Working Paper No: 40/2015 January 2015 LSE Health

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THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

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Working Paper No. 40/2015

First published in January 2015 by:
LSE Health
The London School of Economics and Political Science
Houghton Street
London WC2A 2AE

British Library Cataloguing in Publication Data. A catalogue record for this publication is available from the British Library.
ISSN 2047-8879

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Abstract

Background: Family planning and pregnancy (FPP) in rheumatoid arthritis (RA) is largely unknown to both physicians and patients. There is a paucity of data describing the safety of antirheumatic medications in pregnant women with RA. The need to understand the impact of drug use in pregnancy on the mother and foetus pre- and post-partum is today more pressing than ever.

Objectives: The objectives of this review were (a) to explore the evidence of drug use during pregnancy in women with RA and the potential impact of drugs on mother and baby pre- and post-partum; (b) to investigate the ethical considerations related to treatment (or lack of treatment) of pregnant women suffering from RA; (c) to raise awareness among patients and healthcare professionals with regard to the potential risks of RA treatment in pregnancy for both mother and foetus; and (d) to explore the existence of guidelines for treating RA in pregnant women.

Methodology: A systematic search was performed in the electronic databases of MEDLINE (through PubMed resource) and Scopus from January 2000 to June 2013. The studies were selected and included based on the PICOS approach. Studies were included if they contained primary data on the influence of RA medications on the disease activity of pregnant women with RA, as well as any foetal complications and birth outcomes. Ethical considerations, guidelines, prevalence, costs and access to drugs were also investigated.

Results: 31 studies were included in the systematic review. In most cases disease activity decreased during pregnancy and flared post-partum, but it was not clear if this was due to medication use or the beneficial effect of pregnancy itself. Results showed an association between use of prednisone during pregnancy and premature delivery. Methotrexate (MTX) was associated with an increased risk of preterm births, spontaneous abortions and foetal malformations. There was no substantial risk of adverse pregnancy outcomes due to leflunomide (LEF) exposure among women who underwent wash-out procedure with cholestyramine. Anti-TNFs were associated with a moderate risk of spontaneous abortions, but no clear conclusion could be drawn about their safety for the foetus. Most rheumatologists agreed that pregnancy is contraindicated in women treated with MTX and LEF and, when pregnancy occurs either therapeutic termination or birth control are required.

The termination rate was lower in pregnancies exposed to anti-TNFs and there were cases of women who intentionally opted to continue anti-TNF therapy during pregnancy. Studies confirmed the lack of specific national or international guidelines for the treatment of pregnant RA patients. Only one study discussed the issue of access to medications and particularly the reimbursement granted to persons diagnosed with a chronic disease. There were no studies referring to costs of drugs in RA pregnant patients.

Conclusions: This is the first systematic review that investigates the impact of drug use in pregnant patients with RA. Results showed that different RA agents have different effects on disease activity, pregnancy outcomes and congenital anomalies, although further research is essential to increase the information available. The creation of national and international guidelines is crucial for the management of pregnant women with RA.

Contents

List of Abbreviations

ACPA	Anti-citrullinated protein antibody
AS	Ankylosing spondylitis
DMARDs	Disease-modifying antirheumatic drugs
FDA	Food and Drug Administration
FPP	Family Planning and Pregnancy
HCQ	Hydroxychloroquine
HLA	Human Leukocyte Antigen
IgG	Immunoglobin G
JIA	Juvenile idiopathic arthritis
JRA	Juvenile rheumatoid arthritis
LEF	Leflunomide
MTX	Methotrexate
NSAIDs	Nonsteroidal anti-inflammatory drugs
OECD	Organisation for Economic Cooperation and Development
OTIS	Organisation of Teratology Information Specialists
PICOS	Population, interventions, comparators, outcomes, and study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RCTs	Randomised Controlled Trials
RF	Rheumatoid factor
SDS	Standard deviation score
SLE	Systemic lupus erythematosus
SSZ	Sulfasalazine
TNF	Tumor necrosis factor

1. Background

There is a paucity of scientific data describing the use of medication for the treatment of chronic conditions among pregnant women. The tragedy of thalidomide in the 1950's and 1960's led to a much stricter testing for drug licensing (Eichler et al. 2012) and to the pause of clinical research in pregnant women for ethical reasons (Østensen et al. 2006). As a consequence, in post-marketing reports, most data are presented in isolated case reports or observational case series, where a real causal relationship cannot be easily proved (Golding et al. 2007). The safety of drugs used during family planning and pregnancy (FPP) is questionable and their impact on both mother and baby is largely unknown. Moreover, since women among OECD member nations have been conceiving at an increasingly older age over the last decades (average age of conception 27.8 years in 2009) (OECD 2009), there is a higher probability of onset of chronic diseases. This constitutes a global problem, as the prevalence of chronic diseases, which are the major cause of death nowadays, is rapidly increasing worldwide (WHO 2005).

All the above suggests that pharmacologic management of chronic conditions before and especially after conception (Spiegler et al. 2013), continues to be a challenge for health policymakers and physicians. In fact for most medicines there is little or no guidance regarding their appropriate use and effects on pregnant women and their unborn babies. This is accentuated by the fact that the choice to leave a pregnant woman untreated can have adverse effects for the foetus as well as the mother (Feibus 2008).

Rheumatoid arthritis (RA) is an autoimmune disorder that principally affects the skeletal system and connective tissue (Reed et al. 2006). Although RA tends to have a late onset (Jawaheer et al. 2011), the disease occurs before the age of 30 in 1 every 5 diagnosed women and before the age of 40 in 2 every 5 diagnosed women (Mecacci et al. 2007).

Studies have emphasised the current paucity of evidence regarding the use of various medications for the treatment of RA during pregnancy (Adams et al. 2012, Hazes et al. 2011) and FPP in RA lacks medical consensus or guidelines (Perinatal Medicine 2011). In the US, the classification of the Food and Drug Administration (FDA) has a specific category to define risk and safety of medications during pregnancy (Meadows 2001). However, this classification system is almost exclusively based on animal data and does not provide any

detailed advice on treatment (Golding et al. 2007). Therefore, physicians are often forced to assess the potential risks of a medication taken early in pregnancy, or to decide whether continuing or discontinuing therapy during pregnancy, for fear of harming the foetus (Chambers et al. 2006). With regard to teratogenic risk of most antirheumatic drugs, information coming from controlled studies is either conflicting or absent (Chan and Hernández-Díaz 2004). As a result, there have been cases of women who decided to avoid or interrupt their pregnancies, as well as to suspend or postpone their treatments (Clowse et al 2012).

During the previous years, the abundant availability of new disease-modifying antirheumatic drugs (DMARDs) has raised questions about their safety during pregnancy and their effect on the foetus (Chambers et al. 2007). Some of them, such as sulfasalazine (SSZ) and the antimalarial hydroxychloroquine (HCQ), are used during pregnancy, while others, like methotrexate (MTX) and leflunomide (LEF), have proved to be teratogenic in animal studies and they are contraindicated during pregnancy (Østensen and Förger 2009). Nevertheless, the reason for the exclusion is not their proven teratogenicity, but the absence of proven safety for the foetus (Østensen and Förger 2009). With regard to biological therapies (TNF-α inhibitors or anti-TNFs), the limited available knowledge is coming from case reports and national therapy registers and therefore they are not recommended during pregnancy (Märker-Hermann and Fischer-Betz 2010).

Moreover, rheumatologists have to consider some singular features of RA before establishing a therapeutic regimen for a pregnant patient: (a) 54-94% of the patients with RA experience a spontaneous improvement or even remission of their disease activity during pregnancy (Märker-Hermann and Fischer-Betz 2010); (b) RA tends to relapse severely post-partum in more than 70% of cases (Mecacci et al. 2007); (c) in contrast to what was believed in the past, approximately one fourth of patients continue to have active disease or even deterioration of RA during pregnancy (Tandon et al. 2006) and require pharmacotherapy. In fact, 10–25% of women whose disease remains active during pregnancy need to continue drug use (Østensen 2001); and (d) there are considerable risks for the mother and foetus if RA is left untreated (Rindfleisch and Muller 2005).

Against this background, this review was designed with the following objectives: (a) to explore the evidence of drug use during pregnancy in women with RA and the potential

impact of drugs on mother and foetus pre- and post-partum; (b) to investigate the ethical considerations related to treatment (or lack of treatment) of pregnant women suffering from RA; (c) to raise awareness among patients and healthcare professionals about the potential risk related to RA treatment in pregnancy for both mother and foetus; (d) to investigate the socioeconomic impact and costs related to pregnancies of RA patients, as well as access to medication; (e) to explore the existence of guidelines for treating RA in pregnant women; and (f) to explore the availability of any prevalence data on RA in pregnant women and on drug use in pregnant RA patients.

The study is structured into four parts. In part one, the methodology and search strategies are presented. Part two gives an overview of the results of the systematic review. Part three provides a discussion on the implications for policy making. Finally, some conclusions are given.

2. Methodology

A systematic literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al. 2009) for the identification, screening, eligibility and inclusion of articles.

2.1 Search strategy

The search strategy involved the following four steps. First, a broad systematic search was performed in the electronic databases of MEDLINE (through PubMed resource) and Scopus for the period from January 2000 to June 2013. Search terms and their combinations are set out in Table 1. Databases were searched using the primary terms “rheumatoid arthritis” AND “pregnancy OR pregnant” (column 1), in combination with a term associated with drug use (column 2). Second, appropriate filters were set to restrict results to studies published in English and undertaken on humans and, particularly, on female populations. Third, duplicate studies were identified and removed. Fourth, further studies were identified and included from the references found in the retrieved publications.

Table 1: Search Terms

Column 1	Column 2 *Combined with (individually)*
rheumatoid arthritis AND	drug use
pregnancy OR	medication use
Pregnant	medication
	medications
	treatment
	therapy
	pharmacotherapy
	pharmaceutical use
	management

2.2 Selection and inclusion criteria

The primary endpoint of the review was any clinical outcome for mother and foetus pre- and post-partum. Any influence of RA medications on the disease activity of pregnant women, as well as any foetal complications and birth outcomes were examined. The identified literature was also searched for any references or materials related to ethical considerations, guidelines, prevalence, access and costs. Only studies reporting primary data were regarded as eligible and they were selected according to the inclusion criteria based on the PICOS approach outlined in Table 2. Although it was anticipated that no randomised controlled trials (RCTs) would be retrieved from the search, they were part of the inclusion criteria, as they constitute a basic source of primary data.

2.3 Data extraction

The data collected for each article were extracted into an Excel spread sheet and included (a) information about the study (study type, study objective, country of origin, sample size, conditions studied); (b) interventions (medication studied); (c) baseline characteristics of the study population (maternal age, ethnical background, years from diagnosis, timing of exposure to rheumatoid arthritis agents in relation to conception; (d) clinical outcomes

(disease-related outcome, birth outcome, foetal complications); (e) further endpoints (ethical considerations, guidelines, prevalence, access, costs).

Table 2: Inclusion criteria

P (Population)	Pregnant women diagnosed with RA before pregnancy.
I (Interventions)	Any drug intervention or combination of drug interventions or lack of drug intervention given for the treatment of RA during pregnancy.
C (Comparator)	N/A
O (Outcomes)	Any clinical outcome for mother and foetus pre- and post- partum, ethical considerations, referral to guidelines, prevalence, access and costs.
S (Study design)	Cohort studies, clinical trials, studies based on registry data, case studies, surveys/interviews.

Systematic Reviews. CRD's guidance for undertaking reviews in health care. (2008). York: Centre for Reviews and Dissemination, University of York.

2.4 Limitations

The methodology of this systematic review is not without limitations. Although case studies and case reports provide anecdotal evidence and they are very prone to bias (Doherty 1994), they were also considered for inclusion in the systematic review. The reason for this was that they would enable the identification of information in relation to the subject under investigation, particularly in light of the absence of RCTs and the strong ethical considerations concerning drug use in pregnancy. It was expected that they would offer valuable information on the issues that concern women with RA when it comes to childbearing and on the way women, their partners and their doctors made decisions about FPP considering the risks involved for mother and the baby with regard to treatment.

Another limitation of the methodology is that while dosing of medication is important during pregnancy, as different doses have a different impact on the mother and the foetus, this matter was not taken into account.

3. Results

3.1 Search results

265 citations were identified in both MEDLINE and Scopus. The flow of information through the different phases of the systematic review is depicted in Figure 1. Duplicates between the two databases were removed (n = 104). The 161 remaining studies were reviewed by three researchers in terms of title and abstract to gauge their suitability for inclusion in the first instance.

102 studies were excluded because: a) 37 studies dealt with a topic irrelevant to the purpose of this study; (b) 10 studies were of irrelevant design. For instance, there were 4 Q&A articles and one letter; (c) 5 studies studied conditions other than RA;[1] (d) 16 studies were not specific to pregnancy;[2] (e) 6 studies were conducted on animals; and (f) 28 studies had no information on drug use but instead focused on the ameliorating effect of pregnancy on RA, the immunological modifications during gestation, the mechanisms responsible for remission and the post-partum relapses of the disease.

Subsequently, the remaining studies (n = 59) were downloaded and read in order to decide whether or not they met the inclusion criteria. The same selection process was applied to 18 additional studies identified through the reference lists and to one study identified in Google. The reason that these studies were not retrieved through the database search is because they did not include the term "rheumatoid arthritis" in the title or abstract, but rather used the terms "chronic inflammatory disorders" or "rheumatic diseases", as they reported many different rheumatic conditions.

In the final stage, 47 studies were excluded because: (a) the study design was not relevant (n = 36); (b) they were in a language other than English (n = 3); (c) they did not examine the impact of medications (n = 4); (d) the patient population was not pregnant (n = 2); (e) they studied a condition other than RA (n = 1); and (f) there was no information on RA (n = 1). 31

[1] For example, one article studied acute renal failure syndrome in a pregnant woman with primary Sjögren's syndrome. Nevertheless it appeared in the initial search because the abstract contained the term "rheumatoid arthritis", mentioning that *"the patient exhibited no other clinical or laboratory findings indicative of other collagenous disease and/or RA"*.

[2] For example, one study discussed if hormonal replacement therapy might reduce the risk for RA in women whereas another study assessed the infliximab continuation rates in patients with RA in everyday practice.

studies from 11 countries were finally included. These included: 15 cohort studies, 1 longitudinal investigation, 10 case studies (8 case reports and 2 case series) and 5 surveys. Appendix 1 contains the characteristics of the studies.

Different drugs for the treatment of RA were examined independently or in combination. DMARDs were examined in the majority of studies: HCQ in 3 studies; LEF in 5 studies;

Figure 1: Flow chart of the study selection process

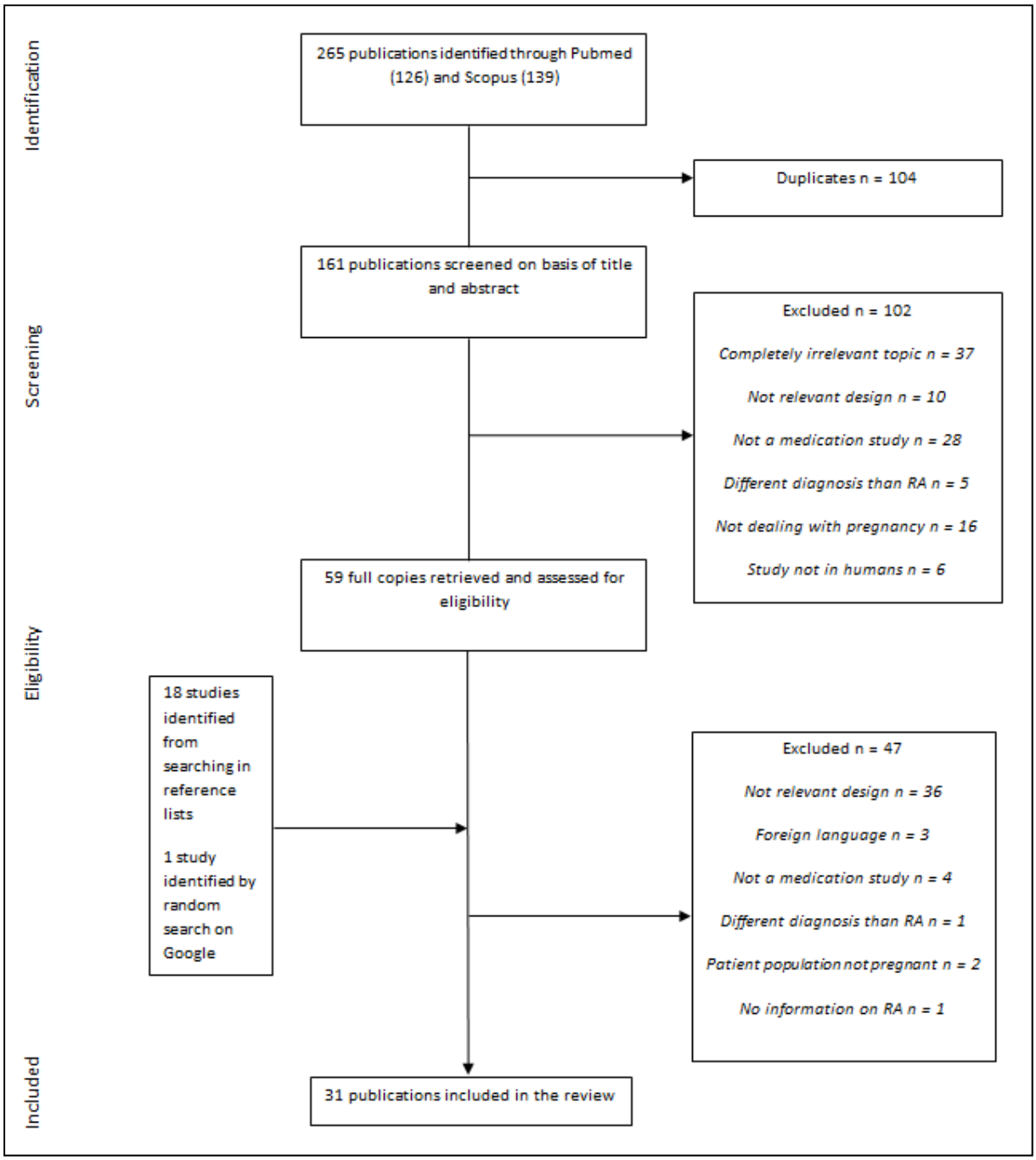

Table 3: Main outcomes addressed in the included studies

Author	Disease-related outcomes	Birth outcomes	Foetal complications	Ethical issues	Guidelines	Prevalence	Costs	Access
Almarzouqi et al. 2007	✓	✓	✓	✓				
Artama et al. 2011			✓			✓		✓
Berthelot et al. 2009		✓	✓					
Cassina et al. 2012	✓	✓	✓					
Chakravarty et al. 2003		✓	✓	✓				
Chakravarty et al. 2011		✓	✓	✓				
Chambers et al. 2010		✓	✓					
Crocker et al. 2000	✓							
Cush 2005		✓	✓			✓		
de Man et al. 2008	✓							
de Man et al. 2009	✓	✓						
Förger et al. 2012	✓							
Hajdyla-Banaś et al. 2009		✓		✓				
Katz et al. 2004		✓	✓					
Kuriya et al. 2011		✓				✓		
Lewden et al. 2004		✓	✓					
Motta et al. 2005		✓	✓					
Østensen et al. 2004	✓	✓						
Østensen et al. 2007		✓	✓	✓				
Østensen and Raio 2005	✓	✓	✓	✓				
Park-Wyllie et al. 2000		✓	✓	✓				
Roux et al. 2007		✓	✓					
Scioscia et al. 2011	✓	✓	✓					
Sheikh 2007	✓	✓						
Sills et al. 2001	✓	✓						
Sinha and Patient 2006		✓		✓				
Thompson & Bashook 2010					✓			
Umeda et al. 2010	✓	✓		✓				
Verstappen et al. 2011	✓	✓	✓	✓				
Viktil et al. 2009						✓		
Vroom et al. 2008				✓	✓	✓		

MTX in 7 studies; SSZ in 4 studies; gold in 2 studies; azathioprine in 1 study; and salazopyrine in 1 study. Biologics were also examined, such as the anti-TNFs etanercept in 10 studies; adalimumab in 4 studies, infliximab in 6 studies; and anakinra in 1 study. The anti-CD20 rituximab was investigated in 1 study. Prednisone was examined in 8 studies. NSAIDs were examined in 3 studies and penicillin in one study.

The findings of this systematic review pertain to disease-related outcomes, birth outcomes, foetal complications, ethical considerations, guidelines, costs, access to drugs and prevalence. The endpoints addressed in the included studies are shown in Table 3, whereas the outcomes are presented in Appendix 2.

3.2 Disease-related outcomes

Six prospective cohort studies (Østensen et al. 2004, de Man et al. 2008, de Man et al. 2009, Verstappen et al. 2011, Cassina et al. 2012, Förger et al. 2012), one retrospective chart review (Almarzouqi et al. 2009), one longitudinal investigation (Crocker et al. 2000) and five case studies (Sills et al. 2001, Sheikh 2007, Umeda et al. 2010, Østensen and Raio 2005, Scioscia et al. 2011) (reporting six cases) investigated the activity of RA in pregnant patients and the impact that medications for RA had on disease activity during pregnancy. Two prospective cohort studies (Verstappen et al. 2011, Cassina et al. 2012) investigated different indications, including RA and juvenile rheumatoid arthritis (JRA), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), scleroderma, juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS) and adult-onset Still's disease. Results from both of these studies referred to the entire cohort and not specifically to the RA cases.

Two prospective cohort studies (Østensen et al. 2004 and de Man et al. 2008) analysed the activity of RA in 94 patients during and after pregnancy. In most patients the disease activity decreased during pregnancy and flared post-partum. In the 6 patients who were treated with biologic drugs less than one year before conception, disease activity was measured and resulted to be moderate to high in the first trimester. Patients included in the study were only treated with SSZ and low-dose prednisone during pregnancy. The combination of these two drugs cannot by itself reduce the disease activity, so the cause of the observed decrease must be attributed to the beneficial effect of pregnancy. De Man et al. (2009) drew the same

conclusion investigating RA activity in 152 pregnant patients treated with prednisone, SSZ and HCQ.

Förger et al. (2012) investigated pregnancy-related changes of RF isotypes and ACPA and their association with disease activity and treatment with DMARDs and TNF-inhibitors in 22 RA patients. Of these, 16 patients experienced improvement or persistent low disease activity during pregnancy (group 1). By contrast, 6 patients had persistent active disease throughout pregnancy (group 2). The gestational DMARD therapy and the pre-conceptional use of DMARD and TNF-inhibitors in group 1 most probably supported the disease ameliorating effect of pregnancy. Conversely, Crocker et al. (2000) found that RA remissions are most probably due to the pregnancy rather than drugs.

Three case reports (Umeda et al. 2010, Scioscia et al. 2011, Sills et al. 2001) examined the RA activity of four pregnant patients pre- and post-partum after treatment with the anti-TNF etanercept. All four women experienced a remission of their symptoms during pregnancy, which persisted for at least nine months after delivery. Another anti-TNF, infliximab, was examined in a case of a woman with RA who did not ameliorate during pregnancy (Østensen and Raio 2005). Last dose had been administered 10 days before pregnancy. No treatment during pregnancy was able to relieve her symptoms and infliximab plus MTX were restarted one week after delivery.

Almarzouqi et al. (2007) investigated the effects of gold in RA patients while planning pregnancy. RA flared in 3 out of 15 pregnancies and was controlled in 12 out of 15 pregnancies. The disease flared 2-20 weeks postpartum in 13/15 completed pregnancies, and 2-6 weeks postpartum after 5 spontaneous abortions. Two women did not experience postpartum flare.

3.4 Birth outcomes

The majority of studies (n = 24) reported birth outcomes such as live births, stillbirths, elective terminations, spontaneous abortions (miscarriages), full-term and premature deliveries, and birth weight. Results are presented according to the medication taken by the mother during pregnancy.

3.4.1 Prednisone

In a study by de Man et al. (2009), the use of prednisone was connected only with the actual birth weight, and not with the birth weight SDS. This implies that prednisone influences birth weight indirectly, because there is a higher chance of delivering the baby prematurely.
Park-Wyllie et al. (2000) also investigated the "relative foetal safety" of treatment with prednisone for several indications in pregnancy including RA. The rate of babies who were born alive was similar among the exposed group and the controls. Elective terminations were more frequent in the exposed group, and babies were smaller, born earlier and more likely to be premature.

3.4.2 Methotrexate

Lewden et al. (2004) assessed the safety of low dose MTX during the first trimester of pregnancy in 27 women, of whom 22 were suffering from RA. They found that the rate of preterm births (16.7%) was relatively high in comparison with the rate in all singleton births reported in France (5.4%). There were also 5 elective abortions, 4 miscarriages, 19 live births and 3 preterm births. Exposure to MTX was also investigated in a survey by Chakravarty et al. (2003), along with concomitant exposure to LEF, etanercept and infliximab. A total of 65 pregnancies exposed to the above DMARDs were reported, 39 of which in patients taking MTX. Of these, 21 women delivered full-term, healthy infants, 7 patients had spontaneous abortions (one after exposure to both MTX and etanercept) and 8 underwent elective terminations.

3.4.3 Leflunomide

Hajdyla-Banaś et al. (2009) reported two cases of LEF-exposed pregnancies. Mothers underwent a LEF wash-out procedure with cholestyramine as soon as they learned about their pregnancy. They both delivered full-term healthy infants. The wash-out procedure was also assessed in the study by Chambers et al. (2010), where 64 women with RA were treated with LEF at some point during their pregnancy (61 received cholestyramine) and 108 were not. Gestational age at delivery and birth weight were the only outcomes that differed significantly between the two groups. Researchers attributed this to confounding factors and

to the necessity of more frequent and higher-dose therapy with corticosteroids due to more severe underlying disease. They concluded that there is no substantial increased risk of adverse pregnancy outcomes due to LEF exposure among women who undergo the elimination procedure early in pregnancy.

In another study (Cassina et al. 2012), 16 women were treated with LEF during the first trimester of their pregnancy (group 1) and 29 were exposed to LEF prior to conception (group 2). All 16 pregnancies of group 1 and 27 of the pregnancies in group 2 resulted in live births.

3.4.4 TNF alfa inhibitors

Verstappen et al. (2011) examined the impact of the anti-TNFs adalimumab, etanercept and infliximab on 14, 48 and 9 pregnancies respectively. Women who were using anti-TNFs at the time of conception presented an increased spontaneous abortion rate, especially if they were also using MTX or LEF. However, this should not only be explained by the simultaneous therapy with MTX and/or LEF, as rates were also high in women exposed to anti-TNFs at conception but not taking MTX and/or LEF. This means that treatment with anti-TNFs at conception may imply an increased risk of spontaneous abortion, but disease severity and concurrent therapy may play a role as well.

In a large case series (Katz et al. 2004) reporting pregnancy outcomes in women with RA and Crohn's disease (CD) exposed to infliximab, where 72 out of 96 patients also received concomitant medication, there was no significant increase of adverse outcomes following exposure to infliximab shortly before conception or during pregnancy. The rates of live births (n = 64), miscarriages (n = 14) and therapeutic terminations (n = 18) were similar to those expected in a healthy population. Infliximab use also seemed to be safe pre-conceptionally and during pregnancy as shown in a case report by Østensen and Raio (2005).

In another case series of 15 patients including 4 RA cases Berthelot et al. (2009) drew no conclusion regarding the safety of anti-TNFs during conception or pregnancy, as no significant adverse outcomes were reported. With specific regard to the 4 RA patients, two mothers treated respectively with adalimumab and infliximab had both normal deliveries. A

third woman treated with etanercept had a miscarriege at 4 weeks of gestation and the fourth one, treated with both etanercept and MTX, asked for a therapeutic termination at 6 weeks. A therapeutic termination due to etanercept exposure was also presented in a brief report of 3 cases (Roux et al. 2007). In this study, one of the cases was treated with adalimumab and the other with etanercept; both women gave birth to healthy infants, although one of them was premature (32 weeks) and had a low birth weight (2600 g). Etanercept also seemed to be safe during pregnancy in 4 case studies (Sills et al. 2001, Sinha and Patient 2006, Umeda et al. 2010, Scioscia et al. 2011) reporting 5 pregnancies which ended in full-term babies with normal birth weights.

3.4.5 Antimalarials

In a study by Motta *et al.* (2005) HCQ appeared to be safe during pregnancy and lactation. In total, 40 infants were examined, 2 of whom born by RA patients. Preterm delivery was the most frequently observed complication (8 pregnancies, 20.5%), but researchers could not say whether this was attributed to the HCQ intake or to the maternal disease state. One baby was born at less than 32 weeks and weighted less than 1500 g; she required intensive care. 4 babies (10%) weighted less than they should at their gestational age. Antimalarials were also investigated by Østensen et al. (2004), where 10 RA patients and 9 AS patients were also treated with SSZ, or low dose prednisone, and NSAIDs. 17 out of 19 patients did not encounter any adverse events in their pregnancies and gave birth to full-term healthy babies.

3.4.6 Studies looking at different medications

Kuriya *et al.* (2011) invastigated the distribution of RA medicines by therapeutic class, including NSAIDs/coxibs, glucocorticoids, non-biologic DMARDs and biologic DMARDs. They found that more frequent abortions were associated with exposure to NSAIDs/coxibs, although it was very difficult to decide whether abortions were due to the higher exposure itself, or to greater disease activity, which might have required higher drug exposure.

In a survey conducted by Østensen et al. (2007) patients with different kinds of arthritis reported outcomes of pregnancies exposed to immunosuppressive and biologic drugs. 22 out of 28 pregnancies exposed to drugs like antimalarials, SSZ, cyclosporine and azathioprine

resulted in live births. There were two miscarriages. Two pregnancies exposed to etanercept resulted in live births, one pregnancy exposed to LEF ended in a miscarriage and 3 pregnancies exposed to MTX resulted in one miscarriage and two induced abortions.

3.5 Foetal complications

In 17 of the 31 studies included in the systematic review, a total of 113 foetal complications were identified, 96 of which concerned pregnant women with RA. The remaining 17 foetal complications were found in cohorts of mothers suffering from different chronic diseases, including RA, but treated with the same medication. Results for these cases are presented collectively.

No significant malformations were detected by Motta et al. (2005) in women treated with HCQ during pregnancy, despite the drug's ability to cross the placenta. Three additional studies (Berthelot et al. 2009, Scioscia et al. 2011, Cush 2005) examining the safety and impact of anti-TNF found no congenital malformations. Anti-TNFs also appeared to be safe in a study (Roux et al. 2007) that observed only 1 adrenal congenital hyperplasia with 21-hydroxylase deficiency. However, this was inherited from the father, and was successfully treated with prednisone.

3.5.1 Minor malformations

Almarzouqi et al. (2007) reported the cases of 2 babies who were born with minor congenital malformations (1 weakness of extraocular muscle and 1 blocked tear ducts) to women treated with gold while planning pregnancy.

One child whose mother was exposed to MTX (7.5 mg/week) and SSZ (3 g/day) for RA until 8.3 gestational weeks developed minor neonatal anomalies (bilateral metatarsus varus and right eylid angioma) in a study by Lewden et al. (2004).

Verstappen *et al.* (2011) reported 4 congenital malformations: 1 congenital dislocation of the hip and 1 pyloric stenosis in two infants whose mothers were exposed to anti-TNFs at

conception; 1 winking jaw syndrome and 1 strawberry birth mark in two infants whose mothers were exposed to anti-TNFs prior to conception.

A pattern of 3 minor malformations (short nose, flat nasal bridge, long philtrum) was reported by Cassina et al. (2012) in an infant born to a mother with RA who was exposed to LEF and NSAIDs during the first two trimesters of her pregnancy.

3.5.2 Major malformations

Cassina et al. (2012) reported major malformations in two children who were exposed to LEF and prednisone during gestation (one aplasia cutis congenita to both thighs and one Pierre-Robin sequence, spina bifida occulta, patent ductus arteriosus, chondrodysplasia punctata, and congenital heart block). No major malformations were detected in the cohort of mothers who were treated with LEF prior to conception. The same study also reported two functional anomalies: severe sensorineural hearing loss in an infant exposed to LEF during pregnancy and intrauterine growth restriction and cerebral palsy in an infant whose mother suffered from JRA, diabetes, hypertension and asthma.

In a study (Chambers 2010) investigating pregnancy outcomes in 64 women who received LEF and underwent the wash-out procedure, 3 major structural defects in live births were reported: 1 occult spinal dysraphism; 1 unilateral ureteropelvic junction obstruction and multicystic kidney disease; and 1 microcephaly. There was also a baby born with 2 functional problems (hydronephrosis grade 2 and bilateral vesicoureteral reflux). A pattern of three or more minor structural anomalies were observed in 24 cases.

In a survey conducted by Chakravarty et al. (2003) rheumatologists were concerned about the teratogenicity of MTX and LEF, but they were less certain about the risk of exposure to either etanercept or infliximab for the developing fetus. They reported 3 congenital malformations in infants exposed to MTX. No congenital malformations or adverse events were reported with LEF, etanercept and infliximab.

Two fetal abnormalities were reported in a study (Katz et al. 2004) examining infliximab exposure during pregnancy. One of these was an intestinal malrotation in an infant born to a

mother suffering from RA who had received infliximab before conception and during pregnancy. She was also receiving LEF.

Park-Wyllie *et al.* (2000) investigated the relative fetal safety of prednisone therapy in pregnant women suffering from different diseases (RA among them) and did not detect any statistical difference in the rate of major anomalies between exposed and non-exposed mothers (P = 0.03). There were 4 major anomalies in 4 out of 111 born infants in the exposed group and 3 major anomalies in 3 out of 172 born infants in the unexposed group. This study found that the risk of oral cleft palate for children without exposure to corticosteroids is one per 1,000 live births, and that this risk increases to 1.3-3.3 per 1,000 live births after exposure to corticosteroids in the first trimester of pregnancy.

Lewden et al. (2004) assessed the risk of major malformations in pregnant women with chronic inflammatory disorders, including RA, treated with low-dose MTX in the first trimester. Two children had documented neonatal pathological conditions: the first one, who was premature, experienced hyaline membrane disease and neonatal jaundice, and the other had transient respiratory distress and jaundice.

Chakravarty et al. (2011) reported the pregnancy outcomes of 231 pregnancies exposed to rituximab. Most results were biased by simultaneous therapy with potentially teratogenic drugs and severe underlying disease. An infant born to a mother with RA had neonatal thrombocytopenia.

3.6 Ethical considerations

11 studies discussed the ethical considerations regarding continuation of treatment in pregnant women with RA and elective terminations of pregnancy due to medication exposure, either by the doctor's or the patient's own choice. Doctors also advised birth control, especially during the use of known teratogens such as MTX and LEF.

In the study by Verstappen et al. (2011) 20 patients were receiving MTX and LEF at the moment of conception. It is unclear whether or not they were informed about the drugs' harmful effects. However, the fact that a small number of them used oral contraception,

shows that these pregnancies were probably not planned. Despite the exposure to anti-TNFs at conception, few of the patients chose to terminate the pregnancy. The termination rate was 19% in those exposed simultaneously to anti-TNFs and MTX or LEF at conception, but only 8% in those exposed exclusively to anti-TNFs.

In a survey by Chakravarty et al. (2003), rheumatologists almost uniformly agreed that pregnancy is contraindicated in women taking MTX (95%) or LEF (92.7%), and that the use of reliable methods of birth control is required. However, they were less diligent in monitoring the continuous use of birth control with their patients during their subsequent visits. The study indicates that rheumatologists are concerned about the teratogenicity of MTX and LEF. Furthermore, some of them recommended the termination of pregnancies that occurred while patients were taking these medications. In another survey (Vroom et al. 2008) 9 out of 15 rheumatologists advised their patients to stop taking MTX and LEF as soon as a pregnancy was detected.

Østensen and colleagues (2007) found that most of the women treated with MTX and LEF were advised to practice contraception during treatment and for some time after discontinuation. However, one-third of women did not follow the advice. Østensen and Raio (2005) reported that when a patient expressed her wish for pregnancy, she was advised to stop taking MTX immediately. In another study (Hajdyla-Banaś et al. 2009) reporting two cases of LEF exposure in early pregnancy, both mothers were informed that LEF could have been potentially embryo- and fetotoxic, and that they had to avoid pregnancy while being treated with LEF therapy and for two years after the completion of the therapy. Nevertheless, both women became pregnant and underwent a wash-out procedure with cholestyramine.

In their study Park-Wyllie et al. (2000) discussed that although prednisone has never been proved to have teratogenic effects in humans, some doctors rely on data from animal studies that show that it can cause cleft lip or palate. Consequently, doctors advise patients to not use prednisone in pregnancy. This may have played a role for a number of the 16 women who opted for abortion after being exposed to prednisone. In a study by Almarzouqi et al. (2007) 4 out of 14 women continued to use gold until they gave birth, whereas the remaining 10 discontinued the treatment once they found out to be pregnant. Only one woman stopped using gold 4 weeks before conception. When a decision to continue gold during gestation is made, doctors discuss the typical dangers for the exposed infants.

Chakravarty et al. (2011) discussed maternal exposure to rituximab and reported four clinical trials reports where patients were unblinded to placebo immediately after having discovered to be pregnant; three of the four pregnancies were terminated despite unblinding.

Two studies (Sinha and Patient 2006, Umeda et al. 2010) reported two cases of women with RA who continued etanercept treatment during pregnancy. The first woman planned for pregnancy fully aware that there was no evidence of the effects of etanercept on the foetus. She was counseled thoroughly and finally agreed to take the risks. The second woman was also counseled by her doctors about the risks of etanercept when she expressed her wish to become a mother. They told her that the drug should be administered to pregnant patients only if the benefits from treatment are greater than the potential risks; she continued to take the drug prior to conception and stopped it immediately after she learned that she was pregnant. Nevertheless, her arthritis during pregnancy flared. Being eager to resume etanercept, she consulted the Pregnancy and Medicine Information Center of National Center for Child Health and Development and she resumed treatment at 20 weeks of gestation.

3.7 Guidelines

Thompson & Bashook (2010) conducted a survey to ask physicians what were the key information that patients must know about MTX and what were the most important reasons to call their doctor when taking the drug. 53 out of 141 rheumatologists answered that it was important to advise women to avoid pregnancy. The recommendation given to patients was: "MTX can harm an unborn child. If you are having sex or thinking of having sex and could get pregnant, consult your doctor about continuing to take MTX." Further, 20 out of 135 rheumatologists replied that a pregnancy or planning a pregnancy were good reason to call a rheumatologist. The recommendation given to patients was: "Stop MTX and immediately call your doctor if you become pregnant while taking MTX".

In another survey (Vroom et al. 2008), 9 out of 15 Dutch rheumatologists advised to stop MTX and LEF at least 3 months before intending to become pregnant, in accordance with national and international guidelines, or to stop medication as soon as women knew that they were pregnant. 5 out of 15 rheumatologists pointed out that azathioprine, cyclosporine and HCQ could be taken if necessary, but 10 out of 15 were reluctant to prescribe these drugs in

case patients were pregnant. 5 of the 9 hospitals in the survey reported that they did not use any particular written guidelines" for the therapeutic management of RA patients who are or wish to become pregnant. 4 hospitals indicated that they used written guidelines; 2 hospitals had a specific section regarding pregnancy in their leaflets and 2 hospitals used guidelines that contained pregnancy risk classifications and background material about known or possible teratogenic effects of the drugs. The hospitals mostly used international and national books, international literature in PubMed, international and national guidelines such as the American College of Rheumatology and the Dutch Society of Rheumatology. 11 out of 15 rheumatologists believed that the existing information or guidelines were sufficient, but 5 thought that national guidelines should be created. The shortage of data was believed to be the most important problem.

3.8 Costs and access to drugs

The only study (Artama et al. 2011) that discussed the issue of access to medication was from Finland, where special reimbursement is given to persons diagnosed with a chronic disease: there is a lower special refund category of 72% and an upper special refund category of 100%. The study found that the proportion of women with one or more special reimbursement was slightly higher in parturients (6.5%) than in women with termination of pregnancy (6.0%). There were no studies referring to costs of drugs in RA pregnant patients.

3.9 Prevalence

Two studies reported information on prevalence of drug use in pregnant women with RA (Cush 2005, Viktil et al. 2009). Two other studies reported data of prevalence of RA in pregnant women (Artama et al. 2011, Vroom et al. 2008) and one study reported both (Kuriya et al. 2011).

3.9.1 Prevalence of pregnant women with RA

According to a nationwide register-based surveillance system (Artama et al. 2011) RA was amongst the most frequent chronic diseases in Finland, along with asthma, hypothyroidism,

epilepsy, and diabetes. According to the Finnish national health registers, anti-inflammatory and antirheumatic products were used by 3.5% of women whose pregnancies resulted in deliveries and by 4.3% of women who terminated their pregnancies. In a survey by Vroom et al. (2008), all 15 rheumatologists reported that every year they did not see more than 20 pregnant patients; the majority was suffering from RA. This indicates that very few women use DMARDs in pregnancy and therefore doctors have limited experience with such cases. In another study by Kuriya et al. (2011), 393 pregnancies were detected among 34,169 women with RA.

3.9.2 Prevalence of drug use in pregnant women with RA

In a survey by Cush (2005), rheumatologists reported that 454 patients became pregnant while on biologics and 142 patients used these drugs throughout the pregnancy. Viktil et al. (2009) explored the use of antirheumatic drugs in pregnancy, reporting that 1411 women used at least one antirheumatic drug during pregnancy. Kuriya et al. (2011) reported that 24% of women with RA received at least one DMARD during the period before conception. In addition, 23% of women whose pregnancies resulted in deliveries used more than one DMARD during pregnancy, but the amount of use decreased from the first to the third trimester. Similarly, NSAIDs/coxibs were used significantly less compared to the use before pregnancy. On the other hand, doctors prescribed more glucocorticoids during pregnancy than before pregnancy. Biologic drugs were prescribed in 12.5% of pregnancies.

4. Discussion

4.1 Remission in pregnancy: the role of drugs

The results of this systematic review confirmed the remission of RA symptoms during pregnancy and the flare of the disease postpartum in the majority of cases. Some studies included in the review attributed this remission to the beneficial effect of pregnancy itself; DMARDs are remarkably reduced for fear of side effects on the foetus, and the commonly used therapeutic regimens –like the combination of SSZ and low-dose prednisone- are not enough to induce remission. According to Märker-Hermann and Fischer-Betz (2010), this reduction of RA activity, which usually starts during the first trimester of pregnancy and can

continue in the following trimesters, may be due to three factors: (a) an increase in anti-inflammatory cytokine levels; (b) the HLA-disparate fetal microchimerism; and (c) the increased galactosylation of immunoglobulin G (IgG) N-glycans.

Other studies in the review suggested that since RA is treated more aggressively nowadays, women enter pregnancy in a low level of disease activity. Research has shown that the pre-conceptional use of DMARDs and TNF-inhibitors most probably support the disease-ameliorating effect of pregnancy (Mikuls et al. 2004, Danis VA 1992, Ronnelid et al. 2005). The continuation of treatment in RA patients who plan to become pregnant might therefore be particularly important (Förger et al. 2012). Especially in the case of planned pregnancies, the aim for the physician is to induce remission or substantial improvement in disease activity using the most effective therapy available. As soon as stable improvement is achieved, therapy should be changed to include only drugs compatible with pregnancy (Østensen and Förger 2009).

Yet, results have reported cases of RA pregnant patients in which the disease flared. In such cases treatment is absolutely necessary and therapy with low-dose prednisone, SSZ, HCQ and perhaps TNF-inhibitors may be the best approach (Artama et al. 2011). A better understanding of the immunologic changes during pregnancy may lead to new approaches to RA treatment (Clowse 2008).

4.2 Pregnancy outcomes and congenital malformations

This systematic review indicates that the lower the level of disease the better the pregnancy outcome, although sometimes it is not clear whether negative outcomes are due to the increased disease activity itself, or the pharmacotherapy. There are no suggestions in the literature that women with RA are exposed to an increased risk of unfavourable pregnancy outcomes (Buyon 1998). However, the risk associated with potential drug toxicity of specific drugs cannot be excluded (Mecacci et al. 2007). The most crucial period for a woman with RA who wants to become a mother is before conception, when the use of some DMARDs may be teratogenic, as in the case of MTX and LEF (Andreoli et al 2010). Although recent systematic reviews showed that exposure to MTX and LEF at conception does not increase the risk of adverse pregnancy outcomes (Martìnez Lopez et al. 2009, Chambers et al. 2010),

the current study showed that rates of spontaneous abortions and premature births are highest among women treated pre- or post-conceptionally with these DMARDs. Also, conforming to the conventional wisdom, the current study showed no increased risk of adverse pregnancy outcomes for RA patients who underwent a LEF wash-out procedure with cholestyramine as soon as they knew they were pregnant (*Märker-Hermann and Fischer-Betz 2010*, Cassina et al. 2012, Andreoli et al. 2010). While this may help physicians to counsel patients who inadvertently become pregnant, the common clinical practice if pregnancy is desired is the discontinuation of LEF several months before conception (Andreoli et al. 2010) and of MTX at least three months before conception (Donnenfeld et al. 1994), as the major concern about these drugs is teratogenicity. The current study reported cases of minor and major malformations in children of women exposed to LEF during pregnancy.

There have been cases of minor and major congenital anomalies in foetuses exposed to MTX as well, although no cases of aminopterin syndrome, the most common malformation attributed to MTX (Schuna 1998), have been reported. Literature suggests that the critical period for MTX-induced teratogenicity is from 9 to 10 weeks of gestation (i.e. 6-8 weeks after conception) (Feldkamp and Carey 1993). During this time pharmacologically active metabolites can be retained for several weeks in various human tissues, resulting in a continuous foetal exposure, even when the drug has been stopped immediately before conception (Bannwarth et al. 1996).

The most appropriate choice for a RA patient planning pregnancy is the treatment with anti-TNF agents. However, clinicians advise patients to avoid their use during pregnancy due to limited available data on their safety (Skomsvoll et al. 2007, Andreoli et al. 2010, Østensen and Förger 2009). The current results highlight that exposure to anti-TNF therapy at conception is relatively safe, although it may imply an increased risk of spontaneous abortions. However, disease severity and other antirheumatic drugs must also be considered as possible factors. Moreover, current results showed a small excess risk of congenital malformations with anti-TNF exposure at conception. In the literature there are reports of congenital malformations; however, the incidence of these events appears to be far below the 3% rate of congenital anomalies found in the general population (Østensen et al. 2008 and Ali et al. 2010).

The studies included in this review showed that the use of prednisone is associated with a relatively increased risk of premature deliveries, which in turn influences the baby's birth weight, but not with an increased risk of congenital malformations. One thing to consider when assessing these results is that birth weight was reported without correction for gestational age; moreover, there were no prospective measurements of RA activity during pregnancy (Skomsvoll et al. 1998, Chakravarty et al. 2006, Reed et al. 2006, Wolfberg et al. 2004). No human studies found an increased risk of major congenital malformations associated to the use of corticosteroids (Viktil et al. 2009). However, two studies included in this systematic review found an association between corticosteroids and oral clefts.

This systematic review found that the antimalarial HCQ seems to be safe during pregnancy and lactation. An increased rate of preterm delivery found in one study was not clearly attributed to the HCQ, but mostly to the maternal disease state. In an evidence-based guideline it was recommended to continue HCQ during pregnancy and lactation (Østensen et al. 2006).

4.3 Ethical considerations

This systematic review reported a few pregnancy terminations in patients exposed to LEF or MTX and anti-TNFs either before or after conception. Although most of these cases involved unplanned pregnancies, studies did not specify whether the decision for termination was the patient's or the doctor's. Some pregnancies occurred despite the use of contraception, which raises the issue of adherence to the doctor's advice regarding birth control, as confirmed by the literature (Østensen et al. 2007). The surveys included in the review indicated that rheumatologists required women in childbearing age exposed to LEF and MTX to use birth control and to immediately suspend the treatment with LEF, MTX and anti-TNFs as soon as a pregnancy was diagnosed. Nevertheless, there were few cases of women who continued taking MTX or LEF during the first and second trimesters (Viktil et al. 2009) and other cases of women who took the risk on their own responsibility to continue anti-TNF therapy during pregnancy. Literature suggests that it is particularly important for FPP to discuss contraception with patients exposed to certain medications as early as possible (Clowse 2010, Partlett and Roussou 2011) and that therapeutic decisions must consider the welfare of both the patient and the future child (Østensen 2009).

Even less is known from the literature on the concerns of women with RA on becoming pregnant and experiencing motherhood, not only due to the impact of their medications on the foetuses, but also due to their ability to take care of their children. This may be an explanation on the lower rates of pregnancy in women suffering from RA compared with healthy women that were reported in the literature (Hazes et al. 1990, Da Silva and Spector 1992, Skomsvoll et al. 2001). A recent study investigating the family plans of 14 women with RA (Meade et al. 2013) showed that the disease had played a significant role on their decisions to become mothers. Women were most concerned about the support they would get from their partners, family and doctors, the value of motherhood which and their capacity to care for a child. They were also concerned about the uncertainty of the actual impact of their drug use on the child, as well as the impact that a potential therapy discontinuation would have on their disease activity.

4.4 Prevalence

This systematic review reported some data on prevalence of RA in pregnant women and prevalence of drug use in pregnant women with RA. Nevertheless, these data cannot be used to illustrate a specific pattern of prevalence of RA in pregnancy. Data concerning drug use suggested that corticosteroids such as prednisone are widely used during pregnancy, especially in the period prior to conception, whereas the use of DMARDs generally decreases. Additionally, drug use declines from the first to the third trimester. A study by Reed et al. conducted in Washington State (Reed et al. 2006) reported 243 live births born to women with RA from 1987 to 2011. As there are approximately 1400 infants born to mothers with RA in the US annually (Chakravarty et al. 2006),this means that most American rheumatologists will only see a few pregnant women with RA during 1 year of practice, stressing the importance of establishing large databases from multiple clinical centres in order to acquire significant epidemiologic data.

4.5 Socioeconomic impact

This systematic review has not revealed any studies looking at the socio-economic impact of anti-rheumatic treatment during pregnancy. Generally, research has shown that impact of RA on society is high due to therapy requirements and loss in productivity. Disease severity,

disease activity, age and socioeconomic status were found to be the factors that have the greater effect on cost increase in RA (Furneri et al. 2012). Healthcare expenditures can reach the amount of €4000–6000 per patient per year in Europe and North America (Huscher et al 2014). Because RA causes physical disability, it is not only linked with direct costs; indirect costs are also substantial and are connected with productivity loss associated with absenteeism and presenteeism (Tanaka et al. 2013). Although there are too many studies investigating RA costs in the last decades, there is a lack of research on costs and socioeconomic impact of RA during pregnancy, although two issues can arise and be further explored in the future.

First, the good probability of remission of RA during pregnancy means that patients will cease treatment. This could lead to a potential decrease in drug costs as it has been shown that not only sustained remission, but even a remission for a short period of time or a decrease in disease activity can substantially reduce healthcare service utilisation costs, including hospitalisation and physician visits. A study from Canada showed that healthcare costs of patients who had achieved a brief period of low disease activity were $2104 less (mean annual difference) than those who remained in moderate or high disease activity (Barnabe et al. 2013).

Second, most women with RA choose to discontinue treatment with conventional DMARDs that have been proven to be teratogenic, such as MTX or LEF, as soon as they decide to become mothers or as soon as they know they are pregnant. This can lead to a potential decline in costs. Nevertheless, some of these women may choose to switch treatment and opt for biologic agents such as anti-TNFs. This can lead to an increase in costs, as DMARDs are generally inexpensive, whereas anti-TNF therapy can significantly raise direct costs (Furneri et al. 2012), even as much as a 3-fold to 6-fold increase (Huscher et al. 2014).

Studies have shown that even the choice of a particular anti-TNF drug can have an impact on costs, with etanercept being proved to be more cost-effective (Schabert et al. 2013, Joyce et al. 2014). Etanercept had a 17% cost advantage compared to adalimumab and a 30% cost advantage compared to infliximab. In our systematic review many women chose to use etanercept during their pregnancy.

4.6 Limitations

The results of this systematic review revealed the complexity of studies in this area. Although a large number of women whose infants have been exposed to antirheumatic drugs have been investigated, a clear interpretation of the results is difficult. The studies varied in design and in some of these the population size was insufficient to draw specific conclusions about the effects of medications to pregnant women with RA and to foetuses. Furthermore, not all observational studies had a control group, and even the larger ones that had one, reported results for several indications and not specifically for RA.

Additionally, the studies included in this review reported on the impact of different RA agents, with different mechanisms of action, clinical efficacy and adverse effect profile. While results in this review were presented separately for each agent when possible, a clear interpretation of the impact of individual drugs and combinations of drugs is difficult.

Another limitation of this study is that it did not report any outcomes of pregnancies that were exposed indirectly to RA medications through the mother's partner. Four studies providing results on indirect exposure of the foetus to RA medications at conception have been reported in the literature (Chakravarty et al. 2011, Katz et al. 2004, Viktil et al. 2009, Østensen et al. 2007). While there are high levels of awareness about maternal drug use in pregnancy, drug exposure in fathers shortly before conception should be further explored in the future.

5. Conclusions and Policy Implications

5.1 Safety

A number of salient policy issues arose from this systematic review. One of them was the safety of the RA medications when used during pregnancy. This review proves that there is a scarcity of studies investigating the safety of anti-rheumatic drugs in pregnant women. The disease improvement in pregnancy often allows the safe discontinuation of potentially harmful agents such as LEF and MTX (Golding et al. 2007), but additional research is needed to establish the safety of anti-TNFs, as well as the potential long-term developmental consequences arising in children after *in utero exposure* (Ali et al. 2010).

5.2 Risk

Another policy issue that merits consideration is the potential risks to which mothers and foetuses are exposed while taking RA medications during pregnancy. Immunosuppressive drugs can cross the placenta and enter into the foetal circulation (Little 1997); this raises concerns over the potential adverse effects that may occur during the development of the foetus, such as the occurrence of congenital malformations (Motta et al. 2008). The assessment of the relative risk ascribed to immunosuppressive drug use is difficult, since the concurrent use of other medications, as well as the impact of the disease activity itself, may confound the explanation of pregnancy outcome (Motta et al. 2008). Because of the lack of information, physicians focus on the potential risk and not on the potential benefit for the patients and their unborn babies, frequently opting for therapeutic terminations. Therefore it is important that physicians, when choosing whether continuing or not a medication, balance the overall risks and benefits for both mother and foetus. When a decision to discontinue medication is made, it is also vital that the patient is closely supervised to ensure a prompt intervention in case of relapse.

5.3 Guidelines and pregnancy registries

The current study revealed a lack of guidelines for the treatment of pregnant RA patients. Information and recommendations on use of RA medications during pregnancy from international and national books, national societies of rheumatology, articles and textbooks are insufficient and differ considerably. Even the recommendations given by the manufacturer of a specific drug may vary in different countries. Furthermore, although the FDA pregnancy classification offers some guidance for physicians who treat pregnant RA patients, this needs to be updated with human data (Chambers et al. 2006). All the above are obviously poor sources for evidence-based clinical decision making (Hazes et al. 2011).

This is the reason why pregnancy registries have started to be increasingly used as a post-marketing tool for gathering safety data for new and previously marketed drugs (Chambers et al. 2006). The Organisation of Teratology Information Specialists (OTIS) (Chambers et al. 2006) in the US and Canada provides risk counselling on pregnancy and breastfeeding drug effects to nearly 100,000 pregnant women and physicians per year. OTIS also conducts

pregnancy outcome studies such as the Autoimmune Diseases in Pregnancy Project in collaboration with rheumatologists, pharmaceutical company sponsors, and pregnant women who want to contribute to increase the knowledge on safety of RA medications during pregnancy (Chambers et al. 2006).

Official national and international guidelines are urgently needed and this will require collaborative support from government agencies, non-profit organizations, academic and public health professionals, and healthcare providers (Lagoy et al. 2005). This issue is of particular importance for clinicians in order to ensure safe and beneficial use of drugs during pregnancy.

5.4 Conclusions

The results of this systematic review showed that different RA agents have different effects on disease activity, pregnancy outcomes and congenital anomalies. They also showed that there are hardly no primary data studies that look into issues such as the socioeconomic impact of the use of RA medication in pregnancy as well as access to drugs and prevalence. Additionally, ethical issues have not been much discussed and guidelines are scarce. Further research is essential to enhance the understanding on the effects of RA agents, particularly when a new drug is marketed and likely to be used by women of reproductive age. Evidence-based risk evaluation in collaboration with the rheumatologist are essential in order to decide about the future of the pregnancy, especially in situations where patients choose to continue therapy with proven teratogens. For this reason, the creation of national and international guidelines is crucial for a better management of pregnant women with RA.

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Appendix 1. Characteristics of studies included in the systematic review.

Author	Study design	Study origin	Study objective	Pathology of mother	RA medication n,dose	Disease duration (RA)	Timing of drug exposure relative to conception	Comedication	Ethnical background	Maternal age
Almarzouqi et al. 2007	Retrospective chart review	Canada	To review the experience and outcome of pregnancies in women taking gold while planning pregnancy.	RA	gold sodium aurothiomalate n = 13 gold sodium aurothioglucose n = 1 Mean doses: 25-50 mg/wk, 50 mg/2 wks, 60 mg/wk, 5-10 mg/wk, 10 mg every 2 weeks	Mean (range), years: 8.5 (1-16)	<12 months in 7 pregnancies 13-24 months in 4 pregnancies 25-34 months in 2 pregnancies 2-10 years in 7 pregnancies	DMARDs HCQ SSZ	N/A	Mean (range): 34.5 (24-41)
Artama et al. 2011	National Surveillance System	Finland	To get basic information on the use of prescribed drugs during pregnancy and to achieve more detailed information on drug exposure-outcome associations with data obtained from the Finnish national health registers.	asthma hypothyroidism, epilepsy, diabetes, other chronic diseases	anti-inflammatory and antirheumatic products	N/A	N/A	N/A	N/A	N/A
Berthelot et al. 2009	Case series	France	To report on the outcome of 15 cases of pregnancies in women treated with anti-TNF drugs during conception or pregnancy	Spondylarthropathies, RA, Juvenile idiopathic arthritis, PsA	n patients = 15 (with RA) anti-TNFs : infliximab (n = 3), adalimumab (n = 2), or etanercept (n = 10) infliximab n = 1 3 mg/kg adalimumab n = 1 40 mg every other week etanercept n = 2	N/A	Anti-TNF 1-48 months before pregnancy (median: 8 months). 1 RA patient under anti-TNF and MTX at time of conception 3 RA patients discontinued DMARDs >3 months before conception	N/A	N/A	Average 30.75
Cassina et al. 2012	Prospective cohort study	USA/Canada	To expand on the previously published data with a description of birth outcomes	RA, JRA, PsA, SLE, scleroderma	LEF n = 45, Group 1 (n = 16) 81.3% underwent at >1 washout procedure with cholestyramine after	N/A	Mean ± SD gestational timing of the last dose of LEF 7.1 ± 7.9 weeks postconception. ¥	Systemic steroids during the first trimester of pregnancy	White/non-Hispanic Group 1: 6 (37.5%) Group 2: 22	Mean ± SD years ¥ Group 1: 29.9 ± 7.9 Group 2:

			among women who did not meet the previous cohort study criteria but who were exposed to LEF either during pregnancy or prior to conception.		LEF therapy was discontinued during pregnancy. Group 2 (n = 29) 65.5% discontinued leflunomide therapy during the last 15 weeks before conception. 72.4% underwent the cholestyramine washout procedure after conception in all but one case.			(51.7%). ¥ MTX in 3 women exposed to leflunomide during pregnancy (18.8%). ¥	(75.9%) Hispanic Group 1: 4 (25.0%), Group 2: 5 (17.2%) Black Group 1: 5 (31.3%), Group 2: 2 (6.9%) Asian Group 1: 1 (6.3%), Group 2: 0 ¥	29.9 ± 4.6
Chakravarty et al. 2003	Survey	USA	To describe the practices of rheumatologists when prescribing the DMARDs MTX, LEF, ET and IN to women of childbearing age with RA and the pregnancy outcomes of patients who become pregnant while taking these medications.	RA	DMARDs at conception, n pregnancies=39 MTX n = 39 pregnancies LEF n = 10 pregnancies Etanercept n = 15 pregnancies Infliximab n = 2 pregnancies	N/A	N/A	N/A	N/A	N/A
Chakravarty et al. 2011	Global drug safety database	Global	To report on pregnancy outcomes after maternal exposure to rituximab		rituximab n = 231 RA n = 41 out of 53 pregnancies occurring in industry sponsored or cosponsored trials	N/A	N/A	MTX in more than half cases	N/A	N/A
Chambers et al. 2010	Prospective cohort study	US/Canada	To investigate pregnancy outcomes in women who received LEF and were treated with cholestyramine during pregnancy.	RA, JRA	Cohort n = 250 LEF (Mean dose ± SD, range: 17.6 ± 5.1 [2.5–100.0]) n = 64 Cholestryramine, washout procedure n = 61/64, Systemic steroid use n = 44/64, NSAID use n = 38/64, Disease-matched comparison group n = 108, Systemic steroid use n = 69/108 NSAID use n = 42/108	N/A	Last dose of LEF on average 3.1 weeks after conception. Latest exposure ending at 8.6 weeks after conception.		LEF group: White/Non-Hispanic 73.4%, Hispanic 12.5%, Black 9.4%,Asian 4.7%	Mean, ± SD :LEF group: 31.7 ± 6.1

					Healthy comparison group n = 78, Systemic steroid use n = 2/78 NSAID use n = 11/78					
Crocker et al. 2000	Longitudinal investigation	UK	To confirm whether changes to neutrophil function occur in pregnant patients with RA, and therefore provide an explanation for the ameliorating affects of pregnancy on RA.	RA	healthy pregnant women n = 9 pregnant patients with RA n = 9 (2 stopped treatment at the start of pregnancy and 7 continued low doses of prednisone or methylprednisolone [2.5±10 mg/d]) age matched non-pregnant patients with RA n = 12 (NSAIDs but no form of second line treatment) healthy controls n = 22	N/A	N/A	N/A	N/A	9 pregnant patients with RA (mean age 30, range 23±38)
Cush 2005	Survey	USA	To explore physicians' preferences on RA biological drug use.	RA	TNF inhibitors	N/A	N/A	N/A	N/A	N/A
de Man et al. 2008	Prospective cohort study	Netherlands	To prospectively determine the disease activity during pregnancy in RA patients treated in an era of new treatment options.	RA	Cohort n = 84 Prednisone (oral) (Median daily dose 7.5 mg [0.5–20 mg] before conception and throughout pregnancy) 1st trim. n = 30 (36%) , 2nd trim. n = 30 (36%), 3rd trim. n = 29 (35%) SSZ (Median daily dose 2,000 mg [500–4,000 mg] at all-time points) 1st trim. n = 26 (31%) , 2nd trim. n = 28 (33%), 3rd trim. n = 28 (33%) MTX: 1st trim. n = 0 (0) , 2nd trim. n = 0 (0), 3rd trim. n = 0 (0) LEF: 1st trim. n = 0 (0) , 2nd trim. n = 0 (0), 3rd trim. n = 0 (0) HCQ: 1st trim. n = 2 (2%), 2nd trim. n = 3	Median at first visit (range), years: 4.8 (0.1–28.6)	6 patients received biologic agents <1 year before conception. None of the patients received a combination of biologic agents, prednisone, and MTX <1 year before conception.	NSAIDs and Acetaminophen for pain relief	Caucasian, 3pregnancies occurred in non-white women (2 Asian, 1 African).	Mean ± SD: 31.9 ± 3.3

					(4%), 3rd trim. n = 2 (2%) Biologic agents 1st trim. n = 0 (0) , 2nd trim. n = 0 (0), 3rd trim. n = 0 (0)					
de Man et al. 2009	Prospective cohort study	Netherlands	To determine whether disease activity and prednisone use during pregnancy were independent influences on birth weight and whether their effects on birth weight were mediated via gestational age at delivery.	RA	Cohort n = 152 Prednisone n = 50 (Mean daily dose at 1st, 2nd and 3rd trim. 7.7 mg, 8.0 mg and 7.7 mg respectively) HCQ n = 2 SSZ n = 40	Median at delivery (range), months: 70 (8–356)	All women discontinued MTX at least 3 months before conception	N/A	Caucasian	Mean: 32.5
Förger et al. 2012	Prospective cohort study	Switzerland	To investigate pregnancy related changes of RF isotypes and ACPA and their association with disease activity and therapy in patients with RA.	RA	RA patients n = 22 Impoved/stable disease) n = 16 Active disease n = 6, Healthy controls n = 29, SSZ (1st, 2nd and 3rd tr.): Group 1 n = 6 (38%), 5 (31%) and 4 (25%) Group 2 n = 1 (17%), 1 (17%), 1 (17%) Antimalarials Group 1 n = 2 (13%), 3 (19%), 2 (13%) Group 2 n = 0, 0, 0 Oral prednisone /-solone Group 1: 4 (25%), 6 (38%), 4 (25%) Group 2: 3 (50%), 4 (67%), 5 (83%) NSAID Group 1: 3 (19%), 2 (13%), 1 (6%) No medication Group 1: 4 (25%), 2 (25%), 7 (44%) Group 2: 2 (33%), 1 (17%), 0	At study entry, median years (range): Group 1 (impoved/stable disease): 3.5 (0.83-15) Group 2 (active disease): 4 (0.3-11)	N/A	Sulfasalazine was taken in combination with folic acid	N/A	Median (range) Group 1: 30.5 (23-40) Group 2: 33.5 (25-38)

Hajdyla-Banaś et al. 2009	Case report (2)	Poland	To present clinical management and outcomes of LEF-exposed pregnancies based on very detailed case presentations of such pregnancies reported in Poland for the first time.	RA	LEF (load-dose 100mg on the first 3 days and continued at 20 mg per day) n = 2 1: LEF wash-out procedure with an oral administration of 8g of cholestyramine tid for 11 days. 2: LEF wash-out procedure with an oral augmentation of 8g of cholestyramine tid for 11 days	1: 17 years 2: 4 years	LEF in first 2 months of pregnancy.	N/A	N/A	01:38:00 02:30:00
Katz *et al.*, 2004	Large case series	USA	To report the pregnancy outcomes in women with RA and CD exposed to infliximab.	RA, CD	infliximab n = 96 patients (exposed directly) infliximab n = 15 (exposed indirectly through the partner) RA n = 8 patients exposed directly JRA n = 2 patients exposed indirectly RA n = 2 patients exposed indirectly	N/A	1 RA patient was receiving infliximab at the time of conception	One RA patient was receiving LEF	N/A	Mean (for all cohort), range: 33 (18-43)
Kuriya et al. 2011	Retrospective cohort study	US	To characterize therapies prescribed during pregnancy to women with RA.	RA	n = 393 pregnancies NSAIDs/coxibs n = 31 (11%) Glucocorticoids n = 156 (55.5%) Any DMARD (≥ 1) n = 64 (22.8%) Combination of ≥ 2 DMARDs n = 16 (5.7%) Nonbiologic DMARD (Category B or C) n = 32 (11.4%) Chloroquine n = 0 Cyclosporine n = 0 Gold n = 1 (0.4%) HCQ n = 25 (8.9%) SSZ n = 11 (3.9%) Nonbiologic DMARD (Category D or X) n =	N/A	61.9% no DMARDs 180 days prior to EDC 4.3% ≥3 different DMARDs in the 180 days prior to EDC	2.1% of women with deliveries ≥ 3 comorbidities (low rate according to the Charlson Comorbidity Index)	N/A	Mean Women with a delivery: 32.8 Elective abortions: 33.4 Spontaneous abortions: 33.9

					11 (3.9%) Azathioprine n = 1 (0.4%) LEF n = 3 (1.1%) Adalimumab n = 7 (2.5%) Biologic DMARD (Category B or C) n = 35 (12.5%) MTX n = 8 (2.9%) Anakinra n = 1 (0.4%) Etanercept n = 23 (8.2%) Infliximab n = 6 (2.1%) Rituximab n = 0					
Lewden et al. 2004	Prospective collaborative study	France	To assess the risk of major malformations in pregnant women with chronic inflammatory disorders treated with low dose MTX during the first trimester of pregnancy.	RA Takayasu's arteritis PsA dermatomyositis AS	MTX (less than 15 mg/week) n = 27 (28 pregnancies) RA cases n = 22	N/A	¥ 16 patients discontinued MTX during the first 4 gestational weeks,10 treated between week 5 to 8, 1 discontinued MTX after week 8, 1 started MTX after week 6 for a 5-week period (all other patients had initiated treatment before pregnancy).	NSAIDs and corticosteroids	N/A	Mean ± SD: 32.9 ± 4.8
Motta et al. 2005	Prospective observational study	Italy	To determine the effect of HCQ treatment during pregnancy and lactation on babies of mothers affected by rheumatic diseases.	SLE,Mixed connective tissue disease, Subacute cutaneous lupus erythematosus, Undifferentiated connective tissue disease,Primary antiphospholipid syndrome, RA, Sjogren's syndrome, Antiphospholipid syndrome within SLE, SLE - polimyositis overlap syndrome	HCQ (200 mg/day, plaquentil) n = 40 infants (39 mothers, one twin pregnancy), RA cases n = 2 infants born	N/A	1 year or more before pregnancy, during gestation and after delivery	steroids and low-dose acetylsalicylic acis as antiplatelet agent, azathioprine (1 mother), cyclosporin-A (1 mother), aspirin+heparin	N/A	N/A

Østensen et al. 2004	Prospective study	Switzerland	To analyse the disease course of patients with RA and AS during and after pregnancy by validated clinical instruments for measurement of disease activity, and assess their usefulness in pregnant patients.	RA, AS	RA cases n = 10, AS cases n = 9, Antimalarials, Salazopyrine (DMARD), SSZ n = 9 RA cases,Low dose prednisone (10 mg/day) n = 3 RA cases , NSAIDs until week 32	Median (range), years: 3 (0–10)	N/A	N/A	N/A	28 (25-37)
Østensen *et al.*, 2007	Survey	Switzerland	To investigate the attitude of patients towards immunosuppressive and biological drugs in relation to reproduction and the outcome of pregnancies exposed to these drugs.	Rheumatic diseases, Patient survey: RA, AS, PsA, juvenile arthritis, other arthritis	Patient survey pregnancies n = 34, salazopyrine n = 14,antimalarials n = 10,cyclosporine n = 1,azathioprine n = 1, LEF n = 1,MTX n = 3,comb. of antimalarials and salazopyrine n = 1, etanercept n = 3, Rheumatologists' survey pregnancies n = 19, DMARDs	Median: 6 (1-36) for females and 8 (1-37) for males	N/A	N/A	N/A	Median(range) 35 (30-38)
Østensen and Raio, 2005	Case study (1)	Switzerland	To report the case of a woman with RA whose condition did not improve during pregnancy.	RA	n = 1, Infliximab last dose 10 days before pregnancy occurred, SSZ (2 g/day) after positive pregnancy test, Methylprednisolone injection at gestational week 4, Nimesulide (100 mg twice daily from gestational week 8 until week 18), Oral prednisone (7.5 mg/day) plus calcium and vitamin D3, 2 corticosteroid injections	3 years	Last infusion of infliximab 10 days before she became pregnant.	Folate 5 mg, 3 times/week	N/A	25

					at week 15 and week 17 and 1 at weeks 26 and 30					
Park-Wyllie et al. 2000	Prospective cohort study and meta-analysis	Canada	To investigate the relative fetal safety of maternal prednisone therapy.	CD,Asthma, Ulcerative colitis, RA, Bell's palsy, Transplant, Lupus, Sarxcoidosis, other indications	prednisone (5-80 mg/day) n = 184, RA cases n = 18 (10%),Controls n = 188	N/A	138 (75%) women were exposed in the first trimester of pregnancy ¥	N/A	N/A	prednisone: 30 ± 5,controls: 31 ± 5
Roux et al. 2007	Concise report (3)	France	To report experience of anti-TNF-α use in pregnancy, and review the international literature.	RA	anti-TNFs, adalimumab (40 mg twice a month) n = 1, etanercept (25 mg twice a week) n = 1, etanercept (25 mg twice a week) n = 1	1: 4 years, 2: 8 years,3: 4 years	1: Adalimumab 1 month prior to conception, a single injection since conception 2: Etanercept at least 2 months 3: Etanercept 8 monthes before conception, 1 month after conception	N/A	N/A	01:37:00,2: N/A,03:21:00
Scioscia et al. 2011	Case report (2)	Italy	To explore safety of the TNF inhibitor etanercept during pregnancy and lactation.	RA	Etanercept n = 2	> 5 years	N/A	paracetamol when necessary	N/A	01:23:00, 02:28:00
Sheikh 2007	Case report (1)	USA	To report a case of new-onset penicillin allergy during pregnancy in a woman with RA.	RA	n = 1, oral amoxilin during the first trimester	N/A	N/A	levothyroxine for hypothyroidism	N/A	39
Sills et al. 2001	Case report (1)	USA	To explore the safety of etanercept for infertility patients planning ovulation induction.	RA	Etanercept (25 mg twice weekly) n = 1	>1 year	Sustained 16 month treatment interval was discontinued 1 month before fertility therapy	N/A	Caucasian	32
Sinha and Patient 2006	Case report (1)	UK	To explore the safety of etanercept during pregnancy in a woman with RA.	RA	Etanercept (anti-TNF) (25 mg/day) n = 1	from 2000	Etanercept at conception and throughout pregnancy	N/A	Caucasian	34

Thompson and Bashook 2010	Survey	Canada	To determine what key information patients must know about MTX and the key reasons they should call their doctor while they are taking MTX.	RA	MTX	N/A	N/A	N/A	N/A	N/A
Umeda et al. 2010	Case report (1)	Japan	To explore safety of the TNF inhibitor etanercept during pregnancy.	RA	etanercept (25 mgX2/week, discontinued at 6 weeks, resumed at 20 weeks) n = 1	6 years	approximately 7 months	Prednisolone	N/A	29
Verstappen et al. 2011	Prospective cohort study	UK	To summarise the pregnancy outcomes in women treated with anti-TNF in the British Society for Rheumatology Biologics Register.	RA, PsA, JIA, AS, Adult-onset Still's disease, SLE	Cohort n = 128 Group Ia: anti-TNF and MTX and/or LEF at conception n=20 patients, 21 pregnancies [16 RA] Group Ib: anti-TNF at conception n=44 patients, 50 pregnancies [36 RA] Control group III: no exposure to anti-TNF n=10 patients, 10 pregnancies [10 RA] Group II: to anti-TNF prior to conception n=54 patients, 59 pregnancies [46 RA] anti-TNFs at conception: adalimumab n = 14 in total etanercept n = 48 in total	N/A	N/A	N/A	N/A	Mean (SD) Group Ia: 29.7 (8.1) Group Ib: 34.4 (5.2) Group II: 32.6 (4.9) Group III: 32.5 (5.2)
Viktil et al. 2009	Population-based cohort study	Norway	To explore the use of antirheumatic drugs in pregnant women and expectant fathers.	Rheumatic diseases	n = 1411 patients (women) prednisolone (1st, 2nd, 3rd trim.) n = 152, 160, 150 NSAIDs n = 167, 47, 16 Sulfazalazin n = 54, 33, 33 HCQ n = 18, 18, 11 Azathioprin n = 40, 32,	N/A	N/A	N/A	N/A	Mean, range 31 (19-45)

					30 LEF n = 2, 0, 0 MTX n = 1, 1, 0 Etanercept n = 11, 1, 1 Adalimumab n = 2, 1, 0					
Vroom et al. 2008	Survey	Netherlands	To explore, among Dutch rheumatologists, aspects such as attitude towards guidelines, pharmacotherapy and information needs in the treatment of pregnant as well as non-pregnant RA patients.	RA	N/A	N/A	N/A	N/A	N/A	N/A
¥ Data given for all indications included in the study and not specifically for RA.										

Appendix 2

Main outcomes of the review

Author	Disease related outcomes
Almarzouqi et al. 2007	RA flared during 3/15 completed pregnancies, and was controlled in 12/15. RA flared 2-20 weeks postpartum in 13/15 completed pregnancies and 2-6 weeks postpartum after 5 spontaneous abortions. Two women did not experience postpartum flare.
Cassina et al. 2012	Women who discontinued LEF within the last 15 weeks had a higher mean global impact score on the measure of RA disease severity/symptoms obtained from the mother at the time of enrolment.
Crocker et al. 2000	Stimulated neutrophil LUCL was significantly reduced in both pregnant women with RA and healthy pregnant women in the 2nd (fMLP 43% and 69%, ZAS 43% and 59%, respectively) and 3rd trimesters (fMLP 24% and 44%, ZAS 32% and 38%, respectively). Responses returned to normal within 8 weeks of delivery and unstimulated levels remained unchanged throughout pregnancy. Basal and stimulated CD11b, CD18, and CD62L expression showed no variations throughout gestation for both pregnancy groups. Likewise, stimulated lactoferrin release and plasma lactoferrin remained unchanged. Moreover, resting neutrophils and stimulated cells from patients with RA, including pregnant subjects, showed a marked increase in LUCL, but a reduction in CD11b, CD18, and CD62L. Low dose prednisolone and methylprednisolone had no effect on neutrophil parameters over the period of treatment with NSAIDs.
de Man et al. 2008	Disease activity decreased with statistical significance (P = 0.035) during pregnancy and increased post-partum. In patients with at least moderate disease activity in the first trimester (n = 52), at least 48% had a moderate response during pregnancy. In patients with low disease activity in the first trimester (n = 32), disease activity was stable during pregnancy. 39% per cent of patients had at least a moderate flare postpartum. Despite reduction in drug use, a decrease in disease activity was still observed, therefore this must be considered as a consequence of the beneficial effect of pregnancy itself.
de Man et al. 2009	The median disease activity throughout pregnancy (DAS28-CRP) decreased from 3.8 during the 1st trimester to 3.3 during the 3rd trimester, indicating that disease activity was well-controlled.
Förger et al. 2012	16/22 (73%) RA patients experienced improvement or persistent low disease activity during pregnancy reaching a DAS28-CRP below 3.2 at the third trimester. Among these, 13 had a DAS28-CRP below 2.6. 6/22 (27%) RA patients had persistent active disease throughout pregnancy. Disease activity differed significantly between group 1 and group 2 (P <0.001). More patients with low active disease during pregnancy were on pregnancy compatible DMARD therapy or on TNF-inhibitors before conception. Significantly more patients of group 1 received pregnancy compatible DMARDs therapy such as SSZ and antimalarials or TNF-inhibitors within the 4 months before conception (P = 0.025). More patients of group 1 remained on SSZ and antimalarials during gestation. The gestational DMARD therapy and the pre-conceptional use of DMARD and TNF-inhibitors most probably supported the disease ameliorating effect of pregnancy in most RA patients and suppressed levels of ACPA.
Østensen et al. 2004	Most patients with RA showed sustained or increased improvement of disease activity during pregnancy. 1 patient with RA with persistent low back pain showed high patient assessment scores despite remission documented by the joint count. 3 patients with RA were in remission in the 3rd trimester and 4 other patients were improved. 1 patient had disease onset at the start of her first pregnancy and 1 patient entered pregnancy with active arthritis in large joints. Both patients continued to have active disease during pregnancy and needed repeated intraarticular injections of corticosteroids in actively inflamed joints. Aggravation of disease activity in 6 patients with RA was detected at 6 and 12 weeks post-partum, decreasing after starting DMARDs and/or prednisone. 1 patient with RA remained in the pregnancy induced remission throughout the observation period. The 2 patients with RA with active disease during pregnancy improved after the start of DMARDs post-partum.

Østensen and Raio 2005	Patient suffered an arthritis flare in both shoulder joints, the right elbow and several proximal inter phalangeal joints 5 weeks after withdrawal of infliximab. She received a methyleprdnisolone injection at week 4 and started nimesulide at week 8. After 15 weeks of pregnancy, the patient's right elbow, metacarpophalangeal, metatarsophalangeal and shoulder joints were without symptoms; however, arthritis of the right hip was shown by ultrasonography. After two corticosteroid injections at week 15 and week 17 in the right hip joint, all joint symptoms decreased between weeks 19 and 25. In the following months, acute arthritis occurred and was again treated by corticosteroid injection at gestational weeks 26 and 30. The patient's joint symptoms were much improved 4 months after delivery.
Scioscia et al. 2011	Both women were in complete remission with etanercept treatment before pregnancy. Both pregnancies were uneventful without clinical signs of reactivation of the disease. Steady values of DAS-28(3)-CRP with a slightly raise in the curve during pregnancy were observed, although they were well below the 3.2 threshold. The expected reactivation of the disease after delivery was not observed up to 9 months of follow up.
Sheikh 2007	Because of group B streptococcus colonization, an intravenous infusion of penicillin G was started during labor. Within minutes, severe anaphylaxis was developed. A fluorescent enzyme immunoassay revealed a moderate level of specific IgE to penicilloyl G and penicilloyl V (3.15 kU/L and 2.77 kU/L, respectively. Given the patient's history, these positive results were considered confirmatory of penicillin allergy. It is possible that the alerted immunological status associated with RA and/or treatment with immunomodulatory agents played some role in the development of penicillin sensitivity. (with the sensitization occurring during the 1st trimester with the course of amoxicillin) and/or made her more prone to a severe anaphylactic presentation with subsequent exposure.
Sills et al. 2001	Serum RF titers obtained during pregnancy were consistent with active but low-level disease; symptoms were mild and no therapy was required. Remission 3 months after delivery.
Umeda et al. 2010	Etanercept was discontinued at 6 weeks of pregnancy and prednisolone-alone administration was continued at 7 mg/day. Etanercept was resumed at 20 weeks of pregnancy. Three months after changing agents, her arthritis became worse. The CRP level rose to 1.03 mg/dL and she felt pain in her joints with swelling recurred, although there was no observation on the visual analogue scale, she complained of multiple joint pain and multiple proximal interphalangeal joint swelling. One month after the resumption of etanercept treatment, she recovered from arthritis; all of the symptoms were improved. The CRP level was 0.36 mg/dL with no adverse effects and the DAS28-CRP level was 3.67, indicating moderate level of disease activity.
Verstappen et al. 2011	Baseline DAS28 score n, mean SD ¥ Ia n = 20/20, 6.5 (0.6) Ib n = 40/44, 6.1 (0.2) II n = 52/54, 6.0 (1.0) III n = 10/10 5.1 (1.2) DAS28 score significantly higher in the anti-TNF groups compared with the nb-DMARD group. DAS28 significantly higher in group Ia compared with group II (p=0.0213, unpaired t test). Baseline HAQ score n, mean SD ¥ Ia n = 20/20, 2.2 (0.4) Ib n = 41/44, 1.9 (0.5) II n = 49/54, 1.6 (0.6) III n = 8/10, 1.0 (0.4) HAQ score significantly higher in the anti-TNF groups compared with the nb-DMARD group. HAQ score significantly higher in group Ia compared with group Ib (p=0.0353) and signifi cantly higher in group Ia compared with group II (p<001).
	Birth outcomes

Almarzouqi et al. 2007	Spontaneous abortions in the 1st trim. n = 5; (included 2 spontaneous abortions in a woman with known Robertsonian chromosomal translocation) Healthy babies n = 16 (including a pair of twins)
Berthelot et al. 2009	15 pregnancies: 12 live births, 3 stopped early because of elective termination of miscarriage Results for RA patients: Live born deliveries n = 2 Elective terminations n = 1 Miscarriages n = 1
Cassina et al. 2012	Results specific for RA 1 case with RA and depression, MTX (1st trim.); Pred. (2nd, 3rd trim.): Live birth 36.9 weeks 1 case with RA, asthma, depression, hypothyroidism, type 1 diabetes, MTX (1st trim.); NSAID (1st trim.): Live birth 35.7 weeks 1 case with RA no washout: Live birth 40.9 weeks (twin pregnancy) 1 case with JRA, NSAID (1st trim.): Live birth 39.9 weeks 1 case with low JRA no washout, MTX (1st trim.); Pred. (1st, 2nd, 3rd trim.): Live birth 35.9 weeks 1 case with RA and SLE, Pred. (1st trim.): Live birth 40 weeks 1 case with RA, NSAID (1st, 2nd trim.): Live birth 39.4 weeks; 3 minor malformations 1 case with RA, Pred. (3rd trim.); NSAID (1st trim.): Live birth 35.4 weeks; major malformation 1 case with RA and SLE, Pred. (2nd, 3rd trim.): Live birth 35.6 weeks; major malformations 1 case with RA, NSAID (2nd trim.): Live birth 39.7 weeks
Chakravarty et al. 2003	175 (29%) rheumatologists returned completed surveys. 39 respondents reported 65 pregnancies who were taking DMARDs at conception MTX n = 39 pregnancies LEF n = 10 pregnancies Etanercept n = 15 pregnancies Infliximab n = 2 pregnancies Fullterm healthy deliveries MTX n = 21, LEF n = 2 , etanercept n = 6, infliximab n = 1 Preterm delivery LEF n = 1 Elective abortions MTX n = 8, LEF n = 2, etanercept = 1 Spontaneous abortions MTX n = 7, LEF n = 1, etanercept = 1 (One pregnancy resulted in spontaneous abortion after exposure to both MTX and Etanercept)

Chakravarty et al. 2011	rituximab n = 153 ¥ Live births n = 90/153 (60%) ¥ 1st trim. miscarriages n = 33 pregnancies ¥ Elective terminations n = 28 Outcomes for the 53 pregnancies that occurred in industry sponsored or cosponsored trials (41 RA patients) Preterm deliveries n = 9 ¥ Full-term deliveries n = 22¥ 1st trim. spontaneous abortions n = 21, ≥ 60% were exposed to concomitant teratogenic medications ¥ fetal losses n = 1 at 20 weeks of gestation ¥ Elective terminations n = 17 ¥ Outcomes for live births (n = 90) ¥ Full-term deliveries n = 68 (RA n = 29 pregnancies) ¥ Premature deliveries n = 22 ¥
Chambers et al. 2010	Spontaneous abortion LEF group n = 5 (7.8%), Disease-matched group n = 8 (7.4%), Healthy group n = 3 (3.9%) Liveborn infant LEF group n = 56 (87.5%), Disease-matched group n = 95 (88.0%), Healthy group n = 72 (92.3%) Stillbirth LEF group n = 0, Disease-matched compar. group n = 1 (0.9%), Healthy group n = 0 Elective termination LEF group n = 1 (1.6%), Disease-matched group n = 2 (1.9%), Healthy group n = 0 Gestational weeks Mean ± SD (Range) LEF group 36.9 ± 3.2 (24.1–41.7) Disease-matched group 38.2 ± 2.4 (26.4–41.4) Healthy group 39.3 ± 1.5 (33.9-41.6) Preterm delivery (<37 weeks) LEF group n = 20 (35.7%) Disease-matched group n = 23 (24.5%) Healthy group n = 5 (6.9%) Birth weight full-term infants Mean ± SD gm LEF group 3,116 ± 457 Disease-matched group 3,310 ± 391 Healthy group 3,580 ± 420 Only gestational age at delivery (P < 0.01) and birth weight exhibited a significant difference (P = 0.02) between the LEF group and the disease-matched group.
Cush 2005	Normal deliveries n = 378 Premature babies n = 9 Therapeutic abortions n = 5 Miscarriages n = 25

de Man et al. 2009	Disease activity of 3rd trimester significantly negatively associated with the actual birth weight and the birth weight SDS. Similar results were noted for the 1st and 2nd trimesters as well as when subgroup analyses were performed only in women who had not taken prednisone during the pregnancy. Prednisone use associated only with the actual birth weight, and not with the birth weight SDS. Mean ± SD birth weight (3,379 ± 564 gm) and mean ± SD birth weight SDS (SDS;±0.1 ±1.1), comparable with those in the general population. Gestational age at delivery for prednisone users 38.8 versus 39.9 weeks for non-users (P = 0.001) Delivery for prednisone users more often premature <37 weeks (P = 0.004). No influence of SSZ treatment on gestational age was observed.
Hajdyla-Banaś et al. 2009	1st case: vaginal delivery of a completely healthy, female newborn of 2540g at 41 weeks 2nd case: vaginal delivery of a healthy female newborn of 3200g at 39 weeks
Katz et al. 2004	Live births ¥ n = 64/96 (67%) Miscarriages ¥ n = 14/96 (15%) Therapeutic terminations ¥ n = 18/96 (19%)
Kuriya et al. 2011	Deliveries n = 281 (72%) Elective abortions n = 37 (9%) Spontaneous abortions n = 75 (19%) Compared to women with deliveries, women who experienced abortions were more frequently exposed to NSAIDs/coxibs (P < 0.05). Dispensing of category D/X medications was also higher in women with spontaneous abortions and primarily involved MTX (P < 0.05). 12.5% of women with deliveries and 17.9% of women with abortions were prescribed a biologic DMARD at some point during pregnancy.
Lewden et al. 2004	Elective abortions n = 5 ¥ Spontaneous abortions n = 4 ¥ Live births n = 19 (vaginal deliveries n = 12, cesarean deliveries n = 4, preterm births n = 3) ¥ Rate of preterm births 16.7%, relatively high in comparison with the 5.4% rate in all singleton births reported in France. ¥ Mean gestational age at birth for the 16 full-term babies: 39.2 ± 1.2 weeks ¥ Mean birth weight for 14 full-term children): 3179 ± 465 g ¥
Motta et al. 2005	Preterm delivery n = 8 pregnancies (20.5%) ¥ Only 1 infant was <32 weeks and < 1500 g birth weight and required intensive care Mean gestational age at delivery 37.7 weeks (range 31-41) Mean birth weight 2941 g (range 1420-3970), 4 babies (10%) were small for gestational age HCQ treatment during gestation and lactation appeared to be safe. The relatively high incidence of preterm deliveries may reflect the maternal disease state and not HCQ intake.
Østensen et al. 2004	Miscarriages n = 1 Live births n = 9 Birth weight 3120 (2540–4455)

Østensen et al. 2007	Patient survey Immunosuppressive drugs (antimalarials, SSZ, cyclosporine, azathioprine) n = 28 pregnancies: 2 miscarriages, 22 live births, 4 unknown outcomes Etanercept n = 2 pregnancies: 2 live births LEF n = 1 pregnancy: 1 miscarriage MTX n = 3 pregnancies: 1 miscarriage, 2 induced abortions
Østensen and Raio 2005	The patient delivered a healthy girl weighing 2,540 g at gestational week 37.2. The patient's child has been healthy through the first 4 months after birth.
Park-Wyllie et al. 2000	Live born infants (P = 0.06) ¥ Exposed n = 157/187 (3 sets of twins) Controls n = 171 Stillbirths ¥ Controls n = 1 Fetal death (≥ 26 weeks) ¥ Exposed n = 1/187 Controls n = 1 Elective pregnancy terminations (P = 0.002) ¥ Exposed n = 16/187 Controls n = 2 Birth weight (P = 0.0001), Mean ¥ Exposed 3,112 g Controls 3,428 g Premature (<37 weeks) (P = 0.0001) ¥ Exposed n = 27/158 Controls n = 9/172
Roux et al. 2007	1st case: Healthy infant weighing 2.6 kg delivered at 32 weeks. No neonatal abnormality, child is growing and developing normally. 2nd case: Diagnostic ultrasound detected no abnormality and fetal growth was satisfactory, but the patient opted for therapeutic termination at 2.5 months. 3rd case: Healthy male infant weighing 3.520 kg. A neonatal urinary Escherichia coli infection was treated with ceftriaxone. Neonatal jaundice detected 3 days after birth resolved following phototherapy. The child is developing normally.
Scioscia et al. 2011	Both pregnancies were uneventful
Sheikh 2007	Foetal demise
Sills et al. 2001	Healthy female infant (2659 g, Apgar 8/9) was delivered vaginally at 40 weeks gestation and continued to do well 3 months after delivery.
Sinha and Patient, 2006	Admitted in labour at term gestation and eventually had an emergency caesarian section after a failed trial of forceps. The baby weighed 4,060 g (Apgar score 10/10).
Umeda et al. 2010	Birth of a healthy baby girl at 39 weeks. The baby weighed 2,740 g with an Apgar scoar of 10/10, having no malformation.

Verstappen et al. 2011	Live births ¥ Ia n = 10 (48%), Ib n = 32 (64%), II n = 46 (78%), III n = 10 (100%) Terminations ¥ Ia n = 4 (19%), Ib n = 4 (8%), II n = 2 (3%), III n = 0 Spontaneous abortions ¥ Ia n = 7 (33%), Ib n = 12 (24%), II n = 10 (17%), III n = 1 (10%) Neonatal death ¥ Ia n = 0, Ib n = 1 (2%), II n = 0, III n = 0 Intrauterine death ¥ Ia n = 0, Ib n = 2 (4%), II n = 2 (3%), III n = 0 Premature delivery (≤36 weeks) ¥ Ia n = 3, Ib n = 8, II n = 8, III n = 2 1 full-term baby had a low birth weight ¥
	Foetal complications / Congenital malformations
Almarzouqi et al. 2007	1 baby was born with weakness of one extraocular muscle requiring surgery 1 baby had blocked tear ducts at birth Major congenital anomalies were not seen. Though the sample is small, it does not appear that pregnancy loss or outcome is affected by gold therapy taken at the time of conception.
Artama et al. 2011	An increased risk for major congenital anomalies was observed in offspring of women with RA (aOR=1.38, 95%CI 1.16-1.63)
Berthelot et al. 2009	No malformation was observed, and none have been later diagnosed with developmental troubles.
Cassina et al. 2012	Minor malformations Group 1 n = 1 pattern of short nose, flat nasal bridge, long philtrum (mother with RA) Major malformations Group 1 n = 2: 1 aplasia cutis congenita involving both thighs (surviving member of a twin pregnancy; the other twin was spontaneously aborted, mother with RA) and 1 Pierre-Robin sequence, spina bifida occulta, patent ductus arteriosus, chondrodysplasia punctata, and congenital heart block (mother with RA and SLE). Group 2 n = 0 Functional anomalies Group 1 n = 1: severe sensorineural hearing loss Group 2 n = 1: intrauterine growth restriction and cerebral palsy, delivered by cesarean section at the 31st week of gestation, to a mother with JRA, diabetes, hypertension and asthma.
Chakravarty et al. 2003	Congenital malformations MTX n = 3, LEF n = 0, etanercept n = 0, infliximab n = 0 Respondents were less certain about the risk of either etanercept or infliximab exposure to the developing fetus. Fewer than half of the respondents agreed that pregnancy is contraindicated with use of these medications (38.6% etanercept and 46.5% infliximab.
Chakravarty et al. 2011	Congenital malformations ¥ n = 2 infants (one infant in a set of twins had clubfoot and antother full-term ventral septal defect, patent foramen ovale and patent ductus arteriosus. An infant born to a mother suffering for RA had neonatal thrombocytopenia.

Chambers et al. 2010	Major structural defects in live births LEF group n = 3/56 (5.4%): 1 occult spinal dysraphism; 1 unilateral uretero pelvic junction obstruction and multicystic kidney disease; 1 microcephaly Disease-matched group n = 4/95 (4.2%): 1 PFO with peripheral pulmonic stenosis; 1 ASD with pulmonic valve stenosis; 1 bilateral inguinal hernia and microcephaly; 1 eye defect of posterior chamber Healthy group n = 3/72 (4.2%): 1 unilateral cryptorchidism; 1 Klippel-Trenaunay-Weber syndrome; 1 vocal cord paralysis Major structural defects in pregnancy losses Disease-matched group n = 3/11 (27.3%): 2 trisomy 18; 1 chromosomal anomaly NOS Functional problems LEF group n = 1 hydronephrosis grade 2; 1 bilateral vesicoureteral reflux Disease-matched group n = 1 unilateral hydronephrosis; 1 vesicoureteral reflux with unilateral duplicated collecting system Healthy group n = 1 congenital esotropia; 1 neonatal encephalopathy and seizures secondary to subarachnoid bleed; 1 tracheomalacia Minor structural anomalies ≥ 3 LEF group n = 24/51 (47.1%), Disease-matched group n = 29/90 (32.2%), Healthy group n = 19/65 (29.2%)
Cush 2005	No congenital malformations
Katz et al. 2004	Fetal abnormalities n = 2 1 intestinal malrotation by a mother with RA, who had received infliximab before conception, and continued to receive infliximab after she was pregnant. She was also receiving LEF, which is a known teratogen.
Lewden et al. 2004	Results for 1 RA case 1 child presented with minor neonatal anomalies (bilateral metatarsus varus and right eylid angioma). The mother had been exposed to MTX 7.5 mg/week and SSZ 3 g/day for RA until 8.3 gestational weeks. 2 children had documented neonatal pathological conditions (1 premature child born at gestational week 30 experienced hyaline membrane disease and neonatal jaundice, and 1 child had transient respiratory distress and jaundice). ¥ The size of the sample only allows to rule out a higher than 6-fold increase in the risk of major malformations in patients who discontinued MTX before gestational week 8. ¥
Motta et al. 2005	No significant congenital malformations or neonatal infections. ¥ No infant had history of recurrent infections, probably because the HCQ immune-modulating effect is produced through inhibition of antigen processing and inflammatory cytokines synthesis and release. ¥
Østensen et al. 2007	Patient survey 1 small ventricular septal defect of a mother treated with SSZ and prednisone
Østensen and Raio 2005	Ultrasonography of the fetus was completely normal at week 11. At 18 weeks, ultrasound showed severe oligohydramnios. Premature rupture of the membranes was excluded and nimesulide suspected as the cause of the oligohydramnios.

Park-Wyllie et al. 2000	No statistical difference in the rate of major anomalies between the groups (P = 0.03) ¥ Exposed n = 4/111 ¥ Hirschsprung's disease Double outlet right ventricle, valvar and subvalvar pulmorary stenosis, hypothyroidism, hypospadias Undescended testicle (full term, required intervention) Cleft palate, hypospadias Controls n = 3/172 ¥ Aortic valve stenosis Pyloric stenosis Dysplastic kidney (in the stillborn child) The observed rates of anomalies (3.6% and 2%, respectively) are within the expected baseline rate. No apparent pattern that could suggest causality. ¥
Roux et al. 2007	3rd case: Adrenal congenital hyperplasia with 21 hydroxylase deficiency, known in the father, was detected 5 days after birth and treated with prednisone (5 mg/day).
Scioscia et al. 2011	Normal fetal growth
Verstappen et al. 2011	¥ Ib n = 2: 1 congenital dislocation of the hip and 1 pyloric stenosis II n = 2: 1 winking jaw syndrome and 1 strawberry birth mark
	Ethical considerations
Almarzouqi et al. 2007	Risks of typical gold side effect in exposed infants are discussed with the parents if a decision is made to continue gold in these circumstances.
Chakravarty et al. 2003	Rheumatologists almost uniformly agreed that pregnancy is contraindicated in women taking MTX (95%) or LEF (92.7%), and accordingly required the use of reliable methods of birth control. However, they were less diligent in reviewing continued use of birth control with patients at subsequent visits. A number of them recommended termination of pregnancies that occurred while patients were taking the medications. Their opinions about Etanercept or Infliximab reflect the paucity of data about the safety of the medications during pregnancy, but they were still likely to require birth control.
Chakravarty et al. 2011	In 4 clinical trial reports, patients were unblinded to placebo immediately after pregnancy discovery; 3 pregnancies were terminated despite unblinding.
Hajdyla-Banaś et al. 2009	1st case: In March 2005 because of an active RA LEF was introduced after pregnancy exclusion. The patient was informed that LEF could be potentially harmful to embryo and she must have avoided pregnancy during the therapy and two years after it was completed. 2nd case: The patient was informed that LEF therapy could be potentially embryo- and fetotoxic.
Østensen et al. 2007	Contraception with innunosuppressive therapy was practiced by a majority of women. Most of the women treated with the potentially fetotoxic drugs MTX and LEF were advised to practice contraception during treatment and for some time after withdrawal. However, one-third of women did not follow the advice.
Østensen and Raio 2005	When the patient expressed her wish for pregnancy, she was advised to stop taking MTX immediately, and to continue with infliximab until she missed a period. When a positive pregnancy test was obtained, infliximab was stopped. The patient was advised not to breast-feed.
Park-Wyllie et al. 2000	Although prednisone has never been proved to be a human teratogen, there are clinicians who extrapolate animal studies to suggest that the drug can cause cleft lip or palate and subsequently counsel their patients to avoid therapy during pregnancy. This may have been a factor in some of the 16 exposed women, who chose to terminate their pregnancies after prednisone exposure.
Sinha and Patient, 2006	She planned for pregnancy fully aware of the lack of evidence with the use of etanercept in pregnancy. She was counselled thoroughly and was happy to take the risks.

Umeda et al. 2010	After expressing her wish of pregnancy, doctors explained that the use of etanercept is not contraindicated in pregnant RA patients, but its safety has not been established, but in many cases it was discontinued when signs of pregnancy were shown, leading to successful delivery. They explained that they would increase the dose of prednisolone when her disease activity boosted. On the other hand, they also told her that there were several reports of successful cases of pregnancy without discontinuing etanercept in both Western countries and Japan. After the worsening of her symptoms during pregnancy, doctors advised her to choose between an increased dose of PSL and the concomitant use of SASP, but she rejected it. She eagerly desired to resume etanercept treatment and after taking advice of an obstetrician, she made inquiries to Pregnancy and Medicine Information Center of National Center for Child Health and Development. In response to the answer of etanercept treatment being possible, etanercept was resumed at 20 weeks.
Verstappen et al. 2011	¥ 20 patients became pregnant while receiving 'X' class drugs. It is not known whether they were informed about the detrimental effects of these drugs, although we it is known that a few patients became pregnant while using oral contraceptives, which suggests that these were unplanned pregnancies.
Vroom et al. 2008	9/15 rheumatologists recommended their patients to stop medication as soon as pregnancy was known. The existence of guidelines, or the type of hospital, did not influence this.
	Prevalence, costs, access issues
Artama et al. 2011	One or more special reimbursement in parturients = 6.5% in WWTOP = 6.0% ¥ Most frequent chronic diseases identified: asthma, hypothyroidism, epilepsy, RA (0.6% and 0.4%) and diabetes. ¥
Cush 2005	Prevalence of RA patients who became pregnant or took TNF inhibitors during pregnancy Never seen 77% 1-3 cases 21% Calculated total events n = 493 pregnancies Prevalence of patients who became pregnant while on biologics n = 454 patients TNF inhibitor therapy throughout the pregnancy n = 142 patients
Kuriya et al. 2011	393 pregnancies were identified among 34,169 women with RA. Approximately 24% of women with RA received a DMARD before conception. At any point, 23% of women with deliveries were dispensed ≥1 DMARD. The proportion of use declined from the first to the third trimester. Use of NSAIDs/coxibs and exposure to category D/X medications were significantly lower compared to prepregnancy use ($P < 0.05$). In contrast, more women were prescribed glucocorticoids during pregnancy than before pregnancy. Use of biologics occurred in 12.5% of pregnancies. Women with abortions were more frequently exposed to NSAIDs/coxibs ($P < 0.05$). Dispensing of category D/X medications was also higher in women with spontaneous abortions and involved MTX.
Viktil et al., 2009	During the 18-month observation period for each pregnancy, 1411 women (1.3% of the women) redeemed at least one antirheumatic drug. Of these, 45% received at least one drug during 3 months prior to conception, and 28% in the 1st trimester. 4 women redeemed prescriptions for MTX during the 3 months prior to conception, and 2 women did so during the pregnancy. 1 of the 4 women on LEF, received the drug 3 months before conception, and 2 of them during the 1st trimester. Among the women using etanercept, 19 redeemed the prescription 3 months before pregnancy, 22 during the 1st trimester, 1 in both the 2nd and 3rd trimesters.
Vroom et al. 2008	Each of the 15 respondents reported seeing at most 20 pregnant patients per year, mainly RA patients. This indicates that the group of women using DMARDs during pregnancy is very small and experience of such use will remain limited.

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