The use of a birth defects case-control monitoring system in studying the safety of medication use in pregnancy
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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.
CHAPTER 3

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.
Selection of controls in case-control studies

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>
<thead>
<tr>
<th>Drug groups (ATC-code)</th>
<th>Genetic population</th>
<th>Source population</th>
<th>Rate Ratio</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibacterials for systemic use (J01)</strong></td>
<td>26</td>
<td>630</td>
<td>0.8</td>
<td>0.5 – 1.2</td>
</tr>
<tr>
<td><strong>Antiemetics (A03FA01, A04A, N05AB04, R06AD, R06AE)</strong></td>
<td>23</td>
<td>590</td>
<td>0.7</td>
<td>0.5 – 1.1</td>
</tr>
<tr>
<td><strong>Gynaecological anti-infectives &amp; antiseptics (G01)</strong></td>
<td>23</td>
<td>418</td>
<td>1.1</td>
<td>0.7 – 1.6</td>
</tr>
<tr>
<td><strong>Gonadotropins &amp; other ovulation stimulants (G03G)</strong></td>
<td>19</td>
<td>223</td>
<td>1.6</td>
<td>1.0 – 2.6</td>
</tr>
<tr>
<td><strong>Corticosteroids. dermatologic preparations (D07)</strong></td>
<td>18</td>
<td>369</td>
<td>0.9</td>
<td>0.6 – 1.5</td>
</tr>
<tr>
<td><strong>Anti-asmatics (R03)</strong></td>
<td>13</td>
<td>226</td>
<td>1.1</td>
<td>0.6 – 1.9</td>
</tr>
<tr>
<td><strong>Antipsychotics exc. prochlorperazine and antidepressants (N05A. excl. N05AB04; N06A)</strong></td>
<td>12</td>
<td>171</td>
<td>1.4</td>
<td>0.8 – 2.4</td>
</tr>
<tr>
<td><strong>Corticosteroids for systemic use (H02)</strong></td>
<td>4</td>
<td>50</td>
<td>1.5</td>
<td>0.6 – 4.3</td>
</tr>
<tr>
<td><strong>Antimigraine medication (N02C)</strong></td>
<td>4</td>
<td>28</td>
<td>2.7</td>
<td>1.0 – 7.8</td>
</tr>
<tr>
<td><strong>Antidiarrheals. intestinal and anti-inflammatory/anti-infective agents (A07)</strong></td>
<td>4</td>
<td>56</td>
<td>1.4</td>
<td>0.5 – 3.8</td>
</tr>
<tr>
<td><strong>Anxiolytics. hypnotics and sedatives (N05B. N05C)</strong></td>
<td>4</td>
<td>137</td>
<td>0.6</td>
<td>0.2 – 1.5</td>
</tr>
<tr>
<td><strong>Drug used in diabetes (A10)</strong></td>
<td>3</td>
<td>32</td>
<td>1.8</td>
<td>0.6 – 5.9</td>
</tr>
<tr>
<td><strong>Anti-epileptics (N03A)</strong></td>
<td>3</td>
<td>28</td>
<td>2.1</td>
<td>0.6 – 6.8</td>
</tr>
<tr>
<td><strong>Thyroid therapy (H03)</strong></td>
<td>2</td>
<td>84</td>
<td>0.5</td>
<td>0.1 – 1.9</td>
</tr>
<tr>
<td><strong>Antibiotics &amp; chemotherapeutics for dermatological use (D06)</strong></td>
<td>1</td>
<td>82</td>
<td>0.2</td>
<td>0.03 – 1.7</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Drug groups (ATC-code)</th>
<th>&lt;=30</th>
<th></th>
<th>&gt;=30</th>
<th></th>
<th>Adjusted rate ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Genetic population</td>
<td>Source population</td>
<td>Genetic population</td>
<td>Source population</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=231</td>
<td>%</td>
<td>n=6247</td>
<td>%</td>
<td>n=334</td>
<td>%</td>
</tr>
<tr>
<td>Antipsychotics exc. prochlorperazine and antidepressants (N05A. excl. N05AB04; N06A)</td>
<td>3</td>
<td>1.3</td>
<td>78</td>
<td>1.2</td>
<td>9</td>
<td>2.7</td>
</tr>
<tr>
<td>Thyroid therapy (H03)</td>
<td>2</td>
<td>0.9</td>
<td>30</td>
<td>0.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Drugs used in diabetes (A10)</td>
<td>0</td>
<td>0.0</td>
<td>14</td>
<td>0.2</td>
<td>3</td>
<td>0.9</td>
</tr>
<tr>
<td>Anxiolytics. hypnotics and sedatives (N05B. N05C)</td>
<td>1</td>
<td>0.4</td>
<td>57</td>
<td>0.9</td>
<td>3</td>
<td>0.9</td>
</tr>
<tr>
<td>Gonadotropins and ovulation stim (G03G)</td>
<td>7</td>
<td>3.0</td>
<td>91</td>
<td>1.5</td>
<td>12</td>
<td>3.6</td>
</tr>
<tr>
<td>Antiemetics (A03FA01. A04A. N05AB04. R06AD. R06AE)</td>
<td>11</td>
<td>4.8</td>
<td>372</td>
<td>6.0</td>
<td>12</td>
<td>3.6</td>
</tr>
</tbody>
</table>
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.\textsuperscript{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%\textsuperscript{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.\textsuperscript{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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We would like to thank Prof. Charles Buys for his thoughtful comments on a previous version of this paper.
Reference List