetic disorder associated with a heart defect, or without post mortem examination data, we had 615 controls, consisting of 272 with a chromosomal disorder and 343 with a monogenetic disorder.

Table 1 presents the characteristics of our cases and controls. Significant differences can be observed for year of birth (cases more often came from the period 2002-2006), maternal age (higher among controls), mother's educational level (more highly educated mothers among controls) and pregnancy outcome (more terminations, miscarriages and stillbirths among the controls). The excluded controls more often came from the period 2002-2006 than the included controls (55.6%, vs 39.7%, p=0.000) and comprised fewer live births (30.3% vs 86.5%, p=0.000). The difference in pregnancy outcome between included and excluded controls remained after stratifying for year of birth.

A total of 27 mothers had taken an SSRI during pregnancy. Of these, ten case mothers (1.5%) and six mothers from the control group (1.0%) had used paroxetine in the first trimester. Mothers who used another type of SSRI (n=5) or who used paroxetine outside the first trimester or at an unknown time in pregnancy (n=6), were excluded from the case-control analyses. Table 2 presents the characteristics of the 16 exposed children and the 1,266 non-exposed children. Significant differences were observed for year of birth (exposed pregnancies were more often from the period 2002-2006) and maternal smoking (more smokers among exposed pregnancies). Mean maternal age did not differ significantly between the exposed and non-exposed children. The use of paroxetine in the first trimester did not differ significantly between excluded and included controls (0.6% vs 1.0%, p=0.72).

Table 3 presents the 10 exposed cases and lists type of heart defect and daily dose of medication taken. For most of the exposed cases and controls, the prescribed daily dose

Table 1. Characteristics of cases (children and foetuses with isolated heart defects) and controls (children and foetuses with genetic disorders without heart defects)

		Cases		Controls		
		Isolated heart defects		Genetic disorders		
		n=678	%	n=615	%	p
Year of birth	1997-2001	362	53.4	371	60.3	0.01
	2002-2006	316	46.6	244	39.7	
Maternal age	mean (SD)	30.3 (4.7)		31.1 (4.9)		0.01
	missing	*28*		*21*		
Educational level	low	78	12.3	82	14.6	0.02
	middle	325	51.1	240	42.8	
	high	233	36.6	239	42.6	
	missing	*42*		*54*		
Smoking	yes	163	25.2	133	23.0	0.38
	no	483	74.8	445	77.0	
	missing	*32*		*37*		
Alcohol	yes	164	25.5	130	22.4	0.21
	no	479	74.5	450	77.6	
	missing	*35*		*35*		
Gravidity	1	243	37.4	205	34.7	0.32
	>1	407	62.6	386	65.3	
	missing	*28*		*24*		
Pregnancy outcome	LB	582	85.8	532	86.5	0.00
	LB but died	97	11.7	21	3.4	
	T	1	0.1	11	1.8	
	M	6	0.9	35	5.7	
	SB	10	1.5	16	2.6	
BMI	<19	46	7.3	31	5.6	0.24
	19-24	312	49.8	299	54.1	
	>24	269	42.9	223	40.3	
	missing	*51*		*62*		
Correct use	yes	236	35.7	219	37.1	0.62
of folic acid	no	425	64.3	372	62.9	
	missing	*17*		*24*		
Diabetes	yes	5	0.7	3	0.5	0.73*
	no	667	99.3	591	99.5	
	missing	*6*		*21*		
Epilepsy	yes	8	1.2	8	1.3	0.8
	no	664	98.8	586	98.7	
	missing	*6*		*21*		

* p-value calculated with Fisher Exact test.

SD standard deviation, LB live birth, T termination of pregnancy, M miscarriage, SB stillbirth, BMI body mass index

Table 2. Characteristics of children and foetuses exposed to paroxetine in utero in the first trimester and of non-exposed children and foetuses.

		Exposed to paroxetine in 1st trimester		Not exposed		
		n=16	%	n=1266	%	p
Year of birth	1997-2001	5	31.2	721	57.0	0.039
	2002-2006	11	68.8	545	43.0	
Maternal age	mean (SD)	32.0 (6.4)		30.7 (4.8)		0.289
	missing	*1*		*48*		
Educational level	low	2	13.3	155	13.2	Low/ middle vs high 0.101
	middle	4	26.7	558	47.6	
	high	9	60.0	459	39.2	
	missing	*1*		*94*		
Smoking	yes	8	53.3	285	23.8	0.013*
	no	7	46.7	913	76.2	
	missing	*1*		*68*		
Alcohol	yes	4	26.7	289	24.1	0.767*
	no	11	73.3	908	75.9	
	missing	*1*		*69*		
Gravidity	1	4	26.7	441	36.3	0.440
	>1	11	73.3	774	63.7	
	missing			*51*		
Pregnancy outcome	LB	14	87.5	1189	93.9	0.259*
	T, M, SB	2	12.5	77	6.1	
BMI	<19	1	6.7	76	6.6	Low/ middle vs high 0.700
	19-24	7	46.7	597	51.7	
	>24	7	46.7	482	41.7	
	missing	*1*		*111*		
Correct use of folic acid	yes	5	31.2	448	36.6	0.660
	no	11	68.8	777	63.4	
	missing			*41*		
Diabetes	yes	1	6.2	7	0.6	0.098*
	no	15	93.2	1232	99.4	
	missing			*27*		
Epilepsy	yes	0	0%	16	1.3	1.000*
	no	16	100%	1223	98.7	
	missing			*27*		

* p-value calculated with Fisher Exact test.

SD standard deviation; LB live birth including children who died after birth; T termination of pregnancy; M miscarriage; SB stillbirth; BMI body mass index

Table 3. Cases with an isolated heart defect after maternal exposure to paroxetine in the first trimester of pregnancy showing year of birth, daily dose taken by the mother, diagnosis and phenotypic subgroup

Case #	Year of birth	Daily dose (in mg)	Diagnosis	Phenotypic subgroup
1	1998	30	ASD II	ASD
2	1999	20	transposition of great arteries, AVSD and heart in right thorax	Other
3	2000	20	patent ductus arteriosus (surgically corrected)	Other
4	2000	20	coarctation of aorta	Left-sided defects
5	2002	20	VSD, muscular	VSD
6	2003	20	ASD, sinus venosus superior type	ASD
7	2003	20	ASD II	ASD
8	2003	10	pulmonary valve stenosis	Right-sided defects
9	2004	20	aortic valve stenosis	Left-sided defects
10	2004	20	coarctation of aorta	Left-sided defects

VSD ventricular septum defect; ASD atrial septum defect; AVSD atrium ventricular septum defect.

Table 4. Comparison of crude and adjusted odds ratios for congenital heart defects in cases and controls after maternal exposure to paroxetine in the first trimester

	Exposed	Non-exposed	OR	95% CI	AdjOR**	95% CI	p-value***
Controls	6	605	ref				
All heart defects	10	661	1.5	(0.6-4.2)	1.5	(0.5-4.0)	0.476
VSD	1	182	0.6	(0.1-4.6)	0.5	(0.1-4.2)	0.528
ASD	3	53	5.7	(1.4-23.5)	5.7	(1.4-23.7)	0.016
Septal defects*	4	245	1.6	(0.5-5.9)	1.6	(0.4-5.6)	0.493
Right-sided defects	1	101	1.0	(0.1-8.3)	0.9	(0.1-7.6)	0.926
Left-sided defects	3	126	2.4	(0.6-9.7)	2.1	(0.5-8.7)	0.292
Other defects	2	189	1.1	(0.2-5.3)	1.0	(0.2-5.2)	0.967

VSD, ventricular septum defect; ASD, atrial septum defect; OR, odds ratio; adjOR, adjusted odds ratio.
* Septal defects also includes children and foetuses with both a VSD and ASD; ** OR adjusted for year of birth; *** p-value obtained from logistic regression.

was 20 mg. The mother of one case took 10 mg per day and the mother of another case took 30 mg per day. Among the controls, one mother took 40 mg per day.

Because only year of birth differed between cases and controls and exposed and non-exposed subjects, we adjusted for year of birth in the case-control analyses. Table

4 shows the crude and adjusted ORs for the occurrence of heart defects after use of paroxetine. Whereas no significantly increased OR was found for heart defects overall (adjOR=1.5; 95% CI: 0.5-4.0), a significantly increased OR was found specifically for atrium septum defects (ASD, AdjOR=5.7; 95% CI: 1.4-23.5) after use of paroxetine during the first trimester of pregnancy. Among the three exposed cases with an ASD, one had an ASD sinus venosus superior type. Because this type of ASD is anatomically different from the ASD secundum type, we repeated the analyses for ASD secundum only. The OR decreased slightly and was borderline significant (AdjOR=5.1; 95% CI: 1.0-26.1).

DISCUSSION

Our study represents a case-control study on the use of paroxetine during the first trimester of pregnancy and its possible association with specific congenital heart defects. After use of paroxetine, we found a significantly increased OR for ASD, not for the occurrence of isolated heart defects in general.

Heart defects, as a group, are very heterogeneous: the development of the heart is a complex process and a wide variety of heart defects can occur. Heart defects can be very complex, involving several parts of the heart, or relatively simple, such as ventricular septum defects. Sometimes the heart is affected by two or more separate defects or extra-cardiac defects are also present. A specific exposure is not expected to increase the risk for congenital (heart) defects in general. In studying risk factors it is therefore important to create homogeneous groups. In this study, by including only cases with isolated heart defects, we tried to create a case group that was homogeneous as much as possible. Moreover we performed sub-analyses on specific phenotypes of heart defects. The finding of an increased risk for ASDs only and not for all heart defects as a group may be the result of multiple testing, but is in line with the expected specificity of teratogenic effects. However, because the number of exposed cases and controls was relatively small, the 95% confidence intervals are wide and the results need to be interpreted carefully.

Most cohort studies on risks of maternal SSRI and paroxetine use have evaluated the association with heart defects in general. Cole et al[3] observed an increased risk for all malformations after the use of paroxetine (adjOR=1.76; 95% CI: 1.18-2.64), but not for cardiovascular malformations (adjOR=1.46; 95% CI: 0.74-2.88). They used an administrative database from a health care insurer and compared malformation rates with a cohort of mothers using other antidepressants. They only included liveborn children with malformations in their study. In another cohort study[5], an increased risk for cardiovascular malformations after first trimester use of paroxetine was found (adjOR=1.63; 95% CI: 1.05-2.53). After excluding women with putative confounding characteristics such as high BMI and use of specific other drugs, an increased OR for VSD and/or ASD after

maternal use of paroxetine was found (7 exposed cases, adjOR=3.23 95% CI: 1.30-6.65). They found no association for other SSRIs with cardiovascular defects. Both these cohort studies were included in a meta-analysis of six cohort studies and three case-control studies that concluded that the rate of heart defects in exposed and non-exposed infants closely approximated the rate found in the general population.[15] In a cohort study in British Columbia in which data from several databases, including maternal health and prescription databases, were linked to neonatal records, an increased incidence for ASDs was found when serotonin reuptake inhibitor monotherapy was compared to no exposure (adjusted risk difference 0.21, 95% CI: 0.05-0.36).[16] Paroxetine was the most commonly used SSRI, but the investigators did not analyse the use of paroxetine in particular and the occurrence of ASDs. Results from a recent population-based cohort study from Denmark found an increased risk for septal heart defects after the use of SSRIs and more specifically for sertraline and citalopram and after the use of more than one type of SSRI, but not for paroxetine.[7]

As we mentioned in the Introduction, case-control studies have more statistical power to detect moderately increased risks for specific birth defects. Two large case-control studies, using data from two birth defects surveillance systems, investigated the use of SSRIs in relation to several congenital anomalies.[8,9] Both studies found an increased risk for right ventricular outflow tract obstruction defects after the use of paroxetine (the NBDPS study covered seven exposed cases: adjOR=2.5; 95% CI: 1.0-6.0; while the Slone study covered six exposed cases: adjOR=3.3; 95% CI: 1.3-8.8). Both studies used non-malformed controls and the use of medication shortly before and during pregnancy was retrospectively determined by means of a telephone interview with the mother. Neither study made a statistical adjustment for multiple testing. In our study we could not find a significantly increased risk for right-sided defects, because we only had one paroxetine-exposed case with such a heart defect. A case-control study[10], who used data from health care databases on malformations and medication, only found an association between paroxetine and cardiac malformations when a daily dose of more than 25 mg was taken (5 exposed cases; adjOR,=3.07; 95% CI: 1.00-9.42). They only included liveborn children and the mother's actual use of the medication was not verified. No analyses were performed for specific heart defects.

In conclusion, results from our and other epidemiological studies on paroxetine and congenital (heart) defects are difficult to compare because of differences in study design, exposure and outcome definition. Results from a recent meta-analysis including 20 publications indicate an increased prevalence of combined heart defects associated with first trimester paroxetine use.[17] They also found that variability among individual study findings might be associated with data source, type of publication and age at ascertainment.

Cardiac defects are, however, also associated with several chromosomal and monogenetic disorders. Ongoing research has demonstrated that the genetic basis for heart defects is larger than previously expected.[18] It is possible that, in our study population, we may have a case (or cases) with an isolated heart defect, suffering from a chromosomal or monogenetic disorder that has not yet been discovered or diagnosed. In selecting the case group, the criterion requiring a post mortem examination was not applied. Therefore we cannot fully exclude the possibility that we may have included deceased cases with a heart defect and extra-cardiac defects in the case group. However, any misclassification of cases with an undiagnosed genetic disorder or extra-cardiac anomalies will bias the OR towards no effect.

For the controls, we excluded all children with a genetic disorder and an associated heart defect, and all children in whom the absence of a heart defect was not sufficiently well demonstrated. Because the rate of terminations of pregnancy for genetic disorders is increasing over time in the Netherlands, the excluded controls came more often from the birth years 2002-2006 and included more terminations, miscarriages and stillbirths than the included controls. There was however no association with the use of paroxetine. Thus, excluding controls with a heart defect or without a post mortem examination will not bias our results. The included controls more often came from the birth years 1997-2001 than the cases. The mean maternal age was higher for the controls than for the cases, because maternal age is a risk factor for chromosomal anomalies. Since certain chromosomal and monogenetic disorders are lethal and/or are subject to prenatal screening, there were more terminations, miscarriages and stillbirths among the controls. Maternal age and pregnancy outcome was not associated with exposure status, so we calculated ORs adjusted for year of birth alone. The adjusted ORs were similar to the crude ORs, indicating that year of birth was not a strong confounder. We did not calculate ORs adjusted for other potential confounders such as smoking, maternal disease or use of other (teratogenic) drugs because of the relatively small sample size. In addition it was not possible to take into account any confounding by indication, because good information on depression status of women not using antidepressants was not available.

Depression is associated with several life style factors that are risk factors for birth defects. Although we did not find significant differences for several of these life style factors, such as drinking habits, we cannot rule out the presence of unidentified confounding factors. On the other hand, there may be a plausible biological explanation for the possible teratogenic effect of paroxetine. SSRIs inhibit the re-uptake of serotonin (5-hydroxytryptamine, 5-HT) by binding to the serotonin uptake sites (transporters). This results in an increase of synaptic serotonin levels. Serotonin is known to mediate a wide variety of physiological effects, including developmental functions. Animal studies have shown that serotonin also plays a role in mouse cardiovascular morphogenesis.[19] It is

possible that properties of paroxetine that distinguish it from other SSRIs are associated with the specific teratogenic effects. The specific SSRIs differ in their pharmacokinetic properties.[20] Paroxetine is the most potent serotonin re-uptake blocker available, but its half-life varies depending on dose and duration of use. The cytochrome P450 isoenzymes play an important role in the extensive metabolism of paroxetine, with a high inter-individual variability.

In this study we used prospectively collected pharmacy data and verified the actual use with the mother. Misclassification of exposure might still have occurred if the mother obtained her medication through other sources than her pharmacist and did not reveal this in the telephone interview. However, because we used malformed controls and the same procedure for data collection for cases and controls any misclassification bias will most likely be non-differential. Misclassification of exposure might also have occurred because of the broadly defined exposure window that was not restricted to the period of cardiac development to allow for uncertainty in date of conception and period of medication use. The actual exposure time could also be longer than the period of use because it may take some time for the drug to be eliminated from the body. For these reasons a strictly defined exposure window might also introduce misclassification bias. Moreover, the actual exposure of the foetus to paroxetine is unknown. Measuring serum levels of paroxetine in the developing foetus is not a feasible option. A more appropriate approach might be to include genotypic factors indicating the metabolizing properties of mother and child in studies on teratogenic effects.

In conclusion, we found an increased OR for isolated ASD after maternal use of paroxetine in the month before conception and/or the first trimester, but not for isolated heart defects in general. The absolute risk for ASD remains small. Our results stress the importance of studying possible teratogenic effects of a specific drug on specific birth defects. Results from studies on the use of paroxetine and a possible association with heart defects have not been conclusive. This is possibly due to methodological differences and/or to overlooking biological factors. We therefore recommend that future studies should also include the analysis of biological factors, such as drug eliminating or metabolizing properties, in order to obtain more specific information on the teratogenic risks of paroxetine and other SSRIs.

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CHAPTER 6

General Discussion

When a new drug is put on the market, there is only limited information available on the possible teratogenic risks for various reasons. Post-marketing surveillance is therefore necessary to collect information on the safety of medication use in pregnancy in the human situation. One of the methods to monitor the safety of medication use in pregnancy systematically is through a birth defects case-control monitoring system with ongoing data collection on birth defects and maternal medication use. The potential of such a system, consisting of a prescription database (IADB.nl) and a population-based birth defects registry (Eurocat NNL) is explored in this thesis.

MONITORING DRUG USE IN PREGNANCY

During pregnancy, a large number of women use one or more types of drugs. Through monitoring we learn which drugs are frequently used and will, therefore, be important to study. Frequently used drugs with low teratogenic risk may be of greater importance to public health than high-risk drugs that are rarely taken by pregnant women. The IADB.nl, a population-based prescription database, is an important tool in monitoring the use of drugs among pregnant women. In the drug utilisation study performed with data from the IADB.nl, we found a first trimester prescription rate of 44% (chapter 2.1). The prescription rate increased in the second and third trimesters, due to an increase in the use of drugs that are typically prescribed for pregnancy-related physical complaints, symptoms and illnesses, such as nausea, anaemia, heartburn, and urinary tract or gynaecological infections.

The majority of the drugs prescribed for pregnancy-related symptoms are considered safe for use in pregnancy. Large numbers of pregnant women and women of child-bearing age have taken these drugs without any proven increase in the frequency of malformations or harmful effects on the foetus. The safety of drugs that are prescribed for chronic conditions or for occasional use has often not yet been determined or they are considered (potentially) harmful for the foetus. Results from the drug utilisation study showed that the drugs prescribed most frequently in the first trimester are dermatological corticosteroid preparations (3.9%), anti-bacterials for systemic use (6.3%), preparations for ear, eye, nose and throat complaints (5.2%), anti-emetics (5.8%), iron preparations (5.2%), folic acid and derivates (8.6%), and gynaecological anti-infectives (3.6%). However, these prescription rates are calculated for drug groups consisting of several specific drugs and drug classes with a common indication for prescribing. The actual prescription rates for specific medications are therefore much smaller.

Because we must study sufficient numbers of exposed children to draw valid conclusions on the safety of drugs, it may take some time to detect the teratogenic effect of a new drug. It is also important to monitor trends in use over a longer time period. The

drug utilisation study presented in Chapter 2.2 showed that, during a ten-year period, the use of a selective serotonin reuptake inhibitor (SSRI) in pregnancy increased from 12.2 to 28.5 per 1000 pregnancies. The use of paroxetine (in all SSRI exposed pregnancies) increased in that period from 38% to 60%, whereas the use of fluoxetine decreased from 38% to 20%. Since paroxetine is one of the SSRIs most commonly used by pregnant women, sufficient data are now becoming available to detect moderately increased risks for specific congenital malformations.[1-3] The safety of SSRIs that are less frequently used has not yet been established.

There are several limitations concerning the use of the IADB.nl in drug utilisation studies. First, the IADB.nl does not contain information on medication dispensed by hospital pharmacies, such as certain anti-cancer drugs, or directly prescribed by the treating physician, such as certain vaccinations. Second, the actual use of the prescribed medication is unknown and the length of the pregnancy is standardised at 39 weeks. Medication use may therefore be overestimated, if the mother discontinued taking the drug after she found out she was pregnant, or if use is associated with pre-term birth. Third, if a child could not be linked to the mother, or the pregnancy did not result in a live-born child, or the child has not yet been registered with the pharmacy, the pregnancy will not be identified. Failure to identify a pregnancy when the child is known can mostly be attributed to administrative reasons and selection towards drug-using families seems limited.[4] The detection rate may be improved using less strict criteria, but would most likely lead to a loss of sensitivity, which is not desirable. Since it may take some time for a newborn child to be registered with a pharmacy, the number of unidentified pregnancies may be larger in more recent years than in previous years. This will most likely result in an under-estimation of maternal drug use in more recent years. The usefulness of the IADB.nl could be improved if the IADB.nl could be linked to a database in which births are registered, such as the nationwide Dutch Perinatal Registry. The Dutch Perinatal Registry contains information on the length of pregnancy and on pregnancy outcome, including general information on congenital malformations. However, in studies evaluating the risk of drugs on birth outcome, more precise data is necessary on the birth outcome and timing of drug exposure, and administrative datasets alone are therefore insufficient. For this purpose Eurocat NNL collects very detailed information on congenital malformations and maternal medication use.

SYSTEMATIC SURVEILLANCE OF BIRTH DEFECTS AND MATERNAL MEDICATION USE

One of the major objectives of a birth defects registry is the identification of possible new teratogens at an early stage. Monitoring the prevalence of birth defects over time is not a

sufficiently sensitive method for detecting possible new teratogenic drugs, since known teratogenic drugs, such as certain anti-epileptic drugs, have not caused a detectable increase in all, or in specific, birth defects. It is therefore necessary to use other methods.

In chapter 4, a signal is described that was found in a systematic surveillance study in which the database was screened for combinations of drugs and malformations that are disproportionately present compared to the rest of the database. Such a surveillance study generates a lot of results, which cannot simply be adopted. The large number of tests performed will undoubtedly cause false-positive results. In a case-control surveillance study a number of criteria are set in order to limit the number of tests to be performed and thus the chance of false-positive associations. However, the chance of missing a real association will increase when using more strict inclusion criteria. Because the purpose of a surveillance study is to generate signals that have to be further evaluated, stringent adjustment for multiple testing is not necessary. The criteria chosen in the surveillance study presented in chapter 4 did not allow us to identify associations between very rare medications and rare birth defects or rare patterns of defects, since only birth defects with 10 or more affected children and foetuses, and medication with 10 or more first trimester exposures were included.

To distinguish real signals from false-positive results, it is also important to evaluate the possible signals on a qualitative basis. The qualitative analyses should include a detailed examination of malformations and exposure and additional case-control analysis with adjustment for possible confounders. Evidence for a real teratogenic effect increases if the malformations of the exposed cases are homogeneous and the exposure occurred in a biologically plausible period (before or at the time of development of the effect), and if the association remains statistically significant in an additional case-control analysis, using a well-chosen control group. A plausible biological pathway adds to the evidence, but is not always necessary, since for many birth defects and teratogenic effects the causal pathway has not yet been identified. Nevertheless, even when a signal is still valid after the qualitative analysis, it is possible that the finding may have occurred by chance. Confirmation using other data, or the re-occurrence of the association in the same dataset after more data has been collected, can provide definitive proof for a teratogenic effect.

Because the systematic screening of the database for combinations of specific birth defects and drugs that are disproportionately present requires a certain number of exposed registrations, it is also advisable to periodically search the database for very rare exposures, such as to certain new drugs, and to evaluate any birth defects that occur after these exposures. Again, such an individual evaluation of exposed cases can only generate signals that need to be verified in other databases.

Another approach that has to be further explored, is to compare the first trimester exposure rate of specific drugs among cases with specific birth defects with the first

trimester exposure rates in the general pregnant population estimated from the IADB.nl. This methodology is also referred to as case-population surveillance.[5] However, application of this methodology may be limited to medications used in treatment of chronic conditions, since compliance for medications for short term treatment is more likely to be low.[6]

CASE-CONTROL STUDIES

After a signal is detected through case reports or a surveillance study, the findings need to be replicated or elucidated by many subsequent studies. Consistency of findings adds to the evidence for causality. However, results from several studies are often inconsistent and therefore difficult to interpret. In particular, studies on weak to moderate associations are sensitive to several forms of bias, which may not be evident from the study design. Whereas observational cohort studies are suitable for identifying high-risk teratogens, case-control studies can reveal moderately increased risks for specific birth defects. The Eurocat NNL database is designed to conduct explorative and confirmative case-control studies on possible risk factors for birth defects, with an emphasis on maternal medication use. The following sections will discuss some of the methodological challenges for these case-control studies with reference to Eurocat NNL.

Birth defects are not, in general, a well-defined outcome measure

The prevalence of major birth defects generally lies between 2–3%. The cause of the majority of them is unknown, but both exogenous and genetic factors are most likely involved. Birth defects as a group are very heterogeneous and, from an aetiological point of view, it is not correct to consider birth defects in general as a single outcome. Moderate teratogens can cause specific birth defects, but will not cause all types of birth defects. In case-control studies, analyses should therefore be performed using case groups that are as homogeneous as possible, consisting of a single birth defect or of a group of birth defects with a (theoretically) common aetiology. Furthermore, it is desirable to analyse cases with isolated defects separately from cases in which the defect is associated with a syndrome or other defects (multiple malformed cases), because the aetiology of the birth defect under study in syndromic and multiple malformed cases may well differ from that in isolated cases.

Eurocat NNL collects information on the malformations from medical records and pathology reports. The reporting of children and foetuses with birth defects is not biased with regard to maternal medication use, because active case ascertainment and multiple sources are used. Malformations (up to ten per registered case) are coded using the ICD-9 and ICD-10 classification system (with extension from the British Paediatric

Association). To facilitate the identification of homogeneous case groups, a diagnostic category is attributed to each case, indicating if the malformations are present as isolated malformations, as multiple malformations, or as part of a (genetic) syndrome. A clinical geneticist reviews the coding of each case that has more than one malformation or a (genetic) syndrome diagnosis.

Medication use in pregnancy: importance of specificity and time of exposure

The use of pharmacy data in Eurocat NNL enables not only the study of possible teratogenic risks of specific drugs but also to take into account the timing of exposure.

Potential teratogenic properties are not equally shared among the specific drugs that belong to the same drug class. A classic example is that of thalidomide and glutethimide, which are chemically related and have sedative properties. It is well known that thalidomide causes severe birth defects, whereas glutethimide does not.[7] Among the SSRIs, paroxetine in particular has also been associated with congenital heart defects, but not all SSRIs can be placed together (chapter 5,[8-10]). Because the aetiology is still unknown for many birth defects, we do not know whether the possible teratogenic effect is caused by the shared chemical structure of a drug class or the chemical component that differentiates one drug from the others within that drug class. It is therefore preferable to study the possible teratogenic risks of a specific medication.

In general, the developing embryo is most vulnerable to teratogenic exposure in the first three months after conception when all the major structures and organs are formed. The development of embryonic structures follows a distinct pattern and the potential consequences of a teratogenic effect depends on the stage at which the teratogen interacts with the embryonic development and how it interacts with the embryonic development.[11] Although the prescription date for a medication and the gestational age at delivery are often recorded in the Eurocat database, the exposure definition usually includes the period from 1 month before conception and the first trimester (14 weeks of gestation). This period is chosen to allow for uncertainty in the date of conception and in the exact period of medication use (which may be difficult to establish, for instance for medications prescribed for 'use if necessary'). Also, it may take some time for the drug to be eliminated from the body, so that the actual exposure time is longer than the period of use. However, a broadly defined period may introduce misclassification of exposure if the exposure occurred after the development of the embryonic structure involved in the birth defect. A case-control study on folic acid antagonists and the risk of neural tube defects showed that use of trimethoprim, an antibiotic and folic acid antagonist, in the month before pregnancy or in the third month after the last menstrual period was not associated with an increased risk of neural tube defects, whereas the use of trimethoprim in the first and second months after last menstrual period (period in which the neural tube closes)

did show an increased risk.[12]

The use of an appropriate control group

The selection of an appropriate control group in case-control studies on the possible risks of maternal medication use is of great importance. The control group should be sampled from the same source population as the cases. In theory, a control would be selected as a case if he/she had developed the birth defect under study. The sampling of controls from the source population has to be unrelated to the exposure of interest. Usually, healthy controls without birth defects are preferred. However, Eurocat NNL does not collect information on non-malformed children, so that children and foetuses with other malformations than those under study and/or genetic disorders are used as controls. The use of other malformed controls may introduce selection bias if the drug under study also causes other malformations; this would lead to an underestimation of the effect. An alternative is to use controls with a chromosomal or monogenetic disorder, assuming that the origin of these disorders is most likely not related to maternal medication use. We compared use of prescription medication in the first trimester by mothers of children with a genetic disorder with the prescription rate in the general pregnant population (chapter 3). We saw no significant differences, indicating that the medication use in mothers of children with a genetic disorder was representative for the general pregnant population. However, the use of a control group with genetic disorders should be considered carefully with respect to the methodological consequences.

First, the presence of possible confounding factors, in particular maternal age, should be scrutinised. Maternal age is associated with an increased risk for chromosomal anomalies and might be associated with the use of particular drugs, such as fertility drugs. In that case, age-adjusted odds ratios should be calculated. Second, since a possible relationship between drug exposure and associated defects in infants with a genetic disorder cannot be ruled out, the choice of the most appropriate genetic control group should be considered carefully for each case-control study and this will depend on the study hypothesis and the possibilities of the study-setting. For example, in a case-control study on the use of paroxetine and the occurrence of heart defects, we excluded infants with an associated heart defect and deceased foetuses and infants for which the absence of a heart defects had not been sufficiently determined from the control group that consisted of children with a chromosomal or monogenetic disorder (chapter 5). Third, the use of a genetic control group instead of a control group consisting of other malformed children usually implies there will be a smaller number of controls and therefore less power to detect an association (resulting in large confidence intervals).

The rationale for using controls with a genetic condition is based on the assumption that maternal medication use is not involved in the development of the genetic defect.

Although some known teratogens express mutagenic activity in bioassays[13], associations between maternal medication use and genetic aberrations, such as deletions, mutations or chromosomal abnormalities in the offspring have not yet been identified in the human situation. However, the role of epigenetic events (in which the exposure to environmental factors leads to an alteration in gene expression) is increasingly recognised in teratogenic mechanisms.[14] It would be advisable for Eurocat NNL to expand the data collection to non-malformed children, in order to obtain a non-malformed control group. The possibility of recall bias can be reduced if prospectively collected data, such as pharmacy data, is used for both cases and controls.

Confounding factors

In case-control studies on maternal medication use and the risk of (specific) birth defects, the possible association under study can be complicated by the presence of several confounders. Confounding factors are those that are related both to outcome and exposure. A significant association between an exposure and outcome may be entirely attributed to these confounding factors. For instance, an association between fertility drugs and trisomy 21 could be entirely attributed to maternal age, since both the use of fertility drugs and the occurrence of trisomy 21 are related to maternal age. It is therefore important to identify possible confounding factors and adjust for them in the analysis. Confounders which have been identified and can be easily measured are year of birth, race, geographical region (in international studies), maternal age, smoking habits, alcohol intake, use of other medication and folic acid supplements, underlying disease of the mother, etc. Socio-economic status (measured as educational level, annual income, or based on the home address) is frequently also considered as a confounding variable. The socio-economic status itself is not a causative factor, but is an indicator of life style factors and health status. Eurocat NNL collects information on all these possible confounding factors through the parental questionnaire.

Besides these exogenous factors, biological factors could also be important confounders or effect modifiers. Polymorphisms of genes involved in the folate pathway, such as the gene for 5,10-methylenetetrahydrofolate reductase (MTHFR), have been frequently studied in association with folic acid intake, homocysteine status and risk of neural tube defects, orofacial clefts and other folic-acid-sensitive birth defects.[15-17] Similarly, polymorphisms in detoxification genes or genes encoding drug metabolism enzymes, such as cytochrome P450, could indirectly affect the possible teratogenic risk, by influencing the rate of metabolism of the mother or the developing child. Yet, only a few studies have investigated the interaction of maternal medication use and genetic factors on the risk of birth defects.[18] And, as mentioned above, some environmental factors, such as maternal medication use, may influence gene expression, which could

lead to abnormal embryonic development (epigenetic effects). In order to study the possible interaction between genetic factors and maternal medication use, biological materials, such as blood samples from the child, or from the parents and child, need to be collected on a routine basis.

Sample size considerations

Although case-control studies on the possible risks of maternal medication use have more power to identify small to moderate risks for specific birth defects, it is particularly the rarity of the exposure that limits the power that can be achieved. In Table 1, the sample size needed to detect weak (OR=2), moderate (OR=5) and strong (OR=10) associations is shown for several drug use rates. The number of births that need to be monitored in order to reach a sufficient number of cases is also shown for several prevalence rates. To detect a weak association (OR=2) for a birth defect that is relatively common (prevalence rate of 30 per 10,000 births) in combination with a relatively common exposure (4 per 100 pregnancies), we need approximately 700 cases, or coverage of 230,000 births. In the current situation, with approximately 20,000 births per year in the registration area, more than 10 years of monitoring is needed to achieve the required number of cases. To study the association between neural tube defects and maternal use of anti-epileptics, over 1,000 cases (or coverage of 1.1 million births) are needed to detect an OR of 5. From Table 1 it is clear that Eurocat NNL is able to detect moderate and strong associations for relatively common and rare birth defects (over a maximum period of 15 years of monitoring), but that it is hardly able to study possible teratogenic drugs for very rare specific birth defects. Eurocat NNL also lacks sufficient power to study medications that are very rarely used in pregnancy.

There are several options for increasing the sample size. The first option would be to increase the registration area of Eurocat NNL. In the current situation, Eurocat covers ±10% of all births in the Netherlands and expansion of the registration area to the rest of the Netherlands would thus increase the power of studies dramatically. However, such an expansion to the rest of the Netherlands would be very costly. The data collection is labour intensive and includes active case ascertainment using multiple sources, verification of the diagnosis in medical records, procedures concerning the request for informed consent, collection of data on possible risk factors, and acquisition of pharmacy data. An expansion of the registration area does not appear feasible at this time.

The second option to increase sample size would be to combine data with other birth defects registries. Eurocat NNL is a member of the European Concerted Action on Congenital Anomalies and Twins (EUROCAT), a network of population-based registries for the surveillance of congenital anomalies. Currently, this network is made up of 43 registries from 20 countries, covering 1.5 million births in Europe per year[19], but practices regarding

Table 1. Sample size and number of births covered in a case-control study for several levels of drug exposure rates and malformation prevalence rates.

Exposure rate in controls	OR	Case: control ratio	Sample size		Births covered at prevalence rate (per 10,000)		
			Cases	Controls	30	10	1
4%	2	1:1	686	686	228,667	686,000	6,860,000
		1:2	494	988	164,667	494,000	4,940,000
		1:4	397	1,566	132,333	397,000	3,970,000
	5	1:1	98	98	32,667	98,000	980,000
		1:2	68	136	22,667	68,000	680,000
		1:4	53	212	17,667	53,000	530,000
	10	1:1	40	40	13,333	40,000	400,000
		1:2	28	56	9,333	28,000	280,000
		1:4	21	84	7,000	21,000	210,000
1%	2	1:1	2,597	2,597	865,667	2,597,000	25,970,000
		1:2	1,866	3,732	622,000	1,866,000	18,660,000
		1:4	1,494	5,976	498,000	1,494,000	14,940,000
	5	1:1	355	355	118,333	355,000	3,550,000
		1:2	244	488	81,333	244,000	2,440,000
		1:4	186	744	62,000	186,000	1,860,000
	10	1:1	136	136	45,333	136,000	1,360,000
		1:2	92	184	30,667	92,000	920,000
		1:4	68	272	22,667	68,000	680,000
0.3%	2	1:1	8,549	8,549	2,849,667	8,549,000	85,490,000
		1:2	6,135	12,270	2,045,000	6,135,000	61,350,000
		1:4	4,910	19,640	1,636,667	4,910,000	49,100,000
	5	1:1	1,154	1,154	384,667	1,154,000	11,540,000
		1:2	792	1,584	264,000	792,000	7,920,000
		1:4	601	2,404	200,333	601,000	6,010,000
	10	1:1	434	434	144,667	434,000	4,340,000
		1:2	292	584	97,333	292,000	2,920,000
		1:4	215	860	71,667	215,000	2,150,000

Sample size estimates were calculated with Epi Info (TM) version 3.5.1 based on a two-sided test with a 95% confidence interval and 80% statistical power.

Cells with grey shading represent combinations that need over 15 years of monitoring 20,000 births per year in order to collect the required number of cases.

Note 1. Examples of drugs with exposure rates near the exposure rate of interest: corticosteroids, gynaecological anti-infectives (4%), antihistamines for systemic use (1%), anti-epileptics (0.3%).

Note 2. Examples of birth defects with prevalence rates near the prevalence rate of interest: ventricular septum defects, dysplasia of the hip (30 per 10,000 births); neural tube defects (10 per 10,000 births), gastroschisis, penoscrotal hypospadias (1 per 10,000 births)

drug exposure information vary widely between registries. If it is recorded at all, data on maternal medication use is mainly taken from obstetric records, while some registries use maternal interviews after birth or linkage with a pharmacy database, resulting in a large variation of quality of information on maternal medication use.[20] Nevertheless, the EUROCAT network has the potential to perform post-marketing surveillance studies. Using data from 19 registries with validated data on maternal anti-epileptic drug use, we performed a case-control study on the possible association between maternal use of lamotrigine and the occurrence of orofacial clefts, covering over 5,500 cases with orofacial clefts and 80,000 non-chromosomal controls with other malformations. No significantly increased risk was found and a three-fold risk could be excluded.[21] The potential of the EUROCAT network for drug safety surveillance could be even greater if more registries were able to use sources of prospectively collected data on maternal medication use, such as pharmacy data, and the ATC classification system for the coding of drugs.

Eurocat NNL also contributes data to the Malformation Drug Exposure (MADRE) database that was set up within the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), a network for registries of congenital anomalies from all over the world. MADRE is a drug safety surveillance system, which only includes cases with birth defects and a positive history of first trimester medication use. The primary goal is to generate signals and hypotheses to be tested further by other registries[22], but case-control studies on a specific combination of malformation and a drug are also performed.[23] As in the European network, the quality of the information on maternal medication use varies greatly. To reduce the chance of spurious findings, associations are evaluated across participating programmes, so that whether a given association holds across multiple areas and countries, or among programs can be assessed using different ascertainment approaches.

CONCLUSIONS AND RECOMMENDATIONS FOR THE FUTURE

Since medication use in pregnancy is very common and little is known on possible teratogenic risks for many of the drugs used, it is of great importance to study possible risks of medication use in pregnancy. Although the risk for a specific birth defect may be small for an individual woman, the public health relevance may be large, certainly if the drug is commonly used in pregnancy. Knowledge on possible teratogenic risks of a specific medication can also help the treating physician and mother-to-be to make an informed decision on whether to continue treatment, to switch to another type of drug, or to discontinue treatment. This decision should preferably be taken before the woman becomes pregnant. Finally, the results of epidemiological studies on the possible teratogenic risks of medication use in pregnancy can lead to a better understanding of

the pathogenesis of birth defects and pharmacological effects of certain drugs.

Eurocat NNL, a population-based birth defects registry, and the IADB.nl, a population-based prescription database, together constitute a birth defects case-control monitoring system. Both initiatives cover the same geographical area. In the IADB.nl the use of prescription drugs among women of fertile age and in pregnancy can be monitored to identify drugs that are frequently used in pregnancy, but also to investigate whether potentially teratogenic drugs or certain newly marketed drugs are used by pregnant women. The effectiveness of monitoring medication use in pregnancy could be improved if the data from the IADB.nl could be linked to the perinatal registry. It would be advisable to explore if such a linkage is feasible.

Eurocat collects detailed information on malformations and on medications used in the three months before conception and during pregnancy in order in order to evaluate the possible teratogenic risk of a drug for specific birth defects. Signals of possible new teratogenic drugs can be generated from the database by the systematic surveillance of specific birth defects and specific medications. Identifying the possible teratogenic effects of newly marketed drugs, or drugs which are rarely used in pregnancy, will require individual evaluation of exposed cases in the database. The signals that are found then need to be further investigated in other datasets.

Possible teratogenic risks of specific medications for specific birth defects can be evaluated in case-control studies. In order to increase the possibilities for conducting these case-control studies in the Eurocat database, the use of non-malformed controls, with prospectively collected data on maternal medication use, is now strongly recommended. Since it is becoming clear that there are both exogenous and genetic factors involved in the majority of the birth defects of unknown cause, including biological and genetic factors in studies on possible risk factors should be considered. This will require the routine collection of blood samples, such as on neonatal blood cards, or buccal swabs of the mother and child. Finally, because of the low prevalence of use of a specific medication in the first trimester of pregnancy, identifying a moderately increased risk for specific birth defects will require a large number of cases. Eurocat NNL's relatively small registration area with a maximum of 20,000 births per year is therefore the major limitation in studying the possible teratogenic risks of maternal medication use in the Eurocat database. There are European and worldwide networks for registrations of congenital anomalies (EUROCAT and ICBDSR): the birth defects registries in these networks which have good, prospectively collected, information on maternal medication use, coded according to the ATC classification system, should work together in systematically surveying birth defects and maternal medication use. Other birth defects registries should be encouraged to start collecting data on maternal medication use. By combining data from several birth defects registries with good information on maternal medication use, it is possible to compile

a large enough sample size to identify possible teratogenic risks of medication use in pregnancy as early as possible.

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Summary

Post-marketing surveillance of medication use in pregnancy is of great importance because many women use drugs during pregnancy whereas the possible teratogenic risks are largely unknown. In this thesis, the usefulness of an ongoing birth defects case-control monitoring system in studying the safety of medication use in pregnancy is explored.

Chapter 1 describes several study designs in the post-marketing surveillance of medication use in pregnancy. *Drug utilisation studies* are primarily suitable for gaining insight into the types of drugs used and the prevalence of use in specific time periods before conception and during pregnancy. However, these studies are not suitable for identifying the possible teratogenic risks. Such effects are sometimes detected by alert clinicians, who connect an unusual pattern of malformations or a very rare birth defect to the use of an unusual medication by the mother in pregnancy. These initial observations, presented as *case-reports* or *case-series,* need to be confirmed by epidemiological studies. *Cohort studies* include women who have taken a particular drug in pregnancy and then follow them to determine the pregnancy outcome. The reference group consists of women who did not use the drug of interest in pregnancy. Cohort studies are primarily suitable for identifying high-risk teratogens, because the number of exposed pregnancies is mostly too small to detect mild to moderate risks for birth defects. *Case-control studies* look at cases with a specific birth defect and compare them to a control group with reference to the drug of interest. Case-control studies have more power to detect mild to moderate risks for specific birth defects in association with relatively commonly used drugs. In a *birth defects case-control monitoring system,* information on birth defects and maternal medication use is collected on an ongoing basis. Within such a system it is possible to perform multiple case-control studies on several types of birth defects in association with a wide range of drugs used in pregnancy. Eurocat Northern Netherlands (Eurocat NNL), a population-based birth defects registry, constitutes together with the Interaction Database (IADB.nl), a prescription database, such a birth defects case-control monitoring system.

Chapter 2 presents two drug utilization studies on maternal medication use in pregnancy with data from the IADB.nl. In the first study prescription of drugs to women in the period from two years before to three months after pregnancy was investigated with reference to the type of drugs used and the foetal risk classification. A cohort study was performed in which 5,412 women were included who gave birth to a child between 1994-2003 and for whom complete pharmacy records were available. Drugs were classified into 3 categories: (I) drugs for chronic conditions, (II) drugs for occasional use, and (III) drugs for pregnancy-related symptoms and classified according to the Australian classification system. The prescription rate was calculated as the number of women per 100 who received one or more prescriptions for a given drug within a specified time period. In total, almost

80% of the women received at least one prescription during pregnancy. The increase in prescription rate during pregnancy from 44% in the first trimester to 61% in the third trimester was caused by an increase in prescription rate for drugs for pregnancy-related symptoms. The prescription rates for most drugs for chronic diseases and for occasional use decreased during pregnancy. The results further showed that, although potentially harmful drugs are not frequently prescribed in general, prescription of these drugs is more commonly associated with drugs for occasional use than with drugs for chronic conditions. This warrants more cautious prescription of drugs to healthy women in the fertile age.

The second study was performed after the publication of several studies in which a relationship between the use of selective serotonin re-uptake inhibitors (SSRIs) and the occurrence of birth defects and other adverse pregnancy outcomes was described. The extent of SSRI use before and during pregnancy and its trend over a 10-year period in the Netherlands was investigated. This study included 14,902 women who gave birth to a child between 1995-2004, and for whom complete pharmacy records were available from three months before pregnancy up to delivery. The exposure rate and 95% confidence interval (CI) were calculated as the number of pregnancies per 1000 that were exposed to an SSRI in a defined period (per trimester or in the year preceding delivery). We calculated the exposure rates for 2-year periods: 1995/1996, 1997/1998, 1999/2000, 2001/2002 and 2003/2004. Trends in exposure rates were analysed using the X^2-test for trend. A total of 310 pregnancies were exposed to an SSRI in the year preceding delivery. There was a significant increase in exposure rate from 12.2 (95%CI: 7.0-19.8) in 1995/1996 to 28.5 (95%CI: 23.0-34.9) in 2003/2004, comparable to the increase in exposure in women of fertile age.

In case-control studies on teratogenic risks of maternal drug use during pregnancy, the use of normal or malformed controls may lead to recall-bias or selection bias. This can be avoided by using controls with a genetic disorder since the genetic disorder is probably not caused by maternal medication use. However, researchers are hesitant to use these as controls because it is unknown whether their selection is independent of exposure status. Chapter 3 presents a study that investigated whether first trimester drug use among mothers of children with genetic disorders was representative for the 'general pregnant population'. From the Eurocat database, 565 mothers of infants with a genetic disorder born between 1998-2004 were selected (called the 'genetic population'). The first trimester exposure rate was calculated for prescription-only drugs as the number of exposed women per 100. The exposure rates in the 'genetic population' were then compared with those in the 'general pregnant population', consisting of 10,870 mothers from the IADB.nl who gave birth to a child in the same period, by calculating the rate ratio (RR) and 95% CI. The

mean maternal age at birth was significantly higher for the genetic population (p=0.000). In the genetic population, a higher use was only found for anti-migraine medication (RR=2.7, 95% CI=1.0-7.8) and for ovulation stimulants (RR=1.6; 95% CI=1.0-2.6), but after adjustment for maternal age, the difference in use of ovulation stimulants disappeared. We therefore concluded that, except for anti-migraine medication, first trimester drug use among mothers of infants with genetic disorders seems to be representative for the general pregnant population.

One of the objectives of a birth defects' registry is to identify possible new teratogenic effects at an early stage. Chapter 4 describes a signal, found in a surveillance study in which combinations of specific birth defects and drugs used in the first trimester of pregnancy were systematically evaluated. The database of Eurocat NNL, birth years 1997-2007, was systematically screened for combinations of drugs and malformations that were disproportionately present compared to the rest of the database. Combinations with at least three exposed cases and p<0.01 (Fisher's Exact test) were subjected to detailed analyses, including a detailed specification of malformation and timing of exposure and additional case-control analyses. Among the significant associations found, one between maternal use of fluoxetine, an SSRI, and infantile hypertrophic pyloric stenosis (IHPS) was of particular interest. In total 3/178 (1.7%) of the children with an IHPS were exposed to fluoxetine in the first trimester compared to 8/4077 (0.2%) fluoxetine exposures among the children with other malformations (p=0.009, OR=8.7; 95% CI: 2.3-33.2). The three exposed cases were all isolated and fluoxetine was used in gestational weeks 4–8, 2–8, and 10 weeks before conception to 19 weeks gestation, respectively. In additional case-control analyses, using controls with a genetic disorder and after adjusting for maternal age, and smoking in the first trimester of pregnancy, the adjusted odds ratio was 9.8 (95% CI: 1.5–62.0). Although chance cannot be ruled out, the association between IHPS and fluoxetine was considered as a signal that needs to be verified in other cohorts.

Chapter 5 presents a case-control study that investigated the possible association between the use of paroxetine in early pregnancy and the occurrence of specific heart defects. From the Eurocat NNL database all registrations from birth years 1997-2006 were selected. Cases were defined as foetuses and children with isolated heart defects, while the controls were foetuses and children with a chromosomal or monogenic disorder with no heart defect. Children for whom there was no information on maternal medication use and deceased children and foetuses who were not examined post mortem were excluded. First trimester exposure to paroxetine was compared between cases and controls by calculating adjusted odds ratios (adjOR). Included were 678 cases with isolated heart defects and 615 controls. The first trimester exposure rate was 1.5% for cases and 1.0% for

controls. After excluding mothers who used paroxetine outside the first trimester, or who had used another type of SSRI, we found no significantly increased OR for heart defects overall (10 exposed cases, adjOR=1.5; 95% CI: 0.5-4.0), but we did find a significantly increased OR for atrium septum defects (3 exposed cases, adjOR=5.7; 95% CI: 1.4-23.7). These results suggest that the use of paroxetine in early pregnancy is associated with an increased risk of atrium septum defects. Leading on from this particular study, we would further stress the importance of studying possible teratogenic effects of a drug preferably with respect to well-specified malformations.

In Chapter 6 the feasibility of a birth defects case-control monitoring system in which Eurocat NNL and the IADB.nl collaborate is discussed and recommendations for improvement are made. Drug utilisation studies on medication use in pregnancy can be performed within the IADB.nl, but this database can only be used to identify pregnancies that result in live-born infants and it does not include information on length of the pregnancy or pregnancy outcome. Therefore, the effectivity of monitoring medication use in pregnancy could be improved if data from the IADB.nl could be linked to the Dutch perinatal registry. It would be advisable to explore the feasibility of such a linkage.

The Eurocat database has been designed to conduct case-control studies. The database contains detailed information on malformations, which makes it possible to create homogeneous case groups. This is important because birth defects are very heterogeneous and no teratogenic drug will cause an increase in all birth defects. Another advantage is that the prospectively recorded pharmacy data allows a very strict definition of the exposure period, or can at least identify cases in which the exposure occurred after the period in which the defect developed. Because Eurocat does not collect information on non-malformed children, children with a genetic disorder or with other malformations are used as the controls in case-control studies. In order to increase the possibilities for conducting case-control studies on possible teratogenic risks for birth defects, the use of non-malformed controls, with prospectively collected data on maternal medication use, is strongly recommended. Furthermore, since both exogenous and genetic factors are involved in the majority of birth defects of unknown cause, the inclusion of biological and genetic factors in studies on possible risk factors should be considered.

Finally, Eurocat 's relatively small registration area is the most important limitation in studying possible risks of medication use with this database. Identification of a moderately increased risk for specific birth defects will require a large number of cases, which can only be reached by monitoring birth defects in a larger area, over a longer period of time, or through collaboration with other birth defects registries, the latter being the most efficient way. By combining data from several birth defects registries with good information on maternal medication use, it is possible to compile a large enough sample size to identify potential teratogenic risks of medication use in pregnancy as early as possible.

Samenvatting

Veel vrouwen gebruiken medicijnen tijdens hun zwangerschap. Van veel van deze medicijnen zijn de mogelijke teratogene effecten vaak nog niet goed bekend. Onderzoek naar welke medicijnen gebruikt worden tijdens de zwangerschap en naar mogelijke nadelige effecten hiervan op het ongeboren kind (post-marketing surveillance) is daarom zeer belangrijk. In dit proefschrift wordt onderzocht in hoeverre een doorlopende case-controle monitoring van aangeboren afwijkingen gebruikt kan worden om onderzoek te doen naar veiligheid van medicijngebruik tijdens de zwangerschap.

In Hoofdstuk 1 worden diverse vormen van onderzoek beschreven die gebruikt worden in de post-marketing surveillance van medicijngebruik in de zwangerschap. Studies naar geneesmiddelengebruik *(drug utilisation studies)* dienen voornamelijk om inzicht te verkrijgen in welke geneesmiddelen gebruikt worden tijdens de zwangerschap en hoe vaak. Deze studies zijn echter niet geschikt om onderzoek te doen naar mogelijke teratogene effecten. In sommige gevallen worden teratogene effecten ontdekt door oplettende artsen die een verband vermoeden tussen een zeldzame aangeboren afwijking of een bijzonder patroon van aangeboren afwijkingen bij een kind en het gebruik van een ongewoon medicijn tijdens de zwangerschap door de moeder. Deze observaties, beschreven in zogenaamde *case-reports of case-series*, moeten nader onderzocht worden in epidemiologische studies. In *cohort studies* worden vrouwen die een specifiek medicijn gebruiken tijdens de zwangerschap gevolgd om de uitkomst van de zwangerschap vast te kunnen stellen. De referentie groep bestaat uit zwangere vrouwen die het specifieke medicijn niet hebben gebruikt. Cohort studies zijn voornamelijk geschikt om teratogene medicijnen te identificeren die een hoog risico geven op aangeboren aandoeningen, omdat het aantal blootgestelde zwangerschappen vaak te klein is om een licht tot matig verhoogd risico op aangeboren aandoeningen te kunnen ontdekken. In *case-controle studies* wordt het medicijngebruik tijdens de zwangerschap vergeleken tussen moeders van kinderen met een specifieke aangeboren afwijking en moeders van kinderen zonder deze afwijking. Case-controle studies hebben meer power om licht tot matig verhoogde risico's op specifieke aangeboren afwijkingen te ontdekken voor medicijnen die relatief vaak gebruikt worden. In een *case-controle monitoring systeem* voor aangeboren afwijkingen, wordt informatie over aangeboren afwijkingen en maternaal medicijngebruik verzameld op een doorlopende basis. Met een dergelijk systeem is het mogelijk om verschillende case-controle studies uit te voeren voor diverse aangeboren afwijkingen in relatie tot diverse medicijnen die tijdens de zwangerschap gebruikt worden. Eurocat Noord Nederland (Eurocat NNL) is een registratie voor aangeboren afwijkingen. Samen met de Interactie Database (IADB.nl), een database met informatie over afgeleverde recept-geneesmiddelen, vormen zij een case-controle monitoring systeem voor aangeboren afwijkingen.

Hoofdstuk 2 beschrijft twee studies naar geneesmiddelengebruik tijdens de zwangerschap. Voor deze studies is gebruik gemaakt van gegevens van de IADB.nl. In de eerste studie is onderzocht welke medicijnen voorgeschreven worden en hoe vaak aan vrouwen in de periode van twee jaar voor hun zwangerschap tot 3 maanden na de bevalling. Deze cohort studie bevatte complete apotheekgegevens van 5.412 vrouwen die bevallen zijn in de periode 1994-2003. De medicijnen werden in drie groepen ingedeeld: (I) medicijnen voor chronische aandoeningen, (II) medicijnen voor tijdelijk en kortdurend gebruik en (III) medicijnen voor zwangerschapsgerelateerde klachten. Medicijnen werden tevens geclassificeerd naar foetaal risico volgens het Australische classificatie systeem. De 'prescription rate' werd berekend als het aantal vrouwen per 100 dat een specifiek medicijn op recept voorgeschreven kreeg in een bepaalde tijdsperiode. In totaal, kreeg bijna 80% van de vrouwen tenminste één medicijn op recept voorgeschreven tijdens haar zwangerschap. De 'prescription rate' steeg van 44% in het eerste trimester van de zwangerschap naar 61% in het derde trimester. Deze stijging werd veroorzaakt door een stijging in het voorschrijven van medicijnen voor zwangerschapsgerelateerde klachten. De 'prescription rate' voor de meeste medicijnen voor chronische aandoeningen en voor medicijnen voor tijdelijk en kortdurend gebruik daalden tijdens de zwangerschap. Uit de resultaten kwam ook naar voren dat potentieel schadelijke medicijnen niet frequent voorgeschreven worden, maar dat het gebruik van deze medicijnen vaker voorkomt bij medicijnen voor tijdelijk gebruik dan bij medicijnen voor chronische aandoeningen. Voorzichtigheid is daarom geboden bij het voorschrijven van medicijnen aan gezonde vrouwen in de vruchtbare leeftijd.

De tweede studie werd uitgevoerd nadat verschillende studies waren verschenen waarin associaties tussen het gebruik van selectieve serotonine heropname remmers (SSRIs) en het ontstaan van aangeboren afwijkingen en andere negatieve zwangerschapsuitkomsten werden beschreven. In deze studie is het gebruik van SSRIs voor en tijdens de zwangerschap beschreven over een periode van 10 jaar. In totaal werden 14.902 vrouwen geïncludeerd die bevallen zijn in de periode 1995-2004 en van wie complete apotheek data beschikbaar was over de periode van 3 maanden voor de zwangerschap tot aan de bevalling. De expositie rate en het 95% betrouwbaarheidsinterval (BI) werden berekend als het aantal zwangerschappen per 1.000 die blootgesteld werden aan een SSRI in een bepaalde periode (trimester of het jaar voorafgaand aan de bevalling). Expositie rates werden berekend voor 2-jaar periodes: 1995/1996, 1997/1998, 1999/2000, 2001/2002 and 2003/2004. Trends in expositie rates werden getest met behulp van de Chi kwadraat test voor trend. In totaal waren 310 zwangerschappen blootgesteld aan een SSRI in het jaar voorafgaand aan de bevalling. De expositie rate steeg van 12,2 (95% BI: 7,0-19,8) in 1995/1996 naar 28,5 (95% BI: 23,0-34,9) in 2003/2004, vergelijkbaar met de stijging in expositie rate in vrouwen van vruchtbare leeftijd.

Het gebruik van gezonde controles of controles met andere aangeboren afwijkingen dan die van de cases kan leiden tot recall-bias of selectie bias bij case-control studies naar teratogene effecten van maternaal medicijngebruik tijdens de zwangerschap. Deze vormen van bias kunnen voorkomen worden, wanneer de controles bestaan uit kinderen (en foetussen) met een chromosomale of monogene aandoening, omdat deze genetische aandoeningen zeer waarschijnlijk niet gerelateerd zijn aan het maternaal medicijngebruik tijdens de zwangerschap. Onderzoekers zijn echter terughoudend in het gebruik van genetische controles, omdat onbekend is of de selectie van deze genetische controles onafhankelijk is van expositie status. Hoofdstuk 3 beschrijft een studie waarin onderzocht is of het gebruik van medicijnen in het eerste trimester van de zwangerschap representatief is voor het medicijngebruik in het eerste trimester in de algemene populatie van zwangere vrouwen. Uit de Eurocat database werden 565 moeders geselecteerd van kinderen geboren tussen 1998-2004 met een genetische aandoening (de 'genetische populatie'). De expositie rate in het eerste trimester werd berekend voor medicijnen die alleen op recept verkrijgbaar zijn als het aantal blootgestelde zwangerschappen per 100. De expositie rate van de genetische populatie werd vergeleken met de rate uit de 'algemeen zwangere populatie' door het berekenen van de 'rate ratio' (RR) en het 95% betrouwbaarheidsinterval. Deze algemeen zwangere populatie bestond uit 10.870 vrouwen uit de IADB.nl die bevallen waren in dezelfde periode als de genetische populatie. De gemiddelde leeftijd van de moeder was significant hoger in de genetische populatie (p=0,000). Een significant hoger gebruik werd alleen gevonden voor anti-migraine medicatie (RR=2,7, 95% BI=1,0-7,8) en voor ovulatie stimulerende medicijnen (RR=1,6; 95% BI=1,0-2,6) in de genetische populatie. Nadat gecorrigeerd was voor maternale leeftijd vedween het verschil in gebruik van ovulatie stimulerende medicijnen. Als conclusie werd daarom getrokken dat, behalve voor anti-migraine middelen, het gebruik van medicijnen in het eerste trimester door moeders van kinderen met genetische aandoeningen representatief lijkt te zijn voor het medicijngebruik in het eerste trimester in de algemeen zwangere populatie.

Een van de doelstellingen van een registratie voor aangeboren afwijkingen is het identificeren van mogelijke nieuwe teratogene stoffen in een vroeg stadium. Hoofdstuk 4 beschrijft een signaal dat werd gevonden in een surveillance studie waarin combinaties van specifieke aangeboren afwijkingen en medicijnen op een systematische wijze werden geëvalueerd. In de database van Eurocat, geboortejaren 1997-2007, werd op een systematische wijze gezocht naar combinaties van specifieke aangeboren afwijkingen en medicijnen die vaker aanwezig waren dan verwacht, vergeleken met de rest van de database. Combinaties met tenminste 3 blootgestelde cases en een p<0,01 (gebaseerd op de Fisher Exact test) werden verder onderzocht door een gedetailleerde omschrijving van de afwijkingen en het tijdstip van blootstelling en door additionele case-controle

analyses. Met name de associatie tussen hypertrofische pylorus stenose en fluoxetine, een SSRI, was interessant. In totaal waren 3 van de 178 kinderen met een hypertrofische pylorus stenose (1,7%) blootgesteld aan fluoxetine in het eerste trimester vergeleken met 8 van de 4.077 kinderen (0,2%) met andere aangeboren afwijkingen (p=0,009, OR=8,7, 95% BI: 2,3-33,2). In alle 3 gevallen betrof het een geïsoleerde aandoening en fluoxetine was gebruikt door de moeder in respectievelijk week 4 tot 8 van de zwangerschap, week 2 tot 8 van de zwangerschap en in de periode van 10 weken voor tot 19 weken in de zwangerschap. In de additionele case-controle analyses bestond de controlegroep uit kinderen en foetussen met een genetische aandoening. Na correctie voor maternale leeftijd en roken in het eerste trimester was de odds ratio 9,8 (95% BI: 1,5–62,0). Hoewel toeval niet uitgesloten kon worden, werd de gevonden associatie tussen hypertrofische pylorus stenose en fluoxetine beschouwd als een signaal, dat in andere datasets geverifieerd dient te worden.

Hoofdstuk 5 beschrijft een studie waarin de mogelijke associatie tussen het gebruik van paroxetine in het eerste trimester van de zwangerschap en het ontstaan van specifieke aangeboren hartafwijkingen werd onderzocht met gegevens van de Eurocat database. Cases waren foetussen en kinderen met een geïsoleerde aangeboren hartafwijking, geboren in de periode 1997-2006. Controles waren foetussen en kinderen met een chromosomale of monogene aandoening, zonder hartafwijking. Kinderen waarbij geen informatie was over medicijngebruik van de moeder en overleden kinderen zonder post mortem onderzoek werden geëxcludeerd. De onderzoekspopulatie bestond uit 678 cases met een geïsoleerde hartafwijking en 615 controles. Blootstelling aan paroxetine in het eerste trimester vond plaats in 1,5% van de cases en 1,0% van de controles. Odds ratio's, gecorrigeerd voor geboortejaar, werden berekend na exclusie van de cases en controles waarbij de moeder paroxetine buiten het eerste trimester gebruikte, of waarbij de moeder een ander type SSRI gebruikte. We vonden geen significant verhoogde OR voor aangeboren hartafwijkingen als een groep (gebaseerd op 10 blootgestelde cases, OR=1,5; 95% BI: 0,5-4,0), maar wel voor atrium septum defecten (gebaseerd op 3 blootgestelde cases, OR=5,7; 95% BI: 1,4-23,7). Deze resultaten suggereren dat gebruik van paroxetine in het begin van de zwangerschap geassocieerd is met een verhoogd risico op atrium septum defecten. Tevens benadrukken deze resultaten dat het belangrijk is om mogelijke teratogene effecten van een medicijn te bestuderen in relatie tot specifieke, goed gedefinieerde, aangeboren afwijkingen.

In Hoofdstuk 6 wordt de bruikbaarheid van een *case-controle monitoring systeem* voor aangeboren afwijkingen met gegevens van Eurocat NNL en de IADB.nl bediscussieerd en worden aanbevelingen voor de toekomst gedaan. Met data van de IADB.nl kunnen

studies naar medicijngebruik tijdens de zwangerschap uitgevoerd worden. Omdat de IADB.nl alleen zwangerschappen kan identificeren waarbij het kind levend ter wereld komt en omdat de IADB.nl geen informatie heeft over de lengte van de zwangerschap of over de zwangerschapsuitkomst, zou de effectiviteit van de database verbeterd kunnen worden wanneer de IADB.nl gekoppeld wordt aan de perinatale registratie in Nederland. Geadviseerd wordt om te onderzoeken of een dergelijke koppeling mogelijk is.

De Eurocat database is ontworpen voor het uitvoeren van case-controle studies. De database bevat gedetailleerde informatie over aangeboren afwijkingen, waardoor het mogelijk is om homogene case groepen te maken. Dit is belangrijk, omdat aangeboren afwijkingen zeer divers van aard zijn en medicatie niet eenzelfde teratogene effect zal hebben op alle aangeboren afwijkingen. Het gebruik van prospectief verzamelde medicijngegevens van de apotheek maakt het mogelijk om de blootstellingperiode strikt te definiëren. Omdat Eurocat geen gegevens verzamelt over kinderen zonder aangeboren afwijkingen, worden foetussen en kinderen met chromosomale en monogene aandoeningen of met andere aangeboren afwijkingen gebruikt als controles in case-controle studies. Het gebruik van gezonde controles zonder aangeboren afwijkingen wordt aanbevolen om de mogelijkheden te vergroten voor case-controle studies naar risico's van medicijngebruik tijdens de zwangerschap. Voorwaarde daarbij is wel dat informatie over medicijngebruik op eenzelfde prospectieve wijze wordt verzameld. Daarnaast wordt geadviseerd om biologische en genetische factoren te includeren in studies naar mogelijke risicofactoren, omdat bij de meerderheid van de aangeboren afwijkingen met onbekende oorzaak zowel exogene als genetische factoren een rol zullen spelen.

De belangrijkste beperking in studies naar risico's van medicijngebruik tijdens de zwangerschap met de Eurocat database is het relatief kleine registratiegebied. Om een licht tot matig verhoogd risico te kunnen detecteren voor een specifieke aangeboren afwijking is een groot aantal cases nodig. Dit aantal kan alleen behaald worden wanneer het registratiegebied aanzienlijk vergroot wordt, door het verzamelen van gegevens gedurende een lange periode, of door samen te werken met andere registraties van aangeboren afwijkingen. Deze laatste optie is de meest efficiënte manier om grote aantallen cases te kunnen includeren in case-controle onderzoek. Door gegevens van verschillende registraties voor aangeboren afwijkingen met goede informatie over medicijngebruik tijdens de zwangerschap bij elkaar te voegen is het mogelijk om een studiepopulatie te genereren die groot genoeg is om in een zo vroeg mogelijk stadium teratogene effecten te kunnen identificeren.

Curriculum Vitae

Marian Karolien Bakker was born in Hoogezand-Sappemeer on February 14, 1972. After she had finished high school at the Dr. Aletta Jacobs college in Hoogezand (*Gymnasium B*) in 1990, she studied Biomedical Health Sciences at the University of Nijmegen and became interested in epidemiology. For her Master's thesis she performed a case-control study on spina bifida and the occupational exposure of the father. She graduated with an MSc level in 1995. Before she joined Eurocat Northern Netherlands as an epidemiologist in 2002, she worked as a staff member for the public health department (*GGD*) in Groningen from 1995-2001 and as an epidemiologist for the regional cancer registry at the Comprehensive Cancer Centre Northern Netherlands (*IKN*) in 2001-2002. Since November 2006 she has been the project leader for Eurocat Northern Netherlands. Marian is married to Berend-Jan Kamps and they are the very proud parents of two daughters, Pien and Nina.

Marian Karolien Bakker werd geboren op 14 februari 1972 in Hoogezand Sappemeer. Nadat ze haar diploma had behaald (Gymnasium B) aan het Dr. Aletta Jacobscollege in Hoogezand in 1990, studeerde ze Biomedische Gezondheidswetenschappen aan de Katholieke Universiteit Nijmegen, afstudeerrichting Epidemiologie. Als afstudeerproject werkte ze mee aan een case-controle onderzoek naar beroepsmatige blootstelling van de vader en spina bifida bij de kinderen. In 1995 rondde ze haar studie af. Voordat Marian bij Eurocat Noord Nederland als epidemioloog in dienst trad in 2002, werkte ze van 1995-2001 als beleidsmedewerker bij de Gemeenschappelijke Gezondheidsdienst Groningen en van 2001-2002 als epidemioloog bij de regionale kankerregistratie van het Integrale Kankercentrum Noord Nederland. Sinds november 2006 is ze projectleider van Eurocat Noord Nederland. Marian is getrouwd met Berend-Jan Kamps. Samen zijn ze de zeer trotse ouders van twee dochters, Pien en Nina.

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