General Introduction
Background

For a long time it was thought the placenta protects the foetus against all possible harmful influences.\(^1\) Despite earlier publications on possible negative effects for the unborn child as radiation and measles,\(^2,3\) it was the thalidomide tragedy at the end of the 1950s and early 1960s that increased the awareness of the fact that the placenta is not a perfect barrier to protect the foetus.\(^4\) Thalidomide, prescribed for anxiety, insomnia, gastritis, tension and as an anti-emetic drug in pregnancy, was marketed as a safe drug for adults as well as for children.\(^5\) But, despite the apparent absence of any toxic effect, it turned out to cause phocomelia and other congenital anomalies in thousands of children exposed in utero.\(^6-9\)

The thalidomide case was the beginning of birth defects research, and the term teratogenicity came into use, meaning the ability to interfere with normal foetal development. Initially, research was focused on obviously noticeable defects. Later, it became clear that the manifestation of teratogenicity also includes infertility, spontaneous abortions, intrauterine death, premature birth, low birth weight, pre- or postnatal growth delay, (neuro)behavioural disorders and organ function disorders.\(^4\) The latter might be difficult to detect, like in the case of diethylstilbestrol (DES). Daughters of women using DES during pregnancy were more likely to develop clear cell adenocarcinoma in early adulthood.\(^10\)

Moreover, recently it was suggested that the sons of these daughters have an increased risk on hypospadias.\(^11\) This illustrates not only the possible long-term effects of intrauterine exposure but it also shows our lack of knowledge of the mechanisms of teratogenic substances like some drugs.

In contrast, also some benefits of intrauterine exposure have been established over the years. The most obvious example is the protective effect of folic acid on neural tube defects and probably also on other anomalies.\(^12-14\)

Studying safety of intrauterine drug exposure

Although it is generally recommended not to use medicines during pregnancy unless it is absolutely necessary, several studies show that up to 80% of women do take at least one type of drug during pregnancy.\(^15-18\) Establishing the safety of drugs used by women of childbearing age is thus of high importance. The two options to establish this safety are animal studies and observational epidemiological studies in humans with data of pregnant women that were already exposed to the drug. The first is very useful in many cases, for example with isotretinoin where animal studies prevented a disaster in humans like thalidomide.\(^19\) Unfortunately, results from animal studies can not simply be translated into
risks in humans. A drug can be teratogenic in one species while it has little or no effect in another, as was the case for thalidomide. Teratogenic effects cannot be detected in human trials before marketing a drug. Not only because of the small numbers in these trials but also because women that might become pregnant are mostly excluded from these studies. This leaves us with the unfortunate situation that possible teratogenic effects are mostly discovered after the release of the drug on the market and also after it has been used by pregnant women.

Studying teratogenicity in humans and some limitations encountered
The diversity in numbers of both drugs and congenital anomalies, and therefore the many possible combinations between them which could all be subjects to study, is an enormous challenge for researchers in this field. To study possible associations between a drug and a congenital anomaly, large datasets with detailed information on drug exposure, the outcome and many other variables that might influence the study are needed. The low exposure rates in pregnancy of some drugs, like the disease modifying anti-rheumatic drugs (DMARDs), increase this challenge.

Fortunately, much effort has been made over the years to collect data necessary to study drug-anomaly associations. In Groningen, the EUROCAT Northern Netherlands registry for congenital anomalies was established in 1981 to collect data on children and foetuses with anomalies in the region. Until 1996, all information about the pregnancy outcome, and the mother's condition, diseases and drug use was collected through the physician or midwife who reported the birth. Since 1997, data collection is extended with a questionnaire to the parents and pharmacy data of the mother which provides researchers with complete and detailed information about drug exposure. Comparable registries are established in many locations all over the world. Still, one registry does not always have the number of cases needed to investigate specific associations. To tackle this problem, several drugs or defects can be joined and investigated as a group. Such groups can be formed based on drugs being from the same class or anomalies categorised according to the embryologic tissue of origin. Although grouping increases the numbers in the analyses, it is known that teratogenic effects cannot be predicted reliable from the class of drugs a specific compound belongs to, nor from the existing knowledge of pharmacology and toxicology. Chemical relationships are not generally predictive of teratogenesis as can best be illustrated by the structural relation between thalidomide and glutethimide: there is only a slight difference in structure but there is no evidence of teratogenicity of the latter. Furthermore, by joining drugs or defects an existing association can be diluted by the group
members and therefore overseen. Another solution for increasing the power of a study is collaboration of different registries. In Europe, over 40 registries participate in the EUROCAT network. Other examples of collaboration are the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)\(^{23}\) and the National Birth Defects Prevention Network (NBDPN)\(^{24}\) in the US.

**Counselling women of reproductive age about (anti)teratogenic effects**

The first eight weeks of pregnancy are most critical for developing anomalies.\(^{25}\) Although most Dutch pregnancies are planned thus reasoned behaviour can be planned as well, all pregnancies are only recognised after a few weeks. Therefore exposure of the foetus to teratogens can easily take place in that period. Furthermore, due to long half lives of certain drugs e.g. chloroquine for malaria prophylaxis (3-5 days), clomiphene to induce ovulation (5-7 days), and leflunomide to treat rheumatoid arthritis (2 weeks),\(^{26}\) the drug can be still in the mother's body during early pregnancy even if it was used before pregnancy. Informing women of reproductive age about their drugs is therefore important.

Widespread preconception care is not present in the Netherlands. Therefore, most women only consult a health care provider about their pregnancy after actually getting pregnant. But, due to the unique situation that most Dutch citizens are registered in one community pharmacy, which keeps their medication history, pharmacists can use this relationship to provide certain populations with specific information. Besides the obvious role of the pharmacy to check whether a new prescription does not conflict with existing medication, pharmacies can also be pro-active and educate people on health issues that might be of interest to them. They can for example educate women of childbearing age about the risks of drugs they get prescribed. Moreover, since over 70% of the Dutch women take prescribed contraceptives before their first pregnancy,\(^{27}\) they can reach even those women that do not use other drugs but do visit their pharmacy regularly to collect their contraceptives. Thus, in spite of the lack of organized preconception care, education about teratogenic risks of drugs but also about the protecting effect of folic acid on birth defects can be organized through pharmacies. To be able to do so, pharmacies have to develop strategies to implement this form of patient education in their daily practice.

**Objectives and outline of the thesis**

From the foregoing it is clear that, for establishing the risks and benefits of intrauterine exposure, epidemiological studies have to be performed. Fortunately, ongoing data
collection provides the possibility to do so. Nevertheless, broadening data collection methods or collaboration might improve the possibilities of these studies. Subsequently, new insights should be communicated with the population that actually needs the information, e.g. the women of reproductive age. Therefore, three objectives are formulated in this thesis:

A. To study risks and benefits of intrauterine exposure in relation to congenital anomalies;
B. To investigate the strengths and limitations of current available datasets with respect to studying associations between intrauterine exposure and congenital anomalies;
C. To investigate if and how pharmacies can counsel women of reproductive age about decreasing risks on congenital anomalies, for example by using folic acid supplements.

This thesis consists of three consecutive parts, each dealing with one of the objectives. The intake of folic acid is a repeating theme throughout the thesis. In the first part of the thesis, part A, periconceptional exposure to drugs and/or folic acid is topic of study. After describing drug use among pregnant and non-pregnant women (chapter 1) three studies are presented with folic acid as communal factor (chapters 2 to 4). The last chapter of this part of the thesis describes the association between preconceptional clomiphene use and the occurrence of hypospadias among male offspring. This study demonstrates the limited methodological possibilities if exposure is rare and numbers are small.

In part B, improvements to overcome certain limitations of current available data are explored. In chapter 6, the potential of the EUROCAT network to study teratogenicity of drugs is described. Chapter 7 describes the actions that were undertaken to gather data on non-malformed children as controls for the births in the EUROCAT Northern Netherlands registration.

The following goal is to reach women of childbearing age and to educate them about teratogenic risks. Studies on the possibilities to do so are clustered in part C of the thesis, all with folic acid education as topic. First, determinants of the use of folic acid were studied to provide health care providers with tools to educate this specific population (chapter 8). Subsequently, a pilot study is presented on the introduction of pro-active patient education in daily pharmacy practice (chapter 9) and the effect of this intervention on the knowledge and use of folic acid among the target population (chapter 10).
References


23. www.icbd.org

24. www.nbdpn.org

