General introduction
Recently it was confirmed that about two-third of the Dutch population suffering from a rheumatic disease are younger than 65 years of age. Even more important, about 10% of them are of childbearing age (20-39 years). Especially at young age early and effective treatment of a rheumatic disease is of great necessity. During the past decades several new disease modifying anti-rheumatic drugs (DMARDs) have been developed.

Before new drugs are approved to the market animal testing should illustrate effectiveness and safety as well as possible teratogenic and embryo toxic properties. However, results from animal testing do not always predict the teratogenic effects of drugs in humans. This became very clear after the thalidomide disaster in the last century. Routine screening in rodents did not show any teratogenic effects of thalidomide and therefore it was thought to be safe. Thalidomide was used in the treatment of different disorders such as anxiety, insomnia, gastritis and tension; it was furthermore promoted as a safe anti-emetic drug during pregnancy. The drug was withdrawn from the market a few years after its introduction due to severe teratogenic effects causing limb defects, ear malformations and/or hearing loss, ocular anomalies and various other anomalies. The use of thalidomide showed us that although the drug was thought to be safe from animal studies, it was clearly not safe in humans. The thalidomide disaster demonstrated the importance of pharmacovigilance and in particular of research on drug use in relation to birth defects in humans.

**Pregnancy, drug use and risks: issues encountered**

Before risks associated with drug use during pregnancy can be identified, drug utilization studies should be performed to identify the magnitude of the problem. Drug utilizations studies showed that drug use during pregnancy varies, estimations range from 44 to 99%. Variation in these estimations occurs due to the inclusion or exclusion of for example folic acid and the use of over-the-counter (OTC) drugs as well as data sources used. Drugs for chronic conditions and occasional or incidental use are prescribed less during pregnancy in contrast to drugs which are regularly used during pregnancy such as folic acid, anti-emetic...
General Introduction

drugs and antacids. For identification of drugs prescribed during pregnancy several national and international databases are available. The Groningen Interaction Database (IADB.nl) contains pharmacy dispensing data; prescribed drugs dispense during a certain period can be identified and in this way the expected exposure (when the patient is adherent to her therapy) can be determined. The general practice research database (GPRD, UK) is also able to identify possible exposure; data are collected at the general practitioner including date and name of drugs prescribed. Claim or health insurance databases are used as well in an attempt to identify drug exposure. Nevertheless, these databases are only able to identify possible exposure; none of these databases can determine the actual use of the drug. Interviews with patients or questionnaires can be useful to determine whether drugs are actually being used during pregnancy. However, this type of data collection may introduce recall bias due to time between use of the drug and the interview or questionnaire.

Approximately 65% of all congenital malformations are of unknown origin; 20-25% of all congenital malformations are explained by genetic defects and environmental factors. From the latter chemicals and drugs account for only 8-11% of all birth defects. Congenital malformations can be divided into major and minor malformations, the risk of major congenital malformation among the general population is estimated between 1 and 3%. In principle drugs could be classified in high-risk teratogens such as thalidomide and isotretinoin, moderate-risk teratogens and low-risk teratogens. It is believed that moderate-risk teratogens cause an increase of a specific birth defect by a factor somewhere between 2 and 10 compared to the baseline risk for that specific birth defect.

To identify teratogens in the post-marketing setting two main study designs have been developed; follow-up studies and case-control surveillances. Follow-up studies are able to identify women exposed to a certain drug; high-risk teratogens can be identified efficiently and small numbers suffice. However, in follow-up studies relatively small samples are recruited and they lack statistical power, therefore they are insufficient to identify moderate- and low-risk teratogens. Case-
control studies have more substantial statistical power and are therefore more appropriate to identify moderate- or low-risk teratogens.  

*Rheumatic diseases, pharmacotherapy and pregnancy: changing policies*

**Pregnancy in rheumatic diseases**

In the past women with a rheumatic disease were told not to have children for several reasons related to their chronic disease. The treatment of rheumatic diseases focused on symptom control with non-steroidal anti-inflammatory drugs (NSAIDs) to achieve pain relief and decrease of the swelling.  

It was thought that the damage caused to the joints leads to inability of the women to take care of a child. Insight on the course of the disease during pregnancy and changes in the pharmacotherapy changed this perspective. It is believed that RA does not compromise fetal outcome and approximately 75% of the RA patients experience an improvement of their symptoms during pregnancy. In about 65% of the pregnancies remission of RA is described and drugs can be stopped. In contrast, women with systemic lupus erythematosus (SLE) often have symptoms during pregnancy followed by an active disease after delivery, therefore the disease should be well controlled with drugs. In women with SLE fetal outcome can be affected, adverse outcomes such as fetal death, preterm birth and intrauterine growth retardation are seen. In many other rheumatic diseases such as ankylosing spondylitis (Bechterew disease), Behçet’s disease and juvenile chronic arthritis fetal outcome does not seem to be affected.  

**Pharmacotherapy in rheumatic disease**

Disease modifying anti-rheumatic drugs (DMARDs) are the main drugs used in nowadays treatment of rheumatic diseases. The treatment focuses on the prevention or control of joint damage as soon as a rheumatic disease is discovered. Guidelines state methotrexate to be the first choice DMARD, due to its effectiveness, safety and low costs. If methotrexate single therapy fails, other DMARDs such as hydroxychloroquine, sulfasalazine or leflunomide can be added. A new group of DMARDs, the “biologicals”, are recently introduced in the treatment of rheumatic diseases: namely the tumor necrosis factor alfa (TNFα)
blocking drugs etanercept, adalimumab and infliximab. They are prescribed to patients who do not respond to a combination of other DMARDs\textsuperscript{20}, although there is evidence that they are also effective in the first line treatment \textsuperscript{21}. Other DMARDs traditionally being used in the treatment of rheumatic diseases are gold preparations (gold sodium thiomalate, aurothioglucose and an oral variant: auranofin), chloroquine and hydroxychloroquine (antimalarial drug), azathioprine and cyclosporine (immunosuppressive drugs), d-penicillamine and cyclophosphamide (alkylating agent)\textsuperscript{16}. Newer biologicals recently admitted to the market for the treatment of rheumatic diseases are anakinra (interleukin-1 receptor antagonist), abatacept (anti-CTLA-4: costimulation blocker) and rituximab (chimeric anti-CD20 monoclonal antibody).\textsuperscript{15,18,20,22,23}

Pharmacotherapy in rheumatic diseases during pregnancy
Many of the DMARDs can not be used or should be used with caution during pregnancy. In order to guide health care providers in prescribing drugs to pregnant women several classification systems have been developed. The United States (FDA), Australia and Sweden all developed their own classification system\textsuperscript{24-27}. Each drug can be classified according to these systems (see appendix 1) and although the systems may vary, general recommendations do apply for most drugs. Methotrexate and leflunomide are considered to be teratogenic and should therefore not be used before or during pregnancy. Drugs such as cyclosporin, cyclophosphamide, penicillamine, TNF\textalpha blocking drugs, anakinra, and rituximab should be avoided during pregnancy. Information for many of these drugs is scarce and recommendations lack animal or human data or are based on inadequate animal or human studies, case reports, or small exposed cohorts.\textsuperscript{28,29} Hydroxychloroquine, chloroquine and azathioprine should also be avoided during pregnancy, although for these drugs therapy benefits may outweigh potentials risks for the fetus. This has to be judged individually in every single case. Sulfasalazine is the only drug that is safe according to the risk classification systems\textsuperscript{24-27}. 
Pharmacotherapy in rheumatic diseases during pregnancy: the dilemmas

Patients with a rheumatic disease will have many questions about their disease and drug use in relation to pregnancy. ‘Do I want to become pregnant with this disease, can my baby get the disease as well, does a pregnancy influence my disease, can I take drugs while I am pregnant and can I take care of my child with this disease?’ are just a few of the dilemmas women have to deal with. Clinicians and their patients have to discuss their options, using guidelines, information leaflets and experience. However, in many cases the available information is limited and evidence and experience is scarce, leading to difficult choices for the clinician and their patients.

Nowadays the Internet is a widely used medium and the search for information might look easy. The Internet provides more than a million websites about ‘rheumatoid arthritis’ and ‘systemic lupus erythematosus’, and in relation to pregnancy about half a million websites are available. In addition, information can be obtained from books, leaflets, magazines, other patients, family and friends and health care professionals. National as well as international associations of rheumatism patients and rheumatism associations and organizations of professionals try to support patients with informative websites. They translate the scientific information and considerations into a compact and understandable text on the website or in leaflets.

Some of the information that can be found on the Internet will be misleading, incomplete or even untrue. For the patient it might be difficult to distinguish between information that is reliable and useful and information that is not. The bulk of information might lead to more questions rather than to answers. Questions which can be posed to health care professionals such as the rheumatologist or general practitioner but also Internet forums show wide ranges of questions asked and answers given. Topics on these forums vary from general questions about RA and pregnancy to very specific questions about continuation or discontinuation of drugs before and during pregnancy. Other patients respond by sharing their experiences and knowledge or refer to informative websites. It was seen that patients felt empowered by participation in online support groups. The total
search for information hopefully leads to answers, although evidence on drug use during pregnancy is often scarce and women might be left with the questions.

Objectives of this thesis
In this thesis the following objectives are formulated and explored:
1. The current knowledge on DMARD use during pregnancy;
2. Drugs used in rheumatic diseases among pregnant women;
3. Risks associated with the use of DMARDs during pregnancy
4. The perspective of rheumatologists on the treatment of pregnant and non-pregnant female patients;
5. The way female patients handle questions and information about the use of their drugs and their disease around pregnancy.

Current knowledge from literature on DMARD use during pregnancy mainly focused on studies performed in patients with a rheumatic disease will be discussed in chapter 1.
The use of NSAIDs and acetylsalicylic acid (ASA) as well as a detailed description of the use of sulfasalazine, azathioprine and methotrexate before, during and after pregnancy in the Netherlands will be discussed in chapter 2 and 3.
Chapter 4 and 5 will describe the use of DMARDs in the United Kingdom and risks associated with the use of DMARDs in relation to gestational age and birth defects.
Chapter 6 will discuss the perspective of Dutch rheumatologists on the treatment of pregnant patients as well as non-pregnant patients.
Chapter 7 will discuss women’s questions about a rheumatic disease, drugs and a (recent) pregnancy or a (past) desire to become pregnant.
At the end of this thesis the overall findings and conclusions of this thesis will be discussed and recommendation for future research will be made.
Reference List

4  Bakker MK, Jentink J, Vroom F, Van Den Berg PB, de Walle HE, de Jong-van den Berg LT. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. BJOG 2006 May;113(5):559-68.
25 Farmacotherapeutisch Kompas; Medisch farmaceutische voorlichting. Amstelveen: Commissie Farmaceutische Hulp van het College voor zorgverzekeringen; 2005.
### Appendix 1

<table>
<thead>
<tr>
<th>FDA pregnancy risk category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.</td>
</tr>
<tr>
<td>B</td>
<td>Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).</td>
</tr>
<tr>
<td>C</td>
<td>Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.</td>
</tr>
<tr>
<td>D</td>
<td>There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).</td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.</td>
</tr>
<tr>
<td>Australian pregnancy risk category</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>A</td>
<td>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 fetus having been observed.</td>
</tr>
<tr>
<td>B1</td>
<td>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 fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.</td>
</tr>
<tr>
<td>B2</td>
<td>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 fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.</td>
</tr>
<tr>
<td>B3</td>
<td>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 fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.</td>
</tr>
<tr>
<td>C</td>
<td>Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.</td>
</tr>
<tr>
<td>D</td>
<td>Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.</td>
</tr>
<tr>
<td>X</td>
<td>Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.</td>
</tr>
<tr>
<td>Category</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>Medicinal products which may be assumed to have been used by a large number of pregnant women and women of child-bearing age without any identified disturbance in the reproductive process, e.g. an increased incidence of malformations or other direct or indirect effects on the fetus. This category comprises: drugs that have been available for many years; those that have been used by many pregnant women and women of child-bearing age and; drugs for which satisfactory retrospective studies in pregnant women are considered to have been carried out.</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>Medicinal products which may be assumed to have been used only by a limited number of pregnant women and women of child-bearing age without any identified disturbance in the reproductive process having been noted so far, e.g. an increased incidence of malformations or other direct or indirect harmful effects on the fetus. As experience of effects of medicinal products in man is limited in this category, results of reproduction toxicity studies in animals are indicated by allocation to one of 3 subgroups B1, B2 or B3 according to the following definitions:</td>
</tr>
<tr>
<td><strong>B1</strong></td>
<td>Reproduction toxicity studies have not given evidence of an increased incidence of fetal damage or other deleterious effects on the reproductive process.</td>
</tr>
<tr>
<td><strong>B2</strong></td>
<td>Reproduction toxicity studies are inadequate or lacking, but available data do not indicate an increased incidence of fetal damage or other deleterious effects on the reproductive process.</td>
</tr>
<tr>
<td><strong>B3</strong></td>
<td>Reproduction toxicity studies in animals have revealed an increased incidence of fetal damage or other deleterious effects on the reproductive process, the significance of which is considered uncertain in humans.</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>Medicinal products, which by their pharmacological effects have caused, or must be suspected of causing, disturbances in the reproductive process that may involve risk to the fetus without being directly teratogenic. If experimental studies in animals have indicated an increased occurrence of fetal injuries or other disturbances of the reproductive process of uncertain insignificance in humans, these findings are to be stated for drugs in this category.</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>Medicinal products which have caused an increased incidence of fetal malformations or other permanent damage in humans, or which, on the basis of e.g. reproduction toxicity studies, must be suspected of doing so. This category comprises drugs with primary teratogenic effects that may directly or indirectly have a harmful effect on the fetus.</td>
</tr>
</tbody>
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