The use of a birth defects case-control monitoring system in studying the safety of medication use in pregnancy
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CHAPTER 1

Introduction
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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 When these reports were published, thalidomide and other drugs that contained thalidomide were withdrawn from the market.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 level6 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.\textsuperscript{3,10} 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\textsuperscript{11}, or from cohort studies.\textsuperscript{12,13} Such drug utilisation studies can reveal whether potentially teratogenic drugs are prescribed in pregnancy and to what extent.\textsuperscript{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.\textsuperscript{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, and within databases from Teratology Information Services (TIS). 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.

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 or within a national or international network of birth defects registries, such as the European Concerted Action on Congenital Anomalies and Twins (EUROCAT). 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.

<table>
<thead>
<tr>
<th>Drug utilisation studies</th>
<th>Case reports and series</th>
<th>Cohort studies</th>
<th>Case-control studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Descriptive / analytical</strong></td>
<td>Descriptive</td>
<td>Analytical</td>
<td>Analytical</td>
</tr>
<tr>
<td><strong>Purpose</strong></td>
<td>To investigate type of drugs used in pregnancy</td>
<td>To report on possible new teratogenic drugs (hypothesis generating)</td>
<td>To study possible risks and safety of medication use in pregnancy</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Large automated databases (prescription databases, health insurance databases)</td>
<td>Clinical practice</td>
<td>Pregnancy registries, Databases from Teratology Information Services (TIS) and their networks, Linked automated databases</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Cost-effective</td>
<td>Can detect early on any associations between rare birth defects and rare exposures</td>
<td>Prospective data collection</td>
</tr>
<tr>
<td></td>
<td>Large numbers can easily be obtained</td>
<td>Suitable to study: • uncommon exposures (newly marketed drugs), • wide range of adverse birth outcomes besides birth defects</td>
<td>Suitable for detecting high-risk teratogens</td>
</tr>
<tr>
<td></td>
<td>Can serve as reference for analytical studies</td>
<td>Information available on possible risk factors and confounders (pregnancy and TIS databases)</td>
<td>More efficient in data collection</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>No information on the use of OTC medication</td>
<td>Depends on alert clinicians</td>
<td>Selective inclusion of patients</td>
</tr>
<tr>
<td></td>
<td>No information on the actual use of prescribed medication</td>
<td>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</td>
<td>Sensitive to selective loss-to-follow-up (biased to adverse outcomes)</td>
</tr>
<tr>
<td></td>
<td>No information on the actual length of gestation</td>
<td>Differences in quality of data</td>
<td>Differences in quality of data</td>
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<tr>
<td></td>
<td></td>
<td>Costly</td>
<td>Costly</td>
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<tr>
<td></td>
<td></td>
<td>Linkage of automated databases: lower data quality</td>
<td></td>
</tr>
</tbody>
</table>
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 Study27 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 worldwide 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 drugs30 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. 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. 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.

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 assess 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.
References


Chapter 1


