Summary and General Discussion
Summary

Rheumatic diseases occur in about two third of the Dutch population, about 10% of them is of childbearing age. An early and effective treatment is of great necessity and the development of new drugs are necessary. The last decades many new drugs were developed in the treatment of rheumatic diseases, such as several TNFα drugs (Tumor Necrosis factor). Drugs such as methotrexate and azathioprine, used as an anti-cancer drug and immunosuppressive drug after transplantation respectively, were also introduced in the treatment of rheumatic diseases. All these drugs are considered to be part of the disease modifying anti-rheumatic drugs (DMARDs).

The get some inside on the current knowledge on the safety of these DMARDs during pregnancy, chapter 1 reviews the studies describing the safety of DMARDs during pregnancy. The review underscores the gross absence of data on safety and risks of DMARDs before and during pregnancy. Follow-up studies and case-control surveillance are suitable to identify teratogens after marketing approval. Apart from two case-control studies and one cohort, mostly small exposed cohorts or individual cases were studied, as could be seen in the review. Methotrexate is categorized as X by the FDA, meaning that the possible risk clearly outweighs any positive benefits. The results presented in the review reconfirm this status. Azathioprine is categorized as a drug that despite indications of fetal risks can be considered during pregnancy if the benefits of therapy outweigh the potential risks. The results shown in the review are in line with these recommendations, azathioprine seems to be generally safe in pregnancy. Sulfasalazine is also considered to be generally safe during pregnancy, which was underscored by the studies described in the review. Results of the studies presented in the review with respect to hydroxychloroquine suggest that this drug can be safely used during pregnancy in the treatment of SLE (systemic lupus erythematosus) and RA (rheumatoid arthritis) in moderate dosages, which is in contrast with the FDA categorization. However, it must noted that these conclusions are based on small exposed cohorts. With respect to the other DMARDs, such as leflunomide, gold preparations and TNFα drugs, information is even more limited; only small exposed
cohorts or case reports were found. Because pregnant women are usually excluded from clinical trials, case-reports and case-series are the first signals for the clinical practice of an adverse effect or pregnancy outcome after drug use. However with respect to DMARDs these case reports and case-series were almost never followed by analytical studies as case control surveillance or follow up studies. Perhaps more time is needed to collect enough data to conduct proper case-control or cohort studies.

Chapter 2, 3 and 4 were performed to see whether DMARDs and another group of anti-rheumatic drugs, NSAIDs (non-steroidal anti-inflammatory drugs), were used before and during pregnancy. If these drugs would not have been used during pregnancy, safety would not have been an issue. However, as is shown in these chapters, DMARDs as well as NSAIDs were used before and during pregnancy. With respect to NSAIDs (chapter 2), a warning was issued in 2005 by the EMEA (European Medicines Agency) about the use of these drugs in the first two trimesters of pregnancy. Based on recent studies, which describe associations between NSAIDs and several different birth defects, it was recommended not to use these drugs in the first trimesters unless strictly indicated. In a drug utilization study based on IADB.nl prescription data, we showed that in 3.9% of the pregnancies NSAIDs (or Acetylsalicylic acid) were prescribed during pregnancy, in 2.9% of the pregnancies these drugs were prescribed during the first trimester. Data on over-the-counter use of NSAIDs was not included in this study, so it is assumed that the actual NSAID use is even higher. Our data show the prescribing of NSAIDs before the warning issued by the EMEA, it is therefore necessary to further investigate the prescribing of these drugs after the warning issued in 2005.

Chapter 3 describes the use of sulfasalazine, azathioprine and methotrexate round pregnancy. Results showed that 35 women received a prescription for sulfasalazine, azathioprine and/or methotrexate before their first pregnancy. Methotrexate was not continued during pregnancy, which is in accordance with national and international guidelines. Azathioprine was continued during pregnancy by 60% of the women who received this drug also before pregnancy, for sulfasalazine 38% of the women continued their drug during pregnancy. Co-medications of women receiving sulfasalazine as their initial DMARD are anti-
inflammatory and anti-rheumatic drugs and analgesics. For women receiving azathioprine as their initial DMARD corticosteroids and intestinal anti-inflammatory drugs were mostly prescribed as co-medication. No specific prescription patterns were found in the use of DMARDs among pregnant women. Based on the results presented in chapter 3 it was concluded that prescribing of DMARDs and related co-medication is based on the characteristics of the individual patient.

In chapter 4 the General Practice Research Database (GPRD), was used to investigate the prescribing of DMARDs before and during pregnancy in the UK general practice.

The results showed that in 1100 pregnancies a DMARD was prescribed just before or during pregnancy. Most often the drugs were prescribed as a malaria prophylaxis (chloroquine), but also azathioprine, hydroxychloroquine and sulfasalazine were prescribed. Methotrexate and leflunomide were prescribed less often. The majority of the women to whom sulfasalazine or azathioprine was prescribed in the three months leading up to pregnancy, continued to have them prescribed during pregnancy. The other drugs were mainly stopped during the first trimester of pregnancy. The other drugs were mainly stopped during the first trimester of pregnancy. Methotrexate was continued during pregnancy in some cases, this is not in accordance with national prescribing guidelines. Reasons for continuation of this drug can not be obtained using this database, but might partly be explained by unplanned pregnancies. In general, the prescribing of DMARDs around pregnancy decreased; this may be partly owing to guidelines being followed but also owing to the uncertainty of DMARD safety during pregnancy. For most products the frequency and duration of exposure increased in the second trimester of pregnancy compared to the previous period. The differences found between the use of DMARDs during pregnancy in the Netherlands and the UK might be explained by cultural differences or by the use of a different kind of data.

The detailed information on DMARD exposure and available information about diagnoses and birth outcome in the GPRD can be used to evaluate any associations between DMARD exposure and selected birth outcomes, which has been described in chapter 5. No increased risk of pregnancy termination or general congenital malformations associated with any DMARD during the first trimester was noted. The use of azathioprine in the second trimester was associated with an
increased risk of preterm birth when compared with women to whom no DMARD was prescribed at all (OR 3.25 95%CI 1.82-5.78). Similar results associating azathioprine use with preterm birth were found in other studies, although larger studies are needed to confirm the findings. The results also showed an increased relative risk (odds ratio), although not significant, of preterm birth related to 2nd and 3rd trimester exposure of hydroxychloroquine. Hydroxychloroquine is mostly prescribed in SLE and SLE has been associated in earlier studies with preterm birth. Whether the underlying disease (SLE) is the confounding factor or that the drug is associated with this increase, could not be concluded from our data. This study was conducted to investigate the associations between DMARD use and birth defects to generate hypothesis. When investigating a relation between the increase of a specific birth defect and drug use, a detailed level of recording is necessary. It has been demonstrated that the completeness of recording of prescribing in the GPRD is high; however the recording of birth defects is not as detailed and complete. It was noted that for the exposure to azathioprine, cyclosporin and chloroquine a rather high relative risk (point estimated) was seen in relation to a hernia although not significant.

Besides insight on the use and safety of DMARDs during pregnancy, insight on current clinical practice is of importance to see whether for example treatment or counseling needs to be changed. Interviews with rheumatologists (chapter 6) revealed that although the evidence with respect to the use of DMARDs during pregnancy is scarce, there was no major need for supplementary guidelines. The lack of evidence was rather obvious and also shown in the review (chapter 1). Guidelines with respect to the use of sulfasalazine, methotrexate and leflunomide during pregnancy were clear, according to the respondents. Sulfasalazine can be continued during pregnancy, the latter two need to be stopped before conception. The respondents also indicated that drugs such as azathioprine, cyclosporine and hydroxychloroquine could be used during pregnancy if necessary and after careful consideration. Methotrexate and sulfasalazine would be the drug of first choice in regular treatment of RA. However, in pregnancy the rheumatologist indicated a preference for sulfasalazine or discontinuation of the drugs at all. Experience with pregnancy was mostly limited, at most 20 pregnant patients or patients wishing to
be become pregnant were annually seen by the rheumatologists. Therefore rheumatologists give their patient a tailor made advice, based on the individual characteristics. It was felt that guidelines would probably not contribute to a better advice. Overall, the Dutch rheumatologists are of the view that there is sufficient information on the treatment of RA in pregnant women or women wishing to become pregnant.

In the last chapter we describe women’s experience; what are their questions when using DMARDs and having a child wish. By means of a questionnaire women with a rheumatic disease were approached (n=50) to explore the questions they had and answers they retrieved about drug use and pregnancy. Most women were diagnosed with rheumatoid arthritis or Ankylosing spondylitis. The reported use of methotrexate and TNFα drugs decreased as soon as women consciously want to become pregnant, the reported use of sulfasalazine increased. About two-third of the women responding to the questionnaire indicated that their questions were satisfactory answered. Most reported questions were about medication use before and during pregnancy and the harmfulness for the baby. Women indicated that the rheumatologists and the media (including internet) were the most reported sources for information and answers to their questions. About forty percent judged that the available information is sufficient, the majority of the women indicated that a specific leaflet on pregnancy and drugs would be of added value. Doubts and/or fears remained or increased after receiving information for the majority of the women.

This thesis explored the field of DMARD and drug use during pregnancy. From literature it was shown that there is a gross absence on safety data of DMARD use during pregnancy. This was indicated by rheumatologists and patients as well. In line with these findings, the patients expressed a need for a specific leaflet on pregnancy and drug use. Rheumatologists, however, indicated that there was no major need for supplementary guidelines. DMARDs are being used before and during pregnancy, however a specific pattern was not found. From the data it can be concluded that the patients receive a tailor made advice with respect to drug treatment during pregnancy, which was also indicated by the rheumatologists.
From the safety data it became clear that DMARDs were not associated with any specific birth defects. An increased association between azathioprine use in the second trimester and pre-term birth was seen but these finding should be confirmed by larger studies.
General discussion

This thesis aimed to explore in particular a safer use of disease modifying anti-rheumatic drugs (DMARDs) among female pregnant patients. On the one hand, post marketing studies can be performed not only to identify the use of DMARDs but also to see whether these drugs are prescribed according to guidelines. Subsequently, the safety of these drugs during pregnancy can be determined by performing risk assessment studies (follow-up or surveillance). On the other hand, it has to be identified whether women using DMARDs or rheumatologists prescribing DMARDs encounter difficulties regarding the use/prescribing of these drugs during pregnancy.

The complexity of elements involved

A young patient with a rheumatic disease wishing to become pregnant, is not a situation a rheumatologists encounters on a daily basis (chapter 6). The woman will have questions specifically about her disease and the use of her drugs in relation to pregnancy (chapter 7). According to rheumatologists recommendations on drugs such as sulfasalazine and methotrexate before and during pregnancy are clear. However, for more recent introduced drugs such as TNFα-drugs recommendations are less clear, mainly due to the lack of evidence on these drugs (chapter 1 and 6).

The example shown in box 1 shows that not only women using DMARDs have questions, also rheumatologists have questions about the drugs they prescribe during pregnancy. What does the rheumatologist need in order to provide answers to his patients? Where can the woman find (more) answers to her questions? How can researchers help the rheumatologists as well as the patient to fulfill the needs they have? It becomes clear that the treatment of young women who are pregnant or desire to become pregnant is rather complex as a variety of factors must be taken into account. Each of the latter should be investigated and discussed from the point of view of the patient, rheumatologist and researcher.
**Box 1. Factors involved: an example**

A woman indicates to her rheumatologist that she wants to become pregnant and wonders if she should stop her drugs. The woman is using methotrexate, etanercept, prednisone and naproxen on demand. With advice from the rheumatologist she stops both DMARDs and continues with the other drugs, after 6 months she will start trying to conceive. However, due to increased disease activity after a few months the use of DMARDs has to be reconsidered. The patient wishes she had known about this possibility of increased disease activity, this would have prepared her better, she said. In concordance with the rheumatologist she starts using etanercept again and then, unexpectedly, she becomes pregnant. She is really worried about the consequences of the use of etanercept for her unborn child. She looks for information to reassure her but the Internet shows different things and she does not know what to believe and what not. On some Internet sites she finds women who ended their pregnancy, but others say healthy children are born after the use of etanercept. She does not know what to do and discusses this with her rheumatologist. It is recommended not to use etanercept during pregnancy, confirms the rheumatologist, but there are also no indications that this drug poses a big teratogenic risk. Inofficially, it is even said that this drug can be used up to conception. The rheumatologist sais that is all he knows, at the moment no more information is available. She finds some reassurance in this answer, although she is still worried.

Drug utilization and safety studies
Drug utilization studies are a first step towards assessing the safety of a drug. When it is known if drugs are being prescribed to pregnant women, the magnitude of the problem can be determined.

*Drug utilization: NSAIDs*
Women with a rheumatic disease are often prescribed DMARDs in combination with NSAIDs (Non steroidal anti-inflammatory drugs). In a 2005 warning, it was stated by the Dutch registration authorities and others that NSAIDs and ASA (acetylsalicylic acid) should not be prescribed during the first trimester of
pregnancy unless this was strictly indicated, as might be the case in severe rheumatic diseases \(^1\-^3\). This thesis shows that nevertheless 2.9% of the women were prescribed a NSAID or ASA during the first trimester (chapter 2). Over the counter NSAIDs were not taken into account in the IADB.nl (Interaction Database), so it can be assumed that even more women are exposed to a NSAID, especially in the first trimester when pregnancy might still be unknown. On the other hand, since a standardized gestational period was used, an overestimation of actual use is also to be expected. Either way, NSAIDs and ASA were prescribed in the first trimester of pregnancy and the question that remains is: ‘Should physicians prescribing these drugs be more careful or are they careful enough?’ To draw conclusions from the effect of the warning issued in 2005, data from 2005 onwards should show if prescribing has changed since then. Preliminary data show a slight decrease in the proportion of prescriptions, although not significant. To investigate whether these drugs are being prescribed according to guidelines, indications regarding NSAIDs are being prescribed are of added value. Since diagnoses are not available in the IADB.nl, a database such as the GPRD (general practice research database) might be helpful \(^4\). However, physicians who prescribe these drugs, should always be careful prescribing these drugs to women in the fertile age, especially when they suspect pregnancy is an issue.

Drug utilization: DMARDs

Chapter 3 showed that in the Netherlands approximately three per 1000 women (CI 95% 0.20-0.40) were prescribed a DMARD before pregnancy, and during pregnancy this was one per 1000 (13/12177; CI 95% 0.06-0.18). The results from this study indicate that prescribing of these drugs before and during pregnancy was based on the individual situation of the patient since patterns of prescribing were not found. In the United Kingdom (UK) one per 1000 women (CI 95% 0.12-0.14) was prescribed a DMARD before pregnancy as well as during pregnancy (CI 95% 0.13-0.15), as was shown in chapter 4 of this thesis. The decrease in prescribing of DMARDs round pregnancy will be partly due to guidelines being followed. Also the uncertainty of continuation or discontinuation of the DMARDs during pregnancy might have an influence.
In the Netherlands teratogenic drugs, such as methotrexate and leflunomide, were not prescribed before and during pregnancy in contrast to the UK. In both countries sulfasalazine and azathioprine were continued during pregnancy which is in concordance with recommendations. Hydroxychloroquine and chloroquine are hardly prescribed during pregnancy in the Netherlands in contrast to the UK where more than 100 women received a prescription for these drugs.

**Explaining the differences: general issues discussed**

The IADB.nl contains pharmacy dispensing data, so the prescriptions were prescribed by physicians (GP or specialist) and dispensed to the patient. The GPRD contains data from the general practitioner (GP), and records only drug prescribed by the GP. Drugs prescribed by the specialist will be registered as ‘letter from the specialist’ (or a comparable record) and a prescription will not be detected as such. In addition, the UK uses a traffic light system for prescribing drugs. This system distinguishes between drugs prescribed by the GP only (green), prescribed by the specialist as well as the GP (shared care, amber) and drugs prescribed by the specialist only (red). Some DMARDs, TNFα-drugs are red, some others, azathioprine, sulfasalazine, are labeled amber. Amber means that the drug is initiated by the specialist and can be prescribed by the GP further on in the treatment. The combination of these factors might explain the difference found between the Netherlands and the UK. For both databases used in these utilization studies, it has to be noted that they do not reflect actual use of the DMARDs. This limitation can be handled by taking into account the continuity of prescribing. It can be assumed that DMARDs are being prescribed and dispensed on a regular basis. To calculate not only the number of prescriptions, but also the time for which the drugs is being prescribed, assumptions on continued use can be made. If drugs are being prescribed continuously, it can be assumed that these drugs are being taken. Olesen et al showed that drugs used for chronic conditions were reported to be used always.

Cultural difference may also contribute to a difference in the use of drugs during pregnancy. In France it was estimated that 99% of the women received a
prescription for at least one drug during pregnancy (including vitamins). In Norway drug prescription during pregnancy was estimated at 85%, in the US, 64% of the women were dispensed a drug (or medical supply) during pregnancy. In the UK, it was estimated that approximately 65% of the women received a prescription for a drug during pregnancy, in the Netherlands, 79% of the women were prescribed a drug during pregnancy. From these studies it appears that there are small differences between the UK and the Netherlands in prescribing drugs during pregnancy.

The prevalence of rheumatic diseases in the UK and the Netherlands are comparable and guidelines towards drug use in rheumatic diseases are in principle the same. It is therefore not to be expected that these factors contribute to the difference determined between the UK and the Netherlands.

Explaining the differences: individual DMARDs discussed

In the Netherlands, 8-24% of the pregnancies are unplanned, in the UK this is estimated at approximately 33%. This higher number of unplanned pregnancies in the UK might contribute to the use of methotrexate and leflunomide in the first trimester of pregnancy. In the Netherlands, women who received one prescription of hydroxychloroquine or chloroquine and no other DMARD were excluded because it was assumed that these drugs were prescribed for malaria prophylaxis. In the UK these women were not excluded, which makes it difficult to compare the use of hydroxychloroquine and chloroquine. However, the number of women receiving hydroxychloroquine or chloroquine for another indication as malaria, is still much higher in the UK as seen in the Netherlands.

It should be discussed if the prescribing of DMARDs in both countries has to be improved and whether strict guidelines will help doing this. In addition, it should be investigated why the prescription of these drugs such as methotrexate and leflunomide was continued in the UK, and if guidelines with respect to these drugs need to be changed or other measures should be taken.
**Drug safety: DMARDs**

Since DMARDs are being used in daily practice, risk assessment studies can be performed to assess safety. To investigate the use of drugs in relation to birth defects, data need to be as detailed as possible. Meijer et al.\(^{24}\) described the importance of studying possible associations between drug use and birth defects at the most detailed level. They showed that the use of clomiphene was not associated with hypospadias in general, but a significantly increased Odds ratio was found for a severe form of hypospadias. This particular study was performed with data of EUROCAT Northern Netherlands (NNL), which records detailed information on birth defects as well as drugs prescribed and drugs actually used.\(^{25}\)

The GPRD is one of the largest databases used in pharmacoepidemiology research,\(^ {4,26}\), but is not as detailed as the EUROCAT NNL or EUROCAT Central\(^ {27}\) with respect to the registration of birth defects. However, data from the GPRD can be used to detect a possible signal on the use of drugs in association with a certain birth defect. Using the GPRD (chapter 5), associations between azathioprine in the second trimester and prematurity was found (OR 3.25 (1.82,5.78)). This effect has been described before\(^ {28,29}\) and it has to be discussed if and how these findings should be translated into guidelines on the use of azathioprine during pregnancy. With respect to birth defects no associations were found. If a significant association would be found this could be regarded as a signal and this should be further investigated in databases such as EUROCAT NNL, EUROCAT Central\(^ {25}\) or Slone Epidemiology Center Birth Defects Study\(^ {30}\).

**Rheumatologists perspectives and needs**

Rheumatologists are the main health care providers for patients with a rheumatic disease. Rheumatologists are often confronted with a lack of evidence on the use of anti-rheumatic drugs during pregnancy (chapter 1 & 6)

**Evidence on DMARD use in pregnancy**

There is usually some time difference between approval of a drug to the market and the first reports on teratogenic effects. Methotrexate, nowadays recognized as a teratogenic drug, was approved for the market in 1953 (FDA), reports on
teratogenic effects were first published in 1960’s 17. Sulfasalazine was approved to the international market in 1944, case reports on teratogenic effects were published in 1980’s 17. Sulfasalazine is nowadays considered to be safe. Chapter 1 showed that most studies reporting on risks of DMARD exposure during pregnancy are based on case-reports or small exposed cohorts. A single case-report or small exposed cohort can, on its own, not be used to identify teratogenic effects. However, a combination of all case-reports and exposed cohorts might yield a signal which should lead to a detailed investigation. Case-control surveillances and follow-up studies are the most appropriate observational studies to detect moderate or high risk teratogens respectively. Follow-up studies only need limited numbers to identify a high teratogen drug, however, to identify moderate teratogens larger numbers are needed.31 Norgard et al.32 evaluated the teratogenic risk of sulfasalazine using in a case-control study, after signals became clear from case-reports and small exposed cohorts without an external control group. This, however, is an exception, in chapter 1 only two case-control studies 32;33 on the use of sulfasalazine during pregnancy and 1 large cohort on the use of azathioprine during pregnancy 34, were found.

Guidelines
It is reported by the rheumatologists that there is not a major need for supplementary guidelines. They are well aware of current recommendations and the lack of evidence with respect to the use of DMARDs during pregnancy, and they inform their patients accordingly. Guidelines are developed using current evidence, knowledge and experience of clinicians, giving physicians a tool to help treat their patients. There is always some time lag between the development of the guideline and its implementation in daily practice, and in rare situations this time lag may be considerable. The situation of women with a rheumatic disease and a desire to become pregnant does not occur very often and the benefit of guidelines needs to be wondered. It would be prudent, in the case of women with a rheumatic disease, to think a rigid guideline would be appropriate, the development of a dynamic guideline would be more appropriate. The development of this guideline should be initiated by the rheumatologists, but also other health care providers like
obstetricians and clinical pharmacists should be involved. The GPs, who have a more regular contact with their patients, pharmacists, who are experts when it comes to drugs, gynecologists, who might be involved in the treatment of complicated cases of rheumatic patients, should all be involved. The dynamic guidelines should focus on DMARD use, but also the use of NSAIDs and corticosteroids should be taken into account. Organizations as the CBO (Centraal Begeleidings Orgaan) or the NVR (Nederlandse Vereniging van Reumatologie) could regulate this process. The panel of experts should generate a list of recommendations on each specific drug, where most common situations and exceptions should be addressed as well. These guidelines should be updated on a regular basis; e.g. once every two years, but they should also be updated when new information on these drugs become available such as safety updates. The recommendations can also be used by other physicians prescribing these drugs for other indications, although the effects of the indications should be reckoned with. Updates by means of courses or news letters might also be used to regularly inform rheumatologists on how to treat a woman with a rheumatic disease wishing to become pregnant.

Patients perspective
Chapter 7 of this thesis showed that women with a rheumatic disease had many questions about the use of their drugs and pregnancy. Most questions were about the use of drugs before or during pregnancy and fortunately most women received a satisfying answer to their questions.

Information sources
Information on the use of drugs in rheumatic diseases during pregnancy can be obtained at many different places, with the rheumatologist as the main source of information (chapter 7).
In a rheumatic disease, drugs are being dispensed in a regular manner and the pharmacy should be able to provide information on drug use during pregnancy. However, pharmacists are hardly consulted on drug use and pregnancy. If patients
are not aware that they can obtain their information in a pharmacy, they will not pose their questions there.

The Internet was mentioned as a source of information as well. Using the Internet you basically can find whatever you need, however, for many people it is difficult to distinguish between information that is true and useful and information that is not. Sources behind a website are often unknown or hard to identify. It is essential for the patient to know which of the information that was obtained provides the answers he/she needs. Websites from the National Association of Rheumatic Patients (Reuma Patienten Bond) and Dutch league against Rheumatism are helpful. They provide information leaflets, and links to other websites. In the northern and eastern Netherlands, some hospitals have information leaflets on the use of rheumatic drugs during pregnancy. However, a specific leaflet on the use of rheumatic drugs that contains information on DMARDs, NSAIDs as well as corticosteroids that is available to the general public, does not exist.

Questions and information
Women with a rheumatic disease had a lot of questions on drug use and pregnancy (chapter 7). Fortunately most questions were answered, but also a lot of questions will remain. It is impossible to answer all the questions, since not all the answers are known. Women with a rheumatic disease were mainly concerned on the use of their drug before and during pregnancy, less about the relapse of the disease after pregnancy and about drug use when breastfeeding. The majority of the responders in this study wanted to become pregnant at the time of the questionnaire. This might explain why a smaller proportion of the women had questions on the issues after pregnancy. It is, however, important to know what kind of questions women have on the use of their drugs during pregnancy, in order to be able to provide the answers needed. It seems that especially questions on drug use before and during pregnancy concern women, so it would be helpful to address these kinds of questions for example by developing a specific information leaflet.
The available information was found insufficient by the majority of the women, and many women reported no change or an increase in their doubts and fears about drug use and pregnancy. For those who experienced an increase, it was difficult to determine what caused the increase of doubts and fears, but the lack of evidence plays a major role. When using sulfasalazine, answers might be more clear, since there is more information available on the use of this drug during pregnancy. TNF-α-drugs and other biological agents are just recently approved for the market. Experience in general, but also of the individual rheumatologist is small, which makes it difficult to provide answers. Situations where rheumatologists might express their own fears and doubts about the use of a TNF-α-drug but still recommend continuing the drug might occur. All risks and benefits have to be considered, including patient’s disease and wishes. This might result in continuation of TNF-α in one case and discontinuation in another case.

Final remarks
This thesis explores, in particular, the safe use of DMARDs among female pregnant patients. It was shown that in the Netherlands DMARDs were prescribed on an individual basis. In the Netherlands guidelines with respect to methotrexate were followed, in contrast with the prescribing of methotrexate in the UK, which was continued during pregnancy. The use of both sulfasalazine and azathioprine was continued during pregnancy in the UK and the Netherlands, which is in concordance with recommendations. The use of azathioprine was associated with preterm birth, and it should be discussed whether recommendations with respect to the use of azathioprine in pregnancy should be changed. There is a lack of evidence with respect to the use of DMARDs during pregnancy which was acknowledged both by the women using these drugs as well as rheumatologists prescribing these drugs. Development of a dynamic guideline should be considered to support the rheumatologists. To keep the rheumatologists better informed, these guidelines should be updated more often than it is the case with rigid guidelines to keep the rheumatologists better updated. A special information leaflet on DMARDs and pregnancy would be considered of added value for women using these drugs.
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