CLINICAL ASPECTS OF PREGNANCY-INDUCED AMELIORATION OF RHEUMATOID ARTHRITIS PARA-STUDY

Yaël A. de Man

All rheumatologists working in the Netherlands were contacted by mail twice a year from the start in May, 2002, till May, 2008. They were asked to recruit patients with RA who had a wish to conceive or who were already pregnant (preferably in their first trimester). Patients were eligible for the study if they fulfilled the 1987 revised criteria of the American College of Rheumatology (ACR) for RA and had a good understanding of the Dutch language. During the study the patients' own rheumatologists provided patient care. Patients were visited six or seven times at their home address. They were visited before conception (if possible), at each trimester (8-12 weeks of gestation, 18-22 weeks, and 28-32 weeks) and three times postpartum (4-6 weeks, 12 weeks and 26 weeks) (see Figure 2.1.1). The visit before conception took place if the woman had a wish to conceive, i.e. she and her partner did not use any contraceptives. If a woman did not conceive within a year after the first visit, another visit took place. Data collected before conception was classed as 'before pregnancy'. Medical and obstetrical history were taken at the first visit by interview. Erosions were ascertained from the patients' medical records. Pregnancy outcome was ascertained, only if complicated, from patients' medical records.

Clinical Aspects of Pregnancy-induced Amelioration of Rheumatoid Arthritis

PARA-study

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PARA-study

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PARA-studie

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INTRODUCTION

"Kon ik maar altijd zwanger zijn!"

citaat 80-jarige patiënte met reumatoïde artritis

"If only I could have been pregnant forever!" This is a quote from an 80-year-old lady with rheumatoid arthritis (RA), who developed RA before the discovery of cortisone in 1950, which was the primary treatment for RA. Female patients suffering from rheumatoid arthritis (RA) reported in those days that only pregnancy induced a spontaneous and considerable improvement of their disease. Outside pregnancy no other situation could relieve their pain and the swelling of their disabling joint disease. Postpartum, however, almost all patients reported a flare of their disease again.

Rheumatoid arthritis is a chronic, systemic, inflammatory autoimmune disease leading to destructive arthropathy, which can be accompanied by extra-articular manifestations (1). Fortunately, in recent decades the pharmacological treatment of RA has improved considerably. The reduction of inflammation and destruction by treatment has contributed to the preservation of functionality in RA patients nowadays (2). One can imagine that because of these achievements in treatment, RA patients with a wish to conceive now face other questions: first about the possibilities of using current pharmacological treatment before and during pregnancy, especially regarding outcome of pregnancy, and secondly what they can expect regarding their parenting function postpartum if the disease may flare (3, 4).

As early as in 1938, Hench was the first physician to describe the phenomenon of spontaneous improvement of disease activity among his patients (5). Up to now several attempts have been made to reveal the pathogenesis of the improvement, however, it has still not been elucidated (6). Even the hormonal changes as explanation have not yet been proven (7), despite the fact that the risk of RA developing in women who had been pregnant or had used or were still using oral contraceptives, decreases (8, 9). In order to elucidate the mechanism it is important to study immunological, biochemical, and hormonal changes in time combined with objective disease activity scores, preferably collected prospectively, in order to avoid selection bias. Only with accurately collected data on several time points from before pregnancy, during pregnancy and postpartum, might one get insight into changes and associate these with the favourable course of the disease during pregnancy, but also with the disease flare in the postpartum period.

Despite a considerable number of previous studies conducted in the field of pregnancy and RA, a large prospective study from preconception or early pregnancy onwards was lacking. For that reason a nationwide prospective cohort study on pregnancy and RA was conducted (the PARA-study, acronym for Pregnancy-induced Amelioration of Rheumatoid Arthritis-study) in the Netherlands between 2002 and 2009. This study aims to describe the clinical course before, during and after pregnancy for patients and health professionals in rheumatology, and strives to study the pathogenesis of the improvement during pregnancy and flare postpartum. Such a prospective design of the study will give a high level of evidence examining causal relations between the improvement of RA during pregnancy and the deterioration of RA postpartum.

The work presented in this thesis aims (I) to prospectively study disease activity of rheumatoid arthritis (RA) before, during and after pregnancy, (II) to explore associations of the pregnancy-induced amelioration of RA between the clinical characteristics and immunological changes in autoantibodies, (III) to determine the influence of disease activity and medication use on pregnancy outcome, and, finally, (IV) to address clinical aspects in parenting function postpartum.

In this chapter, firstly an introduction on pregnancy and rheumatic diseases is given, including an extensive review on the clinical course of RA during and after pregnancy, and on pregnancy outcome in RA women (section 1.1); and secondly, antirheumatic treatment during pregnancy and postpartum is discussed in detail (section 1.2).

In chapter two after a brief outline of the PARA-study, objective and validated disease activity scores for RA (Disease Activity Score of 28 joints) and functionality scores (Health Assessment Questionnaire) for use during pregnancy will be defined. Up to now no validated measurement tools for functionality and disease activity during pregnancy have been defined, and previous studies used all kinds of scoring methods (10, 11).

In chapter three, the course of disease activity of RA during pregnancy and postpartum will be determined with defined and validated measurement tools in an era of new treatment options (section 3.1). Subsequently, pregnancy-induced changes in autoantibody levels will be determined, and patients' characteristics (presence or absence of autoantibodies) will be associated with the course of disease activity of RA during pregnancy and postpartum (section 3.2).

In chapter four disease activity of RA and prednisone use during pregnancy and its influences on birth weight and other pregnancy outcomes will be addressed,

since unfavourable pregnancy outcomes were previously demonstrated in rheumatic diseases (6, 12, 13).

In chapter five parental function expressed in parenting disability scores will be for the first time described postpartum and it will be associated with patients' characteristics in order to find (modifiable) factors for better parental function postpartum (3).

Finally, in chapter six all the results described in this thesis will be discussed in a broader context. Some methodological considerations, implications for clinical practice, and recommendations for future research regarding pregnancy and RA will be put forward.

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1.1

PREGNANCY IN RHEUMATIC DISEASES: AN OVERVIEW

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INTRODUCTION

Pregnancy has an important impact on many rheumatic diseases. This may be either a dramatic improvement like in rheumatoid arthritis (RA) or a deterioration as in systemic lupus erythematosus (SLE). In addition, the disease may influence the outcome of the pregnancy by causing recurrent spontaneous abortions, still birth, or congenital abnormalities. The changes in the course of rheumatic diseases during pregnancy can be explained by the major changes in the immune system of the mother in order to enable her to maintain the partially non-self foetus. The immunological phenomena that are part of the rheumatic diseases may influence the pregnancy itself and the health of the foetus.

As soon as a patient indicates that she wants to become pregnant, the physician needs to pay extra attention. The medication has to be changed often and the physician should be alert to potential decreased fertility or frequent early miscarriages. Sometimes the gynaecologist has to be consulted at an early stage. Depending on the underlying disease, the frequency of the clinic visits has to be increased to monitor the woman and foetus in close cooperation with a specialized obstetrician. The delivery can cause problems either for the mother or for the child and needs specialist supervision. After delivery, breastfeeding and the risk of a flare in some of the rheumatic diseases require adjustments of the medication. Additional non-medical measures might be needed to lighten the physical task of the mother in caring for her baby. This chapter deals with the influence of pregnancy on the course and outcome of the rheumatic diseases, the effect of the rheumatic diseases on the course and outcome of the pregnancy for mother (obstetric complications), and child, fertility and disease management before, during, and after pregnancy.

RHEUMATOID ARTHRITIS

Effect of pregnancy on maternal disease

Amelioration of signs and symptoms of RA during pregnancy is a consistent finding throughout the RA literature, starting with the classical observation by Hench in 1938 (1). The improvement of RA occurs in about 75 percent of the patients. In retrospective studies, improvement of the arthritis is reported in 54-83 percent (2), in prospective studies in 66-86 percent (2, 3). The most recent and largest study showed widespread variability of disease response during pregnancy with 16 percent of the patients experiencing a complete remission (3) in contrast to the high remission rate of 53 percent reported previously (2). The reported amelioration of RA in pregnancy is probably an underestimation of

the favourable effect of pregnancy as patients will diminish or stop their antirheumatic medication during gestation. The improvement of RA starts in the first trimester of the pregnancy to reach its peak in the second and third trimesters.

RA typically deteriorates after delivery starting in the first month postpartum. After 3-4 months postpartum, most women will experience disease recurrence. Up to 90 percent of the women will get active disease after childbirth, irrespective of whether they had a remission during pregnancy or not (2).

Prediction of the pregnancy effect on RA

The disease response during previous pregnancies is predictive for the disease response in subsequent pregnancies (2, 3). The postpartum flare - or the absence of a postpartum flare - cannot be predicted. Presence of rheumatoid factor, age, disease duration, functional class, or parity have no influence on the RA response during or after pregnancy.

Pregnancy in relation to onset and outcome of RA

RA onset

Women who never had children have an approximately two-fold risk of developing RA compared to women who have children (2, 4, 5). This conclusion can also be reversed by stating that women who have been pregnant have an approximately two-fold reduced risk of developing RA compared to nulliparous women. Notably, one hardly sees women develop RA during pregnancy, but the onset of RA in the postpartum period is a well-known phenomenon. This has been confirmed in several studies showing a reduced risk of onset during pregnancy, odds ratios between 0.2 and 0.6, and an increased risk of onset in the 3-month postpartum period, odds ratios between 3.4 and 5.6 (2, 6, 7). Breastfeeding, in particular after the first pregnancy, has been implicated as being responsible for the increased risk of RA onset after pregnancy or for the postpartum flare in established RA (8, 9). Whether pregnancy really reduces the risk of RA or just delays the onset of symptoms through its ameliorating effect on the disease is still debated, though the latter explanation appears the most acceptable. There are some studies that question a reduced lifetime risk of RA due to pregnancy or breastfeeding (10, 11).

Outcome of RA

Patients often ask whether pregnancy will affect the ultimate outcome of their disease. The amelioration during pregnancy and postpartum flare appear to have no net effect on the prognosis of RA (2). In the only prospective study trying to answer this question, a trend was found to a more favourable outcome

in patients who had ever been pregnant compared to women who were never pregnant; this trend was, however, not significant (12). Table 1.1.1 summarizes the clinical observations in relation to RA and pregnancy.

Table 1.1.1: Clinical observations in relation to RA and pregnancy

Issues	Clinical observation
During pregnancy	
Disease activity	Amelioration or remission in about 75% (peak third trimester)
Onset RA	A two- to five-fold decreased risk to develop RA during pregnancy in healthy women
Obstetric problems (pre-eclampsia)	None, or probably none
Foetal outcome	No significant differences compared to healthy women and their babies
Delivery	No problems, unless severe hip arthritis
Postpartum	
Disease activity	Flare in 90% of patients within 6 months
Breastfeeding	Breastfeeding may increase the risk to develop (two- to five-fold) or deteriorate RA postpartum
Maternal care	Need for extra assistance for mother and child
Long-term (>10 years)	No adverse effect but also no apparent favourable effect
Fertility	Equal to healthy women
Fecundity	Possibly decreased

Mechanisms explaining the favourable effect of pregnancy

The possible mechanisms by which pregnancy decreases disease activity in RA have intrigued doctors and scientists for many decades with no conclusive explanation till now. Doctors have tried to copy the favourable effect by treating patients with blood, placental products, or serum from pregnant women without much success. The hormonal, immunological, and biochemical changes during pregnancy have all been considered as possible causes of the pregnancy-induced remission and postpartum flare in RA (2, 13-16). Increased serum cortisol concentrations did not explain the amelioration of RA probably because the concomitant elevation of steroid binding globulin. The elevated levels of sex hormones also could not satisfactorily explain the pregnancy-induced remission in RA. Treatment with female hormones exerts no or only a modest effect on disease activity in RA (13). Many other hormones are increased during pregnancy. The hormonal shifts are associated with shifts in cytokine profiles. Pregnancy is characterized by a decreased production of T-helper 1 (Th1) cell associated cytokines (like IL-1 and interferon-gamma), an increased production of Th2 cell associated cytokines (like IL-4 and IL-10) and decreased production of pro-inflammatory cytokines (TNF-alpha, IL-12) (13, 17, 18). Since RA is marked by a Th1 cytokine profile, a shift towards a Th2 cytokine profile during

pregnancy is an attractive explanation for a pregnancy-induced remission in RA, however conflicting results are reported (17). Exposure of foetal (paternal) non-self HLA antigens to the mother is also implicated in the causation of pregnancy induced amelioration of RA. Disparity of maternal-foetal HLA-DR and particularly HLA-DQ correlated with amelioration of the arthritis during pregnancy (2). These findings fit well with the fact that not all patients will improve during pregnancy and that a favourable response in a previous pregnancy will predict a similar response in a subsequent pregnancy. The studies till now are, however, not conclusive (19, 20).

Changes in the levels of α-2 pregnancy-associated protein (PAG) parallel the timing of arthritis amelioration during, and return after, pregnancy and are therefore also indicated as a possible explanation for the pregnancy-induced changes in RA. The studies on this topic are also not conclusive (2). Recently, a correlation was found between the increase during pregnancy and decrease postpartum of glycosylation of IgG and the clinical course of RA in that period (21), though the significance of this finding is still not clear. Table 1.1.2 summarizes the possible mechanisms that account for the pregnancy effect on disease activity of RA.

Fertility

Women with RA were found to have smaller family sizes than controls, which could not be attributed to lower fertility (2). Women with RA appear to need a longer time to conceive (lower fecundity). Many possible explanations have been put forward such as ovulatory dysfunction, tubal abnormalities, antibodies to spermatozoa, and hormonal disturbances. Another reason for delayed conception could be a decrease in the frequency of intercourse owing to pain from the arthritis. The physician should be aware of the potential increased time to conception because of pain or low fecundity in order to timely discuss the issue with the woman and, if necessary, refer her to a gynaecologist. Patients often stop or lower their antirheumatic medication the moment they seriously make efforts to get pregnant. When it takes a long time before the woman conceives—or knows she cannot conceive—she is also without adequate antirheumatic medication for an unnecessarily long time, a situation that should be avoided.

Table 1.1.2: Possible mechanisms that account for the pregnancy effect on disease activity of RA

Mechanisms	Account for amelioration of RA
Hormonal	
Cortisol	Probably not; serum levels rise along with steroid binding globulin
Female sex hormones	Explain insufficiently the amelioration of RA and when given as a treatment it has at the most a modest effect on disease activity
Immunological	
Cytokines	
Shift in Th1 (IL1 and INF-γ) and Th2 (IL-4 and IL-10) cytokine profiles	Possible; not yet determined for well-defined RA patients, but there are conflicting results in literature
Decreased pro-inflammatory (TNF-α, IL-12)	Possible; not yet determined for well-defined RA patients
Regulatory T-cells	Possibly beneficial effect of Treg on disease activity, not yet determined in high number of RA patients
Increased phagocyte and recurring lymphocyte gene activity, molecular activation of monocytes	Possibly associated with postpartum flare; not yet determined in high numbers of RA patients
Maternal–foetal HLA disparity HLA–DR, HLA–DQ	Possible HLA–DQ correlates, but there are conflicting results in literature
Biochemical	
Increased α-2 pregnancy-associated protein (PAG) levels	Possible; changes in PAG parallels the timing of amelioration and deterioration of RA during pregnancy
Increased glycosylation of IgG	Possible; levels change along with the clinical course

Obstetric problems and foetal outcome

Labour and delivery are usually uneventful in women with RA and there is no increased risk of foetal loss. There are few studies showing a increased risks for pre-eclampsia, caesarean delivery, prematurity, lower birth weight (however, not small for gestational age (SGA)) and longer hospitalization at birth among infants born to women with rheumatoid arthritis compared to the general population (22-25). In those studies, the case groups did not only include well-defined RA but also ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), and inflammatory arthritis, which prohibits specific conclusions for RA. An influence of disease activity of RA during pregnancy on birth weight was suggested, however, could not be discriminated from the influence of medication use during pregnancy (22). In rare cases, a normal vaginal delivery is not possible because of severe hip arthritis. If a caesarean section under general anaesthesia is required, special precaution has to be taken in case of atlanto-axial subluxation of the spine.

ANKYLOSING SPONDYLITIS

Effect of pregnancy on maternal disease

Unlike the pregnancy effects in RA, disease activity in AS does not substantially change during pregnancy. Amelioration of the disease is found in 20-31 percent, aggravation in 28-33 percent, and no change in 33-60 percent. A postpartum aggravation of AS is seen in 45-87 percent of the women depending on whether women were studied retrospectively or prospectively (26-29). In retrospect, women tend to forget their postpartum deterioration. The differences in the percentages are due to the heterogeneity of the studied populations. In general, spinal disease remains unchanged during pregnancy while peripheral arthritis and uveitis are suppressed during gestation and tend to exacerbate after delivery. The postpartum flare correlates with the disease activity during conception (28).

Prediction of pregnancy effect on AS

Improvement of AS activity during pregnancy - if any - is predicted by a history of peripheral arthritis. Women carrying a female foetus appear to fare better than women pregnant with a male foetus (28). This effect may be attributed to hormonal differences in pregnancies of a male or female child. Patients who get pregnant during active disease tend to have active disease in the postpartum period and - in case of spinal disease - will also experience many problems during pregnancy because of unchanged or even aggravated disease activity. Patients with predominantly spinal disease are therefore advised not to get pregnant during a very active period of their disease. Postpartum flares in AS have no relation with breastfeeding or the return of menses after delivery (26).

Pregnancy in relation to the onset of AS

The onset of AS symptoms typically occurs at the childbearing age. Consequently, the onset of AS around pregnancy would not be rare. Ostensen and Ostensen (1998) found a pregnancy-related onset of AS in 21 percent of 939 studied patients (28). For AS not associated with psoriasis or inflammatory bowel disease, the onset of AS seems to be slightly more often in the post-partum period than during pregnancy. This slightly increased onset postpartum can be explained in several ways: (i) high physical demands on the mother in caring for her new-born; (ii) a methodological flaw, comparing the 9 months risk of onset during pregnancy with the 6 months postpartum risk; (iii) a real increased postpartum risk of onset of AS. The risk of pregnancy-related onset of AS - if any - appears to be low.

Fertility

In a large multinational study, women with AS had 2.4 pregnancies per woman, with an average of two children per woman (28). These figures do not differ from the situation in the general population of those countries, indicating that there is no decreased fertility in AS.

Obstetric problems and foetal outcome

Foetal outcome is not compromised in AS (27, 28). Women with AS have no increased risk for foetal loss, prematurity, or low birth weight. Delivery may be a problem in advanced hip disease. This is, however, rarely the case in this age group and a normal vaginal delivery can be expected. Caesarean section was reported more frequently in AS women (28 percent) than expected from the figures reported for healthy women in North America and Europe (28). In 58 percent, AS was mentioned as the reason for the caesarean section. The decision to perform a caesarean section may be influenced by the inclination of the obstetrician to choose primary surgical delivery for women with inflammatory joint disease of the pelvic region and not by actual peri-partum problems.

JUVENILE IDIOPATHIC ARTHRITIS

The onset of JIA is by definition before the childbearing age, so all patients will be confronted with the possible effects of their disease on reproduction and fertility. In a recent study, at least one-third of female JIA patients were advised against having children, in particular by doctors (30). There are no good reasons for such negative advice, however, since the outcome of pregnancy in JIA is good.

Effect of pregnancy on maternal disease

The effect of pregnancy on disease activity in JIA is very similar to that in RA (30-32). About 60 percent of the patients will experience amelioration and 10–20 percent an aggravation. The favourable effect of pregnancy on disease activity is pre-eminently seen in patients with polyarticular disease, although patients with pauciarticular disease also showed a high remission rate of the disease during pregnancy (32). The remission rate during pregnancy of systemic disease is generally much lower than the remission rate of the other forms of JIA.

Postpartum flares are common, even in women who did not have a change in their disease activity during pregnancy. In about 60 percent, the disease will flare in the postpartum period, mostly in the first 6 months after delivery. In the

study of pauciarticular JIA the postpartum flare seemed to be predicted by active disease before pregnancy and by breastfeeding (32). The flare related to breastfeeding occurred only when the breastfeeding was stopped. Analogous to RA, the experience of previous pregnancies appears to predict the response of the disease to subsequent pregnancies.

Pregnancy complications and foetal outcome

Pregnancy generally passes without much extra problems. Consequences of the JIA influence the mode of delivery; severe hip involvement may prevent normal vaginal delivery. This problem is probably encountered more often in JIA than in RA because of the relative long duration of the disease in JIA. Similarly, patients with JIA may have more problems in caring for their babies than RA patients because of the more extensive joint impairments.

Early case series showed no evidence of adverse foetal outcome in terms of increased abortion rate, still birth, pre-term birth, or intrauterine growth retardation. In a recent controlled study, however, a significantly higher rate of miscarriages was seen in JIA patients than in healthy controls, 20.8 and 9.5 percent, respectively (30).

Fertility

Fertility appears to be normal in JIA, but patients report more difficulties in getting pregnant during 1 year of unprotected intercourse than healthy controls (30).The lower chance to conceive (fecundity) may be due to the higher frequency of gynaecological problems that were also found more often in the JIA patients than in the healthy controls. Ultimately, the number of pregnancies was similar for JIA and healthy controls with an average of 2.3 pregnancy per woman.

SYSTEMIC LUPUS ERYTHEMATOSUS

In pregnancies associated with SLE both maternal and foetal problems are common. Adolescents with SLE should preferably be given special attention regarding fertility and pregnancy in a translation clinic (33). Maternal disease outcome and maternal obstetric complications will be discussed separately from foetal and neonatal outcome (Table 1.1.3a and b).

Table 1.1.3a: Consequences of pregnancy in SLE, maternal perspective

Consequences	Risk factors
Maternal perspective	
Effect of pregnancy on SLE flares	
More than two-fold risk of flares	Active disease before conception
No time preference of flares	
Flares not more severe than outside pregnancy	
Effect of SLE on pregnancy: obstetric complications	
Hypertension	Renal flare, prednisone
Pre-eclampsia	Renal flare, prednisone
Thrombosis	
- deep venous thrombosis	Antiphospholipid syndrome
- stroke	Antiphospholipid syndrome
Diabetes mellitus	Prednisone
Hyperglycaemia	Prednisone
Bladder infections	Medications?
Premature rupture of membranes	Probably multifactorial
More frequent caesarean section	Multifactorial
Rare obstetric complications (uterine rupture, bilateral retinal detachment during labour, severe retinopathy, HELLP)	Renal flare, APLS, and medication

The maternal perspective

Effect of pregnancy on maternal disease: lupus flare

Despite all the conflicting results in the literature, there is some agreement that the frequency of flares is higher in pregnant than in non-pregnant SLE patients (34-36). Considering the often heterogeneous patient populations studied and the very different ways flares were assessed, the similarity of the results in the different studies support the clinical impression that SLE patients tend to flare during pregnancy. In nearly all studies the frequencies of flares during pregnancy were higher than 57 percent, with flare rates ranging from 0.06 to 0.136 per patient-month, compared to very consistent flare rates in control groups of 0.039–0.054 per patient-month. The flares during pregnancy are not more severe than outside pregnancy and they mostly affect the skin and the joints (34, 36), though others found less musculoskeletal flares and more renal and haematologic flares (35). One should realize that the frequency, nature, and severity of the flares are not only determined by pregnancy itself but also by

the change in medication because of the pregnancy. Monitoring disease activity of SLE during pregnancy can be performed with the lupus activity index during pregnancy (37). The disease manifestations, the pregnancy, and the medication together will determine the morbidity of mother and child. Hypertension develops frequently during pregnancy as well as mild oedema and proteinuria and may progress into (pre)eclampsia mimicking a flare of the disease. In general, pregnancy does not lead to worsening of renal function in patients with previous lupus nephritis, but the combination of pre-eclampsia and renal disease may rapidly lead to serious morbidity requiring clear differentiation between a renal flare and (pre)eclampsia and subsequent adequate therapy; high dose immunosuppression or delivery, respectively.

Prediction of lupus flare

A flare can occur at any time during pregnancy or the puerperium (38). There is no specific postpartum risk of a flare. It is not possible to predict when or if an individual patient will flare and what the nature of the flare will be, though quiescent disease in the year prior to conception seems to be associated with fewer disease flares during pregnancy (39). Low-dose prednisone (10 mg/day) does not prevent flares occurring. Close monitoring of the patient during the whole pregnancy and the puerperium is necessary, since most patients can or will not plan their pregnancy exclusively after a year without disease activity.

Mechanisms explaining pregnancy flares

During pregnancy, strong hormonal and immunologic changes are required to permit the woman to carry a child that is partly non-self. SLE is strongly associated with female sex hormones since the female to male ratio of SLE is about 10:1. In particular, female sex hormones will rise during pregnancy, which in turn stimulate prolactin production. Prolactin is known to be an immunomodulator with multiple effects on the immune system. Prolactin receptors are expressed in a number of cells, including T- and B-lymphocytes, and belong to the family of cytokine receptors. Prolactin levels were found to be associated with SLE activity in some studies, but not in others (34, 35, 40, 41). Use of bromocriptine during pregnancy was tested in SLE patients and suggests that it possibly reduces unfavourable pregnancy outcome, however, this have to be confirmed in a randomised clinical trial (41, 42).

In contrast with the possibly favourable effect in RA, the shift from Th1 to Th2 cytokines in pregnancy may be deleterious in SLE. The Th2 cytokines are responsible for the humoral immunity and a shift towards a Th2 cytokine profile may therefore worsen an antibody-mediated disease like SLE (18).

Table 1.1.3b: Consequences of pregnancy in SLE, foetal perspective

Consequences	Risk factors
Foetal perspective	
Overall a two-fold risk of foetal loss	
First trimester	
- probable increased frequency of spontaneous abortions	Active disease? APLS?
Second and third trimesters	
- increased frequency of foetal loss	Antiphospholipid syndrome (particularly in LA)
	Low renal function
	Low serum C3
Pre-term birth and intrauterine growth retardation	
- 24-59% pre-term deliveries	Active disease in general
	Renal disease and hypertension
	Prednisone
	Poor obstetric history (anticoagulant therapy because of antiphospholipid syndrome)
Neonatal outcome	
Neonatal lupus syndrome	
Transient	
- skin rashes	Anti-SSA/Ro and Anti-SSB/La
- cytopaenias	
- hepatosplenomegaly	
- myocarditis/pericarditis	
Permanent	
- neurocognitive abnormalities	
- complete heart block	Anti-SSA/Ro and Anti-SSB/La
Neonatal antiphospholipid syndrome (extremely rare)	Primary APLS/ secondary APLS in SLE

Obstetric complications

Obstetric morbidity is a serious problem in SLE. Obstetric morbidity is higher in lupus patients than in controls. In particular, hypertension, pre-eclampsia, diabetes mellitus, hyperglycaemia, and bladder infections are common with a four- to six-fold increased risk compared to controls (25, 35). Corticosteroid therapy strongly contributes to this comorbidity, particularly in patients taking more than 10 mg/day. Lupus patients are more likely to have premature rupture of membranes and they require also more frequently caesarean sections. The rare, but more serious obstetric complications are uterine rupture, bilateral retinal detachment during labour, severe retinopathy, deep venous thrombosis, and recurrent liver necrosis (43) and stroke (both associated with secondary antiphospholipid syndrome, APLS) and the HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets). The APLS-associated complications

can occur in patients who are already receiving antithrombotic treatment. Women with APLS and a previous arterial thromboembolism should be discouraged to become pregnant because of the high risk of recurrent thromboembolism, even with anticoagulant treatment (35, 44, 45). A substantial proportion of all thrombotic events in women with APLS occurs during pregnancy or in the postpartum period.

Fertility

SLE does not apparently affect fertility (46), unless patients have been treated previously with cyclophosphamide. Despite the fact that women who have, or later develop, SLE are at greater risk of pregnancy loss, their ultimate family size is comparable to that of healthy controls (47). However, infertility may be a factor in a small group of women with high levels of APL antibodies seeking help for inability to conceive (48). Some clinicians recommend that infertile women with APLS should be treated with heparin/aspirin when they are undergoing *in vitro* fertilization. In particular, women with APL antibodies against phosphatidylethanolamine (PE) or phosphatidylserine (PS) appear to have low success rates with *in vitro* fertilization. In these women, treatment with intravenous immunoglobulin might help if heparin/aspirin fails.

The foetal perspective

Foetal loss

There is an increased foetal loss in SLE pregnancies, in particular in the second trimester. Most studies report foetal loss in 20-30 percent of the SLE pregnancies, which is more than a twofold risk of foetal loss compared to controls (35, 36, 39, 44, 47). Secondary APLS is strongly associated with foetal loss in the second trimester, but not with foetal loss in the first trimester. The risk of foetal loss in APLS is strong for the presence of lupus anticoagulant (LA) (odds ratio 27.7), but less strong for anticardiolipin (odds ratio 1.7). Other risk factors for foetal loss are impaired renal function and active disease, for example, measured by low serum C3, and placental compromise (35, 36, 49).

Pre-term birth

The rate of pre-term delivery in SLE patients ranges from 24 to 59 percent. Disease activity, measured with whatever marker for SLE activity, is probably the most important risk factor for pre-term birth (35). Renal disease with proteinuria in the nephrotic range and hypertension are particularly important in causing prematurity. High prednisone doses either as a marker of active (renal) disease, or by a direct effect contributes to the prematurity risk. In addition, poor obstetric history also predicts pre-term birth. Prematurity in SLE is often

multifactorial and preventive measures should include optimal antihypertensive treatment, treatment of SLE activity and treatment of secondary APLS.

Women with SLE are also at risk for foetal growth impairment and foetal distress caused by placental insufficiency. Placental pathology in SLE patients is characterized by decidual vasculopathy and infarction. The latter feature in particular can be extensive in APLS patients (48).

Neonatal outcome

Women with circulating anti-52 kDa SSA/Ro or SSB/La antibodies are at risk of having a child with neonatal lupus syndrome. Transient symptoms of neonatal lupus are rash, cytopaenias, hepatosplenomegaly, and myocarditis/pericarditis. A permanent, and potentially lethal, manifestation of neonatal lupus is complete congenital heart block. Mortality in congenital heart block may accumulate to 20 percent in utero. Of the new-born babies with a congenital heart block 64 percent need a pacemaker (50). The risk of having a subsequent child with congenital heart block appears to be between 12 and 16 percent (48). Series of foetal echocardiograms are indicated between weeks 16 and 24 of gestation to follow the foetal cardiac function in women with anti-SSA/Ro, anti-SSB/La antibodies or with a previous child with congenital heart block. Oral dexamethasone and/or plasmapheresis have been used to attenuate or to reverse the serious complication of congenital heart block in utero with varying degree of success (50, 51). Another extremely rare complication of women with SLE and secondary APLS can be a neonatal antiphospholipid syndrome. Its occurrence may depend on the passage of antibodies through the placenta or, by the production of de novo antibodies by the fetus (52). In later life, offspring of patients with SLE showed neuropsychological abnormalities in learning and memory and behaviour domains. These abnormalities were not associated with neither the development of SLE in the offspring nor disease activity during the pregnancy in the mother (53).

Patient management with SLE pregnancy

Successful pregnancies are now possible in 85 percent of the women with SLE. This is only made possible through partnership between expert rheumatologists, obstetricians, and neonatologists. SLE still carries a high risk for adverse pregnancy outcome. Counselling and obstetric care ideally begins before conception (25, 39, 54). Risk factors can be assessed and treatment can be optimized aiming at a quiescent disease at least 6 months before conception. A series of laboratory assessments will provide the baseline measures for further follow up during pregnancy and the potential risk factors for adverse outcome (Table 1.1.4). In normal pregnancy the C3 and C4 should rise. Monthly monitoring - if necessary more often - by rheumatologist, obstetrician, and

possibly other specialists may pick up important change that have to be acted upon. Particular attention has to be given to disease flare, renal deterioration, hypertension, and adverse foetal development. The medication has to be adapted to the patient's needs depending on disease activity, prior obstetric history, presence of APLS, presence of anti-SSA/Ro or anti-SSB/La antibodies, and the course of the present pregnancy. Management of lupus flares can be problematic because of the limitations on medications that can be used safely during pregnancy. Mild flares can be treated with prednisone, although high doses of prednisone are not favoured because of the increased risk of obstetric problems and pre-term birth. For moderate to major flares intravenous methylprednisolone pulse therapy, 1000 mg/day, for 3 days may be an option combined with azathioprine, which has been used without much problem in lupus flares during pregnancy. Hydroxychloroquine has been shown to control disease activity during pregnancy and can be continued during pregnancy in SLE without harm to the foetus (35, 39). Treatment with NSAIDs after the second trimester is not advised because of the potential adverse effect on the foetal renal and cardiac system. The preferred treatment for APLS nowadays is a combination of low-dose aspirin and low-molecular-weight heparin that can be given for the duration of pregnancy (35, 44). The use of prednisone to prevent APLS complications is not advocated anymore because of the lack of effect and the risk of prednisone associated obstetric complications such as diabetes mellitus, hypertension, pre-eclampsia, and pre-term delivery (Table 1.1.3). Antihypertensive treatment is often necessary in lupus pregnancy but should not be too aggressive because of the differential effect on maternal hypertension and placental blood flow. Antihypertensives that are most commonly used in SLE pregnancies include methyldopa, hydralazine, and—in more severe hypertension - labetolol. Patients who are chronically on thiazide diuretics or nifedipine because of renal disease could potentially remain on these drugs if closely monitored. ACE inhibitors should be stopped because of effects on foetal kidney development (39).

Prednisone and hydrocortisone are inactivated in the placenta and therefore have little effect on the foetus. Dexamethasone and betamethasone do cross the placenta in an unmetabolized form and are therefore used if the foetus has to be treated, for example, in case of anti-SSA/Ro or anti-SSB/La foetal myocardiopathy.

Approaching delivery, the team has to include a neonatologist. Obstetric management during labour is not dissimilar from normal pregnancy care. Stress dose steroids should be administered to patients who are on prolonged courses of steroids. Any antithrombotic therapy should be stopped if labour is imminent. Because of the high-risk nature of SLE pregnancies, the rate of caesarean

sections will be higher than usual. The usual precautions for anaesthesia and surgery should be taken in case of prednisone and/or anticoagulant use. After delivery the newly born baby has to be observed for signs and symptoms of neonatal lupus. There are no objections against breastfeeding, unless certain medications prevent it because of risk for the baby.

Table 1.1.4: Baseline laboratory assessments in SLE-pregnancy

Investigations	Parameter
Immunological	ANA titre
	Anti-dsDNA and titre
	Anti-SSA/Ro
	Anti-SSB/La
	Anticardiolipin IgM and IgG
	Lupus anticoagulant (LA)
	Complement levels: C3, C4, and CH50
Haematological and chemical	Haemoglobin
	Haematocrit
	Leucocytes
	Platelets
	Full serum electrolyte panel
	Serum creatinine
	Liver enzymes
	Glucose
Urinalysis	24 h creatinine clearance
	24 h total protein
	Sediment

SCLERODERMA

Effect of pregnancy on maternal disease

Pregnancy in general does not change the disease status of scleroderma. The few studies that systematically evaluated the disease status during pregnancy reported no change in 72-88 percent, improvement in 5-14 percent, and worsening in 7-14 percent of scleroderma patients (55, 56). Scleroderma symptoms such as oedema, arthralgias, gastrointestinal reflux, and mild shortness of breath are also common in normal pregnancy. Raynaud's phenomenon usually improves, but will come back after delivery. Hypertension, a frequent symptom during pregnancy, should be aggressively treated, since renal crisis is the most serious complication of scleroderma and cause of death in scleroderma pregnancies. The presence of hypertension and proteinuria related to pre-eclampsia could be confused with a renal crisis and it may be difficult to distinguish between the presence of pre-eclampsia or scleroderma renal crisis per se or a renal crisis in scleroderma induced by pregnancy. Recent studies showed far fewer episodes of renal crises than earlier anecdotal

case reports (55, 56). Women with symptoms of scleroderma of less than 4 years, those with diffuse cutaneous scleroderma and those who have antitopoisomerase antibodies (anti-Scl70) have a greater risk of aggressive disease than those with longstanding disease with anticentromere antibodies (55). Women with early progressive disease are therefore more at risk of renal crisis during pregnancy than women with limited scleroderma or longstanding stable disease. Prednisone therapy is another precipitating factor for renal crisis in scleroderma and should therefore be avoided, particularly during pregnancy. The overall outcome of scleroderma is not influenced by pregnancy; the 10-year cumulative survival for women with and without a pregnancy was similar (Table 1.1.5).

Table 1.1.5: Clinical observations in relation to scleroderma and pregnancy

Issues	Clinical observation
During pregnancy	
Disease activity	No change in 72–88%, 5–14% improvement, 7–14% worsening
	Only Raynaud's phenomenon usually improves
Onset scleroderma	No relation between the timing of onset and pregnancy
	Parous women have threefold decreased risk of developing scleroderma
Obstetric problems	Hypertension: treat aggressively
Measures - Need frequent evaluations of blood pressure, urinalysis and foetal growth by ultrasound - Prednisone is contraindicated	Renal crises: most serious complication that can cause death in scleroderma patients. Must be treated with ACE-inhibitor - Risk factors of renal crisis: early progressive disease (<4 year), diffuse cutaneous scleroderma, presence of anti-topoisomerase antibodies (anti-Scl70) and prednisone therapy - Low risk of renal crisis: longstanding disease with anti-centromere antibodies
	Pre-eclampsia: difficult to distinguish from renal crisis in scleroderma induced by pregnancy
Foetal outcome	Slightly increased risk of prematurity and miscarriages in diffuse scleroderma
Delivery	Caution with the use of beta-adrenergic agonists to prevent pre-term labour, because of its potential side-effects of myocardial ischaemia and pulmonary oedema
	In case of general anaesthesia difficult intubation because of restricted opening of scleroderma mouth
	Special care needed for surgical repair of caesarean wound and episiotomy
Postpartum	
Disease activity	Raynaud's comes back
Long-term (>10 years)	Overall outcome and 10-year cumulative survival is not influenced by pregnancy
Fertility	No evidence of decreased fertility in scleroderma patients

Pregnancy in relation to onset of scleroderma

There is no relation between the onset of scleroderma and pregnancy. The disease can develop during as well as outside pregnancy with similar risks. Parity has been implicated in the causation of scleroderma through persistent, HLA similar (but not entirely identical), foetal microchimerism disrupting the maternal immunoregulatory mechanisms (57, 58). Parous women and women who had abortive pregnancy, however, were found to have three-fold decreased risk of scleroderma compared to nulliparous women, which excludes the possibility of pregnancy itself being a risk factor for the development of scleroderma (59).

Fertility

The most recent studies show no evidence of decreased fertility in scleroderma (60), though older studies suggested that fertility was decreased (55). Patients with systemic sclerosis are more often nulliparous than controls. When nulliparity was adjusted for number of women who never married, women who were sexually active, and women who chose not to have children, the differences from the controls disappeared. Only 2-5 percent of both the scleroderma and control women who attempted to become pregnant was unsuccessful. All other determinants of fertility were also similar in both groups (60).

Foetal outcome

Pregnancy outcome in scleroderma is variable but the overall adverse pregnancy outcome rate is increased in most case-control studies (55). Scleroderma patients are more likely to have adverse pregnancy outcome after disease onset than before, in particular, prematurity. An increased rate of miscarriages and prematurity is reported especially in patients with longstanding diffuse scleroderma but not in limited scleroderma. Recent studies show, however, more favourable pregnancy outcomes in scleroderma than the older case series (60). The current consensus is that the overall success of pregnancy in scleroderma is good, and only in the diffuse disease is there a slight increased risk of adverse pregnancy outcome, in particular, prematurity.

Patient management of scleroderma pregnancy

The overall outcome of pregnancy in scleroderma is favourable though, in the individual patient, the risk of maternal harm and foetal prematurity may be substantial (61). Careful management of the pregnant scleroderma patient is therefore indicated. Patients with early diffuse scleroderma should wait to become pregnant until their disease stabilizes and the risk of renal crisis has decreased. Patients with longstanding diffuse systemic sclerosis and extensive

organ involvement have to be assessed regarding the risk of serious health problems during the physical demands of pregnancy. When cardiac, renal, or lung function are greatly impaired the patient should be strongly advised against pregnancy. This decision is based on the abnormalities found and is independent of the fact that scleroderma is the cause of these abnormalities.

Management of the pregnant scleroderma patient includes frequent evaluation of blood pressure, urinalysis, and foetal growth by ultrasound. Prednisone therapy is contraindicated because of the risk of a renal crisis. Patients with diffuse scleroderma are advised to monitor their blood pressure very frequently, if possible several times a week, by home monitoring. Even a slight elevation in blood pressure compared to previous levels should be considered potentially serious and be treated promptly. In case of (suspicion of) a renal crisis the first choice of treatment is an ACE inhibitor; this could make the difference in the life or death of the mother and the foetus. ACE inhibitors have been reported to cause foetal abnormalities, but successful use in pregnancies has been documented. The risk of renal failure and foetal loss may outweigh the risk of the birth defects associated with the use of ACE inhibitors and justify the use of these drugs in pregnancy of a scleroderma patient.

Antacids and anti-reflux measures can manage common problems such as oesophageal dysmotility. The use of histamine blockers and proton pump blockers has not been reported to cause significant problems in pregnancy.
The risk of pre-term labour, in particular in diffuse scleroderma, is increased. The use of beta-adrenergic agonists to prevent pre-term labour particularly in this patient group should be used with great caution, because of the potential side effects of myocardial ischaemia and pulmonary oedema. Before delivery venous access should be secured because of the potential difficulties finding access in the taut skin. General anaesthesia should be avoided because of the difficulties in intubating a scleroderma patient with a minimal mouth opening and the risk of aspiration. An epidural block can normally be used without problem. If a caesarean section is indicated, the wound normally heals without difficulty if care is taken in the surgical repair. The same applies for an episiotomy incision.

If the baby is born full term, no special care has to be taken.

DERMATOMYOSITIS/POLYMYOSITIS

Pregnancy in dermatomyositis (DM) or polymyositis (PM) is infrequent because of the rarity of the disease and the late age at onset. In over 85 percent of the patients, the disease starts after childbearing age. The knowledge about pregnancy in DM/PM, is based on some case series and several case reports

(62-65) and can best be divided into: (i) influence of pregnancy on childhood DM/PM; (ii) influence of pregnancy on adult DM/PM; and (iii) onset of DM/PM related to pregnancy (Table 1.1.6).

Table 1.1.6: Clinical observations in relation to dermatomyositis/polymyositis and pregnancy

Issues	Clinical observation
Child DM/PM	
Risk of flare during pregnancy	Low
Foetal outcome	Favourable
Adult DM/PM	
Risk of flare during pregnancy	Low
Foetal outcome	Moderate-poor (± 50% at term)
	Risk factor for adverse outcome: active disease at start of pregnancy
Onset of DM/PM during pregnancy	
Risk of uncontrollable disease	High
Foetal outcome	Moderate-poor (± 50% adverse outcome)
	Remarkable postpartum remission reported

Maternal disease and pregnancy outcome

All reported cases of childhood DM/PM started their pregnancy in an inactive phase of their disease. Two patients had an abortion (one spontaneously, one induced) and a flare post-abortion. Of the remaining eight patients, only two (25 percent) flared during pregnancy. Seven out of 10 patients (70 percent) had full term new-borns. One baby was born prematurely. In adult DM/PM, 88 percent of the patients remained stable during pregnancy and the corticosteroid dosages were not changed. The pregnancy outcome was worse than in childhood DM/PM with only 50 percent full-term new-borns. Of eight pregnancies two ended with an abortion, one in pre-term birth and one in neonatal death of a pair of twins.

Risk for adverse outcome of pregnancy

It appears that the outcome is best in mothers with inactive disease (n = 12), with 72 percent full term birth, 11 percent spontaneous abortions and no pre-term birth (when excluding the induced abortion). In active disease (n = 14) the outcome is worse with only 47 percent full-term birth, 33 percent foetal loss, and 13 percent premature birth. The babies did not show any sign of an autoimmune disease. Recently three cases of a pregnant patients with active DM were described who were successfully treated with IVIG. This might suggest that IVIG therapy is a possible therapeutic option in active DM during pregnancy, given its corticosteroid-sparing effect and the reduced risk of steroid-related side effects (66-68).

Onset of DM/PM during pregnancy

There are several case reports of DM/PM starting during pregnancy, mostly in the first, sometimes in the second and rarely in the third trimester (62, 63). The group of patients with onset of DM/PM during pregnancy has the poorest outcome of pregnancy with over 50 percent foetal death. Conversely, pregnancy appeared to have a negative influence on the disease in the mother, with very active therapy-resistant disease during pregnancy. In some of these cases, patients showed remarkable postpartum remissions.

PRIMARY SJÖGREN'S SYNDROME

There are few studies on pregnancy in primary Sjögren's syndrome. Fertility, parity, and sexual activity of patients with primary Sjögren's syndrome do not appear to differ from that of the healthy population. There are, however, some contradictory results on the risk of foetal loss (69-72). In some studies the risk of foetal loss is approximately two-fold increased and comparable to that of SLE, while in other studies no such risk is observed. Foetal growth retardation and pre-term birth are not problems in primary Sjögren's syndrome. APLS antibodies or antibodies to SSA/Ro or SSB/La appeared to play no major role in the increased risk of foetal loss in Sjögren's patients. There may be the risk of congenital heart block, but only few prospective data are available.

RARE DISEASES

Adult onset Still's disease

Reviewing the scarce case reports, pregnancy seems to have no effect on adult onset Still's disease, and conversely, adult onset Still's disease has no obvious influence on pregnancy, foetal growth, or infant maturity and health (73, 74).

Vasculitis syndromes

Polyarteritis nodosa

Polyarteritis nodosa (PAN) developing during pregnancy has an extremely bad prognosis. All seven women diagnosed during gestation or in the immediate postpartum period died within 6 weeks postpartum (75-77). This grave prognosis may be explained to a certain extent by difficulties in diagnosing PAN in the setting of pregnancy and by the very active disease during pregnancy. Pregnant women with a known, quiescent PAN have a much better prognosis, with only one in four women experiencing an exacerbation. Perinatal outcome was surprisingly good, with approximately 70 percent survival of the child.

Wegener's granulomatosis

About 30 pregnancies have now been reported in Wegener's granulomatosis (WG) of which half occurred during or immediately after pregnancy (76-79). If the disease is inactive prior to pregnancy the chance of disease activation during pregnancy is not particularly high and the foetal outcome is generally favourable. In contrast, obstetric problems, such as pre-eclampsia, prematurity, and foetal deaths occurred when maternal disease was not controlled.

Takayasu arteritis

Pregnancy does not seem to worsen Takayasu arteritis, although symptoms common to both the disease and pregnancy—such as hypertension and abdominal discomfort—have to be correctly interpreted (77, 80, 81). There is an increased risk of foetal loss, intrauterine growth retardation, and pre-term birth. All patients with poor perinatal outcome had abdominal aortic involvement and a significant delay in seeking medical attention.

Behçet's disease

In women with Behçet's disease, convincing reports of both pregnancy-related flares and remissions, mainly of mucocutaneous involvement, are found in the literature. Gestational exacerbations of the more serious manifestations of Behçet's including major eye problems, vasculitis, and CNS disease are uncommon. Also, foetal development and survival is generally good in Behçet's syndrome (75, 77, 82, 83).

The general advice for management of pregnancy in a vasculitis syndrome is that pregnancy should be planned during a remission of the disease. If vasculitis activity reappears, rigorous treatment of the vasculitis is required in order to protect mother and child against serious morbidity and mortality. If necessary, cyclophosphamide pulse therapy in the second and third trimesters should be considered as a therapeutic option, since maximal suppression of the vasculitis activity is the goal.

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1.2

ANTIRHEUMATIC DRUGS IN PREGNANCY AND LACTATION

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INTRODUCTION

The inflammatory rheumatic diseases predominantly affect women, often in the childbearing years. Antirheumatic drugs are necessary to control the disease and many times the medication cannot be stopped in pregnancy because of risk of a disease flare potentially threatening the health of mother and child. Some drugs appear to be safe during pregnancy, though an association between drugs and malformations is hard to exclude totally. It therefore seems prudent to stop all medications during pregnancy if possible. In general, the outcome for mother and child is best if pregnancy occurs in a period of disease remission (1). Often, pregnancy will or cannot be planned in a period of remission or, conversely, the disease will flare during pregnancy and the doctor will face the question which antirheumatic drugs to use during pregnancy. The most critical phase for the foetal outcome in relation to use of medication is in the first weeks of pregnancy during conception, embryogenesis, and organogenesis. It is therefore important that a pregnancy is carefully planned and the antirheumatic medication is adapted as soon as the patient seriously wishes to conceive.

There are virtually no controlled data on the safety of drug use during pregnancy, since pregnant women are always excluded from randomized controlled trials. Placental transfer has been described for the majority of antirheumatic drugs. The foetal concentrations of drugs can vary considerably compared to the maternal concentrations depending on the type and dosage of the drug, duration of treatment, and timing. Both protein binding and hepatic metabolism in the foetus differ from those in the mother and depend on the stage of development of the foetus. The first trimester and the few weeks before delivery are the most vulnerable periods for the foetus: the former because of the early foetal development and the potential risk of malformations during foetal organogenesis (teratogenesis), the latter because of the risk of functional abnormalities and post-natal problems in the neonate due to exposure to a specific drug.

Knowledge about safety for mother and child during pregnancy comes from observations during long-term clinical experience, case series, and case reports. The last of these tends to overestimate adverse effects of drugs on the foetus due to publication bias. Animal studies may provide some guidance in the usage of drugs during pregnancy though they cannot be easily extrapolated to the human situation. Physicians should be aware of the potential adverse effects of antirheumatic drugs during conception, pregnancy, and lactation, and should carefully weigh the risks and the benefits of these medications for mother and child. Comprehensive management of the patient starting before conception is prerequisite for an optimal outcome. Recently the prescribing

patterns of rheumatologists regarding DMARDs in rheumatic diseases were described (2). This chapter describes what is known about the effects of antirheumatic drugs on fertility, conception, pregnancy, and lactation for both mother and child. This information is summarized in Tables 1.2.1 - 1.2.6 . This chapter is based on some excellent reviews (3-12) and the information from the Micromedex and a Dutch pharmacologic registry containing information on antirheumatic drugs during pregnancy and lactation (13, 14).

Table 1.2.1 Use of NSAIDs and corticosteroids in pregnancy

	Aspirin		NSAIDs		
	High dose	Low dose	Non-selective COX	COX-2 selective	Corticosteroids
Fertility	No effect	May promote embryo implantation	Probably to a small degree: interference with follicle development	Unknown	No effect
Teratogenicity	Possibly	No	Possibly	Unknown	High dose: possibly risk of oral clefts (after first trimester exposure)
Late pregnancy	Contraindicated for bleeding risk and foetal renovascular complications	For complicated SLE and positive effect on hypertension and preeclampsia	Contraindicated for fetal bleeding risk and postpartum bleeding and premature closure of ductus arteriosus	Probably as non-selective COX-inhibitors	Maternal: obstetric complications (gestational diabetes, hypertension, sodium retention, edema, premature rupture of membranes and osteoporosis) Child: hypercortisolism
Risk/benefit ratio [a]	Negative	Positive	Neutral–Negative (third trimester)	Negative because of unknown data	Neutral–Positive depending on disease
FDA category [b]	C D (3rd trimester)	—	B–D (third trimester)	C	B (prednisone/hydrocortisone) C (dexamethasone/betamethasone)
Breastfeeding [c]	Unsafe	With caution	Usually compatible	No reports of use	Compatible up to dose 20 mg/day

[a] Positive, disease is worse than the drug; neutral, always better to stop the drug if possible; negative, drug is always worse than the disease.
[b] FDA category: A, no foetal risk in controlled studies; B, no risk in animals, no controlled human studies; or abnormalities in animal studies but not in controlled human studies; C, studies show teratogenic or embryocidal effects in animals, but no controlled human studies; or no studies are available in either human or animals; D, positive evidence for foetal abnormalities but potential benefits may outweigh potential risks; X, contra-indicated.
[c] According to the Micromedex and 'Farmacotherpeutisch Kompas' advice (13, 14).

Table 1.2.2 Use of conventional DMARDs in pregnancy

	Hydroxy-chloroquine	Sulfasalazine	Gold	D -Penicillamine
Fertility	No effect	Women: no effect Men: reversible infertility	No effect	Unknown
Teratogenicity	Probably not in average dose (< 6.5 mg/kg body weight)	No	Probably not (little data)	Definite: physical defects, tissue abnormalities
Late pregnancy	No problems	No problems	Little data	Connective tissue abnormalities (cutis laxa)
Risk/benefit ratio [a]	Positive in SLE	Positive	Neutral	Negative
FDA category [b]	C (in high doses)	B	C	D
Breastfeeding [c]	Use with caution	Use with caution	Use with caution	No reports of use

[a] Positive, disease is worse than the drug; neutral, always better to stop the drug if possible; negative, drug is always worse than the disease.
[b] FDA category: A, no foetal risk in controlled studies; B, no risk in animals, no controlled human studies; or abnormalities in animal studies but not in controlled human studies; C, studies show teratogenic or embryocidal effects in animals, but no controlled human studies; or no studies are available in either human or animals; D, positive evidence for foetal abnormalities but potential benefits may outweigh potential risks; X, contra-indicated.
[c] According to the Micromedex and 'Farmacotherpeutisch Kompas' advice (13, 14).

Table 1.2.3 Use of cytotoxic medications in pregnancy

	Methotrexate	Azathioprine	Mycophenolate Mofetil	Cyclophosphamide
Fertility	Wimen: no effect Men: oligospermia, reversible sterility, discontinue 3 months before conception	Women/ Men: Possibly no effect	--	Definite adverse effect Women: Infertility: increased risk with high cumulative doses and age >31 years Men: decrease fertility (not reversible)
Teratogenicity	Definite: ossification and neural tube defects and is abortifacient	Possibly not	Possibly; animal studies indicate teratogenicity, human cases reports showed multiple malformations	Definite: facial cleft, limb defects, craniofacial dysmorphism
Late pregnancy	Growth retardation and myelosuppression	Variety of adverse effects; foetal immunosuppression	--	Myelotoxicity and growth retardation
Risk/benefit ratio [a]	Negative	Neutral–Positive depending on disease	Negative	Negative in first trimester Neutral–Positive in second half of pregnancy depending on disease
FDA category [b]	X (high doses)	D	C	D
Breastfeeding [c]	Contra-indicated	No reports of use	Contra-indicated	Contra-indicated

[a] Positive, disease is worse than the drug; neutral, always better to stop the drug if possible; negative, drug is always worse than the disease.
[b] FDA category: A, no foetal risk in controlled studies; B, no risk in animals, no controlled human studies; or abnormalities in animal studies but not in controlled human studies; C, studies show teratogenic or embryocidal effects in animals, but no controlled human studies; or no studies are available in either human or animals; D, positive evidence for foetal abnormalities but potential benefits may outweigh potential risks; X, contra-indicated.
[c] According to the Micromedex and 'Farmacotherpeutisch Kompas' advice (13, 14).

Table 1.2.4 Use of new antirheumatic drugs in pregnancy

	Cyclosporine A	Leflunomide	TNF-alfa blockade
Fertility	Women/Men: No effect	Not known	Not known: may even facilitate ovulation induction
Teratogenicity	Probably not	Definite in animals; human not known	Possibly not, no teratogenicity found in animal studies
Late pregnancy	Growth retardation Prematurity	Not known	Not known
Risk/benefit ratio [a]	Negative–Neutral depending on disease	Negative	Possibly Neutral–Positive
FDA category [b]	C	X	B (etanercept) [c] B (infliximab) B (adalimumab)
Breastfeeding [d]	Contra-indicated	Contra-indicated	No data

[a] Positive, disease is worse than the drug; neutral, always better to stop the drug if possible; negative; drug is always worse than the disease.
[b] FDA category: A, no foetal risk in controlled studies; B, no risk in animals, no controlled human studies; or abnormalities in animal studies but not in controlled human studies; C, studies show teratogenic or embryocidal effects in animals, but no controlled human studies; or no studies are available in either human or animals; D, positive evidence for foetal abnormalities but potential benefits may outweigh potential risks; X, contra-indicated.
[c] High doses of these drugs have been tested in animals, without leading to teratogenicity, controlled human studies have not been done.
[d] According to the Micromedex and 'Farmacotherpeutisch Kompas' advice (13, 14).

Table 1.2.5 Use of miscellaneous antirheumatic drugs in pregnancy

	Anakinra	Rituximab	Paracetamol	Intravenous immunoglobulins	Colchicine
Fertility	Not known	Not known	No effect	Probably no effect	Probably no effect
Teratogenicity	Possibly not; No malformations in animals	Not known	No	No effect	Probably not
Late pregnancy	Not known	Cytopaenia in newborns	No problems	No problems	No problems
Risk/benefit ratio [a]	Possibly Neutral	Negative	Neutral–Positive	Neutral–Positive depending on disease	Positive depending on disease
FDA category [b]	B	C	B	C	C
Breastfeeding [c]	Contra-indicated	Contra-indicated	Compatible	Unknown, probably compatible	Compatible

[a] Positive, disease is worse than the drug; neutral, always better to stop the drug if possible; negative, drug is always worse than the disease.
[b] FDA category: A, no foetal risk in controlled studies; B, no risk in animals, no controlled human studies; or abnormalities in animal studies but not in controlled human studies; C, studies show teratogenic or embryocidal effects in animals, but no controlled human studies; or no studies are available in either human or animals; D, positive evidence for foetal abnormalities but potential benefits may outweigh potential risks; X, contra-indicated.
[c] According to the Micromedex and 'Farmacotherpeutisch Kompas' advice (13, 14).

Table 1.2.6 Summary of recommendations

1. Aspirin Low dose, ≤ 80 mg/day of aspirin can be used safely throughout pregnancy without evident risk of foetal malformations, clotting problems in either mother or child, or abnormality in foetal renal function or premature closure of the ductus arteriosus. Cautious use of low dose of aspirin during breastfeeding will not adversely affect the child. High, anti-inflammatory doses of aspirin should be avoided during all stages of pregnancy, in particular in the last trimester.
2. NSAIDs can be safely used in the first and second trimester of pregnancy, if necessary to control maternal disease. Recently, a higher risk on miscarriages was found in women using NSAIDs in a population based study, however the study's retrospective design may limit the reliability of the results (15, 16). There is no consistent reported risk of foetal malformation. Indomethacin may induce oligohydramnios as they can inhibit fetal renal urinary output. NSAIDs should be stopped in the last 6–8 weeks of pregnancy because of the prostaglandin inhibiting effects on mother and child potentially leading to a delayed labour, renal, and vascular effects on the child and perinatal bleeding in mother and child. NSAIDs with a short half-life and inactive metabolites, such as ibuprofen, flurbiprofen, and diclofenac may be used more safely, in particular during breastfeeding (17). Since only trace amounts of NSAIDs will appear in breast milk, breastfeeding is recommended to be compatible with NSAID use. There is a lack of data on the new COX-2 selective inhibitors in pregnancy and their use in pregnant or lactating women should be avoided.
3. Corticosteroids Low dose of prednisone is considered safe in pregnancy for both mother and child. High doses (1–2 mg/kg/day) should be avoided during the first trimester because of the possible risk of oral cleft in the child. Prednisone and hydrocortisone are inactivated to cortisone in the placenta. The fluorinated corticosteroids, dexamethasone, and betamethasone, will pass the placenta and are only used to treat the foetus, if necessary. The lowest possible dose of prednisone needed to control the maternal disease should be used to minimize the risk for gestational diabetes and hypertension. Calcium and vitamin D supplementation for prevention of osteopaenia is advisable. Emergency surgery, caesarean section and prolonged labour are indications for 'stress doses' of corticosteroids. Breastfeeding is compatible with prednisone doses up to 20 mg/day, 3–4 h before actual breastfeeding.
4. Antimalarials The favourable effects of hydroxychloroquine in preventing flares in SLE outweigh the potential risk for the unborn child. No adverse effects on the child have been found in the doses of hydroxychloroquine of 200–400 mg/day commonly used to treat the rheumatic diseases. Breastfeeding should be undertaken cautiously because of the long elimination half-life and the risk of accumulation.
5. Sulfasalazine can be safely used prior to and during all stages of pregnancy. Men with a wish to produce offspring should stop the drug because of its adverse effect on spermatozoa. This effect is reversible after discontinuation of the drug. Breastfeeding is compatible with sulfasalazine treatment though should be advised with caution because of the rare event that the mother is a slow acetylator.
6. Gold Common practice is to continue gold treatment until pregnancy is recognized and then stop the treatment. There seems no risk of foetal malformation, although this is based on very limited information (18). Gold therapy is compatible with breastfeeding, but it seems most prudent to avoid nursing because of the possible toxic effect on the infant
7. Penicillamine should be stopped in women who wish to become pregnant because of the serious risk of congenital malformations and the far better alternatives available for the treatment of the rheumatic diseases during pregnancy

Table 1.2.6 (continued) Summary of recommendations

8. Methotrexate is contra-indicated in the treatment of the rheumatic diseases during pregnancy. The rate of abortion and congenital abnormalities is significantly increased particularly with exposure during the first trimester. Strict contraception is needed when a patient is on methotrexate. Fertility appears not to be adversely effected by prior methotrexate use. Women and men who wish to conceive have to stop methotrexate treatment 4–6 months prior to conception. Continuation of folate supplementation is advised to prevent adverse outcome due to folic deficiency. Breastfeeding is contra-indicated because of excretion of methotrexate in breast milk.
9. Azathioprine Women with severe rheumatic diseases that are otherwise hard to control may use azathioprine during pregnancy. No apparent congenital malformations are known with doses of azathioprine up to approximately 2 mg/kg/day. Exposure to azathioprine throughout pregnancy may lead to immunosuppression and low blood cell counts in the neonate. Strict adjustment of the azathioprine dosage to maintain normal maternal blood cell counts may prevent neonatal abnormalities. Breastfeeding is not recommended.
10. Cyclophosphamide treatment leads to infertility in particular after cumulative doses and in patients aged over 30 years. Cryopreservation of semen and oocytes can help to preserve the changes of future offspring. Oral contraception is advised to possibly protect ovarian function during cyclophosphamide treatment. Adequate contraception is anyhow necessary because of the teratogenicity of the drug. Exposure to cyclophosphamide during the first trimester of pregnancy leads to congenital malformation and should be avoided. Treatment with cyclophosphamide during the second half of pregnancy may be considered in case of severe, life threatening disease of the mother. Breastfeeding is contra-indicated
11. Cyclosporine A is apparently not associated with congenital malformation, but can cause prematurity and intra-uterine growth retardation. Long-term effect of intrauterine exposure is not known. It is generally advised not to use cyclosporine during pregnancy unless the severity of the maternal disease urges to do so. Breastfeeding should be discouraged in women using cyclosporine.
12. Leflunomide is contra-indicated during pregnancy and safe contraception during its use is warranted. Due to the long half-life and slow elimination time, leflunomide should be washed out in both male and female patients who wish to conceive. The wash-out procedure consists of 8 g of cholestyramine three times daily for 11 days, followed by two separate tests to verify whether the drug has been eliminated. If blood levels remain high the procedure has to be repeated. Without a wash-out the levels of leflunomide may stay too high for pregnancy for up to 2 years. Breastfeeding is considered unsafe
13. Biologicals Little information on use of any of the biologicals (etanercept, infliximab, adalimumab, anakinra) during human pregnancy has been published until now. Based on the minimal or lack of data on human pregnancy the teratogenic risk is undetermined. Until now, use is not recommended during pregnancy and lactation. At least 5 months before conception and/or before breastfeeding will be given, the use of infliximab and adalimumab should be stopped
14. Colchicine is considered safe during pregnancy as well as during breastfeeding. Fertility is probably not decreased with the possible exception of men taking colchicine because of Behçet's disease.

GENERAL CONSIDERATIONS OF ANTIRHEUMATIC TREATMENT DURING PREGNANCY

Treatment of (rheumatoid) arthritis

The majority of the patients with rheumatoid arthritis (RA) improve during pregnancy and in most cases the antirheumatic treatment can be stopped as soon as the woman becomes pregnant. The same applies for arthritis symptoms in other rheumatic diseases, such as juvenile idiopathic arthritis and peripheral arthritis in spondyloarthropathies (19). Cytotoxic drugs have to be stopped before conception, because of the teratogenic effect on the foetus. This holds for both male and female patients. In case of an arthritis flare during pregnancy, the symptoms can often be safely controlled with intra-articular steroids, non-steroidal anti-inflammatory drugs (NSAIDs) or, if necessary, low dose oral prednisone.

Treatment of systemic lupus erythematosus (SLE) and other systemic diseases during pregnancy

SLE and other systemic rheumatic diseases should be planned when the disease is quiescent. Similar to RA treatment with cytotoxic drugs should be stopped several months before conception because of the teratogenic effect on the foetus. In SLE, there is a possible risk of a flare during pregnancy and treatment may be necessary. Both the disease and the treatment may harm mother and child. It can be difficult to interpret whether an adverse outcome of mother or child is due to the disease manifestations or to the drug treatment (see also previous chapter). A rheumatologist and an obstetrician with expertise in treating these kinds of patient should frequently see every mother with SLE throughout pregnancy (20).

Aspirin

Aspirin is the oldest and most commonly used NSAID and is the most often researched NSAID during pregnancy. In high doses it has adverse effects on both mother and child, whereas in low doses it is safe.

Effects on the mother

High doses of aspirin in the third trimester inhibit uterine contractility and prolong labour and gestation. Labour may be complicated by pre- and post-partum haemorrhage. Low-dose aspirin appears to be safe and is even of benefit in patients at risk for pregnancy-induced hypertension and preeclampsia. Low-dose aspirin is prescribed in patients with SLE and antiphospholipid syndrome at risk for recurrent foetal loss.

Effects on the child

There are several conflicting reports on teratogenicity of high doses of aspirin in the first trimester of pregnancy in animals as well in humans (4, 5, 7, 13, 21, 22). There is no evident teratogenic effect of low dose aspirin. High doses of aspirin in the perinatal period lead to clotting defects in mother and child through irreversible binding to platelet cyclooxygenase enzymes. The mother can experience increased blood loss during delivery. An increased incidence of intra-cerebral haemorrhage in the newborns exposed to aspirin in the last weeks before delivery has been reported (4, 5, 21). This problem has been found in newborns exposed to a total of 325-650 mg/day within 1 week prior to delivery. Nowadays, more than 10 000 pregnancies have been exposed to 60–80 mg/day of aspirin that has been shown to have a positive effect on interleukin-3, a cytokine that affects pregnancy and foetal development. No adverse effect of low-dose aspirin of 80 mg/day or lesser on clotting ability, renal function, or ductus arteriosus in the newborn has been demonstrated. Doses up to 80 mg/day of aspirin can be used safely throughout pregnancy.

Breastfeeding

Aspirin is found in breast milk up to approximately 20 percent of the amount ingested by the mother. Peak salicylate concentrations in milk occur about 2 h after peak serum levels in the mother. In case of high anti-inflammatory doses of aspirin ingested by the mother the child is potentially at risk of developing salicylate intoxication and bleeding problems during lactation. It is therefore recommended that aspirin can be used during breastfeeding, but with caution and in low doses.

NSAIDs

The most commonly used antirheumatic drugs during pregnancy are NSAIDs. They readily cross the placenta and block prostaglandin synthesis in a variety of foetal tissues. Because of the prostaglandin blocking effect NSAIDs have been used for pregnancy related indications such as premature labour, polyhydramnion, and pregnancy-induced hypertension.

Far less information is available on the relatively new NSAIDs and pregnancy than on aspirin and pregnancy. The risk of NSAIDs during pregnancy is best researched for indomethacin, sulindac, naproxen, ibuprofen, ketoprofen, and diclofenac (8, 21), mostly because of their ability to suppress premature labour. The potential adverse effects of NSAIDs in pregnancy have been described most extensively for indomethacin (23), though these adverse effects have also been reported to a certain extent for the other NSAIDs. The potential side effects of NSAIDs in pregnancy are linked to their ability to inhibit prostaglandin

synthesis. Dose, duration, and period of gestation are important determinants of the extent of these effects.

Effects on the mother

There is some evidence that women who have problems in conceiving should stop NSAIDs when attempting to become pregnant because of the findings in a variety of animal models indicating that prostaglandin inhibitors block blastocyst implantation (7, 24). Ingestion of NSAIDs near term will significantly delay and prolong labour. There is a serious risk of increased maternal blood loss at delivery. If NSAIDs are stopped at least 1 month before the expected delivery these problems can be avoided.

Effects on the child

NSAIDs can cross the placenta and have been detected in foetal tissues (25). A recent study reported a higher risk on miscarriages in healthy women using NSAIDs compared to non using women, however the cohort's retrospective design limits the reliability of its results (15). A recent study reported no increased risk for any congenital malformation with NSAID use in early pregnancy. But when controlled for maternal age, parity, and smoking habits, in a small number of women there was an increased risk for cardiac defects and of oral facial clefts (26). The general advice from the European Medicines Agency (27) regarding NSAID use during pregnancy is not to give NSAIDs in the first and second trimester of pregnancy, and should not be given unless clearly necessary. If NSAIDs are used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and durations of treatment as short as possible to control maternal disease (4,7,13, 21,28,29).

NSAIDs administered in the last trimester of pregnancy can cause premature constriction of the ductus arteriosus, pulmonary hypertension, impaired renal function, a reduction in foetal urine output, and oligohydramnion. These effects are reversible if the NSAID is stopped (30). Due to the effect on platelets, NSAIDs administered in the perinatal period can cause intracerebral haemorrhage in the child. Discontinuation of NSAIDs 6–8 weeks before delivery is considered safe. Theoretically the effects of the new COX-2 selective inhibitors on the duration of labour and clotting function should be less compared to that of the non-selective COX inhibitors. The effects on the foetal vasculature and renal function are, however, the same as for the non-selective COX inhibitors and for the benefit of the child discontinuation of any NSAID 6–8 weeks prior to the expected delivery is warranted. Because of the lack of data on these new drugs, the COX-2 selective inhibitors are better avoided in pregnant women altogether.

Breastfeeding

Because breast milk has a pH of 6.9-7.6, weak acids are ionized so drugs such as NSAIDs are not readily distributed into the breast milk. Trace amounts of naproxen, piroxicam, ibuprofen, and diclofenac have been reported in breast milk (7, 13). NSAID use is considered compatible with breastfeeding, though some NSAIDs (indomethacin, sulindac) circulate enterohepatically and should therefore be avoided. NSAIDs are contraindicated in the jaundiced neonate because of their property to displace bilirubin and by that increasing the risk of kernicterus.

Paracetamol (acetaminophen)

Paracetamol is the most widely used analgesic during pregnancy. Therapeutic doses are safely used during pregnancy without apparent adverse affects on mother or child. The drug is distributed in breast milk in amount ranging from approximately 1-2 percent of the maternal dose (13). The usage of paracetamol during pregnancy and breastfeeding is considered safe (17).

Since paracetamol is only a moderate painkiller without anti-inflammatory properties the drug is for most pregnant women with an active rheumatic disease often not sufficient to treat the maternal disease.

Glucocorticoids

Glucocorticoid therapy is the mainstay treatment for SLE during pregnancy and is also a popular choice in joint diseases when NSAIDs are insufficient to control the arthritis. Many potentially serious adverse effects of high dose corticosteroids in pregnancy have been reported for both mother and child, although one should realize that active SLE per se, for which the corticosteroids are prescribed, may equally well be the culprit of the observed adverse effects (see previous chapter). The non-fluorinated steroid preparations such as prednisone, prednisolone, and methylprednisolone are the drugs of choice to treat active maternal disease. They are metabolized by placental 11-hydroxygenase, and the foetus is exposed to only 10 percent of the maternal dose. If the foetus has to be treated, for example, in case of immature lungs or foetal carditis due to anti-SSA/SSB antibodies, fluorinated corticosteroids such as dexamethasone and betamethasone are preferred because they are less well metabolized in the placenta and higher doses are available to the foetus.

Effects on the mother

All the well-known side effects of corticosteroids may be more marked when used during pregnancy. Pregnancy is associated with hypertension, hyperglycaemia, striae, osteopaenia, and immunosuppression, the risk of these

conditions will be enhanced by corticosteroid use. Premature rupture of the membranes has been observed during steroid use, although the causative role of corticosteroids cannot be separated from the possible role of a flare of the underlying rheumatic disease.

Effects on the child

Exposure to corticosteroids during pregnancy has been studied in various animal species resulting in reports on deleterious effects on the offspring, including cleft palate. In the human series, no evidence was found for congenital abnormalities due to corticosteroid use in pregnancy (3-5,7,8,21). However, in a meta-analysis of epidemiological studies an increased risk for oral clefts after exposure to corticosteroids during the first trimester was found (31). There are some case reports on masculinization of female infants, growth restriction, neonatal cataract, and adrenal suppression in children exposed to high doses of corticosteroid before birth (8).

Breastfeeding

The dose of corticosteroids found in breast milk is negligible when the mother receives prednisone 20 mg or less. Abstaining from breastfeeding in the 3–4 h after the mother has taken her medication can minimize the dose received by the infant (13).

Chloroquine and hydroxychloroquine

Most observations of the effects of antimalarials during pregnancy have been made in women taking malaria prophylaxis with chloroquine. Hydroxychloroquine is widely used in the treatment of rheumatic diseases. The use of antimalarials in RA is relatively easy to avoid but it is a mainstay of treatment in many patients with SLE and can help to prevent flares during pregnancy.

Effects on the mother

Knowledge is now accumulating about hydroxychloroquine exposure in pregnant SLE patients (3, 7, 8, 32, 33). A double blind, placebo-controlled trial of hydroxychloroquine in lupus pregnancy was published recently (34). Discontinuation of hydroxychloroquine may precipitate a flare of the SLE with harmful consequences for mother and child. For both it appears to be better to continue the hydroxychloroquine therapy during pregnancy since women on hydroxychloroquine experienced less disease activity and better neonatal outcome than women who stopped hydroxychloroquine (34).

Effects on the child

Chloroquine crosses the placenta and accumulates preferentially in melanin-containing structures in the foetal uveal tract and inner ear. In animal models, abnormalities of the foetal eye have been reported as well as in some infants who had been exposed to higher than the daily recommended dose of chloroquine throughout pregnancy (3, 4, 8). No increase in the rate of congenital abnormalities, prematurity, or foetal growth restriction was found in a cohort study of 169 pregnancies of women exposed to chloroquine 300 mg/week for malaria prophylaxis as compared to a four times larger control group.

In the last few years, it has become apparent that hydroxychloroquine used in doses of 200-400 mg/day to prevent SLE flare carries no risk of congenital malformation or adverse neonatal outcome (32-36). Discontinuation of hydroxychloroquine in controlled SLE runs the risk of flares and consequently harms the child. It is therefore advised not to stop hydroxychloroquine during gestation. Moreover, due to the very long elimination time of hydroxychloroquine, the foetus will still be exposed to the drug long after the mother has stopped taking the drug.

Breastfeeding

Low concentrations of hydroxychloroquine are found in breast milk. Although hydroxychloroquine is considered compatible with breastfeeding, the slow elimination rate and the potential accumulation of a toxic amount of hydroxychloroquine in the infant, breastfeeding should be undertaken with caution (13, 14).

Sulfasalazine

Sulfasalazine is an effective treatment for RA in a daily dose up to 3 g/day. About 30 percent of the drug is absorbed in the small intestine; the other 70 percent passes into the colon where it is cleaved into 5-aminosalicylic acid and sulfapyridine. Sulfasalazine and sulfapyridine cross the placenta and foetal blood concentrations will come close to maternal concentrations. The 5-amino salicylic acid has very limited placental transfer. There are data available for the safe use of sulfasalazine in over 2000 pregnancies of women with inflammatory bowel disease (37). There is no reason to assume that the safety of sulfasalazine in pregnant women with arthritis would prove to be different from its safety in pregnant women with inflammatory bowel disease.

Effects on the mother

Sulfasalazine does not adversely affect fertility in women and can therefore safely be prescribed in women who wish to become pregnant. If the arthritis is not adequately controlled after conception the drug can be continued during gestation without problems. In contrast to the situation in women, men have decreased fertility with sulfasalazine due to oligospermia, impaired sperm motility, and an increase in abnormal spermatozoa (3, 7, 37). The decreased fertility has been shown reversible when treatment with the drug is discontinued.

Effects on the child

The wealth of data regarding pregnancy and sulfasalazine use in inflammatory bowel disease shows no increased rate of congenital malformation, prematurity or low gestational weight (4, 7, 37). Theoretically, sulfasalazine may increase the risk of kernicterus when used near term because of its bilirubin-displacing ability. Severe neonatal jaundice, however, has never been reported in connection with maternal sulfasalazine use.

Sulfasalazine is thought to have an effect on folate metabolism and may cause folate deficiency. Folate supplementation would seem prudent both prior to and during pregnancy in women taking sulfasalazine (7, 37). Nowadays, folate supplementation is recommended for all women considering pregnancy.

Breastfeeding

Sulfasalazine concentrations in breast milk may reach 40-50 percent of the concentration found in the mother. Sulfasalazine use is considered compatible with breastfeeding. Substantial adverse effects have been published in some infants, probably because of high drug concentrations in the mother due to slow acetylation. It has been advised to use sulfasalazine with caution during breastfeeding (13).

Gold

Intramuscular gold has been used extensively to treat RA in the past, although the data on its use during pregnancy are very limited (3-5, 7, 8). Gold is not one of the first choice drugs for RA anymore, but it may still be an alternative drug in the treatment of arthritis of women or men who choose to have offspring (18).

Effects on the mother

Rheumatologists often advise their patients to continue gold therapy until pregnancy is recognized and then stop the injections. One approach in long-term gold treatment is to give monthly injections on the first day of menses. Gold does not seem to impair fertility in either women or men. Data on gold

therapy during pregnancy, albeit scarce, does not reveal adverse effects on the mother. Generally, the drug can be stopped during gestation because of the favourable effect of pregnancy itself on the arthritis.

Effects on the child

The limited data on possible adverse effects of gold treatment on the foetus are conflicting and uncontrolled. Gold compounds cross the placenta and are found in foetal tissues. In over 100 reports on gold therapy during pregnancy, no congenital malformations have been observed (8, 18). One case of multiple foetal malformations in a mother who received aurothiomalate has been reported, though a causal relationship between the malformations and the drug was disputed. To date, little is known about the effect of oral gold (auranofin) on the human foetus, but no abnormalities occurred in the few pregnancy reported during oral gold treatment.

Breastfeeding

Gold is excreted in human breast milk in significant amounts. There have been reports of skin rash, nephritis, hepatitis, and blood dyscrasias in children of mothers treated with gold injections while nursing their infants (7, 13). Although gold is usually considered compatible with breastfeeding, caution is recommended because of the long retention of gold in the body and the potential toxic effects in the infant.

Penicillamine

Penicillamine is used in the treatment of RA and scleroderma. Its popularity is, however, waning because of a wider choice of more effective treatments, in particular for RA. The possible risks of this drug during pregnancy definitely outweigh the benefits (4, 7, 8). In contrast, the use of penicillamine in Wilson's disease is crucial for a successful outcome of pregnancy in this disease. Therefore, knowledge about the teratogenicity of penicillamine mainly comes from the experience in the treatment of pregnant women with Wilson's disease.

Effects on the child

In animals as well as in humans a variety of connective tissue abnormalities have been found in the neonates, including cutis laxa, physical defects such as wide nasal bridge, low set ears, flattened face, club feet, inguinal hernia, congenital hip dislocation, and ventricular septal defects have been reported (13). There are also reports on favourable outcomes of pregnancy after prenatal exposure to penicillamine, which make its use acceptable for women with Wilson's disease. The risks of penicillamine during pregnancy are not acceptable for women with a rheumatic disease, for them the risk/benefit ratio is much too high.

Breastfeeding

There are no reports on breastfeeding and mothers on penicillamine should not nurse their infants (13).

Methotrexate

Methotrexate (MTX) is the mainstay drug in the treatment of RA and is also frequently used in many other rheumatic diseases. It is the drug of choice in early RA and patients of child-bearing age will often be on MTX treatment (38).

The experience with MTX during pregnancy mainly comes from women treated with high dose MTX often in combination with other cytotoxic drugs, and from women who have taken the drug to terminate pregnancy, for example, because of an ectopic pregnancy. Also, some very small series of pregnancies exposed to low-dose MTX have been published (3-5, 7, 8). An extensive review on the effects of MTX on pregnancy, fertility, and lactation was published in 1999 (39).

Effects on the mother

MTX does not impair fertility, even in high doses. Oligospermia has been reported, though further studies showed no long-term effects on ovarian or testicular function (39). The presence of MTX in liver tissue has been reported up to 116 days after MTX exposure. The duration of spermatogenesis is approximately 74 days. Consequently, a period of 6 months off MTX therapy seems safe for men before attempting conception.

MTX is a strong abortifacient and has been used for that purpose. It can be expected that exposure to low dose MTX in early pregnancy will lead to an increased abortion rate. In small series of patients exposed to low dose MTX in the first trimester there was indeed an increase in the abortion rate (3-5, 7, 8, 39). Because of the embryo toxicity, women of child bearing age on MTX must use adequate contraception. Women who wish to conceive must stop MTX at least 3-6 months prior to conception and folate supplementation is best continued to avoid folic depletion.

Effects on the child

MTX treatment is associated with increased risk of congenital malformation. Women who wish to continue pregnancy when exposed to MTX in the first trimester have a 20-30 percent chance of an abnormal child (39). The MTX-induced congenital defects are similar to those produced by aminopterin, another folic antagonist. The defects to be expected with severe folate deficiency include neural tube defects resulting in anencephaly, hydrocephaly, meningomyelocele, and ossification defects resulting in craniofacial and limb

defects. Also an increase nuchal translucency was reported after use of low dose MTX, therefore after exposure of the mother to low dose MTX during first trimester, a structural ultrasound at 20 weeks of gestation is strongly advised (40).

Developmental delay has also been reported (41). The most vulnerable period for the development of foetal malformations is 6-8 weeks of gestation (39). Women who wish to continue pregnancy having had exposure during the first trimester of pregnancy should be offered treatment with folinic acid in order to minimize MTX effects on the foetus. MTX exposure in the second and third trimesters of pregnancy is associated with growth retardation and myelosuppression (3, 7, 39, 41).

Breastfeeding

MTX is excreted in breast milk in low concentrations and may accumulate in neonatal tissues. Breastfeeding is contra-indicated because of potentially severe problems in the neonatal infant (7, 13).

Azathioprine

Experience of azathioprine exposure during pregnancy is derived mainly from the treatment of transplantation patients complemented by some reports of treatment in SLE and inflammatory bowel disease (3,4,6-8,13). Azathioprine crosses the placenta, but the foetal liver lacks the enzyme inosate pyrophophorylase and is therefore unable to convert azathioprine to its active and more toxic metabolite, 6-mercaptopurine. This foetal enzyme deficiency theoretically protects the foetus from any teratogenic effect of azathioprine in early pregnancy.

Effects on the mother

There seems to be no adverse effect on fertility and no increase in the abortion rate in women exposed to azathioprine. This drug is used to preserve allografts or to control systemic autoimmune disease. The choice to continue treatment during pregnancy is dependent on the need to treat maternal disease.

Effects on the child

No predominant or specific pattern of malformation has been identified during 40 years of experience. There are some reports of congenital malformations, but a causal relationship with azathioprine is hard to prove. Women with abnormal babies took significantly higher doses of azathioprine than women with normal babies, suggesting some risk for congenital deformities with increasing doses of azathioprine (3,7,8,13). Exposure throughout pregnancy has been associated with a variety of adverse effects including thymic atrophy,

intra-uterine growth retardation, foetal immunosuppression, foetal pancytopaenia, and chromosomal aberrations. Often, the mother received several drugs and it was not possible to blame either one of the drugs or the underlying disease for the adverse effects on the child. It has been suggested that adjustment of the azathioprine dosage to maintain normal maternal blood cell counts might prevent neonatal cytopaenias.

Breastfeeding

Low concentrations of azathioprine have been found in breast milk. Breastfeeding is not recommended because of the potential adverse effects for the child.

Cyclophosphamide

Cyclophosphamide is an alkylating agent only used in rheumatology to treat severe, potentially life threatening disease. The observations of cyclophosphamide exposure during pregnancy are predominantly in women with malignancies (3-8, 13).

Effects on the mother

The adverse effect of cyclophosphamide on fertility in both men and women is well recognized. The key risk factors for ovarian failure after cyclophosphamide exposure are age 31 years or more, total doses of more than 10 g and treatment greater than 15 pulse cycles (5, 7). Men who start cyclophosphamide treatment have the option of cryopreservation of their semen. Cryopreservation of oocytes is much more complicated and often not possible due to the underlying disease. Inhibition of ovulation, for example, by oral contraceptives is believed to protect ovarian follicle viability. Adequate contraception during cyclophosphamide therapy is necessary because of the teratogenic effects of the drug.

Effects on the child

Both in animals and in humans congenital malformations and changes in the foetal genome have been found when exposed to cyclophosphamide in the first trimester of pregnancy, although normal newborns have also been reported. Abnormalities include facial clefts, limb reduction defects, and craniofacial dysmorphisms. Exposure of the foetus to cyclophosphamide in second half of pregnancy may lead to myelotoxicity of the foetus and growth retardation. It is not established whether the latter adverse effect is due to the underlying disease or to the drug. The risk/benefit ratio may permit cyclophosphamide treatment in the second half of pregnancy in case of severe systemic disease of the mother.

Breastfeeding

Cyclophosphamide has been found in substantial amounts in human breast milk. Breastfeeding is therefore unsafe for the newborn child.

Cyclosporine A

More than 600 pregnancies exposed to cyclosporine have been reported, mainly in transplant recipients (3,4,7,8,13,42,43).

Effects on the mother

There is no indication that cyclosporine impairs human fertility. In case of rheumatoid arthritis the drug can be stopped before pregnancy and, if necessary, replaced by an alternative drug more compatible with pregnancy. When the woman is treated because of systemic disease the possible benefits of the treatment have to be weighted against the possible harm the drug can caused during pregnancy. Renal impairment and hypertension are of particular concern during pregnancy.

Effects on the child

Cyclosporine crosses the placenta and foetal levels may reach between 37 and 64 percent of the maternal plasma levels. It has been shown to have embryotoxic and fetotoxic effects in animals, but only at supra-therapeutic dose levels. In women receiving an average dose of cyclosporine of 5 mg/kg/day during pregnancy no increased rate of congenital malformations was seen. The major problems were prematurity and low birth weight in approximately 50 percent of the pregnancies. It is difficult to estimate what the independent contribution of cyclosporine treatment to these pregnancy complications is, since concomitant medication or the underlying disease may cause these problems as well. The effects of foetal exposure to cyclosporine in the long term are not known.

Breastfeeding

Cyclosporine is excreted in human breast milk, therefore breastfeeding should be avoided.

Leflunomide

Leflunomide is a new drug amongst the medications to treat arthritis. There are no data published on leflunomide exposure during human pregnancy (3,7,8,12, 44,45). Animal data indicate that exposure to leflunonide during pregnancy has teratogenic and foetotoxic effects at normal therapeutic levels. The malformations observed include anophthalmia, micro-ophthalmia, and hydrocephalus. In addition, embryolethality and reduced foetal weight were

noted in animals. Due to the long half-life and slow elimination time, leflunomide should be washed out in both male and female patients who wish to conceive (Table 1.2.6). Distribution of leflunomide into breast milk is unknown.

Biologicals

TNF-α inhibition is becoming increasingly popular in the treatment of various rheumatic diseases, in particular, rheumatoid arthritis. There are some reports on human pregnancies exposed to TNF-α inhibitors until now (3,7,8,11,13), however, reports on other biologicals inhibiting IL-1, or B-cel depleting therapies are scarce (3).

Etanercept

Soluble TNF-α receptor fusion protein that crosses the placenta in mice, but does not impair foetal development (11). Studies in rats and rabbits did not find teratogenicity or fetotoxicity with doses by far exceeding the therapeutic human doses. Because of insufficient data in humans it is advised to abstain from pregnancy while on etanercept treatment. In previous reports few fetal and neonatal complications were reported after anti-TNF-α use. The association with VATER in a child born to a woman with psoriatic arthritis and treated with etanercept throughout her pregnancy is alarming and may be attributable to TNF-α inhibition (46). Etanercept levels were measured in a RA patient and showed that it was secreated in human breast milk. Because of the potential for serious adverse effects in nursing infants breastfeeding should be discouraged during etanercept treatment (3).

Infliximab

In mice, no embryo- or foetotoxicity was noted. Only one case of exposure to infliximab in early pregnancy in a woman with inflammatory bowel disease and an adverse outcome (prematurity and death) was reported (47). The patient had active disease at time of conception that also may explain the adverse outcome of the pregnancy. Initial observations in a series of human pregnancies exposed to infliximab in the first trimester did not show an increase in birth defects or adverse pregnancy outcomes (3, 8, 11). Since the safety of infliximab during pregnancy has not been sufficiently documented, safe contraception is recommended during its use. Either no infliximab was secreted in breast milk or the infliximab concentration was undetectable by standard assays. Since TNF-α antagonists and lactation have not been well studied, breastfeeding should probably be avoided while on TNF- α therapy (3).

Adalimumab

Adalimumab is a recombinant human IgG1 monoclonal antibody that binds to human TNF-α with high affinity. Until now only of 2 RA patients information has been reported about adalimumab and pregnancy outcome (11). No breastfeeding will be advised because of the lack of data.

Anakinra

Anakinra is a recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist, which has been used in the treatment of moderate-to-severe RA. There have not been any adequate or well-controlled studies in pregnant women, but reproductive studies on rats and rabbits at doses up to 100 times the human dose have not revealed evidence of impaired fertility or harm to the fetus. Because of the lack of data regarding use in humans, it should be used in pregnancy only if clearly needed. Since it is not known whether anakinra is secreted in human breast milk, it should be avoided during lactation (3).

Rituximab

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen on B-lymphocytes, which has been studied and used in the treatment of SLE and RA. There are only two case-reports of women treated with (high dose) rituximab for Non-Hodgkin's Lymphoma becoming pregnant during therapy (3). Their pregnancies were successful without maternal complications, but one child had transient granulocytopaenia and lymphopaenia at birth, while the other child was born premature at 35 weeks of gestational age. At this time it is advised to avoid rituximab therapy in pregnancy. Whether rituximab is excreted in breast milk is unknown, therefore it should be avoided during lactation.

Intravenous immunoglobulins

Intravenous immunoglobulins are sometimes used in specific autoimmune conditions such as antiphospholipid syndrome, myositis, and autoimmune thrombocytopaenia. Information regarding teratogenicity in animals is limited. In humans, immunoglobulins will cross the placenta after 32 weeks of pregnancy. No harmful effects to the foetus have been reported (10). Care has to be taken to prevent hepatitis virus transfer through the infusion. If necessary for the treatment of the mother, intravenous immunoglobulins may be administered during pregnancy without apparent adverse effect to the foetus. There seems to be no harm in breastfeeding during intravenous immunoglobulins therapy, because of transfer of protective immunoglobulins to the child.

Colchicine

Colchicine is mainly used for gout, which is very uncommon in women of child-bearing age. It is also used in conditions such as Behçet's disease.

Effects on the mother

In high doses, colchicine arrests mitosis through an inhibitory effect on microtubuli. Theoretically colchicine may induce infertility. In men an increased frequency of oligospermia and azoospermia has been found in patients with Behcet's disease but not in patients with Familial Mediterranean Fever (FMF) during treatment with colchicines (48). In women the fertility rate appears to remain normal when on colchicine. With colchicine treatment FMF patients seem to have even higher fertility and better pregnancy outcome than without treatment due to a better control of the disease.

Effects on the child

Colchicine has been found to be teratogenic in mice and transplacental passage has been described in humans (4, 13, 48). In humans treated with colchicine during pregnancy - mainly because of FMF - no increase in the rate of congenital malformations, miscarriages or stillbirths was seen. A slight increase in trisomy 21 was noted in the FMF patients using colchicine during pregnancy, though this was ascribed to a probably slight increased risk for this abnormality in FMF itself (48).

Breastfeeding

Colchicine is excreted in human milk reaching similar levels to that in the serum of the mother (13, 48). However, the estimated daily amount of colchicine ingested by the nursing infant was at least 10 times less than the therapeutic dose (per kilogram) given to the mother. Breastfeeding is considered safe for the child.

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2

METHODOLOGY

2.1

DESIGN OF THE PARA-STUDY

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The Netherlands

PARA-study

Pregnancy-induced Amelioration of Rheumatoid Arthritis

HEALTHY POPULATION

Thirty-two healthy pregnant women were recruited from a midwifery practice, Verloskunde Praktijk Voorburg (VPV), Voorburg, The Netherlands, between July 2002 and January 2004. At first visit women were < 13 weeks pregnant. These healthy women were visited at the same time points during pregnancy as women with rheumatoid arthritis (RA), postpartum, however, they were only visited at 6 and 12 weeks. Same assessments, except joint examination, and same laboratory tests were performed in healthy women and RA women.

PATIENT POPULATION

All rheumatologists working in the Netherlands were contacted by mail twice a year from the start in May, 2002, till May, 2008. They were asked to recruit patients with RA who had a wish to conceive or who were already pregnant (preferably in their first trimester). Patients were eligible for the study if they fulfilled the 1987 revised criteria of the American College of Rheumatology (ACR) for RA and had a good understanding of the Dutch language. During the study the patient's own rheumatologists provided patient care.

DATA COLLECTION

Patients were visited six or seven times at their home address. They were visited before conception (if possible), at each trimester (8-12 weeks of gestation, 18-22 weeks, and 28-32 weeks) and three times postpartum (4-6 weeks, 12 weeks and 26 weeks) (see Figure 2.1.1). The visit before conception took place if the woman had a wish to conceive, i.e. she and her partner did not use any contraceptives. If a woman did not conceive within a year after the first visit, another visit took place. Data collected before conception was classed as 'before pregnancy'. Medical and obstetrical history were taken at the first visit by interview. Erosions were ascertained from the patient's medical records. Pregnancy outcome was ascertained, only if complicated, from patient's medical records.

Figure 2.1.1: Study design PARA-study

Conception		Partus						
Before pregnancy	Pregnancy				Postpartum			
	T1 8-12	T2 18-22	T3 28-32		4-6	12	26
Collected	Time (weeks)						
C0	C1	C2	C3		C4	C5	C6
B	B	B	B	CB	B	B	B
U	U	U	U		U	U	U
I	I	I	I		I	I	I
J	J	J	J		J	J	J
						P	

Abbreviations

T	trimester
C	visit
B	blood draw
U	urine sample
CB	cord blood
I	interview
J	joint examination
P	paternal blood

2.2

MEASURING DISEASE ACTIVITY & FUNCTIONALITY DURING PREGNANCY IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Objective. Pregnancy has a favourable effect on the course of rheumatoid arthritis (RA), although the magnitude of this effect is equivocal because RA assessment tools have never been validated in pregnancy. The goal of this study was to assess how pregnancy influences the scoring of the Disease Activity Score in 28 joints (DAS28) and the Health Assessment Questionnaire (HAQ), and how both scores perform in pregnant patients with RA.
Methods. Thirty-two healthy women and 30 pregnant patients with RA were prospectively studied during pregnancy and at postpartum. At each trimester and postpartum the components of the DAS28 (global health (GH), erythrocyte sedimentation rate (ESR), and C-reactive protein level (CRP)) and HAQ scores were determined. Maximal influences of healthy pregnancy on each component of the DAS28 were calculated. The performances of different DAS28 scores and the HAQ were also determined in RA patients. Furthermore, variants of the HAQ were developed within the HAQ scoring rules.
Results. The components of the DAS28 were influenced by healthy pregnancy, with average increases in DAS28 score of 0.22 (GH), 1.1 (ESR), and 0.25 (CRP). The DAS28 calculated with CRP (DAS28-CRP) and without GH performed the best in pregnant RA patients. In healthy pregnancy, the median HAQ increased to 0.50 in the third trimester and was reduced by the HAQ variants to 0.25.
Conclusion. Pregnancy considerably influences the scoring of the DAS28 and HAQ. RA disease activity in pregnant patients should preferably be calculated with DAS28-CRP without GH. Even with HAQ variants, influences of pregnancy on the assessment of functionality cannot be precluded.

INTRODUCTION

Pregnancy has an important impact on rheumatoid arthritis (RA). It is the only natural situation in which affected women can experience complete remission of RA. During pregnancy, patients may experience signs and symptoms of amelioration of RA, followed by deterioration postpartum (1-3). The immunologic phenomena contributing to this favourable effect of pregnancy are of great interest in understanding the pathogenesis of RA.

Because remission has always been defined differently, the retrospective and prospective studies to date have shown substantial variations in disease activity during pregnancy (4-9). Criteria for remission were based variously on changes in clinical assessments, medication, and Health Assessment Questionnaire (HAQ) scores. These studies also used methods that were never validated during pregnancy.

To properly study the course of RA, disease activity and functioning of pregnant patients with RA should be studied prospectively throughout pregnancy using currently accepted scores for the assessment of RA, such as the modified Disease Activity Score including 28-joint counts (DAS28) (10,11) and the HAQ (12,13). However, these widely used RA assessment tools may not be valid for assessing RA during pregnancy. This is because pregnancy itself may influence not only the parameters of the DAS28, i.e., the visual analogue scale (VAS) of global health (GH), erythrocyte sedimentation rate (ESR) (14), or C-reactive protein (CRP) level (15), but also the rating of some categories of the HAQ. For example, a 30-week pregnancy will most certainly cause some difficulties in functioning (16). Some adaptation or correction for the influence of pregnancy on currently accepted scores might therefore be warranted. The goal of our study was to investigate 1) how pregnancy itself influences the scoring of the DAS28 and HAQ and reliability of the DAS28 and HAQ as RA assessment tools in pregnancy, 2) how the HAQ can be adapted for use in pregnant patients with RA, and 3) how different DAS28 formulas and adaptations of HAQ perform during pregnancy in women with RA.

PATIENTS AND METHODS

The Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study is a prospective, nationwide cohort study designed to investigate the amelioration of RA during pregnancy and the postpartum flare. The PARA-study was started in 2002. In this study, healthy women serve as a reference group to determine the pregnancy-induced deviations of current scoring methods and laboratory tests. All participants gave their informed consent.

Patient population

At the time of this study, the data collected on 30 consecutive full pregnancies of 30 patients with RA were available. All patients fulfilled the American College of Rheumatology (formerly the American Rheumatism Association) 1987 classification criteria for RA (17). Patients were visited at each trimester (9-12 weeks of gestation, 20 weeks, and 30 weeks) and twice postpartum (6 weeks and 12 weeks). At each visit patients filled out the HAQ and a VAS GH, and a standardized 28-joint count was performed. At the same time, ESR and CRP level were measured in blood samples.

Healthy women

Thirty-two healthy pregnant women were recruited from a midwifery practice between July 2002 and January 2004. Each woman was < 13 weeks pregnant.

The healthy women were visited at the same time points as the patients. The same assessments and laboratory tests were performed, except for the joint count.

Assessments

Disease activity

The disease activity of patients can be defined by several DAS formulas. In general, a DAS is a statistically derived index combining tender joints, swollen joints, a laboratory parameter for inflammation (ESR or CRP), and global disease activity. In this study, the DAS28 was chosen as an assessment tool for disease activity.

Currently, 4 formulas are available to calculate the DAS28 (see Appendix 2.2). In general, these 4 variants are composed of a 28-joint count for swelling and for pain, combined with either an ESR or CRP level and with or without a VAS GH (10). Joint examinations were performed for pain and swelling as recommended by the European League Against Rheumatism (EULAR) Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT) (18). GH was scored on a VAS from 0 (very well) to 100 (very poor). ESR was measured in mm/hour by the Westergren technique using a StaRRsed analyzer (Mechatronics LLC, Etten-Leur, The Netherlands). CRP level was measured in mg/dL by Tinaquant CRP (Roche Diagnostics, Mannheim, Germany).

A sensitivity analysis of the performance of the 4 DAS28 formulas in pregnant women was performed. For this purpose, we first determined the pregnancy-induced deviations of each component of the DAS28 observed in the healthy women. For each healthy woman, the third trimester and 12 weeks postpartum values of each component of the DAS28 were entered into the DAS28 formulas. Then the pregnancy-induced deviation in DAS28 for each component was calculated by subtracting the results of each woman separately at these different time points. Subsequently, the mean pregnancy-induced deviations in DAS28 were calculated for each component using the results of all healthy women. Finally, the mean pregnancy-induced deviations were entered into the 4 different DAS28 formulas to perform the sensitivity analysis.

Patients with RA were categorized according to their disease activity as determined by the 4 different DAS28 formulas in the third trimester of their pregnancy. This was rated according to the 4 criteria for categorizing disease activity as defined by ESCISIT (18). The categories are defined as high disease activity (DAS28 score > 5.1), intermediate disease activity (3.2 < DAS28 score

≤ 5.1), low disease activity (2.6 < DAS28 ≤ 3.2), and clinical remission (DAS28 score ≤ 2.6) (10).

Functionality

The conventional HAQ score was determined using the validated Dutch translation of the Stanford HAQ, which considers the use of devices and aids (12,13,19). In a consensus meeting with researchers of our department, we defined the items and categories that might be most influenced by pregnancy. To determine whether the assumptions of the consensus meeting were valid, we calculated the percentages of our healthy women scoring on the individual HAQ items. Based on the consensus and the rating of the individual HAQ items, modification of the conventional HAQ into 2 HAQ variants was recommended, both within the HAQ scoring rules (12). The first HAQ variant (HAQv1) was calculated on the basis of 6 rather than 8 categories, omitting arising and doing activities. The second HAQ variant (HAQv2) was calculated without selected items per category, i.e., dressing, getting in and out of bed, climbing 5 steps, getting in and out of a bath, bending down to get clothes from the floor, and getting in and out of a car. The 2 HAQ variants were calculated for patients with RA as well as for the healthy women. Finally, the performances of the conventional HAQ scores and the 2 HAQ variants were compared for all time points. The pregnancy-induced deviations of the conventional HAQ and of the 2 HAQ variants were calculated by the subtraction of the third trimester HAQ scores from that of 6 weeks postpartum.

Statistical analysis

Disease activity. Continuous variables were presented as the mean ±SD, i.e., VAS GH, ESR, and CRP level. Student's t-test was used to compare different time points of the continuous variables. Patients with RA were categorized in the 4 disease activity groups according the 4 different DAS28 formulas in the third trimester.

Functionality. HAQ scores were presented as medians and interquartile ranges. The differences in HAQ scores between the first and third trimester and between conventional HAQ and HAQ variants were tested by Wilcoxon's nonparametric test. A difference in HAQ score of > 0.25 between 2 time points was considered to be clinically relevant (12). A 2-sided p value < 0.05 was considered statistically significant. SPSS for Windows, version 12.0 (SPSS, Chicago, IL) was used.

Ethics

This study was in compliance with the Helsinki declaration, and the ethical committee at the Erasmus University Medical Center Rotterdam approved this study.

RESULTS

Demographics

All 30 patients and 32 participating healthy women had successful pregnancies. As shown in Table 2.2.1, mean age, percentage of nulliparity, and parity were comparable between the healthy women and the patients with RA.

Table 2.2.1: Demographics of subjects

Baseline characteristics	Patient group (n = 30)	Healthy women (n = 32)	p
Mean age at first trimester (years) (sd)	30 ± 3.7	32 ± 4.4	NS
Number of nulliparous women (%)	15 (50)	14 (44)	NS
Mean number of previous pregnancies (sd)	0.9 ± 1.0	1.0 ± 1.1	NS
Median disease duration in months (range)	46 (3 - 343)	--	--
Erosions present (%)	58	--	--
RF present (%)	65	--	--

* RA = rheumatoid factor; RF = rheumatoid factor; NS = not significant.

Pregnancy-induced deviations of components of the DAS28

Healthy women. In the healthy women, the influence of pregnancy was different for each component of the DAS28. Pregnancy influenced the VAS GH to a small extent. The mean VAS GH of the healthy women was almost equal during pregnancy and postpartum (Figure 2.2.1). Despite this result, the mean pregnancy-induced deviation of the 2 possible DAS28 with 4 variables due to VAS GH was 0.22 in healthy women, calculated between the third trimester and 12 weeks postpartum. Pregnancy influenced ESR considerably. The mean ESR of the healthy women differed statistically significantly between pregnancy and postpartum period ($p = 0.03$); ESR increased statistically significantly between the first and third trimesters ($p = 0.01$) from 10 mm/hour to 33 mm/hour. The calculations of the mean ESR at the third trimester excluded 1 woman who had sinusitis (ESR 120 mm/hour). The mean ESR returned to normal (< 20 mm/ hour) directly postpartum (Figure 2.2.1). The mean pregnancy-induced deviations of the DAS28 using ESR with 4 variables (DAS28-ESR-4) and the DAS28-ESR with 3 variables (DAS28-ESR-3) due to ESR were 1.07 and 1.16, respectively, in healthy women, regarding the different ESR levels at the third trimester and 12 weeks postpartum. Pregnancy influenced CRP levels slightly. The mean CRP levels of the pregnant healthy women differed statistically

significantly from those postpartum (p = 0.03). The mean CRP levels were equal between the first trimester (0.7 mg/dL) and the third trimester (1.0 mg/dL) (Figure 2.2.1). The calculations at the third trimester excluded 1 woman who had sinusitis (CRP level 7.6 mg/dL). The mean CRP level returned to normal (< 0.7 mg/dL) directly postpartum. The mean pregnancy-induced deviations of the DAS28 using CRP level with 4 variables (DAS28-CRP-4) and the DAS28-CRP with 3 variables (DAS28-CRP-3) due to CRP were 0.25 and 0.27, respectively, in healthy women, calculated between the third trimester and 12

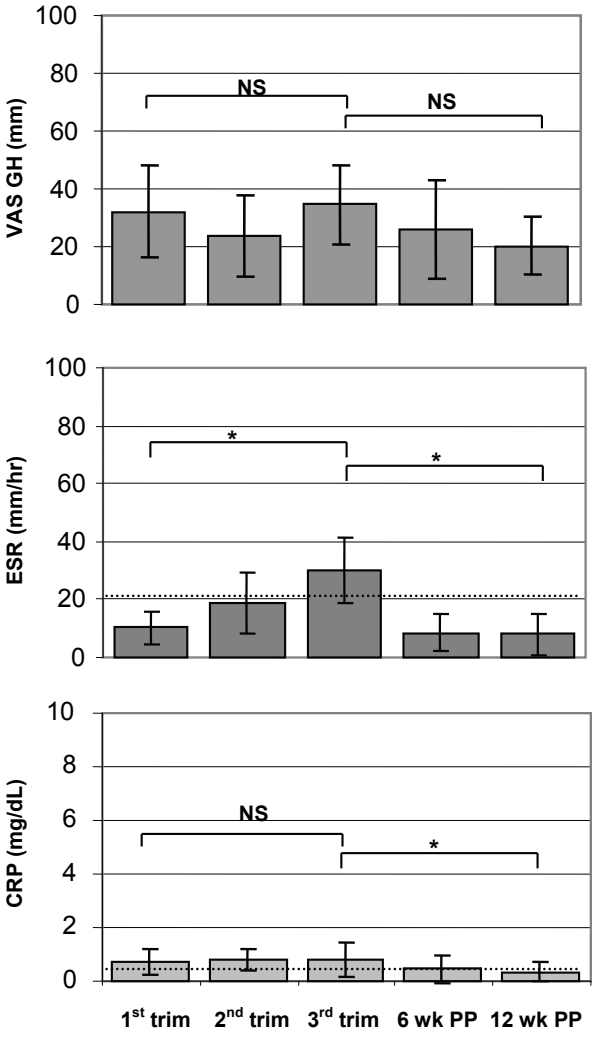

Figure 2.2.1: Values of visual analogue scale (VAS) global health (GH), erythrocyte sedimentation rate (ESR) and C-reactive protein level (CRP) during pregnancy and postpartum (PP) in 32 healthy women are presented in bars as mean ± SE. Normal values (in non-pregnant population) are represented by dotted lines. * p < 0.05. NS = not significant; trim = trimester.

weeks postpartum. The results of the sensitivity analysis of the 4 different DAS28 formulas differed considerably. The calculated mean pregnancy-induced deviations of the VAS GH, ESR, and CRP level for healthy women were added as in the 4 DAS28 formulas (see Appendix 2.2). The total pregnancy-induced deviations per DAS28 were +1.16 for the DAS28-ESR-3, +1.29 for the DAS28-ESR-4, +0.27 for the DAS28-CRP-3, and +0.47 for the DAS28-CRP-4. Thus, healthy pregnancy influenced the DAS28-CRP-3 the least and the DAS28-ESR-4 the most.

RA patients. When, according to the 4 DAS28 variants, patients in their third trimester were categorized in high, intermediate, and low disease activity and remission, large differences were found in the percentages of patients per category (Table 2.2.2). The percentages of clinical remission ranged between 0% and 23%. The highest total percentage (46%) of women with low disease activity or remission during the third trimester was identified by the DAS28-CRP-3, whereas according to the DAS28-ESR-3 and DAS28-ESR-4 the percentage was only 25%.

Pregnancy-induced deviations of the HAQ

Healthy women. Because the healthy women answered more HAQ items "with some difficulty" or "with much difficulty," they had difficulties in functioning during pregnancy. All items defined in the consensus meeting were marked with at least "some difficulty" in > 20% of healthy women (Table 2.2.3). Only 1 item, i.e., walking outdoors, was not defined, but was also marked in > 20% of healthy women in the third trimester.

Table 2.2.2: Percentages of patients with rheumatoid arthritis expressing high, intermediate, and low disease activity or remission in the third trimester based on calculation of disease activity by 4 different DAS28 formulas*

DAS28 variant	High disease activity DAS28 > 5.1	Intermediate disease activity 3.2 < DAS28 ≤ 5.1	Low disease activity 2.6 < DAS28 ≤ 3.2	Remission DAS28 ≤ 2.6
DAS28-CRP-3 n = 30	10	43	23	23
DAS28-CRP-4 n = 30	13	50	20	17
DAS28-ESR-3 n = 28	11	64	25	0
DAS28-ESR-4 n = 28	18	57	14	11

* DAS28 = Disease Activity Score including 28-joint counts; DAS28-CRP-3 = DAS28 using C-reactive protein with 3 variables; DAS28-CRP-4 = DAS28 using C-reactive protein with 4 variables; DAS28-ESR-3 = DAS28 using erythrocyte sedimentation rate with 3 variables; DAS28-ESR-4 = DAS28 using erythrocyte sedimentation rate with 4 variables.

Table 2.2.3: Percentages per item of the Health Assessment Questionnaire (HAQ) categories scored by healthy women in the first, second, and third trimesters and 6 weeks postpartum, showing the items that were marked as at least "with some difficulty" by 20% of the women in the third trimester*

	1st trimester		*2nd trimester*		*3rd trimester*		*6wk pp*	
HAQ CATEGORY Item	Some difficulty	Much difficulty	Some difficulty	Much difficulty	Some difficulty	Much difficulty	Some difficulty	Much difficulty
DRESSING								
HAQ 1.1 Dress yourself, including tying shoelaces and doing buttons †	0	0	16	0	53	0	0	0
ARISING								
HAQ 2.1: Stand up from a straight chair	0	0	13	0	41	0	0	0
HAQ 2.2: get in and out of bed †	3	0	22	0	69	0	0	0
WALKING								
HAQ 4.1: walk outdoors on flat ground	0	0	3	0	28	3	3	0
HAQ 4.2: climb up five steps †	6	0	9	0	22	0	0	0
HYGIENE								
HAQ 5.2: take a tub bath †	0	0	6	0	44	0	0	0
REACHING								
HAQ 6.2: bend down to pick up clothing from the floor	3	0	22	0	69	0	0	0
ACTIVITIES								
HAQ 8.1: run errands and shop	0	0	16	0	47	6	9	0
HAQ 8.2: get in and out of a car †	0	0	16	0	56	3	0	0
HAQ 8.3: do chores like vacuuming or yard work	0	0	32	0	47	9	9	3

* "Unable to do" was never marked. The remaining percentage per item was ascribed to "no difficulty." † Defined at the consensus meeting on the basis that they were likely to be most influenced by pregnancy.

Among the categories marked most frequently during pregnancy were the categories as defined at the consensus meeting, i.e., arising (69%) and doing activities (59%). The category reaching, however, was also marked in 69% of healthy women in the third trimester. However, this third category could not be taken into account in a HAQ variant simultaneously with the other 2 categories, because calculating the HAQ score requires at least 6 categories.

Box plots demonstrated the differences of the HAQ and the 2 HAQ variant scores (HAQv1 and HAQv2) during pregnancy and postpartum (Figure 2.2.2). A third HAQ variant (not shown) was calculated on the basis of omitting items with the highest number of marks, instead of only the items considered in the consensus meeting. The scoring of this third HAQ variant did not perform better than the HAQv2. The median pregnancy-induced deviation in HAQ score

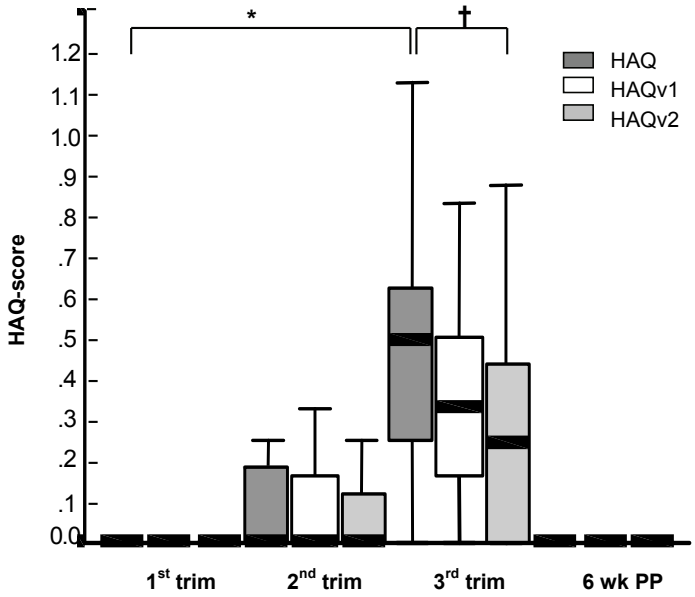

Figure 2.2.2: Box plots of the healthy women showing the distribution Health Assessment Questionnaire (HAQ) scores and the variants from the first trimester (trim) until 6 weeks postpartum (PP). The score at 12 weeks PP (not shown) resembled the 6-week score. Horizontal lines (from bottom) indicate the minimum, lower quartile, median, upper quartile, and maximum, with the exceptions of outliers. HAQv1 = 1st HAQ variant scored without 2 categories (arising and activities); HAQv2 = 2nd HAQ variant scored without items 1.1, 2.2, 4.2, 5.2, 6.2, and 8.2. * p = 0.001, Z = - 4.39 compared with HAQ score at 1st trimester (n = 31). † p = 0.001, Z = - 4.42 compared with HAQ score at 3rd trimester (n = 31).

measured with the HAQ score between the third trimester and 6 weeks postpartum was 0.5. This pregnancy-induced deviation in HAQ score was clinically relevant and statistically significant. Although the use of the HAQv1 and HAQv2 reduced the pregnancy-induced deviation in HAQ scores between the third trimester and 6 weeks postpartum to 0.33 and 0.25, respectively, the influence of pregnancy on the scoring of the HAQ cannot totally be disregarded.

RA patients. Median HAQ scores of the patients with RA increased statistically significantly by 0.31 from the first to the third trimester (p = 0.04) (Table 2.2.4). The median HAQv1 score also increased significantly by 0.42 (p = 0.04). Although the median HAQv2 score increased by 0.17 between the first and the second trimester, it decreased in the third trimester. The median HAQv2 scores between the first and third trimester, however, differed only 0.07 (p = 0.06).

Table 2.2.4: HAQ score and the two HAQ variants of RA women during pregnancy are presented as median and quartile range.*

	1st trimester n = 30	2nd trimester n = 30	3rd trimester n = 29	6wk PP N = 29
HAQ	0.69 (0.4-1.3)	0.88 (0.4-1.3)	1.00† (0.4-1.3)	0.75 (0.2-1.2)
HAQv1	0.58 (0.2-1.1)	0.75 (0.2-1.3)	1.00† (0.5-1.3)	0.75 (0.2-1.2)
HAQv2	0.56 (0.3-1.0)	0.75 (0.5-1.3)	0.63‡ (0.3-1.0)	0.50 (0.2-1.0)

* Values are the median (interquartile range). HAQv1 = 1st HAQ variant scored without 2 categories (arising and activities); HAQv2 = 2nd HAQ variant scored without items 1.1, 2.2, 4.2, 5.2, 6.2, and 8.2. † $p < 0.05$ for HAQ score at 3rd trimester compared with HAQ score at 1st trimester. ‡ Not significant for HAQv2 score at 3rd trimester compared with HAQv2 score at 1st trimester.

DISCUSSION

Our study demonstrates not only that pregnancy influences the scoring of the DAS28 and HAQ, but also that the HAQ variants can be used to reduce the influence of pregnancy on scoring the HAQ. The study also shows that the 2 RA assessment tools that performed best during pregnancy were the DAS28-CRP calculated without GH and the HAQ variant calculated without 6 selected items, although this variant did not totally preclude the influence of pregnancy.

Because the DAS28 had never previously been used in studies of RA in pregnancy, each component of the 4 different DAS28 formulas was first regarded separately in order to properly estimate the contribution pregnancy made to the formulas.

First, we showed that in healthy women, the mean GH score hardly changed during pregnancy, but was higher than postpartum. Although this difference was

small, it still resulted in a mean pregnancy-induced deviation of 0.22 in both DAS28 formulas incorporating the GH. The GH during pregnancy in patients with RA had not been studied before; only patients' global assessment of RA had been studied. In 2004, Ostensen et al (8) prospectively studied patients' global assessments of RA in 10 pregnancies from preconception until 24 weeks postpartum. Patient assessment decreased by an average of 15 mm during pregnancy, and increased by 10 mm postpartum. The differences in GH measured in our 30 patients with RA during pregnancy and postpartum did not completely follow this pattern, because the mean GH of patients with RA decreased by only 1 mm during pregnancy and increased by 12 mm postpartum. During pregnancy, the GH and the patient's global assessment of RA may not be interchangeable, because the former scored health and disease activity together, whereas the latter scored only disease activity. The mean increases postpartum in the GH (12 mm) and in patients' global assessment of RA (10 mm) were comparable. This suggests that outside pregnancy both assessment tools solely scored the difference in disease activity of RA, which will have the greatest influence on the GH postpartum. Based on these findings, we suggest that, during pregnancy, DAS28 formulas can be better used without GH.

Second, in line with previous studies (14), our study demonstrates that ESR increases substantially during pregnancy. On the basis of earlier studies, 30% of patients with RA should be in clinical remission during pregnancy (4-6). The percentages of our patients with RA in clinical remission as determined by the DAS28-ESR formulas with or without GH were only 11% and 0%, respectively, at the third trimester. The DAS28-ESR will therefore certainly be unreliable, and therefore it is not a useful tool for assessing RA during pregnancy.

Third, during healthy pregnancy, a reference CRP level is lacking, especially because it is unknown whether CRP levels rise or fall. In our healthy women the levels measured were slightly higher during pregnancy, but the CRP levels did not increase as pregnancy proceeded. In gynaecologists' daily practice, CRP level is already a useful marker of inflammation and infection, and is starting to be used in high-risk obstetrics such as gestational diabetes and pre-eclampsia (20). The higher CRP level we found during pregnancy agrees nicely with the slightly higher mean CRP levels (0.45 mg/dL) in early pregnancy (4 weeks of gestation) determined in women who became pregnant after in vitro fertilization procedure, and with the lower levels (0.13 mg/dL) in women in whom the procedure had failed (15). The higher CRP levels during pregnancy resulted in a pregnancy-induced deviation of the DAS28 of +0.25, which therefore performs better than that of the ESR (deviation of +1.1). The DAS28-CRP might therefore be a more reliable tool for assessing RA during pregnancy.

Last, although the joint scores of the DAS28 have never been designed for use in non-RA patients, it is conceivable that pregnancy potentially results in a joint score due to oedema or to pain. Therefore, we performed joint counts in an additional 34 healthy pregnant women in different stages of pregnancy (7 in the first trimester, 10 in the second trimester, 17 in the third trimester). None of the examined women had swollen joints, and only 2 of them had 1 painful joint each. There was neither a correlation between oedema and the presence of painful or swollen joints nor between the stage of pregnancy and the presence of painful or swollen joints. Therefore, we are convinced that the sensitivity analyses performed without joint scores but with ESR or CRP level, and with or without a GH are still valid.

In total, of the 4 DAS28 formulas, the DAS28-CRP calculated without GH was shown by the sensitivity analysis to be the least influenced by pregnancy itself. Therefore, this might be the best tool for scoring disease activity during pregnancy. Patients in their third trimester of pregnancy were categorized into different disease activity groups according to their DAS28-CRP score. DAS28-CRP calculated without GH showed the highest percentage of patients in clinical remission. The use of DAS28-CRP may still result in some overestimation of disease activity because CRP level is elevated during pregnancy compared with non-pregnancy, and therefore it may result in an underestimation of the percentage in clinical remission. Because a gold standard is not available to measure either the quantity of this underestimation or the percentage of misclassification that occurred, we suggest that pregnant patients with RA are best categorized according to their level of disease activity measured by DAS28-CRP without GH. This is important not only for research purposes but also for clinical practice in keeping an adequate control of disease activity.

The median HAQ score of our pregnant patients with RA was 1.0 at the third trimester, and is comparable with the median HAQ score of 0.9 calculated at the third trimester of 140 pregnant patients with inflammatory arthritis prospectively studied by Barrett et al from late pregnancy to postpartum (5). At the third trimester, the patients in the study by Barrett et al. completed 2 HAQs, one pertaining to recalled disability before pregnancy and one to current disability. Their patients completed the HAQ at 4 and 26 weeks postpartum. However, their recalled disability before pregnancy was higher than all the HAQ scores prospectively measured. This pattern is very different from that of the HAQ we scored prospectively, which increased from the first trimester until the third trimester. The retrospective design of their study may have introduced recall bias. Postpartum, however, the median HAQ scores were again comparable:

our patients had a median score of 0.75 and their patients a median score of 0.60 (5).

In contrast to what we found, Ostensen et al noted no difference at all between HAQ scores measured during pregnancy in 10 prospectively studied pregnancies of patients with RA (8). However, in that study the disease activity of the patients decreased at the same time and therefore one should have expected an increase in functionality. Because this was not the case, an explanation may be that pregnancy had also contributed to stable instead of lower HAQ scores.

Our results of the performance of the HAQ during pregnancy and results of former studies underline the arguments made by Nelson (16): the HAQ is not a good RA assessment tool during pregnancy. Therefore, we used different HAQ variants in an attempt to minimize the influence of healthy pregnancy on the HAQ. In healthy pregnant women, a pregnancy-induced increase in HAQ score was shown by all our variants that applied the HAQ scoring rules, such as the 2 defined in the consensus meeting, and those made on the basis of items with a high number of marks (12,13). Despite this, the HAQ variants calculated without the 6 selected items generally performed best in this study. We have to conclude, however, that even this HAQ variant cannot preclude all influences of pregnancy on the assessment of functionality, and that each HAQ should therefore be used with great care during pregnancy.

In conclusion, pregnancy has various degrees of influence when calculating disease activity by 4 different DAS28 formulas and scoring functionality with the HAQ and HAQ variants. During pregnancy, the DAS28-CRP may therefore be the best tool for calculating disease activity and the percentage of patients with RA in clinical remission. The best tool for measuring functionality may be the HAQ variant from which 6 selected items were omitted.

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APPENDIX 2.2: 4 DAS28 FORMULAS

DAS28 using ESR with 3 or 4 variables (10)

DAS28-ESR-3 = [0.56xSQRT(t28) + 0.28xSQRT(sw28) + 0.70xLn(ESR)]x1.08 + 0.16
DAS28-ESR-4 = 0.56xSQRT(t28) + 0.28xSQRT(sw28) + 0.70xLn(ESR) + 0.014xGH

DAS28 using CRP with 3 or 4 variables (10)

DAS28-CRP-3 = [0.56xSQRT(t28) + 0.28xSQRT(sw28) + 0.36xLn(CRP+1)] x 1.10 + 1.15
DAS28-CRP-4 = 0.56xSQRT(t28) + 0.28xSQRT(sw28) + 0.36xLn(CRP+1) + 0.014xGH + 0.96

t28: The number of tender joints of 28 joints examined for tenderness.
sw28: The number of swollen joints of the 28 joints examined for swollenness.
28 joints: Twenty-eight tender and swollen joint scores include the same joints: shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints and knees.
ESR: Westergren's Erythrocyte Sedimentation Rate, entered in mm/hr.
CRP: C-reactive protein, entered in mg/L (instead of in mg/dL as shown in Figure 2.2.1).
GH: General Health rated on a 100mm Visual Analogue Scale. GH was rated on a line from 0 (very well) to 100 (very poor).

3

DISEASE ACTIVITY

3.1

DISEASE ACTIVITY OF RHEUMATOID ARTHRITIS DURING PREGNANCY: RESULTS FROM A NATIONWIDE PROSPECTIVE STUDY

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Objective. According to common knowledge and retrospective studies, approximately 75–90% of patients with rheumatoid arthritis (RA) will improve during pregnancy. Prospective data on disease activity during pregnancy are limited. Therefore, this study aimed to prospectively determine the disease activity during pregnancy in RA patients treated in an era of new treatment options.
Methods. For 84 RA patients (American College of Rheumatology criteria), a Disease Activity Score in 28 joints (DAS28) and medication use were obtained, before conception if possible, at each trimester of pregnancy and at 6, 12, and 26 weeks postpartum. Improvement and deterioration were determined by assessing changes in DAS28 and by applying the DAS28-derived European League Against Rheumatism (EULAR) response criteria.
Results. Disease activity decreased with statistical significance ($p = 0.035$) during pregnancy and increased postpartum. In patients with at least moderate disease activity in the first trimester ($n = 52$), at least 48% had a moderate response during pregnancy according to EULAR-defined response criteria. In patients with low disease activity in the first trimester ($n = 32$), disease activity was stable during pregnancy. Thirty-nine percent of patients had at least a moderate flare postpartum according to reversed EULAR response criteria. Less medication was used during pregnancy compared with before conception and compared with postpartum.
Conclusion. This study demonstrates that patients achieve remission during pregnancy and deteriorate postpartum, although less frequently than previously described.

INTRODUCTION

Disease activity in patients with rheumatoid arthritis (RA) decreases spontaneously during pregnancy and increases postpartum. These generalities concerning RA rely on previous retrospective studies, which have been largely based on women's self-reports and doctors' observations in an era of restricted treatment options. In the last 7 decades, a substantial number of pregnant patients with RA improved in those studies; however, this number declined over time from 90% to 53% (1).

Until now, only 1 large, prospective study on this subject has been conducted from late pregnancy onward to 6 months postpartum (2). In retrospect, 63% of patients reported improvement in disease activity. At the third trimester, only 16% were in total remission, which was defined as having no swollen joints and receiving no antirheumatic therapy at the time of measurement. That study had 2 main disadvantages. First, objective information on disease activity was not available before conception or during early pregnancy. Second, no validated

scoring systems for disease activity and remission were used. In addition, new treatment options are now available to reduce disease activity before pregnancy, which was not the case with the previous study.

For this reason, we conducted a prospective nationwide cohort study from preconception or early pregnancy onward. This study, the Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study, had 2 main aims. One aim was to measure disease activity in patients with RA using a validated instrument (Disease Activity Score in 28 joints (DAS28)). The second aim was to collect patients' blood and urine samples to perform laboratory investigations into the underlying mechanisms of spontaneous improvement during pregnancy and relapse postpartum.

Here we present the first data of this study regarding the following 3 objectives. The first objective was to calculate the percentages of women in remission during pregnancy and postpartum. The second objective was to prospectively measure whether disease activity decreases during pregnancy and increases postpartum. Disease activity and remission were defined according to the DAS28 with 3 variables: swollen joint count, tender joint count, and C-reactive protein (CRP) level (mg/liter) (DAS28-CRP-3). The third objective was to provide a clear description of what medication was used before, during, and after pregnancy.

PATIENTS AND METHODS

Patient population

All rheumatologists working in The Netherlands were contacted by mail twice a year from the start of the study in May 2002 until November 2006. Rheumatologists were asked to recruit patients with RA who wanted to conceive or who were already pregnant (preferably in their first trimester). Patients were eligible for the study if they fulfilled the 1987 revised criteria of the American College of Rheumatology (ACR; formerly the American Rheumatism Association) for RA (3) and had a good understanding of the Dutch language. During the study, the patients' own rheumatologists provided patient care. The present analysis used data from patients who had information available from prepregnancy or the first trimester to 26 weeks postpartum onward. Women who had a miscarriage in the first trimester or were pregnant with twins were not included. No woman was included twice.

Data collection

Patients were visited 6 or 7 times at their home address. They were visited before conception (if possible), at each trimester (8–12 weeks of gestation, 18–22 weeks, and 28–32 weeks), and 3 times postpartum (6 weeks, 12 weeks, and 26 weeks). The visit before conception took place if the woman had a desire to conceive, i.e., she and her partner did not use any contraceptives. If a woman did not conceive within a year after the first visit, another visit took place. Data collected before conception were classed as “before pregnancy.”

Medical and obstetric history were taken at the first visit by interview. Presence of rheumatoid factor (RF), antibodies to cyclic citrullinated peptide (anti-CCP), and erosions were ascertained from the patients’ medical records. The presence of anti-CCP, IgM-RF, IgG-RF, and IgA-RF in serum from the first visit was also determined. Presence of anti-CCP was determined with the EliA CCP test (Phadia AB, Uppsala, Sweden) and was defined as a serum level >10 units/ml. Positivity for anti-CCP used in the analyses was defined as “ever recorded positive” in the medical records or “tested positive at first visit.” A positive IgM-RF, IgG-RF, or IgA-RF (Hycor Biomedical, Garden Grove, CA) was defined as a serum level higher than the level at which less than 5% of healthy controls tested positive in these tests. Presence of RF was defined as “ever recorded positive” in the medical records or “tested positive at first visit.”

Current medication use was recorded and percentages of use and median daily doses of medication were calculated per time point. At each visit, women provided information about their current pregnancy, and postpartum they provided information on whether or not their newborn was breastfed.

A research physician or research nurse performed a standardized 28-joint count for swelling and pain. Joint examinations were performed for pain and swelling as recommended by the European League Against Rheumatism (EULAR) Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT) (4).CRP levels were measured in serum by Tina-quant CRP (Roche Diagnostic, Mannheim, Germany).

Disease activity was objectively scored using the DAS28-CRP-3 (5). In a previous study, we demonstrated that disease activity can be measured the most reliably during pregnancy with the DAS28-CRP-3 (6), because erythrocyte sedimentation rate increases physiologically during pregnancy.

Data and statistical analysis.

For all patients, the mean disease activity scores were calculated at the time points indicated. The mean individual difference between DAS28 at the first and

third trimesters was calculated. According to the EULAR criteria, remission was defined as a DAS28 < 2.6 (7).

Improvement in disease activity between the first and third trimesters was defined, according to the EULAR response criteria, as good, moderate, or no responders as defined by ESCISIT (Appendix 3.1.A) (6). Because the baseline requirement for the EULAR response criteria is that patients have an initial DAS28 of at least 3.2, 2 subgroups of patients were created, 1 with patients with moderate to high disease activity (DAS28 ≥ 3.2) and 1 with patients with low disease activity (DAS28 < 3.2) in the first trimester. The prerequisite of an initial DAS28 ≥ 3.2 for application of the EULAR response criteria meant that only those patients with a DAS28 ≥ 3.2 in the first trimester could be classified as good, moderate, or no responder (4,7).

Because no classification for deterioration is available yet, we defined flares in disease activity between 6 weeks and 12 or 26 weeks postpartum as severe or moderate based upon “reversed” EULAR response criteria for disease activity (see Appendix 3.1.B). This classification was applied to all patients; there was no baseline DAS28 requirement. Finally, the mean individual difference between DAS28 at 6 weeks and 12 or 26 weeks postpartum was calculated.

The proportions of women in clinical remission and the proportions with low, moderate, or high disease activity before pregnancy, during pregnancy, and postpartum were calculated. The proportions of women in remission were analyzed by generalized estimating equations with an exchangeable correlation structure. This takes into consideration whether patients are already in remission and stay in remission, or whether other patients go into remission.

All time points during and after pregnancy were used to measure changes in DAS28 over time in a linear mixed model with unstructured covariance. This model considers random variation within individuals and random variation between individuals. In subgroup analyses, the disease course of patients with or without RF, anti-CCP, joint erosions, or biologic agent use prior to their desire to conceive was determined. A likelihood ratio test was used to test the differences in disease course between the different subgroups. A 2-sided $p < 0.05$ was considered statistically significant. SPSS for Windows (SPSS, Chicago, IL) version 12.0 was used.

Ethics

This study is in compliance with the Declaration of Helsinki, and the ethical committee at the Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands approved this study.

RESULTS

Patient recruitment data

Up to November 2006, 346 patients were recruited by rheumatologists. Of these, 276 were eligible; however, 111 were not yet pregnant. As shown in Figure 3.1.1, we obtained a complete disease activity data set of 84 pregnancies from the first trimester to 26 weeks postpartum. A detailed description of disease activity, medication, and demographics of these patients is provided. Data from 41 pregnancies were available from before pregnancy.

Demographics

The cohort consisted of patients with RA with a median disease duration of 4.8 years (range 0.1 - 28.6 years) at first visit. This range can be explained by 11 women who had a desire to conceive within 1 year after diagnosis, and by 7 women who had polyarthritis in childhood that developed into an RF-positive and erosive disease that could be classified as RA. RF was positive in 71% of patients and anti-CCP was positive in 68% (Table 3.1.1). Whether or not patients were erosive was documented in 74 pregnancies; of these, 53 (72%) were erosive. Almost half of the pregnancies were first-time pregnancies. Only 3 pregnancies occurred in non-white women (2 Asian, 1 African). Postpartum, 67% of the babies were breastfed, 49% for longer than 6 weeks.

Table 3.1.1. Clinical and demographic features of 84 rheumatoid arthritis patients and their pregnancies (n = 84)*

Baseline characteristics	
Age at delivery, mean ± SD years	31.9 ± 3.3
Disease duration at first visit, median (range) years	4.8 (0.1-28.6)
RF present	60 (71)
Anti-CCP present	57 (68)
Erosions present	53 (72)†
First-time pregnancies	41 (49)

* Values are the number (percentage) unless otherwise indicated. RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide antibodies. † Only data for 74 patients were available for this analysis.

Evaluation of disease activity

Percentages in remission

The total number of patients in remission (DAS28 < 2.6) increased during pregnancy from 17% in the first trimester to 27% in the third trimester ($p = 0.16$), and decreased to 18% in the 12th week postpartum ($p = 0.07$) (Figure 3.1.2). The number of patients in remission increased, despite the remarkable changes in medication use that took place (Table 3.1.2). The percentage of

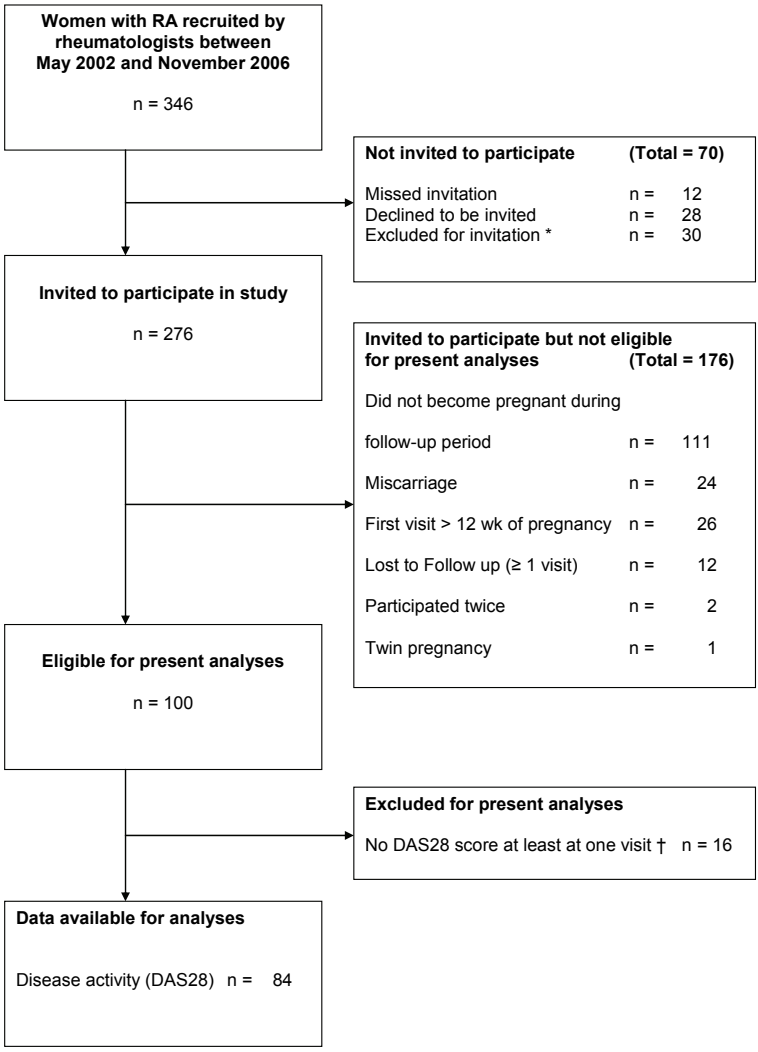

Figure 3.1.1. Flow diagram of the Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study. Patients recruited and final number of patients eligible for the present analyses are shown. * = Excluded for invitation: did not fulfill American College of Rheumatology criteria, did not speak Dutch language. † = Disease Activity Score in 28 joints (DAS28) could not be calculated because either C-reactive protein level or number of swollen or painful joints was missing. RA = rheumatoid arthritis; wk = week.

patients who received methotrexate < 1 year before conception (28%) was reduced to 0% during pregnancy, and the percentage of patients who received non-steroidal anti-inflammatory drugs (NSAIDs) before conception (32%) was reduced to 4% during pregnancy (data not shown in Table 3.1.2). The total number of patients with low disease activity (DAS28 2.6 - 3.2) remained stable

Table 3.1.2: Disease-modifying antirheumatic drug and biologic agent use before pregnancy, during pregnancy, and postpartum*

Medication	Ever used n = 84 n(%)	Used < 1 year before conception n = 84 n (%)	Before pregnancy n = 41 † n (%)	1st trim n = 84 n (%)	2nd trim n = 84 n (%)	3rd trim n = 84 n (%)	6 wk PP n = 84 n (%)	12 wk PP n = 84 n (%)	26 wk PP n = 84 n (%)	Used at 26 wk PP and used < 1 year before conception n/N (%)‡
prednisone (oral)	33 (39)	24 (28)	16 (39)	30 (36)	30 (36)	29 (35)	29 (35)	29 (35)	26 (31)	16/24 (66)
sulfasalazine	65 (77)	41 (49)	17 (41)	26 (31)	28 (33)	28 (33)	27 (32)	31 (37)	31 (37)	28/41 (68)
methotrexate	46 (55)	22 (28) §	0 (0)	0 (0)	0 (0)	0 (0)	20 (24)	28 33)	33 (40)	17/22 (77)
leflunomide	4 (5)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0/1 (0)
hydroxychloroquine	31 (37)	9 (11)	2 (5)	2 (2)	3 (4)	2 (2)	2 (2)	5 (6)	3 (4)	1/2 (50)
biologicals	10 (12)	6 (7)	0 (0)	0 (0)	0 (0)	0 (0)	4 (5)	8 (10)	9 (11)	2/6 (33)
no medication	N/A	N/A	7 (17)	22 (26)	29 (35)	29 (35)	27 (32)	17 (20)	13 (15)	N/A

* Values are the number (percentage) or number/total number (percentage). Trim. = trimester; wks = weeks; PP = postpartum; N/A = not available. † This group only includes patients who were visited before conception. ‡ Number (percentage) of patients who used the same medication 26 weeks postpartum < 1 year before conception. § In 5 patients, the exact cessation date was missing (n = 79). No detailed information was present on whether patients were off medication during a certain time period.

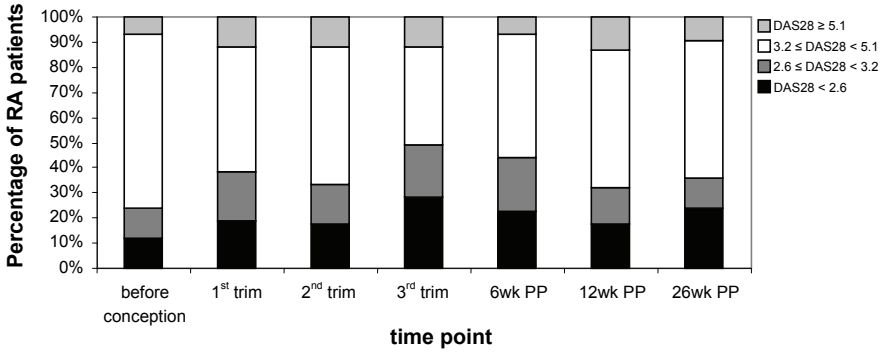

Figure 3.1.2. The percentages of patients grouped, according to Disease Activity Score in 28 joints (DAS28) during pregnancy and postpartum, into remission (DAS28 < 2.6), low disease activity (DAS28 2.6 - 3.2), moderate disease activity (DAS28 3.2 - 5.1), and high disease activity (DAS28 > 5.1). RA = rheumatoid arthritis; trim = trimester; wk = weeks; PP = postpartum.

between the first and third trimesters, but decreased postpartum. Almost half of the patients had at least low disease activity in the third trimester (Figure 3.1.2). The total number of patients with moderate disease activity (DAS28 3.2 - 5.1) decreased during pregnancy, while the total number of patients (n = 10) with high disease activity (DAS28 > 5.1) remained stable during pregnancy.

Changes in disease activity according to DAS28

Altogether, mean disease activity scores decreased during pregnancy and increased postpartum (n = 84; p = 0.035) (Figure 3.1.3). The impact of pregnancy on disease activity in the third trimester was most pronounced in patients who had moderate to high disease activity in the first trimester (mean ± SD = 0.54 ± 0.92 (n = 52), DAS28 4.4 - 3.9; p < 0.001) compared with those with a low disease activity in the first trimester (mean ± SD = 0.23 ± 0.92 (n = 32), DAS28 2.5 - 2.7; p = 0.21). The mean DAS28 increased from 6 weeks to 12 weeks postpartum by 0.30 (95% confidence interval (CI) [0.07;0.48], p = 0.01) from 3.5 to 3.8. In subgroup analyses, the presence of anti-CCP, RF, and erosions did not alter the course of disease activity during pregnancy and postpartum (likelihood ratio tests: p = 0.91, p = 0.98, and p = 0.98, respectively). Biologic agents were used in 6 patients < 1 year prior to conception. Because of the small number, no valid statistical analyses could be performed.

The analysis of patients who were visited before pregnancy (n = 41) showed that the mean disease activity before pregnancy decreased in the third trimester by 0.4 (95% CI [-0.6;-0.03], p = 0.03) from 3.8 to 3.4. The change in DAS28 from before pregnancy to first trimester was not statistically significant in these patients (mean -0.08 (95% CI [-0.3;0.2]; p = 0.61). The change in DAS28 from

before pregnancy to 26 weeks postpartum was not statistically significant (mean -0.22 (95% CI [-0.5;0.1]; p = 0.13).

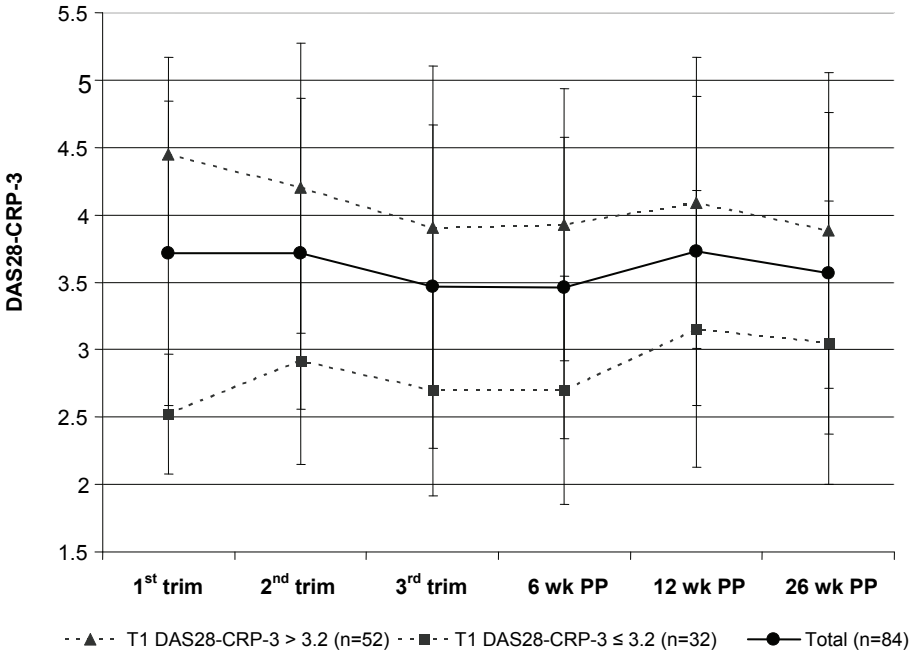

Figure 3.1.3 Disease Activity Score in 28 joints (DAS28) measured with swollen joint count, tender joint count, and C-reactive protein level (DAS28-CRP-3) during and after pregnancy presented as means and 95% confidence intervals. Trim = trimester; wk = weeks; PP = postpartum.

Changes in disease activity according to DAS28-derived EULAR response criteria

Patients who fulfilled the prerequisite for application of EULAR response criteria, namely, those with a DAS28 > 3.2 in the first trimester (n = 52), were classified as good, moderate, and no responders. This analysis showed that 48% of these patients had at least a moderate response during pregnancy (Table 3.1.3).

Of the 6 patients who received biologic agents < 1 year before conception, all had moderate to high disease activity in the first trimester. Similar to the total group (n = 52), 50% had at least a moderate response during pregnancy according to EULAR response criteria and 50% had no response.

Table 3.1.3. Improvement during pregnancy according to the EULAR response criteria, and therefore restricted to patients with moderate disease activity (DAS28 > 3.2) in the first trimester (n = 52)*

Classification (EULAR criteria) between first and third trimester	DAS28 > 3.2 at first trimester
Good response	9 (17.3)
Moderate response	16 (30.8)
No response	27 (51.9)

* Values are the number (percentage). EULAR = European League Against Rheumatism; DAS28 = Disease Activity Score in 28 joints.

Postpartum, RA deteriorated according to the "reversed" EULAR response criteria in 39.3% of all 84 patients (Table 3.1.4). Of the patients with moderate to high disease activity (DAS28 > 3.2) in the first trimester, 2 (3.8%) patients had a severe flare of RA postpartum, 17 (32.7%) patients had at least a moderate flare, and 33 (63.5%) patients had no flare. Of the patients with low disease activity (DAS28 > 3.2) in the first trimester, 1 (3.1%) patient had a severe flare of RA postpartum, 13 (40.6%) patients had at least a moderate flare, and 18 (56.3%) patients had no flare.

Table 3.1.4. Deterioration postpartum according to reversed EULAR response criteria between 6 weeks postpartum and 12 or 26 weeks postpartum, shown for all patients (n = 84)*

Classification (reversed EULAR criteria)	All patients
Severe flare	3 (3.6)
Moderate flare	30 (35.7)
No flare	51 (60.7)

* Values are the number (percentage). EULAR = European League Against Rheumatism.

CRP levels during pregnancy

During pregnancy, mean ± SD CRP levels decreased from 16.2 ± 15.1 mg/liter in the first trimester to 14.2 ± 15.1 mg/liter in the third trimester (not significant). Mean CRP levels increased from 11.3 ± 13.3 mg/liter at 6 weeks postpartum to 14.8 ± 25.1 mg/liter at 12 weeks postpartum, and decreased to 11.5 ± 13.1 mg/liter at 26 weeks postpartum. These differences were not statistically significant.

Evaluation of medication use

In Table 3.1.2, the percentages of disease-modifying antirheumatic drug (DMARD) use are categorized into ever used, used < 1 year before conception, before conception, during pregnancy, and postpartum. The medication used during conception is represented by the columns before pregnancy (n = 41) and first trimester (n = 84). The last column shows the percentage of women who were taking the same medication at 26 weeks postpartum as they were taking at < 1 year before conception.

Very few patients changed from one drug to another during pregnancy. The median daily dosage of prednisone was 7.5 mg (range 0.5 - 20 mg) before conception and did not change throughout pregnancy. The median daily dosage of prednisone increased to 10 mg (range 0.5 - 20 mg) at 6 weeks postpartum and decreased to 7.5 mg (range 0.5 - 20 mg) at 12 and 26 weeks postpartum. The median daily dosage of sulfasalazine was 2,000 mg (range 500 - 4,000 mg) at all time points.

Biologic agents were prescribed before conception in 10 patients. Six patients received biologic agents < 1 year before conception; of these, 2 patients restarted biologic agents postpartum. None of the patients received a combination of biologic agents, prednisone, and methotrexate < 1 year before conception.

Except for DMARDs and biologic agents, NSAIDs were used during pregnancy in 4% of patients, while up to 33% of patients needed them for pain relief postpartum. Acetaminophen was used in only 5 - 10% of patients for pain relief throughout pregnancy and postpartum.

DISCUSSION

The assumption of rheumatologists, based on previous studies, that almost all patients with RA will experience a remission of disease activity during pregnancy does not seem to be valid today. In this nationwide, prospective study, approximately one-quarter of women were in remission in the third trimester, despite the fact that medication use was remarkably reduced during pregnancy compared with before conception. The mean disease activity scores decreased during pregnancy and increased postpartum, and after applying EULAR-defined response criteria, almost half of the women had at least a moderate response during pregnancy and more than one-third had at least a moderate flare postpartum. The postpartum flare may be underestimated because medication use was remarkably increased after delivery.

This is the first study to use the DAS28 as a validated disease activity score to measure disease activity during pregnancy. Therefore, any comparison with previous studies can only be made indirectly. In the present study, 48% of patients who had at least moderate disease activity (DAS28 > 3.2) in the first trimester had an improvement in disease activity during pregnancy. Only one large prospective study has been performed for comparison. In that study, performed by Barrett et al, 140 participants were scored for joint pain and swelling in the third trimester and 1 month and 6 months postpartum (2).

Improvement in RA during pregnancy, however, was recorded retrospectively by self-report. In that study, 65% of the patients retrospectively reported an improvement in pain and swelling compared with before pregnancy. In addition, a combination of smaller prospective studies (a total of 66 pregnancies) showed improvement in disease activity in approximately two-thirds of pregnancies (8-12). That improvement was measured either by Camp index or by tender and swollen joint scores that were rated between 0 and 3 (8-12). Three of these studies selected patients with moderate to high levels of disease activity prior to pregnancy (9,10,12). In our study, changes in disease activity were also measured subjectively by means of a 3-point Likert scale (improved, stable, or deteriorated) between each visit (data not shown). A total of 77% of women reported an improvement at 1 visit, at least, during pregnancy. A difference in outcome between measuring disease activity by DAS28 or patient self-report might also be explained by the fact that in the latter method, patients may also take into consideration their decreased use of medication during pregnancy.

In this study, 27% of patients were in remission in the third trimester according to the DAS28. This is comparable with the percentages of remission shown in previous studies in which other definitions were used. Barrett et al (2), in a manner quite similar to Nelson et al (9), defined remission as using no antirheumatic drugs and having no painful and no swollen joints. In these 2 studies, 16% and 39% of patients, respectively, were in remission in the third trimester. In our study, women had no swollen and no painful joints in the third trimester in 14% of pregnancies, and in only 8% of all pregnancies, no antirheumatic drugs were used.

In the present study, deterioration of RA postpartum was present in at least 39% of all patients with at least a moderate flare according to reversed EULAR response criteria. At least 53% of our patients noted a deterioration on the Likert scale at 12 weeks postpartum compared with 6 weeks postpartum. Barrett et al demonstrated that 62% had more affected joints postpartum, and in ~70% of their patients, a deterioration in disease activity was self-reported at 1 and 6 months postpartum (2). In addition, Barrett et al showed that the median number of affected joints significantly increased from 8 during pregnancy to 10 joints at 6 months postpartum. At the same time, in 50% of those patients, treatment was increased postpartum. In our study, methotrexate and biologic agents were added to the prednisone or sulfasalazine therapy in 40% and 11% of patients, respectively, for adequate disease control postpartum.

The differences in improvement rates during pregnancy and relapse rates postpartum can therefore be explained by various factors. First, subjective measurements seem to show higher percentages of improvement and

deterioration than the objective measurements of disease activity used in this study. Second, in many previous studies, only patients with active disease before pregnancy entered the study. In the present study, all women with RA entered, and a higher percentage of improvement was shown in women with RA with higher disease activity in the first trimester. Finally, as a consequence of better treatment options, the percentages of improvement and deterioration may also be lower today than previously described, because patients may have lower disease activity before pregnancy compared with previous studies and are treated more aggressively postpartum.

Before conception, medication use in patients was remarkably reduced because most DMARDs are contraindicated during pregnancy. Despite this reduction, a decrease in disease activity was still observed, therefore the observed decrease in disease activity during pregnancy must be considered as a consequence of the beneficial effect of pregnancy itself. Another argument that supports the proposal that pregnancy itself has a beneficial effect on disease activity is that treatment of RA during pregnancy was almost completely restricted to sulfasalazine and low-dose prednisone, and it is known that this combination alone is insufficient to induce remission in patients with RA (13).

For daily clinical practice in rheumatology, this study demonstrated that neither presence of RF, as in the study by Barrett et al (2), nor presence of erosions or anti-CCP was associated with improvement during pregnancy or postpartum flare. The levels of RF and anti-CCP in the PARA study were stable during pregnancy until 6 weeks postpartum; only IgM-RF decreased postpartum when treatment was resumed (14). It has previously been suggested that postpartum flare is associated with the cessation of nursing. This assumption, however, could not be tested in the present study because patients have to stop nursing in order to restart treatment when they flare. Furthermore, this study gives rheumatologists additional evidence that patients with low disease activity before pregnancy remain relatively stable, whereas patients with moderate to high disease activity will improve the most.

Up until now, various studies have been undertaken to explain the beneficial effect of pregnancy in RA and many hypotheses have been formulated. Nevertheless, the exact reason is still unknown. Suppression of the immune system by HLA incompatibility between mother and child has been shown to be associated with a favourable disease course (9). In addition, biochemical changes such as elevation of α2-glycoprotein levels during pregnancy (11) and an increase in IgG glycosylation (10) were related to the improvement of disease activity. Finally, as is still hypothesized, a shift in T cell function from a Th1 phenotype to a Th2 may be important (15). The PARA study will provide

excellent opportunities for future laboratory studies on autoantibodies and immune regulation during pregnancy and for epidemiologic investigations of pregnancy outcome related to disease activity during pregnancy.

Finally, the PARA study has some limitations. First, the analyses were restricted to women (n = 84) with a complete data set, because medication use could not otherwise be clearly and correctly interpreted. The missing data were, however, completely random, and when the analyses were repeated including all eligible women (n = 100), similar results were obtained. Second, the present analysis was restricted to all data of singleton pregnancies because twin pregnancies result in more physical problems. Third, pregnancy outcome was self-reported; however, this method was verified with medical charts and was found to be valid and accurate for all data reported (16).

In conclusion, this study demonstrates that during pregnancy, patients go into remission and deteriorate postpartum, although less frequently than previously described.

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APPENDIX 3.1

A. EULAR response criteria for the definition of improvement during pregnancy (6).

DAS28 at 3rd trimester	Decrease of DAS28 1st trimester with		
	> 1.2	*> 0.6 AND ≤ 1.2*	*≤ 0.6*
≤ 3.2	*Good response*	*Moderate response*	*No response*
> 3.2 AND ≤ 5.1	*Moderate response*	*Moderate response*	*No response*
> 5.1	*Moderate response*	*No response*	*No response*

B. 'Reversed' EULAR response criteria for the definition of deterioration postpartum.

DAS28 at 12 or 26 weeks postpartum	Increase of DAS28 6 weeks postpartum with		
	> 1.2	*> 0.6 AND ≤ 1.2*	*≤ 0.6*
> 5.1	*Severe flare*	*Moderate flare*	*No flare*
> 3.2 AND ≤ 5.1	*Moderate flare*	*Moderate flare*	*No flare*
≤ 3.2	*Moderate flare*	*No flare*	*No flare*

3.2

AUTOANTIBODIES DURING PREGNANCY AND POSTPARTUM

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"Women with rheumatoid arthritis negative for anti-CCP and rheumatoid factor are more likely to improve during pregnancy, whereas in autoantibody positive women autoantibody levels are not influenced by pregnancy."

Objectives. To determine whether changes in levels of anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF) are associated with the spontaneous improvement of rheumatoid arthritis (RA) during pregnancy and with the subsequent flare postpartum.
Methods. Disease activity scores from the Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA)-study of 118 patients were available for analysis. Before conception (if applicable), at each trimester and at 6, 12 and 26 weeks postpartum levels of the autoantibodies anti-CCP, IgM-RF, IgG-RF and IgA-RF were determined. Responses in disease activity were classified according EULAR response criteria during pregnancy and postpartum, and associated with the presence or absence of autoantibodies.
Results. The median levels of anti-CCP and all subclasses of RF during pregnancy were stable, whereas postpartum the levels of anti-CCP, IgM-RF and IgA-RF declined. A significantly higher percentage of women without autoantibodies (both anti-CCP and RF negative) improved compared with women positive for either or both autoantibodies (75% vs 39%, p = 0.01). The occurrence of a flare postpartum was comparable between these groups.
Conclusions. Improvement of disease activity of RA during pregnancy was not associated with changes in levels of autoantibodies during pregnancy, however, improvement may occur more frequently in the absence of anti-CCP and RF.

INTRODUCTION

Pregnancy is the only natural situation where improvement of rheumatoid arthritis (RA) occurs and flares after delivery (1). However, the aetiology of this spontaneous improvement of RA during pregnancy and that of the flare postpartum is still unknown (1-5). Insight into this mechanism may enlarge our knowledge on pregnancy-induced remission and also contributes to a better understanding of pathogenic mechanism RA in general.

Evidence for a role of the B cell and autoantibodies in the pathogenesis of RA is accumulating (6-7). Anti-cyclic citrullinated peptide autoantibodies (anti-CCP) and rheumatoid factor (RF) are not only important in diagnosing RA (8,9) and in the prediction of severity of the disease (10,11), but are also thought to play an important role in the pathophysiology of this disease (12). Other evidence in support of B cells is derived from clinical studies demonstrating improvement of disease activity upon treatment with B-cell targeted therapies (13). However, whether changes in B-cell function, as reflected in levels of anti-CCP and RF during pregnancy and postpartum, are associated with improvement of RA during pregnancy or with the flare after delivery is not known.

The two aims of the present study, therefore are (I) to determine whether changes in levels of anti-CCP and RF can be associated with the spontaneous improvement of rheumatoid arthritis (RA) during pregnancy, or with the subsequent flare postpartum, and (II) to determine whether presence or absence of autoantibodies is associated with the disease course of RA patients during pregnancy.

PATIENTS AND METHODS

Patient population

The current study is embedded in the PARA-study, and has been described previously in detail (14). Briefly, all rheumatologists working in the Netherlands were asked to recruit patients with RA, according to the 1987 revised ACR criteria, who had a wish to conceive or who were already pregnant (preferably in their first trimester) (8). During the study the patient's own rheumatologists provided patient care. For present analysis data were collected between May, 2002, till November, 2006. Only data of women were used, that were available from before pregnancy or first trimester till 26 weeks postpartum onwards. Women who had a miscarriage in the first trimester were not included. No woman was included twice.

Data collection

Patients were visited at home, they were visited before conception (prepregnancy), at each trimester (8-12, 20, and 30 weeks of gestation) and three times postpartum (6, 12, and 26 weeks). The visit prepregnancy took place if a woman had a wish to conceive, when she did not conceive within a year after this visit, another visit prior to pregnancy took place. At each visit serum was stored for determination of autoantibodies and disease activity was measured. Presence of anti-CCP, RF, and erosions were ascertained from patient's medical records.

Determination of anti-CCP and RF (IgM, IgG and IgA)

In all sera the levels of anti-CCP antibodies were measured with the ImmunoCAP EliATM CCP test (Phadia AB, Uppsala, Sweden) as routinely used in our diagnostic laboratory. The test was performed according to the manufacturer's instructions. As defined by the manufacturer a positive anti-CCP antibody level was defined as a concentration of anti-CCP antibodies above 10 U/ml. The levels of IgM-RF, IgG-RF and IgA-RF in the sera were all measured by ELISA (HYCOR Biomedical, Inc, California, USA). The cut-off levels were determined in our laboratory by using the sera of 100 healthy voluntary blood bank donors. For each subclass of RF, the level above which only 5% of

healthy controls were tested as positive was defined as the cut-off level. A positive RF was defined in present study as a level above the cut-off level: IgM-RF > 24 IU/mL, IgG-RF > 40 IU/mL, and IgA-RF > 30 IU/mL.

Determination of disease activity

A research physician or research nurse performed a standardized joint count of 28 joints for swelling and pain as recommended by the EULAR Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT) (15). C-reactive protein (CRP) levels were measured in serum by Tina-quant® CRP (Roche Diagnostic GmbH, Mannheim, Germany).
As described previously, disease activity was calculated using a Disease Activity Score of 28 joints (DAS28) with three variables, consisting of a swollen joint count, a tender joint count and a CRP level (mg/L) (DAS28-CRP-3) (16,17).

Data analysis

Levels of autoantibodies during pregnancy and postpartum

To determine whether autoantibody levels changed during pregnancy and after delivery only data of those women were used that were classified as positive for the presence of that autoantibody. Patients were classified as positive either when the presence of an autoantibody was reported in medical records, or when the autoantibody was tested positive at first visit. All other patients were classified as negative. Levels of autoantibodies are expressed as median ± interquartile range (IQR).

To determine whether changes in autoantibody levels were associated with improvement of RA during pregnancy and with the flare after delivery, patients were classified for their clinical response during and after pregnancy.

For classification during pregnancy, improvement of disease activity between the first and third trimesters was defined according to the EULAR response criteria as ‘good’, ‘moderate’ or ‘no’ responders as defined by the ESCISIT (see Appendix 3.2.A) (15,16). Since the baseline requirement for the EULAR response criteria is that patients have an initial DAS28 of at least 3.2, analyses could be performed on a subgroup of patients. Differences in anti-CCP, IgM-RF, IgG-RF, and IgA-RF levels were calculated between the first and third trimesters and compared between ‘responders’ (‘good’ and ‘moderate’ responders combined), and ‘no responders’.

For classification postpartum, flare of disease activity between 6 weeks and 12 weeks, as well as between 6 weeks and 26 weeks was defined according to the

'reversed' EULAR response criteria of disease activity of RA, as described previously (14). These reversed EULAR response criteria classify a flare as 'severe', 'moderate' or 'no' flare. Also for this analysis patients were categorized as having a 'flare' (severe and moderate flare combined) or 'no flare' postpartum (see Appendix 3.2.B). This classification for flares postpartum was applied to all patients; there was no baseline DAS28 requirement. The differences in levels of anti-CCP, IgM-RF, IgG-RF and IgA-RF were calculated between 12 and 6 weeks postpartum and between 26 and 6 weeks postpartum. The largest change in each autoantibody level postpartum was associated with the disease course postpartum.

Disease course during pregnancy and postpartum and presence of autoantibodies

Changes in disease course during pregnancy and postpartum were determined in women who were classified according to the presence of autoantibodies: 'both negative', 'either anti-CCP or RF positive', and 'both positive'. Subsequently it was determined whether the percentages of women who improved during pregnancy and who flared postpartum, were different in these defined groups.

Statistical analysis

Changes in autoantibody levels within patients between different time points were tested for significance by Wilcoxon's test.

Mann-Whitney-U test was used to test for significance the differences in changes in autoantibody levels between different subgroups of patients.

The significance of the association between achievement of clinical improvement, or the occurrence of a flare postpartum and the presence of one or other of the tested autoantibodies, was tested with a Fisher's exact test or Chi-squared test, depending on the number of examined women in each group. A two-sided $p<0.05$ was considered statistically significant. SPSS for Windows (Chicago, IL) version 15.0 was used.

Ethics

This study complies with the Helsinki declaration and the ethical committee at the Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands approved this study.

RESULTS

Patients recruitment data and demographics

From May 2002 until November, 2006, data of 118 pregnancies with a complete dataset from first trimester to 26 weeks postpartum were obtained. Data from 59 pregnancies were also available from before conception. Demographics of patients are given in Table 3.2.1. According to the EULAR response criteria 47% (34/72) of patients with an initial DAS28 3.2 in first trimester, were 'responders' during pregnancy, and postpartum 36% (42/118) of patients had a 'flare' according to the reversed EULAR response criteria.

Table 3.2.1: Demographics and clinical features of 118 RA patients

Baseline characteristics	118 RA patients
Mean age at delivery in years (SD)	32.3 (3.6)
Median disease duration at delivery in years (range)	5.7 (0.7 - 29.7)
Patients with disease duration < 2 years, % (n)	16 (19)
Anti-CCP present, % (n)	62 (73)
RF* present, % (n)	74 (87)
IgM-RF	73 (86)
IgG-RF	33 (39)
IgA-RF	35 (41)
Erosions present, % (n)	70 (81)
DAS28-CRP-3 > 3.2 in first trimester, % (n)	61 (72)
Classification of disease activity during pregnancy	
Good response/ moderate response, % (n)	47 (34)**
no response, % (n)	53 (38)**
Classification of disease activity postpartum	
severe deterioration/ moderate deterioration, % (n)	36 (42)
no deterioration, % (n)	64 (76)
Use of methotrexate prior to wish to conceive, % (n)	58 (68)
Use of (oral) prednisone use prior to pregnancy, % (n)	43 (50)
Use of biologicals prior to wish to conceive, % (n)	10 (12)
Mean number of DMARDs and biologicals ever used prior to wish to conceive, n (SD)	2.5 (1.5)

* RF = rheumatoid factor ** of 72 patients with DAS28-CRP-3 > 3.2 in first trimester

Course of autoantibody levels during pregnancy and postpartum

In Figure 3.2.1(a-d) the courses of the median levels with IQR of autoantibodies during pregnancy are shown. Only levels of patients who were positive for a certain autoantibody are shown. Median levels at first trimester of anti-CCP (200 U/mL, IQR 782, n = 73), IgM-RF (133 IU/mL, IQR 200, n = 86), IgG-RF (48 IU/mL, IQR 66, n = 39), and IgA-RF (61 IU/mL, IQR 49, n = 41) did not change with statistical significance during pregnancy. Postpartum, however, median levels of all autoantibodies, except IgG-RF, statistically significant decreased. Median levels of anti-CCP decreased from 229 U/mL (IQR 850) to 194 U/mL (IQR 497) (n = 73, p = 0.023), median levels of IgM-RF from 152 IU/mL (IQR

252) to 88 IU/mL (IQR 199) (n = 86, p < 0.001) and median levels of IgA-RF from 50 IU/mL (IQR 48) to 42 IU/mL (IQR 58) (n = 41, p = 0.015).

Since autoantibody production might be influenced early in pregnancy, data of 59 women visited before pregnancy were analyzed separately. No statistically significant changes were found between median autoantibody levels before pregnancy and at first trimester (see Table 3.2.2), or between disease activity at these time points (mean DAS28-CRP-3 3.8 and 3.7 respectively).

Table 3.2.2: Median levels of autoantibodies in subgroup analysis of women visited prepregnancy and at first trimester (n = 59). Statistical analyses were performed with Wilcoxon's tests.

Autoantibody	prepregnancy	1st trimester	p
Anti-CCP U/mL (IQR), n = 34	142 (299)	163 (308)	0.84
IgM-RF IU/mL (IQR), n = 43	164 (252)	112 (215)	0.12
IgG-RF IU/mL (IQR), n = 22	44 (32)	47 (53)	0.51
IgA-RF IU/mL (IQR), n = 20	53 (38)	51 (37)	0.78

Course of autoantibody levels in responders versus no responders during pregnancy and postpartum

During pregnancy the change in levels of anti-CCP at first and third trimester were not related to the clinical disease course, classified according to the EULAR response criteria in responders and no responders. Also the changes in serum levels of IgM-RF, IgG-RF or IgA-RF between the first and third trimester were not statistically significantly different between responders en no responders during pregnancy as shown in Table 3.2.3. Postpartum the largest difference in levels of anti-CCP was measured either between 12 and 6 weeks postpartum or between 26 and 6 weeks postpartum. The largest difference in levels of anti-CCP was not associated with a flare postpartum. The median differences in levels of anti-CCP, and median differences in levels of IgM-RF, IgG-RF and IgA-RF postpartum were not associated with a flare (Table 3.2.3).

Disease course during pregnancy and postpartum and presence of autoantibodies

Finally, patients (n = 118) were classified as being positive or negative for a certain autoantibody. In some women anti-CPP (n = 2) or RF (n = 10) was documented as positive in medical charts, although they tested negative at first visit. Neither the presence of anti-CCP, nor of any RF was more likely to be present in responders during pregnancy or in patients with a flare postpartum (all p > 0.05). However, in subsequent analysis on patients classified for autoantibodies as 'both negative' compared with patients classified as 'either-or' or 'both positive' (see Table 3.2.4), the percentage of responders during pregnancy of the first group was significantly higher (75% vs 39%, p = 0.01).

Comparable results were obtained when classification of the autoantibody status was made only by autoantibodies measured at first visit. Postpartum, presence of autoantibodies was not associated with flares (p = 0.42).

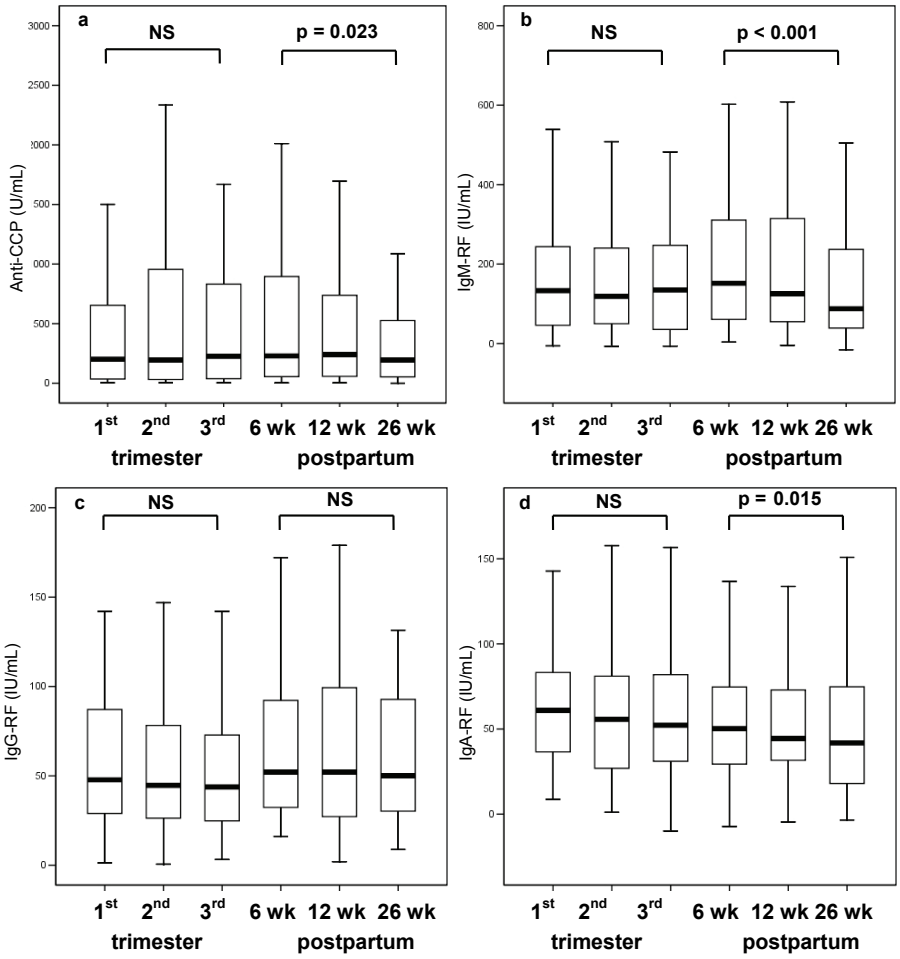

Figure 3.2.1: Boxplots of autoantibody levels in RA women during pregnancy and postpartum (n = 118). a) Levels of anti-CCP (n = 73); b) Levels of IgM-RF (n = 86); c) Levels of IgG-RF (n = 39); d) Levels of IgA-RF (n = 41). Each box represents the 25th-75th centiles; lines inside the boxes represent the medians. Lines outside the boxes represent the 10th and 90th centiles. Statistical analyses were performed by Wilcoxon's tests. (NS = not significant)

Table 3.2.3: Median differences in levels of autoantibodies by different disease courses during (between first and third trimester) and after pregnancy (maximum between 6-12 or 6-26 weeks postpartum).

	Anti-CCP (U/mL)	IgM-RF (IU/mL)	IgG-RF (IU/mL)	IgA-RF (IU/mL)
Responders (n = 34)				
median (IQR; n)	+24 (323; 21)	-0.8 (96; 23)	+1.7 (42; 9)	-0.6 (27; 12)
Non-responders (n = 38)				
median (IQR; n)	+ 7 (149; 28)	+0.1 (87; 32)	-3.5 (23; 20)	+3.2 (26; 18)
Flare (n = 42)				
median (IQR; n)	+15 (124; 24)	+4.2 (97; 28)	+3.9 (37; 13)	-2.2 (19; 15)
No flare (n = 76)				
median (IQR; n)	+4.3 (140; 46)	+5.2 (66; 54)	+8.8 (29; 24)	+4.8 (21; 25)

Table 3.2.4: Patients characteristics and disease activity responses classified according to presence of anti-CCP and RF

	Anti-CCP and RF *both negative* (n = 26)	*Either* Anti-CCP *or* RF *positive* (n = 24)	Anti-CCP and RF *both positive* (n = 68)	p *
Age mean (SD)	31.9 (3.6)	33.5 (4.1)	32.2 (3.5)	0.35
Disease duration median (months)	83	56	57	0.03#
DAS28-CRP-3 > 3.2 at first trimester % (n/N)	62 (16/26)	29 (7/24)	72 (49/68)	0.95
prednisone use during pregnancy % (n/N)	27 (7/26)	46 (11/24)	44 (29/66)	0.11
sulfasalazine use during pregnancy % (n/N)	35 (9/26)	25 (6/24)	36 (24/66)	0.90
responders ** during pregnancy % (n/N)	75 (12/16)	14 (1/7)	43 (21/49)	0.01#
flare *** postpartum % (n/N)	42 (11/26)	33 (8/24)	34 (23/68)	0.42

* Anti-CCP and RF 'both negative' versus combined groups of "either-or" and both positive (ANOVA, Chi-square or Fisher Exact test) ** moderate and good responders combined; analysis is restricted to patients with DAS28-CRP-3 > 3.2 in 1st trimester, n = 72 *** 'moderate and severe' flare postpartum combined # $p \leq 0.05$

DISCUSSION

In this large prospective study of pregnant RA patients, for the first time levels of anti-CCP and subclasses of RF were measured during pregnancy. Anti-CCP remained stable during pregnancy, even in women with spontaneously improved disease activity. As reported previously in smaller studies, similar results were obtained regarding RF (18). Postpartum however, when medication was resumed, levels of all autoantibodies, except IgG-RF, declined. The changes in the measured autoantibody levels, however, were not associated with the disease course during and after pregnancy. But, surprisingly,

women who were negative for both autoantibodies were more likely to improve during pregnancy.

The results of this study are in contrast with changes in autoantibody levels that were found in association with disease course outside pregnancy (19). Outside pregnancy, the levels of autoantibodies (anti-CCP and RF) in relation to clinical disease activity and treatment have been investigated more extensively. In RA patients who were only treated with traditional DMARDs, mainly IgM-RF has been found to correlate positively with clinical disease activity, while IgG-RF, IgA-RF and anti-CCP did not correlate with serum levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or white blood cell counts (20-21). More recent literature describe a decline in the levels of anti-CCP and IgM-RF upon treatment with tumour necrosis factor (TNF) alpha blocking agents (22,23), while the presence of IgA-RF may only be related to a poor clinical response to these biologicals (24-27).

The lack of association between levels of autoantibodies and disease course during pregnancy, brings the study design into question, however:

1 the number of patients included seems sufficient, since postpartum a statistically significant decline in autoantibody levels (anti-CCP, IgM-RF and IgA-RF) was observed;
2 in analogy with previous studies outside pregnancy (21), disease activity in the present cohort may be too well-established to demonstrate changes in autoantibody levels. However, subgroup analysis on only patients with recent (< 2 years, n = 19) RA also failed to demonstrate a decline in autoantibody levels during pregnancy;
3 medication use hardly changed during pregnancy in our cohort, (reported previously(14)), so this is unlikely to have biased our results. Although dosages of medication were changed in 50% of patients during pregnancy, the actual medication remained the same; mainly sulfasalazine (35% of patients) and prednisone (30% of patients). Postpartum, however, the effect of medication use on autoantibody levels such as anti-CCP, IgM-RF and IgA-RF, as in prior studies, might have been preserved since the levels of these antibodies declined in the postpartum period and the use of methotrexate and biologicals was started in over 40% of patients before 26 weeks after delivery.

The finding that women who were negative for both autoantibodies are more likely to improve during pregnancy, supports the hypothesis that RA is a heterogeneous disease with different pathogenic mechanisms involved (28). In analogy with SLE, where presence of auto-antibodies together with increased Th2-mediated responses during pregnancy, may make that disease flare during

pregnancy (29), one can speculate that similar mechanisms are responsible for the observation that disease activity is less likely to improve during pregnancy in RA-patients with autoantibodies (anti-CCP and/or RF).

Although a decrease in levels of autoantibodies during pregnancy was not found in the present study, this study does not rule out that other functions of B cells and autoantibodies might play a role in the improvement of RA during pregnancy. Other functions in the pathogenesis of RA that are attributed to B cells and might be influenced by pregnancy include the production of (inflammatory) cytokines and chemokines, antigen presentation and an important function in the formation of ectopic lymphoid tissue (6). Furthermore it has been shown that during pregnancy the pathogenecity of autoantibodies are modified by differences in glycosylation of IgG (30-32). Since the glycosylation of IgG determines its ability to bind to complement and to Fc receptors, a role for glycosylation of IgG in the pregnancy induced remission of RA has been suggested.

In conclusion, in the world's largest cohort of pregnant RA patients, no association was found between improvement of disease activity during pregnancy and changes in levels of autoantibodies. However, in the absence of autoantibodies (anti-CCP and RF), improvement of RA during pregnancy occurred more frequently. Further investigations will be needed to discover whether improvement during pregnancy is related to other roles of B cells beyond autoantibody production.

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APPENDIX 3.2

A. EULAR response criteria for the definition of improvement during pregnancy (15).

DAS28 at 3rd trimester	Decrease of DAS28 1st trimester with		
	> 1.2	*> 0.6 AND ≤ 1.2*	*≤ 0.6*
≤ 3.2	*Good response*	*Moderate response*	*No response*
> 3.2 AND ≤ 5.1	*Moderate response*	*Moderate response*	*No response*
> 5.1	*Moderate response*	*No response*	*No response*

B. 'Reversed' EULAR response criteria for the definition of deterioration postpartum (14).

DAS28 at 12 or 26 weeks postpartum	Increase of DAS28 6 weeks postpartum with		
	> 1.2	*> 0.6 AND ≤ 1.2*	*≤ 0.6*
> 5.1	*Severe flare*	*Moderate flare*	*No flare*
> 3.2 AND ≤ 5.1	*Moderate flare*	*Moderate flare*	*No flare*
≤ 3.2	*Moderate flare*	*No flare*	*No flare*

4

PREGNANCY OUTCOME

4.1

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PREGNANCY OUTCOME IN RA: RESULTS FROM A NATIONWIDE PROSPECTIVE STUDY

Higher disease activity of RA during pregnancy is associated with lower birth weight

Objective. To determine pregnancy outcome of rheumatoid arthritis (RA) patients in relation to disease activity and prednisone use.
Methods. In a prospective study, pregnant women with RA were visited preconceptionally, if possible, and at each trimester and postpartum. Clinical characteristics, disease activity, medication use, and pregnancy outcome were analyzed. To examine the independent influence of prednisone use and disease activity on birth weight, regression analyses were performed adjusting for gestational age at delivery, sex of newborn, smoking, educational level, parity and assisted reproduction. Kaplan-Meier curve and Log-Rank-test were performed to examine the association between prednisone use and gestational age at delivery.
Results. Data of 152 Caucasian RA patients with singleton pregnancies were available. Both mean birth weight (3379 g, SD 564) and mean birth weight standard deviation score (SDS) (+0.1, SD 1.1), i.e. birth weight adjusted for gestational age and sex of newborn, were comparable to the general population. In multiple linear regression on birth weight and birth weight SDS, adjusted for covariates, only disease activity was associated with lower birth weight ($p = 0.025$). Gestational age at delivery of patients using prednisone was significantly shorter (38^5 vs 39^6 weeks, $p = 0.006$), and their delivery more often premature (< 37 weeks, $p = 0.004$).
Conclusion: Pregnancy outcome in women with well-controlled RA is comparable to the general population. The effect of prednisone on birth weight is mediated by shortening gestational age at delivery, whereas a higher disease activity independently influences birth weight negatively suggesting an immune-mediated mechanism.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic auto-immune disease leading to a destructive arthropathy (1). In the last decades, the pharmacological treatment of RA has improved considerably (2). Irrespective of medical treatment, pregnancy is a special situation that is associated with a spontaneous decrease of disease activity in patients with RA (3-8).

Conversely, pregnancy outcome might be negatively influenced by RA, since unfavourable pregnancy outcome has been demonstrated in several rheumatic diseases (9-13). However, only few studies examined pregnancy outcome in women with RA (5, 10, 11, 13-15). These studies were mostly retrospective, conflicting, and results were easily confounded by selection. Studies regarding the newborns of women with RA showed lower birth weight (11), especially in newborns of women who had high disease activity during pregnancy (15). However, this was done without concerning medication use as a covariate. Low

birth weight, but especially small for gestational age, is not only an important risk factor for perinatal complications, but is also associated with developmental delay (16), metabolic syndrome and cardiovascular disease in children, and in (late) adulthood (17-19). In contrast to the reports that mean birth weight was lower in RA patients compared with healthy controls, the risk of low birth weight defined as <2500 gram, does not seem to be elevated in women with RA (14, 15). However higher rates of small for gestational age (SGA) have been reported as well (11, 13). Furthermore, prednisone use may be associated with both lower birth weight and shorter gestational age at delivery (20), but the only study thus far conducted lacked power to elucidate the influence of disease activity and prednisone use on birth weight separately (15).

Our large prospective nationwide cohort of pregnant women with RA enables us to provide more insight into the influence of RA on pregnancy outcome (8). Measurements of standardized disease activity scores during pregnancy and well-documented medication use make it possible to discriminate the independent effect of these variants on pregnancy outcome, and elucidate their mechanisms.

In addition to this, new insight into pregnancy outcome and birth weight has resulted into the development of birth weight standard deviation score (SDS), in which birth weight is adjusted for gestational age at delivery and sex of newborn (21, 22). This is the first time that birth weight of a cohort of RA patients is analyzed this way.

The objectives of the present study are to determine 1) the pregnancy outcome in women with RA and 2) whether disease activity and prednisone use during pregnancy influences birth weight independently, or whether the effect on birth weight is mediated via gestational age at delivery.

PATIENTS AND METHODS

Current study is embedded in the PARA-study (Pregnancy-induced Amelioration of Rheumatoid Arthritis -study) which is a prospective nationwide study in the Netherlands including women with RA who are visited before pregnancy (if possible), at each trimester during pregnancy, and three times after delivery (6, 12 and 26 weeks postpartum). The PARA study was described in detail previously (8). Briefly, rheumatologists in the Netherlands asked patients with RA to be approached by our research team. Women were eligible if they met the 1987 ACR criteria for RA, had a pregnancy wish or were already pregnant, and had a good understanding of the Dutch language. Women not

already visited preconceptionally were visited from the applicable trimester and onwards.

In the present analysis on pregnancy outcome in women with RA, only singleton pregnancies of Caucasian women who delivered a baby without congenital deformities were included. No women contributed twice, only results of a woman's first application were included. These inclusion criteria were formulated as such, since birth weight is different in non-Caucasians (23), in twin pregnancies, and in newborns with congenital deformities. Finally, inclusion of a second, subsequent pregnancy might introduce bias, since it may be a selection of women with a previously good experience with the course of RA during and after pregnancy and/or with the pregnancy outcome.

Disease activity

Disease activity was measured with a disease activity score (DAS28-CRP-3) with three variables: the total numbers of swollen and tender joints of 28 predefined joints, and C-reactive protein (CRP) level (24). It has previously been shown that disease activity during pregnancy can be measured most reliably with this variant of the DAS28 (25). Joint counts were performed at all visits by a research nurse or medical doctor, and blood samples were drawn for CRP measurements by Tina-Quant®CRP (Roche Diagnostics, GmBH, Mannheim, Germany).

Pregnancy outcome

Clinical characteristics including maternal age at delivery, rheumatologic history, obstetric history, smoking habits, educational level and medication use were collected by interview. The rheumatologic history was ascertained by obtaining information from patient's own rheumatologist on the duration of RA, erosion status, presence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP). Presence of these autoantibodies was determined in our laboratory as well. Smoking habits were obtained by interview before and at first trimester during pregnancy. Only if a patient smoked at first trimester she was defined as smoking during pregnancy. Educational level of a woman was collected, of most of them after the last visit, and was categorized according to the highest level attained; low (≤ 9 yrs: primary school, lower and intermediate secondary schooling or lower vocational training), intermediate (10-14 yrs: higher secondary schooling or intermediate vocational training), and high (≥ 15 years: higher vocational training or university). Medication use was monitored throughout all visits.

Method of conception was obtained by interview and was categorized as spontaneous or assisted reproductive endocrinology techniques. Assisted

techniques included ovulation induction, Intra Uterine Insemination (IUI), In Vitro Fertilization (IVF), or Intracytoplasmic Sperm Injection (ICSI).

Data on pregnancy outcome included spontaneous abortions, intrauterine foetal death, birth weight, gestational age at delivery, gender of child, mode of delivery and location of delivery. Collected pregnancy complications included the incidence of prematurity, small for gestational age, and hypertensive disorders (gestational hypertension and preeclampsia). The data were collected at various visits by interview and analysis of medical charts. Information on the mode of delivery was subdivided into spontaneous birth, instrumental vaginal birth, or caesarean section. Instrumental vaginal birth was defined as use of forceps or ventouse extractor during labour, and the reason was documented as 'failure to progress' or 'foetal distress'. Caesarean sections were documented as either 'elective' or 'emergency'.

Birth weight was assessed in grams and also by birth weight SDS, the use of this reference standard facilitates evaluation of size deviation of the standard at birth (21). Birth weight SDS were calculated by means of following gender specific formulas:

♂

Birth weight SDS =

$$\frac{\sqrt{\text{bweight}} - \left(6.051836581 - 0.600816861 \times \text{ga} + 0.021243304 \times (\text{ga})^2 - 0.000220617 \times (\text{ga})^3\right)}{-3.896362859 + 0.338487494 \times \text{ga} - 0.009363082 \times (\text{ga})^2 + 0.000085226 \times (\text{ga})^3}$$

♀

Birth weight SDS =

$$\frac{\sqrt{\text{bweight}} - \left(8.867334794 - 0.847020906 \times \text{ga} + 0.028264820 \times (\text{ga})^2 - 0.000286775 \times (\text{ga})^3\right)}{-1.776113910 + 0.155674510 \times \text{ga} - 0.004184480 \times (\text{ga})^2 + 0.000036896 \times (\text{ga})^3}$$

With:

bweight = birth weight (kilogram)

ga = gestational age at delivery (weeks)

Small for gestational age (SGA) is defined as a birth weight SDS at least 2 SD below the mean (≤ -2 SD) (26).

The pregnancy complications in present study were defined as follows: spontaneous miscarriage as gestational age of < 16 weeks; prematurity as a delivery < 37 weeks (259 days) of gestational age, gestational hypertension, according to the criteria described by the 'International Society for the Study of Hypertension in Pregnancy', as systolic blood pressure ≥ 140mmHg and/or

diastolic blood pressure ≥ 90mmHg without proteinuria after 20 weeks of gestation in previously normotensive women (27). Preeclampsia was defined as gestational hypertension with concurrent proteinuria (> 2 g/l or 2+) (27, 28).

Statistical Analysis

Descriptive statistics on pregnancy outcome were presented as numbers and percentages.

To compare the pregnancy outcome of present cohort with the general population, two reference groups were used. The first reference group contains results of the general obstetric population registered in 'The Netherlands Perinatal Registry' (PRN). This registry covers almost all deliveries (about 179,000) pregnancies in the Netherlands in 2004 by linking the database of midwifes and general practitioners with the database of obstetricians (29). The vast majority (82%) of the registry consists of the pregnancy outcome of Caucasian women. The second reference group contains results of 'Generation R', which is a population-based prospective cohort study from foetal life until young adulthood of 10,000 pregnancies, conducted in Rotterdam, an urban area in The Netherlands, with children born between 2002 and 2006 (30). No statistical analyses were performed between present cohort and both registries, since inclusion criteria were not exactly comparable, and therefore those registries cannot be used as formal control groups.

To describe the association between disease activity at third trimester and birth weight or birth weight SDS, the following covariates were analyzed by regression analysis; maternal age, parity, smoking status during pregnancy, educational level, gestational age at delivery and sex of newborn (the latter two are not applicable for analyzing birth weight SDS, since these are incorporated in the score). First, simple linear regression was performed. Secondly, multiple regression analysis was performed with all possible explanatory variables that were associated with birth weight or birth weight SDS and those that had a p-value < 0.2 in simple linear regression. Smoking was addressed because of its known negative correlation with birth weight (31). Analyses were performed by multiple linear regression along with disease activity and prednisone use.

A Kaplan-Meier curve visualized the correlation between gestational age at delivery and prednisone use. Differences in gestational age at delivery between prednisone and non-prednisone users were assessed by the Log-rank (Mantel-Cox) test. The difference between the number of prednisone and non-prednisone using women with a gestational age at delivery < 37 weeks were addressed by Fisher's Exact test.

Two sided p-values ≤ 0.05 were considered as statistically significant. All statistical analyses were performed using SPSS version 15.0 for Windows.

Ethics

The PARA-study was approved by the Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands in June 2002. Written informed consent was obtained from all participants.

RESULTS

Patient recruitment

From May 2002 until August 2007, 388 patients were recruited by rheumatologists. Figure 4.1.1 shows the flow sheet of inclusion. After applying the inclusion criteria, only one more woman was excluded, since she was diagnosed with breast cancer during pregnancy. Therefore, 152 Caucasian women with RA with singleton pregnancies were eligible for present analyses.

Demographics

As shown in Table 4.1.1, women had a mean age at delivery of 32.5 years, slightly older than the general population, and had a median disease duration of 70 months (range 8-356 months) at delivery. Only 4.1% of RA patients smoked in the first trimester of pregnancy, this is much lower than documented in the general population reference groups. Artificial reproduction techniques were used in 18% of the patients, this is much more frequent than documented in the PRN reference group (3%).

Because some patients were included in the second or third trimester, DAS28-CRP-3 scores are lacking in 27 patients in first trimester, and in 12 patients in second trimester. Median disease activity throughout pregnancy (DAS28-CRP-3) decreased from 3.8 at the first trimester to 3.3 at the third trimester. These disease activity scores indicate that disease activity was well-controlled in this cohort during pregnancy. Correlation between DAS28-CRP-3 at first and second trimester was 0.715, and between first and third trimester 0.647 (Spearman's correlation coefficients, $p < 0.001$).

Only 10 patients changed prednisone use and/or their dosage throughout pregnancy and at each trimester slightly more than one third of women used prednisone. Prednisone use during the first trimester was strongly correlated with prednisone use during the second and third trimester ($r = 0.880$ and $r = 0.969$, respectively).

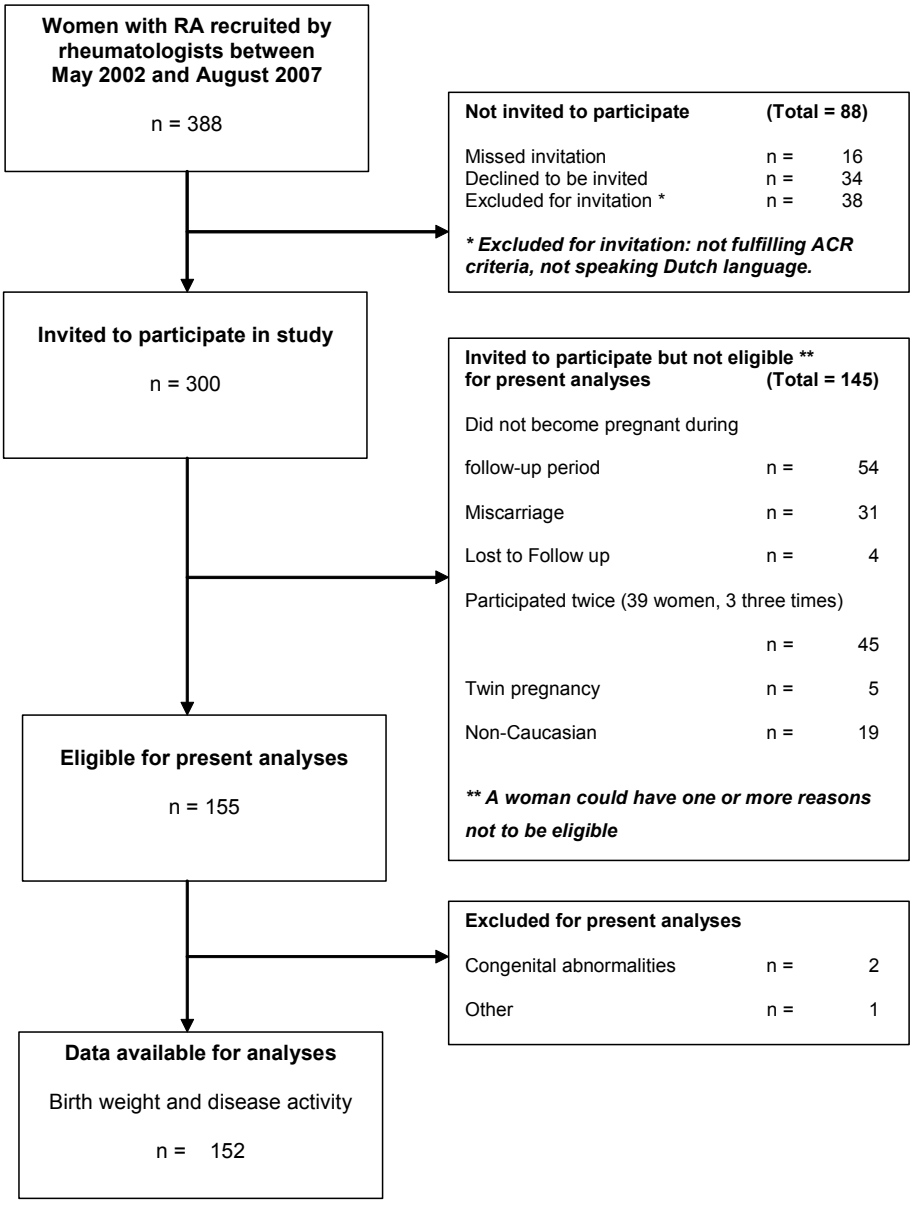

Figure 4.1.1 Flowsheet PARA-study

Table 4.1.1 – Descriptive characteristics of RA patients and reference groups *

	Present cohort	Reference groups	
	RA patients (n = 152)	PRN [b] (n = 175,498)	Generation R [c] (n = 3,659)
Mean age (SD) at delivery, yrs	32.5 (3.7)	30.5 (4.9)	31.2 (4.5)
Median duration (range) of RA at delivery, months	70 (8-356)		
RF status *%(n)*	75 (114)		
Anti-CCP *%(n)*	60 (91)		
Erosions *%(n)*	66 (101)		
Educational level %(n)			
- low	7.2 (11)		5.2[a]
- intermediate	38.2 (58)		37.2
- high	36.1 (55)		56.7
- missing	18.4 (28)		0.8
Parity %(n)			
-nulliparae	57.2 (87)	47	58.6
-multiparae	42.8 (65)	53	39.4
Smoking *%(n)*	4.1 (5)	--	17.0
Conception %(n)			
- Spontaneous	82.2 (125)	97	
- Assisted reproduction technique	17.8 (27)	3	
- ovulation induction	- 6.0 (9)		
- ovulation induction + Intra Uterine Insemination (IUI)	- 3.3 (5)		
- In Vitro Fertilisation (IVF)	- 5.2 (8)		
- IntraCytoplasmic Sperm Injection (ICSI)	- 3.3 (5)		
DAS28-CRP-3 third trimester (N = 148)			
- ≤ 3.2 (low)	47 (69)		
- 3.2-5.1 (intermediate)	44 (66)		
- > 5.1 (high)	9 (13)		
DAS28-CRP-3, mean (IQR)			
-trimester 1 (N = 125)	3.8 (1.0)		
-trimester 2 (N = 140)	3.6 (1.1)		
-trimester 3 (N = 148)	3.3 (1.0)		
Prednisone use %(n)			
-trimester 1 % (N = 127)	36 (46)		
-trimester 2 % (N = 140)	36 (50)		
-trimester 3 % (N = 150)	35 (52)		

* Values are the percentage (number) unless otherwise indicated. [a] Different defined as: low: primary school, intermediate: secondary school, high: higher education (23). PRN = The Netherlands Perinatal Registry, RA = rheumatoid arthritis, IQR = interquartile range.[b] (29); [c] (23)

Pregnancy outcome in women with RA

Pregnancy outcome is shown in Table 4.1.2. The mean birth weight of women with RA is within the normal birth weight range and the mean birth weight SDS was +0.1 (SD 1.1), which is comparable with the standard population.
Twenty-five patients required a caesarean section for delivery. About half of these patients required an elective caesarean section, due to foetal (n = 10 (breech presentation)), maternal (n = 1), or combined reasons (n = 1). The remaining half required an emergency caesarean section due to failure of progress during labor (n = 7), foetal distress (n = 4), or combined reasons (n = 2). Another twenty-five patients (18%) required an instrumental vaginal delivery, this is more frequent than documented in the PRN reference group (10.5%). When RA patients were categorized according to their disease activity at third trimester ('low' versus 'intermediate or high'), caesarean sections were performed significantly more often in the intermediate or high disease activity group (10% versus 22%, Chi-square p = 0.04), while instrumental vaginal births were equally performed in both disease activity groups (25% versus 19%, Chi-square p = 0.43).

The incidence of prematurity was 8.6%, and 3% was born as small for gestational age. The incidences of the hypertensive disorders in women with RA were 7.2% for gestational hypertension (n = 11) and 0.7% for preeclampsia with admission (n =1). Though the number of patients in present cohort is too small to properly study the incidence of these fairly rare complications, it does not seem to differ largely from the general population.

The influence of disease activity and prednisone use on birth weight

Univariate analysis

The association between birth weight and disease activity or prednisone use is shown in Table 4.1.3. We already showed that disease activity at third trimester is highly correlated with disease activity at first and second trimester. Disease activity at third trimester (DAS28-CRP-3) was significantly negatively associated with birth weight expressed in grams, as well as with birth weight SDS ($p < 0.001$ and $p = 0.025$ respectively). Similar data were obtained for disease activity at second and first trimester. Furthermore, prednisone use during pregnancy is significantly associated only with birth weight expressed in grams, but not with birth weight SDS ($p = 0.002$ and $p = 0.256$ respectively). This indicates that prednisone indirectly influences birth weight via gestational age at delivery.

Table 4.1.2 – Pregnancy outcome in RA patients and in reference groups *

	Present cohort	Reference groups	
	RA patients (n = 152)	PRN[a] (n = 179,457)	Generation R[b] (n = 3,659)
Mean birth weight, gram (SD)	3379 (564)	3363	3485 (555)
Mean gestational age at delivery, days (SD)	276 (11.2)	275 (15.7)	278 (11.9)
Mean birth weight SDS (SD)	+0.1 (1.1)		
Gender of child:			
Male	58 (88)	51.3	50.4
Mode of delivery: (n = 147)			
Spontaneous vaginal birth	65 (96)	75.3	
Instrumental vaginal birth	17 (25)	10.5	
- failure to progress	- 56 (14)		
- foetal distress	- 36 (9)		
- combined reason	- 8 (2)		
Caesarean section	17 (25)	14.2	
- elective CS	- 48 (12)	- 6.5	
- emergency CS	- 52 (13)	- 7.7	
Location of delivery child:			
At home	18 (27)	29.4	
Hospital	82 (125)	70.6	
Pregnancy complications:			
Prematurity (<37 weeks)	8.6 (13)	6.2	
Intruterine foetal death	0 (0)		
Birth weight SDS < -2 (SGA)	3.3 (5)		
Hypertensive disorders (verified)	7.2 (11)	8.5	
- Gestational hypertension	- 6.6 (10)	- 7.9	
- Preeclampsia with admission	- 0.7 (1)	- 0.4	

* Values are the percentage (number) unless otherwise indicated. PRN = Netherlands Perinatal Registry, RA = rheumatoid arthritis, SDS = Standard Deviation Score [a](29);[b](23)

To detect potential confounders on the association between birth weight or birth weight SDS and disease activity and prednisone use, simple linear regression analyses was carried out with several factors as independent variables as shown in table 4.1.3.

In simple linear regression on birth weight, parity and gestational age at delivery were most predictive (Table 4.1.3, left column). Multiparae gave birth to heavier newborns, and smoking was not associated with lower birth weight in this cohort. In simple linear regression on birth weight SDS (Table 4.1.3, right column), only parity and maternal age were both statistically significantly associated with birth weight SDS. While all other potential confounders were not significantly associated with birth weight SDS.

Table 4.1.3: Simple linear regression on birth weight and birth weight SDS

	Birth weight		Birth weight SDS	
Simple linear regression	Standardized coefficient (n = 152)[a]	p	Standardized coefficient (n = 152)[a]	p
DAS28-CRP-3 3rd trim	-108.9 [-190.6;-27.2]	0.009	-0.18 [-0.340;-0.023]	0.025
Prednisone use (yes)	-296.5 [-479.3;-113.7]	0.002	-0.21 [-0.574;0.154]	0.256
Gestational age at delivery (days)	+187.7 [142.6;232.7]	<0.001	--	--
Parity (multi)	+383.1 [210.44;555.8]	<0.001	+0.77 [0.438;1.104]	<0.001
Age of mother (years)	+18.5 [-6.0;43.1]	0.137	+0.05 [0.002;0.096]	0.041
Smoking (yes)	-15.0 [-522.5;494.6]	0.954	+0.41 [-0.570;1.389]	0.410
Gender (male)	+99.3 [-83.8;282.3]	0.286	--	--
Education level (low vs high)	-171.0 [-512.5;169.3]	0.321	-0.39 [-1.073;0.292]	0.260
Conception (assisted reproduction)	-5.8 [-243.1;234.6]	0.831	+0.05 [-0.409;0.509]	0.831

[a] n = 117 for education level

Multivariate analyses

In the multivariate analyses, higher disease activity at third trimester is significantly associated with lower birth weight and birth weight SDS after adjustment for all covariates (Table 4.1.4).

Table 4.1.4 - Regression analyses of birth weight and birth weight SDS with disease activity (DAS28-CRP-3 in third trimester) as dependent variable

	Crude			Adjusted		
	n	B [95% CI]	p	n	B [95% CI]	p
DAS28-CRP-3						
Birth weight	148 [a]	-111.9 [-193.6;-30.2]	0.008	117 [b]	-82.6 [-154.5;-10.6]	0.025
				141 [c]	-74.9 [-141.7; -8.0]	0.029
Birth weight SDS	148	-0.181 [-0.34 ; -0.023]	0.025	117 [d]	-0.193 [-0.362;-0.037]	0.025
				141 [e]	-0.174 [-0.331;-0.016]	0.031

[a]: adjusted for sex newborn [b]: adjusted for sex newborn, gestational age at delivery (in days), level of education (low, intermediate, high), smoking (yes/no), age of mother (in years at delivery), parity (0 or > 0), use of assisted reproduction technique (yes/no) , and prednisone use during pregnancy (yes/no) (R Squared = .391 (Adjusted R Squared = .334)) [c]: adjusted for sex newborn, gestational age at delivery (in days), smoking (yes/no), age of mother (in years at delivery), parity (0 or > 0), use of assisted reproduction technique (yes/no), and prednisone use during pregnancy (yes/no) (R Squared = .462 (Adjusted R Squared = .429)) [d]: adjusted for level of education (low, intermediate, high), smoking (yes/no), age of mother (in years at delivery), parity (0 or > 0), use of assisted reproduction technique (yes/no), and prednisone use during pregnancy (yes/no) (R Squared = .161 (Adjusted R Squared = .099)) [e]: adjusted for smoking (yes/no), age of mother (in years at delivery), parity (0 or > 0), use of assisted reproduction technique (yes/no), and prednisone use during pregnancy (yes/no) (R Squared = .179 (Adjusted R Squared = .143))

Prednisone use and gestational age at delivery

Prednisone use is associated with birth weight in grams, but not with birth weight SDS, in the linear regression analyses (Table 4.1.3). Also in multivariate analysis prednisone use during pregnancy was significantly associated with shorter gestational age ($p < 0.001$) after correction for potential confounders as disease activity at third trimester (DAS28-CRP-3), way of delivery (spontaneous versus caesarean section), parity (1 versus > 1), and age of mother. This shows that prednisone is independently associated with lower birth weight via shorter gestational age.

A statistically significant association between prednisone use and gestational age at delivery was also confirmed with a Kaplan Meier curve (Figure 4.1.2).

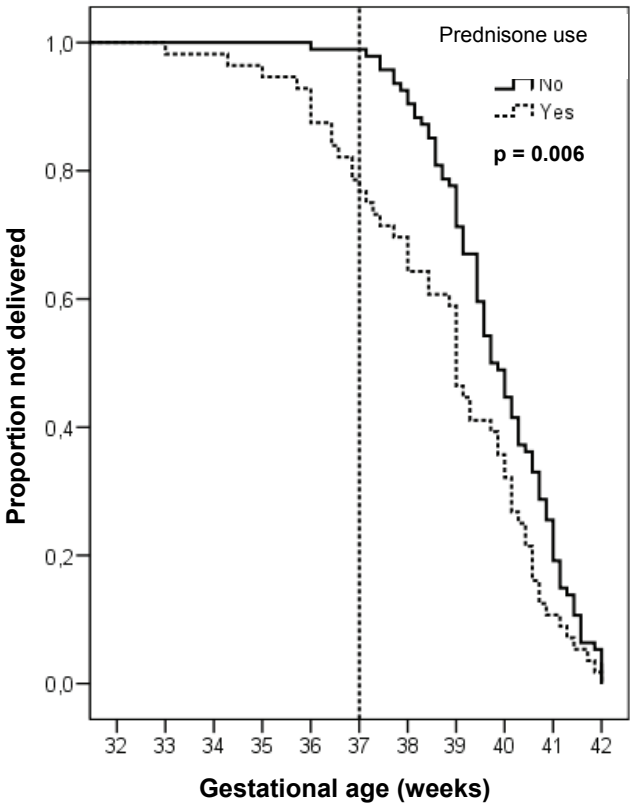

Figure 4.1.2 Kaplan-Meier survival curve showing gestational age at delivery in weeks between the women using prednisone (dotted, n = 56) and no prednisone (black, n = 95). Log-Rank test, Chi-square 7.31, p = 0.006.

Women using prednisone during pregnancy delivered on average one week earlier compared with non-prednisone using women (38.8 weeks, 95% CI [38.2;39.3] versus 39.9 weeks 95% CI [39.6;40.1]). This could not be explained by differences in frequency of induction of labor (14% in both groups) or elective caesarean sections. Patients using prednisone delivered more often < 37 weeks of gestational age, compared with non-prednisone using women (Fisher Exact, p = 0.004).

DISCUSSION

In present prospective study on pregnancy and RA we showed that women with good rheumatology care have a pregnancy outcome comparable to the general obstetric population, and we demonstrated that disease activity and prednisone use during pregnancy were both negatively associated with birth weight. Though, only higher disease activity was associated with lower birth weight SDS, whereas the effect of prednisone on birth weight was mediated by shortening gestational age at delivery. This resulted in significantly more women with prednisone delivering < 37 weeks of gestation.

In this study, we addressed for the first time birth weight of newborns of RA patients with birth weight SDS, in which birth weight was adjusted for gestational age at delivery and sex of newborn (21, 22). Because of this method, we could certify that newborns in present cohort are on average appropriate for gestational age at birth, since the mean birth weight SDS is +0.1SD. Furthermore birth weight SDS enabled us to determine that the effect of disease activity on birth weight was a direct effect (both birth weight SDS as well as birth weight were affected) and that the effect of prednisone was mediated through gestational age (only birth weight but not birth weight SDS was affected).

Almost all studies so far conducted in pregnant women with RA, reported lower birth weight, but still within the normal range, in newborns of RA patients. Almost all studies reported birth weight without correction for gestational age and without prospectively measured disease activity during pregnancy (11, 13, 14, 32). In the present cohort however, we showed that mean birth weight and mean birth weight SDS are in general comparable to the general obstetric population. The discrepancy with previous literature can be explained by several factors. First, RA is treated more aggressively nowadays, which may have resulted in low disease activity in our cohort. Second, in our cohort only few patients smoked and a higher percentage of patients had a higher educational level than the general population; both are associated with higher birth weight. The low percentage of smoking women and the high educational level suggest a healthy cohort effect in this study. On the other hand, in our

cohort women had a higher age and there was a higher percentage of nulliparity, both associated with a lower birth weight.

In present study disease activity of RA during pregnancy is associated with lower birth weight and birth weight SDS. We demonstrated that disease activity at third trimester influenced birth weight negatively and independently of many covariates as prednisone use, parity, smoking, gender of the child, pregnancy duration, maternal age, educational level, and assisted reproduction. In present multiple linear regression analysis, we focused on the role of disease activity and prednisone use during the third trimester, since at that time point our cohort included the most patients. Since disease activity in first, second and third trimester are highly correlated, our data are not suitable for determining whether a certain critical period exists for the effect of disease activity on birth weight.

In general, as a rule of thumb, only a difference in SDS score of 0.5 SDS is considered to be of clinical relevance. Since the estimated mean decrease in SDS score was 0.18 for 1.0 increase in DAS28, our findings may only be clinically relevant for women with high disease activity during pregnancy. Although this small difference in birth weight is unlikely to result in more perinatal complications, a small decrease in birth weight, even within the normal range, has been associated with future developmental delay (16,33), metabolic syndrome and cardiovascular disease (17-19). Whether this holds true for the children born in this study will be subject of further research.

Furthermore, we showed for the first time that prednisone use in women with RA has an indirect negative influence on birth weight by independently influencing gestational age at delivery. This influence of prednisone has already been shown in a study of women using prednisone for a wide spectrum of indications (20). Here we confirm this effect, but now in solely RA patients. This is of clinical importance for obstetricians, since women with RA and prednisone use did more frequently deliver < 37 weeks of gestational age compared with non-prednisone using women, regardless of induction of labor or elective caesarean sections.

There were four more observations in present cohort that need some further discussion. The first is the relatively high number of pregnancies accomplished with assisted reproduction techniques in present cohort. This may be explained by several arguments. The time to conceive in women with RA may be longer, as previously suggested (34), but also women with RA may be more easily referred for artificial reproduction techniques, and lastly, it may be explained by referral bias, because rheumatologists will be more aware of a pregnancy wish

of the patient when it takes longer to conceive, as well as patients with difficulties to conceive may be more interested to participate.

The second observation to discuss is the high rate of instrumental vaginal delivery compared with the general population. However, this should be interpreted against the higher number of nulliparity, since nulliparous women in general need in about 20% instrumental help at vaginal delivery. We could not explain this by a higher disease activity at third trimester.

The third observation to discuss is about caesarean sections. It has been previously documented that caesarean sections are more prevalent among RA patients compared with healthy controls (11, 13, 14). In present study, however, the number of caesarean sections conducted, and the subdivision in elective and emergency seem to be comparable with the general population. The higher number of caesarean sections reported in previous studies may be explained by the fact that women may have had higher disease activity in previous studies. As we showed in our cohort, caesarean sections were significantly more frequent in women with high disease activity.

About the fourth observation on pregnancy complications we can be short. Women with RA have been reported as having an increased risk on premature labor (10, 12, 14), however in present cohort the risk was comparable with the PRN reference group. In our RA patients, only 5 newborns were born (3%) small for gestational age, which is in accordance with the general population. Higher risks on hypertensive disorders (gestational hypertension and preeclampsia) have been described (11, 13), while in other studies this was not (14, 15, 32). We compared our data with the percentage of hypertensive disorders during pregnancy that could be obtained from PRN (all hypertensive disorders combined) and from literature 6-10% (27, 28, 35, 36). The incidence of hypertensive disorders in women with RA in present study seemed to be comparable with the reference groups, however this should be interpreted with caution because of the low number of patients.

The present study has some limitations. Beforehand we showed that patient-reported pregnancy characteristics are generally of good validity and high reliability compared with obstetric records (data not shown). Since the study was not designed as a case control study, comparison with healthy controls can only be made indirectly and should therefore be interpreted cautiously. One of the important limitations is the lack of valid control data for all pregnancy outcomes. Finally a healthy cohort effect may have influenced the results which may even underestimate the results we found. In our opinion, the results of present study can be generalized to Caucasian RA patients with singleton

pregnancies, seen in rheumatology clinics and treated with current available therapies resulting in well-controlled disease. The 'opinion' of rheumatologists that disease activity should be low before pregnancy to have a better pregnancy outcome, seems to hold true.

The mechanism of high disease activity leading to lower birth weight has yet to be elucidated, however some pathophysiological hypotheses might explain this. First, vasculopathy resulting from endothelial dysfunction may contribute to maldevelopment of the placenta. Endothelial dysfunction is a common complication of active RA and is thought to be the initial stage of atherosclerosis. Maldevelopment of the placenta is associated with unfavourable pregnancy outcome (e.g. lower birth weight, hypertension) (37,38, 39). Secondly, a proper fetal development requires lower foetal than maternal cortisol levels. In the placenta the enzyme 11beta-hydroxysteroid dehydrogenase type II (11bHSD2) inactivates the maternal cortisol. High maternal cortisol levels (chronic stress) or low 11beta-hydroxysteroid dehydrogenase type II (11bHSD2) in the placenta (famine), are both associated with decreased birth weight as shown previously (40). Additionally, presence of high pro-inflammatory cytokines as TNF, IL-1 and IL-6, all associated with active RA, can down regulate 11bHSD2 in the placenta (41), and may thus result in lower birth weight. This will be the subject of future studies.

In conclusion, this is the first prospective study in RA women describing pregnancy outcome and extensively linking disease activity and medication use throughout pregnancy to birth weight and birth weight SDS. Although the incidence of pregnancy complications is comparable with the Dutch general obstetric population, among patients with high disease activity more caesarean sections were performed. Furthermore, we showed that newborns of women with higher disease activity and prednisone use had lower birth weight. The effect of prednisone on birth weight is mediated indirectly by shortened gestational age at delivery, whereas disease activity directly influences birth weight. For obstetricians, this study might implicate that they should be aware of a higher incidence of caesarean sections in RA patients with high disease activity, and of an increased risk of preterm delivery by use of prednisone in RA patients. For rheumatologists, it might implicate that they should strive to low disease activity in their patients before and during pregnancy for a better pregnancy outcome.

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5

PARENTING

5.1

PARENTING DISABILITY INDICES OF RA WOMEN PROSPECTIVELY MEASURED POSTPARTUM

Strongly correlated with disease activity and erosive disease

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Background. Rheumatoid arthritis (RA) may affect women's ability to fulfill parenting tasks postpartum.
Objective. To describe parenting disability (PD) of women with RA postpartum and its correlations with disease activity and HAQ scores, define factors influencing PD postpartum, and examine responsiveness of PD scores.
Methods. This study is embedded in the nationwide prospective study on pregnancy and RA, the PARA-study. At 6, 12 and 26 weeks postpartum HAQ-scores and Parenting Disability Index scores (PDI and modified-PDI) were calculated, medication use was registered and disease activity was scored with DAS28-CRP-3. Correlations between PDIs, HAQ, and DAS28 were calculated. GEE was performed with PDIs as dependent variables and covariates DAS28, medication use, duration of RA, and family size. Responsiveness of the PDI to RA flare was assessed.
Results. Data from 100 women with RA were available. Sixty-eight percent was erosive. Mean (SD) PDI scores at three visits postpartum were stable: PDI 0.51(0.42), mPDI 0.64(0.56). PDI scores were significantly correlated with both HAQ and DAS28. Higher disease activity and erosive disease were associated with higher PDI scores postpartum. Activities in which women most frequently encountered difficulty were carrying and bathing the baby and household chores. PDI scores rose significantly in women with a flare postpartum, suggesting responsiveness of PDI scores.
Conclusion. PDI scores postpartum are significantly influenced by disease activity and erosive disease. Health professionals could be advised to lower disease activity to preserve parenting functions. Patients may benefit from joint protective instructions directed toward most affected domains.

INTRODUCTION

Many women with rheumatoid arthritis (RA) are concerned about their parenting capacities after giving birth, since RA tends to flare postpartum in a substantial number of women (1, 2). Perceived inability to fulfill parenting roles, as previously studied, may result in feelings of frustration, guilt, anger and depression (3). The influence of the functionality of women with RA postpartum on parenting, however, has rarely been addressed.

Functionality in RA is measured worldwide with the Health Assessment Questionnaire (HAQ) and is numerically expressed in a HAQ score (4, 5). The HAQ score, however, may not be specific enough to rate functionality of women with RA postpartum, since it concerns only regular daily activities, while women face many unique tasks in caring for their babies.

The Parenting Disability Index (PDI) was developed to measure parenting function and disability and was validated in a sample of women with RA living in northern California, USA (6). In the validation study, only 9 women who had young children (ages 0-5 years) at the time of the study, and 79 women who had young children at the time of their RA diagnosis but answered the questionnaire retrospectively, were included. It appeared that even in that small sample, a substantial proportion of women with RA experienced disability in parenting activities. In the nine women with currently young children, 52% of the activity domains of the PDI were affected. Therefore, the PDI may identify difficulties in care and functionality women with RA are facing postpartum. Furthermore the, PDI may provide information for health professionals to focus care for patients more precisely, and results from larger studies may provide information for women that will help them prepare for potential parenting challenges postpartum.

To study the effects of parenting disability among women with infants in a larger study, the present study was embedded in the PARA-study (Pregnancy-induced Amelioration of Rheumatoid Arthritis study), which provides up to now the largest prospective national cohort of RA patients examined before, during and after pregnancy in the world (2).

The goals of our study were to describe the parenting disability indices (PDIs) over 6 months postpartum, to identify how PDIs are correlated with DAS28 and HAQ, to define (modifiable) factors influencing PDIs postpartum, and to examine the responsiveness of PDI scores to RA flares.

PATIENTS AND METHODS

Patient population

Data for the current study are from the PARA-study, which has been described previously in detail (2). Briefly, all rheumatologists working in the Netherlands were asked to recruit patients with RA, according to the 1987 revised ACR criteria, who wished to conceive or who were already pregnant (preferably in their first trimester). During the study the patient's own rheumatologists provided patient care. For the present analysis, data were collected between August, 2004, and August, 2007. Only data of women who had miscarriages in the first trimester were excluded. Two women were included twice.

Data collection

Patients were visited at home before conception (prepregnancy), at each trimester, and three times postpartum (6 weeks, 12 weeks and 26 weeks). At

each visit women completed questionnaires containing the HAQ, current medications, and, after delivery, the PDI for women with children between 0-5 years. A clinical examination of joints was performed according to the EULAR defined joint count (DAS28) (7) and finally serum was stored for determination of C-reactive protein (CRP) levels, by Tina-quant® CRP (Roche Diagnostic GmbH, Mannheim, Germany).

Parenting Disability Index

The original Parenting Disability questionnaire for women with children between 0 to 5 (including an additional 5 questions) was translated into Dutch by two native Dutch-speaking English translators and was retranslated into English by two native English-speaking translators in order to come to consensus after two versions. All questions could be retained as in the American version. We performed a pilot among 10 women with RA and this revealed adequate responses. Since August 2004 all participants of the PARA-study completed the PDI at each visit. In Appendix 5.1.A-C, all questions of the questionnaire are shown. For this questionnaire a response scale similar to that of the HAQ was used (0 = no difficulty,1 = some difficulty, 2 = a lot of difficulty, 3 = unable to perform), with an additional category “did not perform for reasons other than arthritis”. For all except two function domains, namely “safety” and “getting down to and up from the floor” domains, patients were also asked whether they “did less of the activity because of their arthritis”. Two summary scores were calculated. The first was the “parenting disability index” (PDI), which represents the mean difficulty level across the domains. To calculate the PDI, responses were scored from 0 to 3, and a mean score of all items was calculated. As with the HAQ score, the PDI score could range from 0 to 3, with 0 reflecting no disability, and 3 representing the inability to perform parenting tasks. The second summary score was the “modified PDI” (mPDI) that took also into account responses to the “did less” question. If a patient responded that she did less of an activity, that domain score was increased to a “2,” regardless of the subject’s initial difficulty rating. This is similar to the protocol for scoring the HAQ, in which use of assistive devices or help from other people in a particular functional area increases the score in that area to a “2.”

Covariates

To assess associations with parenting disability, sociodemographic and health characteristics, function, and disease activity were assessed. Sociodemographic and health characteristics included subject age, duration of RA, number of children, and medication use. Functionality with RA was also assessed with the HAQ score (range 0-3), as described previously (4), and disease activity was calculated using a Disease Activity Score of 28 joints (DAS28) with three variables, consisting of a swollen joint count, a tender joint

count and a CRP level (mg/L) (DAS28-CRP-3, range 0-10). Response criteria for improvement, as recommended by the EULAR Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT), and the reverse classification criteria for a postpartum flare, as previously described, were applied (7-9).

Statistical analysis

Descriptive statistics were presented as numbers and percentages.

When comparing PDI scores as new method of measuring functionality postpartum compared with the HAQ, the standard functionality score in RA, correlation coefficients were calculated, as well as whether the differences between the measurements by the two methods (HAQ and PDI) were related to the magnitude of the measurement as defined by Bland and Altman (10).

To determine if parenting disability was associated with disease activity, Pearson's correlation coefficients between PDI and DAS28-CRP-3 at each visit postpartum were calculated and tested for significance.

Data were analyzed with longitudinal regression analysis (generalized estimating equations (GEE)), to adjust for within-patient dependence of the outcome variable (PDIs), using autoregression (AR) with lag one structure. To determine which patient characteristics were associated with postpartum parenting disability, the GEE analyses included the following covariates: disease activity (continuous DAS28 scores), disease duration at partus (< 2 or > 2 years), family size (1 or > 1 children), medication use postpartum (yes/no), erosive disease (Yes/No), and the interaction between medication use and disease activity. If correlation coefficients were > 0.7 between two covariates, one covariate was removed because of possible colinearity.

Responsiveness of PDI scores to RA flares was addressed by comparing PDI scores of two visits (6 and 12 or 6 and 26 weeks postpartum) between women with and without a flare postpartum. The postpartum flare was defined according to reversed EULAR response criteria, as previously described (2). Mean differences in PDI scores between flare and non flare women were compared with ANOVA. The responsiveness of PDI scores to flares were compared with the responsiveness of HAQ scores to flares in present cohort. The Minimal Clinically Important Difference (MCID) of the PDI scores were determined as 0.5 of the SD as a good estimate (11-13), and compared with the MCID of the HAQ in present study.

Two sided p-values ≤ 0.05 were considered as statistically significant. All statistical analyses were performed using SPSS version 15.0 for Windows.

Ethics

The PARA-study complies with the Helsinki declaration and the Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands approved this study in 2002. Written informed consent was obtained from all participants.

RESULTS

Demographics

As shown in Table 5.1.1, the current cohort consists of 100 postpartum periods of 98 women with RA with a mean age of 33 years, 73% were rheumatoid factor positive and 65% anti-CCP positive. Thirty (27/92) percent of patients had a postpartum flare of RA.

Parenting disability indices postpartum

Responses on all questions of the PDI, at 6, 12, and 26 weeks postpartum are shown in the appendices. The five domains in which respondents had the most difficulty at 6 weeks postpartum were: doing other household chores or shopping (63% reported some level of difficulty), picking up or carrying your child (61%), taking your child out in the car (59%), taking care of your child's hygiene needs (53%), and taking care of your child while out of the house (53%). The first four of these domains were consistently rated as the most difficult at all three visits postpartum. The five domains in which women "did less because of arthritis" were consistent over the three visits, with the highest rates at 12 weeks postpartum: Doing other household chores or shopping (50%), picking up or carrying your child (35%), taking your child out in the car (23%), taking care of your child's hygiene needs (34%), and going for walks with your child (32%).

PDI scores

Table 5.1.2 shows the mean PDI and mPDI scores at each postpartum assessment. There was very little change in the mean scores over time. There were no consistent significant correlations between the PDI scores and sociodemographic variables in this cohort: age of mother at delivery (r = 0.06), years of education (r = 0.01), number of children (r = 0.003), and duration of RA at delivery (r = 0.04).

Table 5.1.1: Demographics of study population

	100 postpartum periods of 98 RA patients
Age, mean ± SD years	33.2 ± 3.6
Caucasian, n (%)	96 (96)
Education, mean ± SD years	15 ± 2.7
Disease duration, mean ± SD years	7.9 ± 6.2
Rheumatoid Factor, n (%)	73 (73)
Anti-CCP, n (%)	65 (65)
Erosions, n (%)	68 (68)
HAQ scores: mean ± SD	
before pregnancy (n = 57)	0.74 ± 0.54
6wk PP	0.67 ± 0.5
12wk PP	0.83 ± 0.6
26wk PP	0.74 ± 0.6
No. of children,	
1 child, n (%)	55 (55)
2 children, n (%)	39 (39)
> 2 children, n (%)	6 (6)
DAS28-CRP-3 Mean ± SD (scale 0-10)	
third trimester	3.4 ± 1.1
6 wk postpartum	3.5 ± 1.1
12 wk postpartum	3.6 ± 1.3
26 wk postpartum	3.4 ± 1.2
Methotrexate (re)start, n (%)	
6 wk postpartum	19 (19)
12 wk postpartum	30 (30)
26 wk postpartum	39 (39)
Biologicals (re)start, n (%)	
6 wk postpartum	5 (5)
12 wk postpartum	9 (9)
26 wk postpartum	12(12)
Postpartum disease course:	
Flare (severe/moderate), n (%)	27 (27)
No flare, n (%)	65 (65)
Missing, n (%)	8 (8)

Table 5.1.2: Parenting Disability indices postpartum *

	6wk PP	12wk PP	26 wk PP	95% - CI of the difference 6wk – 12 wk PP ‡	95% - CI of the difference 6wk – 26 wk PP ‡
N:	97	97	96		
PDI:					
Mean ± SD	0.51 ± 0.42	0.57 ± 0.50	0.52 ± 0.48	[-0.13;0.01], NS	[-0.08;0.05], NS
Range	0.00 - 1.50	0.00 - 2.00	0.00 - 2.30		
mPDI:†					
Mean ± SD	0.64 ± 0.56	0.71 ± 0.58	0.65 ± 0.58	[-0.14;0.02], NS	[-0.09;0.07], NS
Range	0.00 - 2.00	0.00 - 2.06	0.00 - 2.30		

* Disability score, without accounting for “doing less” † Disability score, with accounting for “doing less” ‡ Paired T-test of the difference between given time points, NS = Not significant; CI = Confidence Interval; PP = postpartum; wk = weeks.

Associations of parenting disability with functionality and disease activity scores

There was a strong correlation between PDI scores and HAQ scores. The Pearson correlation coefficient at 6 weeks postpartum was 0.78 between PDI and HAQ and 0.72 between mPDI and HAQ. The difference measured between the HAQ and mPDI was not related to the magnitude of the measurements (see Figure 5.1.1).

There was a moderate correlation between HAQ and the DAS28 (r = 0.54). There were also a moderate correlations between PDI scores and the DAS28. Pearson correlation coefficients were on average 0.48 between PDI and DAS28 and 0.46 between mPDI and DAS28.

Factors influencing PDI/mPDI scores postpartum

Evaluating (modifiable) factors contributing to functionality postpartum, the GEE analyses (see Table 5.1.3) revealed that PDI and mPDI were significantly higher when disease activity was higher and when patients had erosive disease. The PDI rose on average 0.15 when DAS28 was 1 point higher, and 0.24 when patients had erosive disease. Results were comparable with mPDI in which mPDI rose 0.16 for each DAS28 point and 0.35 when patients had erosive disease. In the present study, longer disease duration, a higher number of children and the use of medication postpartum did not significantly contribute to PDI scores.

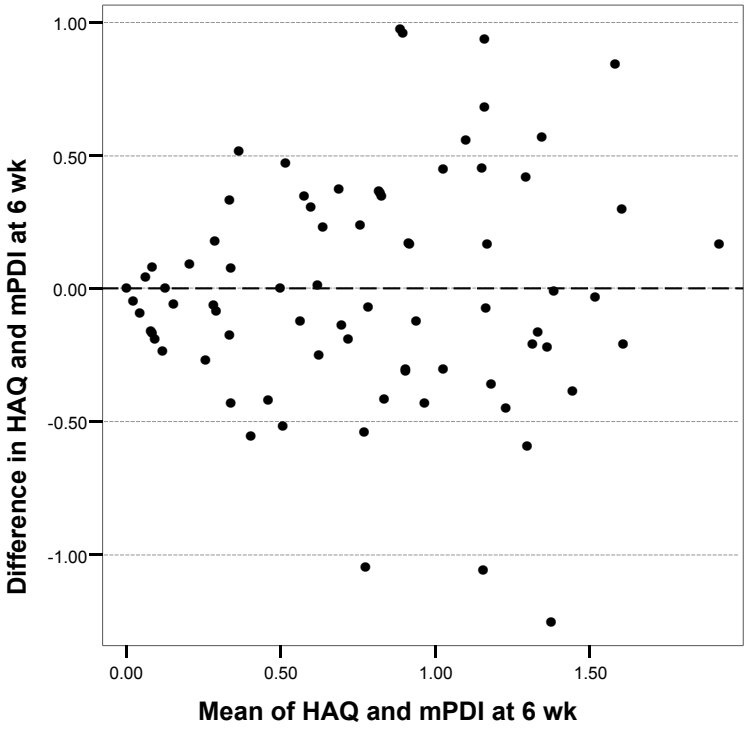

Figure 5.1.1: Plot of the difference between HAQ and mPDI at 6 weeks postpartum against the mean of HAQ and mPDI in each patient. This shows that differences in PDI scores are not related to the magnitude of the mPDI.

The interaction of DAS28 and medication postpartum did not significantly contribute in the GEE analysis, and therefore results are shown without the interaction variable.

Table 5.1.3: Generalized estimating equations (GEE) with PDI or mPDI as dependent variables and following covariates: disease duration at delivery, family size, medication use and erosive disease. An autoregressive with lag one structure was chosen.

	PDI		
	B	95% Wald CI	p
Intercept	-0.119	[-0.301; 0.062]	0.196
DAS28 (continuous)	0.152	[0.106; 0.199]	<0.001 *
Disease duration (> 2 year)	-0.007	[-0.018; 0.005]	0.274
Family size (> 1 child)	0.002	[-0.151; 0.156]	0.986
Medication postpartum (yes)	-0.006	[-0.107; 0.096]	0.910
Erosive disease (yes)	0.243	[0.083; 0.403]	0.003 *

* $p \leq 0.05$

Table 5.1.3 (continued)

	mPDI		
	B	95% Wald CI	p
Intercept	-0.126	[-0.333; 0.081]	0.234
DAS28 (continuous)	0.158	[0.111; 0.206]	<0.001 *
Disease duration (> 2 year)	-0.006	[-0.022; 0.009]	0.432
Family size (> 1 child)	0.063	[-0.133; 0.259]	0.526
Medication postpartum (yes)	0.036	[-0.100; 0.172]	0.602
Erosive disease (yes)	0.347	[0.151; 0.544]	0.001 *

* $p \leq 0.05$

Responsiveness of PDI postpartum

PDI scores in women with a postpartum flare rose significantly, while in women without a flare, PDI scores stayed stable (see Table 5.1.4). ANOVA analyses revealed that women with a flare had a significant change in PDI and mPDI scores compared to women without a flare (between 6 and 12 or 6 and 26 weeks postpartum PDI [F 7.8,df91,p < 0.01]; [F 7.9,df90,p < 0.01], mPDI [F5.5,df91,p = 0.02]; [F8.5,df90,p < 0.01] respectively). This is also true for the HAQ score: in patients with a flare HAQ scores changed significantly (see Table 5.1.4), while they remained stable in non flare patients (ANOVA between 6 and 12 or 6 and 26 weeks postpartum [F 10.56,df 90,p < 0.01] and [F 7.4,df 91,p < 0.01] respectively).

Another way to approach responsiveness is by use of a Minimal Clinically Important Difference (MCID) of the PDI scores. As previously defined, 0.5 of the SD of the measurement is a good estimate of the MCID (11, 12). However this was mostly used for quantification of improvement, here we used it to quantify deterioration in functionality during a flare. The maximum MCIDs of deterioration of PDI and HAQ postpartum was defined as the maximum of all halves of the SD of (m)PDI and HAQ scores at all time points (see Table 5.1.2). This resulted in a MCID of 0.25 for PDI score, a MCID of 0.29 for mPDI score, and a MCID of 0.31 for HAQ score. The proportions of women that met the MCID criterion for PDI scores were 40.7% in the flare group and 23.1% in the non-flare group, for mPDI scores these proportions were 37.0% and 27.7%, respectively. The proportions of women that met the MCID criterion for the HAQ scores were 52.9% in flare women and 18.5% in non-flare women. Another way to give insight into the responsiveness, is by comparing the MCIDs and mean differences of (m)PDI and HAQ scores between the flare and non-flare groups (Table 5.1.4). None of the mean differences in the flare groups was larger than the MCID of the corresponding score.

Table 5.1.4: Mean differences of PDI and HAQ postpartum in women with and without a flare. (paired t-test, CI: confidence interval, NS not significant; ANOVA between non-flare and flare patients, in all subgroups p < 0.01)

Postpartum	Mean difference	95% CI of the difference	p
No flare (n = 65)			
PDI 6wk - 12wk	0.00	[-0.29;0.16]	NS
PDI 6wk - 26wk	-0.05	[-0.12;0.03]	NS
mPDI 6wk - 12wk	0.01	[-0.09;0.10]	NS
mPDI 6wk - 26wk	-0.06	[-0.15;0.03]	NS
HAQ 6wk - 12wk	-0.01	[-0.11;0.08]	NS
HAQ 6wk - 26wk	-0.07	[-0.16;0.15]	NS
Flare (moderate/severe) (n = 27)			
PDI 6wk - 12wk	0.23	[0.06;0.40]	0.01
PDI 6wk - 26wk	0.16	[0.02;0.30]	0.03
mPDI 6wk -12wk	0.22	[0.06;0.38]	0.01
mPDI 6wk -26wk	0.18	[0.03;0.33]	0.02
HAQ 6wk - 12wk	0.29	[0.11;0.48]	0.01
HAQ 6wk - 26wk	0.16	[0.01;0.33]	0.04

DISCUSSION

The present study, embedded in the PARA-study, shows for the first time prospectively measured parenting disability in a large cohort of women with RA postpartum. This study therefore gives detailed information for patients and health professionals about how RA patients function postpartum. Although the overall mean PDI scores of the group did not significantly change between each postpartum visit, in a subgroup of patients with a documented flare, PDI did change significantly. Furthermore, we identified two covariates, a higher disease activity and having erosive disease, that were both associated with higher PDI scores postpartum.

For the first time we were able to show the responsiveness of PDI scores, since we measured the score over time and we were able to compare it with disease course (flare/no flare). Changes in PDI between 0.25-0.29 may be of clinical significance, based on estimates of the MCID from this study. The MCID, however, will have to be confirmed in future longitudinal studies. In the present study also a considerable amount of women without a flare had a clinical significant change in parenting function, this may point to other causes than changes in disease activity contributing to lower parenting function postpartum.

In comparison with the only available results of PDI scores of 9 women with RA and young children (6), PDI scores in present study were lower. Compared to the previous study, our cohort contains younger patients, with a lower HAQ score and also the erosive status might have been lower, which all may have accounted for lower PDI scores. There was also a difference regarding the

number of domains used in the Parenting Disability questionnaire; in previous study 20 questions and in the current study 25 questions. A higher number of domains asked in the latter may have accounted for lower PDI scores. PDI scores calculated with 20 questions in our cohort resulted indeed in slightly higher mean PDI scores postpartum than with 25 questions: at 6wk 0.55, 12 wk 0.61 and 26 wk 0.58. However, as in the previous study, all questions have been answered at least once with some degree of difficulty in current cohort, and the range of scores were identical. Comparable results with the previous conducted study were found regarding HAQ and PDI scores; in both studies, these were highly correlated. An additional study to elucidate the most optimal set of questions from the Parenting Disability questionnaire that correlates even more strongly, might be subject of future research.

In the present study we highlighted the domains that were influenced the most postpartum. These domains were centered on carrying, hygiene needs, using car safety seats, taking care of the child outside the house and doing household chores and shopping. Three of the five domains were also in the top five of domains affected the most in the previous study. Differences could be explained by the fact that women with older children were involved in the previous study. For example, in those women the domain ‘taking care of your child’s hygiene needs’ was less often rated, since this is less difficult with toddlers than with babies. In another study these same items were thought to be of significance in parenting function of RA patients (3).

Although it seems obvious, this is the first study showing that higher disease activity and erosive disease are associated with higher parenting disability of the mother postpartum. Other covariates such as a larger family size, which were previously associated with less parenting disability, were not of significance in the present study (14). Asking for help in child care is often needed, which may indirectly be reflected in the number of domains in present study on which women answered ‘less due to arthritis’. Many women with RA find requesting help very difficult to do, but necessary for completion of daily tasks (3). Further research will be conducted among patients with and without substantial additional help postpartum, in order to determine whether additional household help results in better parenting function. Other strategies, such as adjusting expectations and adaptive approaches to completing tasks, may be applicable rehabilitation and public health interventions targeting mothers living with a chronic illness as RA (14).

Because HAQ and PDI scores are highly correlated and both have comparable responsiveness during a flare postpartum, one could say that there is no need for a PDI. However, in our opinion the Parenting Disability questionnaire

provides much more information of the functioning of a patient just after delivery because of assesses specific tasks related to parenting, which may direct health professionals to give adequate joint protective advices to the tasks with which patients have difficulties. Further research will be focused on women with and without joint protective instructions before delivery and PDI scores after delivery to assess the effectiveness of such instructions on parenting disability.

The present study has some limitations. The PDI was used for the first time in The Netherlands, therefore cultural differences between California and The Netherlands may have influenced the final scores, and another reference group was not available. However, our careful translation and back-translation in addition to pilot testing did not suggest any significant cultural differences. Second, PDI scores were very strongly correlated with disease activity, but were measured in a country with the possibilities for high disease control (mean DAS28 3.4 6 weeks postpartum). Therefore, one should be aware of that if disease is or cannot be maximally controlled, help in parenting may be of greater importance than showed here.

In conclusion, difficulties in the parenting function of women with RA postpartum can be measured with PDI scores. Postpartum parenting disability of patients with RA was significantly influenced by having higher disease activity and erosive disease. Therefore, the treatment goal postpartum should be focussed on modifiable factors such as lowering disease activity and giving joint protective advices before delivery, to preserve the parenting tasks of RA patients.

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Questions Parenting Disability Questionnaire	Difficulty rating at 6 weeks postpartum					
	None	Some	A lot	Unable	Did not do	Did less
1. Diapering, dressing, or helping with dressing	59	39	2	0	0	14
2. Taking care of your child's hygiene needs	47	41	9	2	0	29
3. Feeding your child	52	42	6	0	0	10
4. Picking up or carrying your child	39	51	9	1	0	26
5. Taking care of your child while out of the house	47	37	7	0	9	17
6. Taking your child out in the car	41	37	15	0	7	24
7. Getting down to and up from the floor to play with child	28	29	9	6	27	--
8. Keeping your child out of unsafe situations	37	10	3	0	50	--
9. Getting up with your child, either during the night or early in the morning	49	39	11	0	1	14
10. Playing games or doing other indoor activities with your child	48	28	0	0	24	12
11. Going for walks with your child	55	32	5	0	8	23
12. Playing with your child outdoors	22	13	3	0	62	15
13. Having other children in your home	32	13	2	0	53	9
14. Taking your child to social events or recreational activities	37	14	4	0	44	10
15. Taking care of your child when she or he is sick	61	8	0	0	31	2
16. Maintaining discipline with your child	34	13	2	0	51	4
17. Holding your child in your lap	61	38	0	0	1	7
18. Having energy to be patient with your child	59	29	2	0	10	9
19. Having the energy to be available to listen and talk with your child	44	10	1	0	44	6
20. Keeping, or helping to keep, your child's room and belongings in order	57	30	2	0	11	17
21. Doing other household chores or shopping	37	43	16	0	4	42
22. Using a stroller	61	32	2	0	5	17
23. Using a car seat	48	31	8	0	13	13
24. Opening safety latches or locks	60	32	4	0	4	10
25. Opening medicine or childproof contains	56	26	5	2	11	14

APPENDIX 5.1.B

Questions Parenting Disability Questionnaire	Difficulty rating at 12 weeks postpartum					
	None	Some	A lot	Unable	Did not do	Did less
1. Diapering, dressing, or helping with dressing	56	38	5	0	1	16
2. Taking care of your child's hygiene needs	45	41	15	0	0	34
3. Feeding your child	54	39	7	0	0	9
4. Picking up or carrying your child	31	59	10	0	0	35
5. Taking care of your child while out of the house	48	41	6	0	5	18
6. Taking your child out in the car	38	39	17	1	6	23
7. Getting down to and up from the floor to play with child	27	31	18	5	19	--
8. Keeping your child out of unsafe situations	38	15	1	0	47	--
9. Getting up with your child, either during the night or early in the morning	42	40	17	1	1	20
10. Playing games or doing other indoor activities with your child	49	32	3	0	16	14
11. Going for walks with your child	47	41	10	0	1	32
12. Playing with your child outdoors	23	13	5	0	59	18
13. Having other children in your home	33	14	3	0	50	11
14. Taking your child to social events or recreational activities	46	17	3	1	33	12
15. Taking care of your child when she or he is sick	62	10	2	0	26	3
16. Maintaining discipline with your child	41	13	2	0	43	7
17. Holding your child in your lap	63	33	3	0	1	13
18. Having energy to be patient with your child	58	26	6	0	9	15
19. Having the energy to be available to listen and talk with your child	49	10	1	0	40	7
20. Keeping, or helping to keep, your child's room and belongings in order	59	29	4	0	7	18
21. Doing other household chores or shopping	35	49	16	0	0	50
22. Using a stroller	58	35	6	0	0	16
23. Using a car seat	40	37	11	0	11	14
24. Opening safety latches or locks	56	29	9	0	6	13
25. Opening medicine or childproof contains	48	27	11	1	13	20

Questions Parenting Disability Questionnaire	Difficulty rating at 26 weeks postpartum					
	None	Some	A lot	Unable	Did not do	Did less
1. Diapering, dressing, or helping with dressing	59	43	3	1	0	10
2. Taking care of your child's hygiene needs	43	47	9	0	1	28
3. Feeding your child	64	32	4	0	0	11
4. Picking up or carrying your child	31	48	20	1	0	27
5. Taking care of your child while out of the house	48	43	7	1	1	19
6. Taking your child out in the car	35	45	16	0	4	27
7. Getting down to and up from the floor to play with child	37	34	19	7	3	--
8. Keeping your child out of unsafe situations	46	17	1	0	36	--
9. Getting up with your child, either during the night or early in the morning	53	40	4	1	2	14
10. Playing games or doing other indoor activities with your child	60	33	2	0	4	18
11. Going for walks with your child	59	34	6	0	1	28
12. Playing with your child outdoors	30	17	2	1	50	13
13. Having other children in your home	38	14	2	0	46	8
14. Taking your child to social events or recreational activities	54	26	2	0	18	16
15. Taking care of your child when she or he is sick	65	11	2	1	21	6
16. Maintaining discipline with your child	50	10	1	0	39	9
17. Holding your child in your lap	72	26	2	0	0	13
18. Having energy to be patient with your child	72	20	5	0	2	14
19. Having the energy to be available to listen and talk with your child	59	9	2	0	30	8
20. Keeping, or helping to keep, your child's room and belongings in order	66	24	0	1	9	14
21. Doing other household chores or shopping	38	45	15	1	1	40
22. Using a stroller	63	33	2	1	0	15
23. Using a car seat	44	35	12	0	9	19
24. Opening safety latches or locks	59	30	8	0	2	16
25. Opening medicine or childproof contains	57	26	7	2	7	18

6

GENERAL DISCUSSION

INTRODUCTION

The objectives of this thesis were (I) to prospectively study disease activity of rheumatoid arthritis (RA) before, during and after pregnancy, (II) to explore causal relations of the pregnancy-induced amelioration of RA between the clinical characteristics and immunological changes in autoantibodies, (III) to determine the influence of disease activity and medication use on pregnancy outcome, and, finally, (IV) to address clinical aspects in parenting function postpartum.

Previous, mostly retrospective, studies reported that about 55-85% of women with RA experienced a spontaneous improvement of the disease activity during pregnancy (1-3). Whether this still holds true in a large prospective cohort study from prepregnancy onwards, in an era of new treatment options, is one of the principal research questions addressed in this thesis. Therefore, first, objective disease activity scores and functionality scores were defined for use during pregnancy, secondly, disease activity was measured before conception, during pregnancy and postpartum, and thirdly, associations between disease course during pregnancy and patients' characteristics, with autoantibodies in particular, were addressed.

Another important research question addressed in the present study is about pregnancy outcome in women with RA. In previously performed case-control studies in rheumatic diseases pregnancy outcome was often described as being unfavourable (4-8). Having RA was especially associated with delivering babies of lower birth weight compared with controls, and with higher rates of maternal complications, especially gestational hypertension, (pre)eclampsia, and caesarean sections (4-8). Also higher disease activity during pregnancy was previously suggested as being unfavourable for birth weight, which, however, could not be proven in a statistically significant manner (8). Previous studies had difficulties in distinguishing the effect on disease activity of pregnancy or of medication use, and several studies showed pregnancy outcomes without appropriate corrections for gestational age (4, 6-8). In the present prospective cohort only prevalences of pregnancy-related maternal and child complications could be described. The exclusiveness of the present prospective cohort of pregnant women with RA is that disease activity scores were measured objectively. This, in particular, made it possible to determine the influence of prednisone use and disease activity during pregnancy on birth weight, and on the occurrence of maternal complications.

Finally, our last research question is of great interest to health professionals and patients, and addressed impairments in parenting function postpartum. Detailed information on this special situation postpartum has not been reported in women with RA up to now. The present prospective cohort study addressed this issue by using an objective functionality scoring method of parenting function, 'the parenting disability index (PDI)' (9). Examining the detailed questions on difficulties in parenting function and the association of PDI scores with patients' characteristics will provide information for health professionals and patients and may contribute to the provision of more appropriate care in order to preserve parenting function postpartum.

In this chapter, first the main findings are summarized per objective. Next methodological considerations related to our study design are addressed. The new insights achieved with studies in this thesis are presented subsequently. Then the possible implications for clinical practice are discussed. Finally, directions for future research are discussed.

MAIN FINDINGS

Objective 1: Measuring disease activity during pregnancy

The aim was threefold: First, to assess how pregnancy influences the scoring of the Disease Activity Score in 28 joints (DAS28) (10, 11) and the Health Assessment Questionnaire (HAQ) (12), and how both scores perform in pregnant patients with RA. Second, to prospectively determine the disease activity during pregnancy in RA patients treated in an era of new treatment options. Third, the levels of anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF) were determined during pregnancy and postpartum to correlate with disease activity, and the chance to improve during pregnancy in the presence or absence of autoantibodies was additionally addressed.

Measuring disease activity during pregnancy: Validated instruments

Pregnancy has a favourable effect on the course of rheumatoid arthritis (RA), although we cannot be certain about the magnitude of this effect, because RA assessment tools have never been validated in pregnancy and were mainly subjective (1, 2, 13, 14).

In chapter two it was demonstrated that being pregnant influences the scoring of disease activity and functionality. Disease activity was measured with the DAS28 and functionality with the HAQ. Certain HAQ variants, made within the rules of scoring the HAQ (12, 15), could reduce the influence of pregnancy on functionality scores. The two RA assessment tools for use during pregnancy

which perform best were found to be: for disease activity the DAS28-CRP-3 (calculated with C-reactive protein (CRP in mg/L) but without visual analogue scale (VAS) of global health (GH)), and for functionality the HAQ variant calculated without 6 selected items, although even this variant of the HAQ did not totally preclude the influence of pregnancy. These two well-defined objective assessment tools are indispensable for the present prospective cohort study, and will probably also have their merits in future research.

Measuring disease activity during pregnancy: Disease course during pregnancy and postpartum

As stated before, according to previously conducted retrospective studies, approximately 55–85% of patients with rheumatoid arthritis (RA) will improve during pregnancy (1,13,14). Prospective data on disease activity during pregnancy, however, are limited (2, 6, 16). The assumption of rheumatologists that almost all patients with RA will experience a remission of disease activity during pregnancy does not seem to be valid today, and must be viewed in the context of new treatment options. In this nationwide prospective study disease activity was documented with validated objective instruments and showed that disease activity significantly declines during pregnancy and significantly rises postpartum. Furthermore, it showed that approximately 25% of women were in remission (DAS28-CRP-3 < 2.6) in the third trimester, despite the fact that medication use was remarkably reduced during pregnancy compared with before conception. The difference in reported frequencies of improvement compared with results in the present study may be explained by three arguments: (I) measuring with an objective measurement tool instead of subjective recording of decrease of disease activity, (II) a prospectively conducted study versus retrospectively conducted studies (no recall bias), (III) patients with low and high disease activity participated in the present study, while in previous studies mainly women with high disease activity were selected (selection bias). We found that in women with at least a moderate disease activity (DAS28-CRP-3 > 3.2) at first trimester (62% of participants), almost 50% of them had at least a moderate improvement during pregnancy. Postpartum, we found that more than 33% of all participants had at least a moderate flare. The postpartum flare in the present study, however, may be underestimated because medication use was considerably increased after delivery.

This study demonstrated that neither presence of anti-CCP or RF separately, nor presence of erosions, were associated with improvement during pregnancy or postpartum flare. Finally, this study showed that during pregnancy patients with low disease activity before pregnancy remained relatively stable, and patients with moderate to high disease activity frequently improved.

Measuring disease activity during pregnancy: Associations with autoantibodies

The mechanism underlying the spontaneous clinical improvement of RA during pregnancy and the subsequent flare after delivery is still unexplained. Anti-CCP and RF are thought to play an important role in the pathophysiology of RA (17). Furthermore there is increasing evidence in support of the role of B cells, derived from clinical studies that demonstrate improvement of disease activity upon treatment with B-cell targeted therapies (18). However, whether changes in B-cell function, as reflected in levels of anti-CCP and RF during pregnancy and postpartum, are associated with improvement of RA during pregnancy or with a flare after delivery, was not known. In the present thesis we showed that autoantibody levels were stable during pregnancy, and not related to the improvement of disease activity during pregnancy. Postpartum, all levels of autoantibodies, except of IgG-RF, decreased when medication was resumed, as reported previously (19-21). However, surprisingly, in the absence of both autoantibodies (negative for both anti-CCP and RF) women had significantly more frequently an improvement according to EULAR response criteria during pregnancy, than women positive for one or both of the autoantibodies. This finding may support the hypothesis that RA is a heterogeneous disease with different pathogenic mechanisms involved (22). In analogy with SLE, where the presence of autoantibodies together with increased Th2-mediated responses during pregnancy (23), may result in a disease flare during pregnancy, one can speculate that similar mechanisms are responsible for the observation that disease activity is less likely to improve during pregnancy in RA patients with autoantibodies (anti-CCP and/or RF).

Objective 2: Determining pregnancy outcome in RA

The aim of this study was twofold: firstly to determine the pregnancy outcome of rheumatoid arthritis (RA) patients in relation to disease activity, and secondly in relation to prednisone use. Furthermore, pregnancy outcome might be negatively influenced by RA, since unfavourable pregnancy outcome has been demonstrated in mostly case-control studies in several rheumatic diseases (3, 4, 7, 8, 24). Case definitions in previous studies have always been difficult, and prospective studies are still warranted to find (clinical) associations between adverse pregnancy outcome and, for example, disease activity.

The PARA-study is the world's largest prospective study in women with RA up to now, describing pregnancy outcome and extensively linking disease activity and medication use throughout pregnancy to birth weight and birth weight SDS (standard deviation score), i.e. birth weight adjusted for gestational age and sex of newborn. Although the incidence of pregnancy complications in our cohort was comparable with the Dutch general obstetric population (25), among patients with high disease activity caesarean sections were performed more

frequently. Furthermore, we showed that newborns of women with higher disease activity and prednisone use had a lower birth weight compared to newborns of women with low disease activity and without prednisone use. We described for the first time that the effect of prednisone on a lower birth weight was mediated indirectly by shortened gestational age at delivery, whereas higher disease activity directly negatively influenced birth weight. Both results were strongly suggested in previous studies, however, in those studies the influence on disease activity could not be ascribed with statistical significance to pregnancy or medication use separately (8, 26).

Objective 3: Parental function postpartum

This thesis addresses for the first time an observational study on parenting disability postpartum to describe correlations between PDI scores and disease activity, and other functionality scores (HAQ), so that (modifiable) factors associated with PDI scores postpartum could be defined. Only a few studies have addressed the difficulties parents with RA encounter in parenting up to now (27-29). When modifiable factors are defined, patients can be better prepared for their parenting task postpartum.

Results of this study showed that difficulties in the parenting function of women with RA postpartum can easily be measured with PDI scores, and showed that PDI scores are responsive to changes in time. PDI scores were, as expected, highly correlated with HAQ scores. Two (modifiable) factors influencing parenting disability postpartum could be defined: having higher disease activity postpartum and erosive disease. So lowering disease activity of RA postpartum and providing joint protective advice during pregnancy may be useful for reducing parenting disability postpartum.

METHODOLOGICAL ISSUES

One of the strengths of the studies in this thesis is that all studies were performed in the same study population. This facilitates direct comparison across the studies, though differences in the exact number of persons existed due to the fact that the cohort was still ongoing at the time of analyses, and depended on the outcome measures studied. Each study showed the time frame in which patients enrolled the specific study.

Another strength of the study is that the compliance of the patients, even up to seven visits after inclusion, was over 95%. This was mainly due to visiting participants at home. However, for the interpretation of the findings, some methodological issues should be taken into account. Below, the internal and external validity of the studies described in chapters two to five are discussed.

Internal validity

Internal validity refers to the extent to which results are valid for the study population itself; more specifically the extent to which the results might be distorted by systematic errors. In the following, selection bias and information bias are discussed.

Selection bias

In chapters two to five, data of women participating in a nationwide observational prospective cohort study (PARA-study) were used. Selection bias may have occurred as a result of (I) selective referral of patients by rheumatologists and self-referral of patients to this cohort study, (II) selective non-response, and (III) selective loss to follow-up.

In order to reduce selective referral, all rheumatologists in The Netherlands were informed twice a year about the study and asked to recruit patients. The recruitment may have been selective at two points: women with a long persistent wish to conceive and women with higher disease activity may have been referred more easily. Those women will get more attention because they visited their rheumatologist more frequently. Only a few applications were self-referrals; these were checked with the patient's own rheumatologist to ascertain the presence of RA according to the ACR 1987 criteria (30).

The number of non-responding women for application of the study was very low, since the major selection was already made by rheumatologists. Participating women were highly motivated to enrol the study, and resulted in a follow-up rate of over 95%. Selective loss to follow-up might have been introduced in women with an adverse pregnancy outcome, however, the pregnancy outcome was still recorded by telephone interview, and only a few women preferred not to be visited anymore postpartum or after a miscarriage.

Information bias

One important source of information bias in our study may be the self-report of all clinical and non-clinical risk factors and outcome measures. Self-reports could have biased the results if there had been systematic differences in the answering of questions on risk factors by the outcome measure. In chapter three, we addressed the problem of possible information bias on reported pregnancy outcome separately. We conducted a small study on patient reports and clinical data from obstetricians of 40 participants of the PARA-study. The agreement between patient-reported and obstetric record-based pregnancy outcome and obstetric history, as used in this thesis, was reliable. In those 40 patients, the patient-reported and obstetric record-based results on birth weight

and gestational age were correlated with an intraclass correlation coefficient (ICC) of at least 0.98. Also reports on the frequency of adverse pregnancy outcomes were reliable as reflected in kappas of 1. Of the rare adverse pregnancy outcome, the lowest kappa was 0.65 for eclampsia, 0.78 for gestational hypertension and 0.90 of premature birth. Another issue to address was that self-reports on induction of labour were unreliable, since women often confused this with stimulation of contractions during labour. In conclusion, in the present thesis patient-reported data were likely to be reliable, except for eclampsia and induction of labour. Therefore data of severe pregnancy complications were all verified with obstetric records, as well as for induction of labour.

External validity

The external validity refers to the generalizability of the study findings to persons outside of the study population, e.g. other women with RA and a wish to conceive, or who are already pregnant.

The results of the present cohort study can be generalized to those RA patients under control of rheumatology care in a country with possibilities for high disease control; in the present cohort median DAS28-CRP-3 before pregnancy was 3.9.

In chapter two the objective measurement tools available to describe functionality and disease activity in RA during pregnancy were studied. Since a “gold standard” test is not available during pregnancy we had to make assumptions. For functionality, we were able to perform HAQ scores in 30 healthy pregnant women to measure the influence of pregnancy on the HAQ score. Furthermore rules were already stated by the developers of the HAQ, so the HAQ score could be adapted accordingly (12, 15), in order to obtain still valid functionality scores. However for disease activity this was more complicated. Results of previous literature showed that about 66% of patients reported an improvement during pregnancy, but only 16% of patients had a clinical remission of disease activity defined as no swollen or painful joints at third trimester (2). We decided to choose a variant of the objective disease activity score DAS28.(11) We defined the best performing disease activity score as that DAS28 variant that is most sensitive for recording remission and as the one less influenced by differences in inflammatory parameters (erythrocyte sedimentation rate (ESR) or CRP), and differences in VAS-GH introduced by pregnancy in healthy women. The DAS28-CRP-3 score showed to be influenced the least by pregnancy in that sensitivity analyses, and recorded the most (23%) of women with RA in clinical remission during pregnancy.

It is important to know that this is the first (observational) study that used DAS28-CRP calculated with 3 variables as disease activity score. Furthermore, we used the European League Against Rheumatism (EULAR) response criteria (31), however those were initially designed on the basis of the DAS or DAS28 with ESR (32). Up to now several researchers have shown that DAS28-CRP and DAS28-ESR are not fully comparable in special situations (33, 34). Especially with higher age and with longer disease duration, although these were unlikely to interfere in the present study with the measurements, DAS28-ESR would definitely underestimate the remission rate in RA patients. One should thus be aware of the restrictions of the DAS28-CRP-3, because it has been used as objective measurement tool throughout this thesis.

In chapter three more restrictions concerning measuring disease activity were encountered, first, postpartum a good definition of a flare was absent. Therefore we defined 'reversed' EULAR response criteria, on the basis of the EULAR response criteria (based on DAS28-ESR) (31). These flare criteria need to be confirmed in other cohorts as well, and preferably correlated with patients and rheumatologist's global assessment of disease activity.

A second restriction in chapter three concerns the definition of EULAR-response criteria during pregnancy. Only women with an initial DAS28-CRP-3 > 3.2 at first trimester could be classified for their responses (31). Because of this requirement up to 38% of studied women with RA were excluded from classification of disease response during pregnancy. Also the association between improvement of RA during pregnancy and autoantibodies was only made for women fulfilling that requirement. However, only with good classification of an objectively measured disease activity during pregnancy, can one study clinical associations between pregnancy-induced amelioration and laboratory investigations, that was lacking in previously described studies. Therefore, we chose to make those restrictions for the present analyses.

Another general issue to address here are the concerns of how to interpret medication use during pregnancy. As reported in this study, women were consistent in their kind of medication used during pregnancy, only dosages were adapted in half of them. Interpretation of laboratory findings and disease activity scores should therefore always be interpreted with care. In the present study an underestimation of the effect of pregnancy on disease activity of RA was still likely; women rather decreased than increased their dosage of medication.

Postpartum the interpretation of data regarding medication use may be difficult, since women who decided to breastfeed their child were restricted in medication

use, while other women restarted their medication to prevent a relapse and started using disease-modifying antirheumatic drugs (DMARDs) and/or biologicals soon after delivery. In general, the flare rate postpartum is lower than expected in the present cohort, mainly due to restart of medication soon after delivery, however flares as the natural course of RA postpartum were still observed.

Also in chapter four, where pregnancy outcome is addressed, some issues should be discussed regarding the study design. Since the PARA-study is an observational study, results are restricted to reports of prevalences of adverse pregnancy outcome, without the possibility for statistical analyses with results of healthy controls. This observational study however is the first large observational study of women with RA that can adequately study causal relations between (subgroups of) disease activity or medication use during pregnancy, and pregnancy outcome.

Finally, for chapter five, where parenting disability postpartum is addressed, some minor issues should be discussed on study design. The most important issues are (I) that this was the first time that a Dutch translated version of the parenting questionnaires was used, and (II) that this was the first time that PDI scores were calculated at several time points as an objective score for parenting function postpartum. Another issue to address is the way questionnaires are used. In the present study questionnaires were filled out by women themselves, comparable to the HAQ, whereas the questionnaires were originally developed to collect data of women by telephone interview.

NEW INSIGHTS

The new insights acquired from this thesis are:

I Disease activity and functionality during pregnancy should be measured with (adapted) objective measurement tools only.

II Improvement of disease activity during pregnancy and flares postpartum are still present in women with RA, however in lower percentages (in patients with at least moderate disease activity 48% response during pregnancy, and of all patients 39% flare postpartum), even in an era of more treatment options. Furthermore, women with low disease activity remain stable during pregnancy.

III RA patients without both autoantibodies (anti-CCP and RF) have a higher chance to improve during pregnancy than RA patients with one or both autoantibodies.

IV Higher disease activity is directly associated with lower birth weight, while prednisone use reduces birth weight indirectly via gestational age.

Higher disease activity is also associated with a higher frequency of caesarean sections.

V Postpartum a higher parenting disability is associated with erosive disease and higher disease activity.

IMPLICATIONS FOR CLINICAL PRACTICE

The new insights from this thesis were translated into seven implications for clinical practice:

I During pregnancy in women with RA, disease activity could be measured with DAS28-CRP-3 and functionality can preferably be calculated by means of a HAQ without 6 selected questions to obtain objective data for research, and both scores can possibly be used for monitoring disease activity and functionality in an individual patient.

II Women with RA and a wish to conceive can be informed that if the disease activity of RA can be adequately controlled, currently up to one-half of the women with moderate or high disease activity at first trimester will improve during pregnancy, and of all patients at least one-third of all patients will flare postpartum.

III Women may be informed that in the case of low disease activity before pregnancy, disease activity will remain stable during pregnancy, while women with at least moderate disease activity may have a considerable chance of improving.

IV Women with RA without autoantibodies (anti-CCP and RF) at any time measured during disease course, may have a higher chance of improving during pregnancy.

V Birth weight of the newborn may benefit from good control of disease activity before and during pregnancy, which might implicate that rheumatologists should strive to low disease activity in their patients for a better pregnancy outcome.

VI Obstetricians should be aware of a higher incidence of caesarean sections in RA patients with high disease activity, and of an increased risk of preterm delivery (< 37 weeks) in RA patients using prednisone.

VII Treatment goals postpartum should be focussed on modifiable factors to preserve parenting function of RA patients by giving joint protective advice before delivery and lowering disease activity postpartum.

RECOMMENDATIONS FOR FUTURE RESEARCH

To state new research questions, one must first be aware that performing randomised controlled trials during pregnancy is in general difficult, because of unknown influences on unborn life and for ethical reasons. In these situations an observational study, as the PARA-study, thus provides the highest level of evidence possible to investigate causal relations. In the present thesis we described that RA patients can be properly classified into women with or without improvement during pregnancy, and with or without deterioration postpartum. This facilitates future comparisons between clinical responses and laboratory findings.

A first suggestion for future research is directed towards the question why the disease activity of RA patients improves during pregnancy. Immunological research guided by the clinical observation that the presence of autoantibodies seems to play a role in the persistence of disease activity during pregnancy can be important. Regarding this, biochemical research on glycosylation might be important (35), since this mechanism may change the functional properties of autoantibodies and may result during pregnancy in autoantibodies that are less pathogenic. But also changes in the immune system in general, like the more Th2-guided responses during pregnancy (23), probably as a result of more changes in hormonal status (36) or due to the influence of placental (37) or child characteristics (13, 38, 39), are still of interest for future research.

A second suggestion for future research regarding pregnancy outcome in women with RA is directed towards the pregnancy outcome per DMARD used in the present cohort in order to provide additional information for rheumatologists, when therapy options are restricted and disease activity should be better controlled for the pregnant women (40). Furthermore, ideally a randomised-clinical trial should be conducted, in order to show the effect of DAS28-mediated intensified disease control during pregnancy versus regular care. However, performing this will need an impossibly high number of participants. Another way to support the suggestion that low disease activity during pregnancy is better than moderate to high disease activity, is to perform a study on their children. Lower birth weight of babies of women with high disease activity may influence children's development in growth or health negatively compared with that of children born with a higher birth weight in women with low disease activity. It has been suggested that children with lower birth weight are more susceptible to perform less in school, and to develop already risk factors in their childhood for metabolic diseases for diabetes and/or cardiovascular diseases in adult life (41-44). These indicators for increased risk

are already present at young age, and therefore this could be topic of new research in children born in the PARA-study.

A third suggestion for future research is defining characteristics of women with RA (I) that have not become pregnant yet, and (II) determining associations between the time to conceive and (modifiable) disease characteristics. Elucidating this is of great importance, since many women are treated, because of their wish to conceive, with less medication than needed for adequate disease control. To avoid irreversible loss of functionality due to high disease activity, referral to assisted reproduction techniques may be considered in women with RA. Finally, (III) less fecundity in RA has been described, however the cause has not yet been elucidated (3).

The fourth and final suggestion for future research concerns the measuring of the effect of joint protective advice given to women with RA and erosive disease during pregnancy, and the effect of standardized lowering of disease activity with medication postpartum. Both may independently increase the ability of women to take care of their children. Future research can be conducted with already collected data, and will address the magnitude of the effect of joint protective advice during pregnancy on parenting disability postpartum, in order to generate evidence for adding this into the guidelines for standard care of RA patients during pregnancy.

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SUMMARY

The work presented in this thesis aimed to determine the course of disease activity of rheumatoid arthritis (RA) from before, during, till 6 months after pregnancy, and to define its associations with patients' characteristics and pregnancy outcomes. All in order to elucidate the mechanism of immunological, biochemical, and/or hormonal changes that might explain this favourable effect of pregnancy in RA eventually. Previously mostly retrospectively conducted studies reported up to 90% of women with RA experiencing a spontaneous improvement of the disease activity during pregnancy. Whether this still holds true in a large prospective cohort study from prepregnancy onwards, in an era of new treatment options, is one of the principal research questions addressed in this thesis. Therefore, we conducted a nationwide prospective cohort study on pregnancy and RA (the PARA-study acronym for Pregnancy-induced Amelioration of Rheumatoid Arthritis) in the Netherlands, which was conducted between 2002 and 2009 (chapter two).

MEASURING DISEASE ACTIVITY DURING PREGNANCY

The aim was threefold. First, to assess how pregnancy influences the scoring of the Disease Activity Score in 28 joints (DAS28) and the Health Assessment Questionnaire (HAQ) (chapter two), and how both scores perform in pregnant patients with RA. Second, to prospectively determine the disease activity during pregnancy in RA patients treated in an era of new treatment options. Third, to determine whether changes in levels of anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF), were associated with the spontaneous improvement of rheumatoid arthritis (RA) during pregnancy and with the subsequent flare postpartum (chapter three).

Validated instruments

In chapter two we demonstrated that being pregnant influences the scoring of disease activity and functionality. Disease activity was measured with the DAS28 and functionality with the HAQ. Certain HAQ variants, made within the rules of scoring the HAQ, could reduce the influence of pregnancy on functionality scores. The two RA assessment tools for use during pregnancy which perform best were found to be: for disease activity the DAS28-CRP-3 (calculated without visual analogue scale (VAS) of global health (GH)), and for functionality the HAQ variant calculated without 6 selected items, although even this variant of the HAQ did not totally preclude the influence of pregnancy. These two well-defined objective assessment tools are indispensable for the present prospective cohort study, and will probably also have their merits in future research.

Disease course during pregnancy and postpartum

In chapter three section one we showed that the assumption of rheumatologists that almost all patients with RA will experience a remission of disease activity during pregnancy does not seem to be valid today, and must be viewed in the context of new treatment options. In this nationwide prospective study disease activity was documented with validated objective instruments and showed that approximately one-quarter of women were in remission in the third trimester, despite the fact that medication use was remarkably reduced during pregnancy compared with before conception. Almost half of the women had at least a moderate response in disease activity during pregnancy and more than one-third had at least a moderate flare postpartum. The postpartum flare, however, may be underestimated because medication use was remarkably increased after delivery. In this chapter we demonstrated that neither the presence of RF, or anti-CCP separately, nor the presence of erosions, were associated with improvement during pregnancy or postpartum flare. Finally, this study showed that during pregnancy patients with low disease activity before pregnancy remained relatively stable.

Associations with autoantibodies

In chapter three section two the mechanism underlying the spontaneous clinical improvement of RA during pregnancy and the subsequent flare after delivery was addressed by since RF and anti-CCP are thought to play an important role in the pathophysiology of RA. In the present study we showed that autoantibody levels were stable during pregnancy, and not related to improvement of disease activity during pregnancy. Postpartum, all levels of autoantibodies, except of IgG-RF, decreased when medication was resumed. However, surprisingly, in the absence of both autoantibodies (negative for both anti-CCP and RF) women had statistically significantly more frequently an improvement according to EULAR response criteria, than women positive for one or both of the autoantibodies. This finding may support the hypothesis that RA is a heterogeneous disease with different pathogenic mechanisms involved.

DETERMINING PREGNANCY OUTCOME IN RA

We described the results of this study in chapter four. The aim was twofold, first to determine pregnancy outcome of rheumatoid arthritis (RA) patients in relation to disease activity, and second in relation to prednisone use.

We performed the world's largest prospective study in RA women up to now, describing pregnancy outcome, and extensively linking disease activity and medication use throughout pregnancy to birth weight and birth weight SDS

(standard deviation score). Although the incidence of pregnancy complications in our cohort was comparable with the Dutch general obstetric population, among patients with high disease activity caesarean sections were performed more frequently. Furthermore, we showed that newborns of women with higher disease activity and prednisone use had a lower birth weight compared with newborns of women with low disease activity and without prednisone use. We described for the first time that the effect of prednisone on a lower birth weight was mediated indirectly by shortened gestational age at delivery, whereas higher disease activity directly negatively influenced birth weight.

PARENTING FUNCTION POSTPARTUM

In chapter five we performed for the first time an observational study on parenting disability postpartum to describe correlations between PDI scores and disease activity, and other functionality scores (HAQ), so (modifiable) factors associated with PDI scores postpartum could be defined. Results of this study showed that difficulties in the parenting function of women with RA postpartum can easily be measured with PDI scores, and showed that PDI scores are responsive for changes in time. PDI scores were, as expected, highly correlated with HAQ scores. Two (modifiable) factors influencing parenting disability postpartum could be defined: having higher disease activity postpartum and erosive disease. The three activities in which women most frequently encountered difficulty were carrying and bathing the baby and household chores.

FUTURE RESEARCH

The studies described in this thesis have identified several new insights and recommendations for future research (chapter six); both clinical and laboratory subjects are suggested.

Clinical research

The first hypothesis of future research may be to follow-up the children born from women with high disease activity during pregnancy, to discover whether they have already more risk factors for developing metabolic diseases than children born to women with low disease activity of RA, which may lead to an additional argument for good disease control during pregnancy.

The second hypothesis to address is defining characteristics of women whose pregnancy wish is not fulfilled, and determining associations between the time to conceive and (modifiable) disease characteristics.

Finally a third hypothesis can be tested with already collected data that addresses the magnitude of the effect of joint protective advice during pregnancy on parenting disability postpartum. When there is a significant contribution of given joint protective advice, this will generate evidence for adding this into the guidelines for standard care of RA patients during pregnancy.

Laboratory research

Since we described in the present thesis validated measurement tools to classify disease course during pregnancy, it will facilitate future comparisons between clinical responses and laboratory findings. Immunological research guided by the clinical observation that presence of autoantibodies seems to play a role in the persistence of disease activity during pregnancy could be important. Also biochemical research on glycosylation might be important, since this mechanism may change the sensibility of autoantibodies and may account for different pathogenic effects of autoantibodies during pregnancy. Changed immunological responses, in general, as a switch to more Th2-guided responses during pregnancy, probably due to changes in hormonal status or due to the influence of placental or child characteristics, are still of interest for future research.

SAMENVATTING

Al in de dertiger jaren van de twintigste eeuw werd beschreven dat tijdens zwangerschap de ziekteactiviteit van reumatoïde artritis (RA) spontaan kon verbeteren. Er waren in die tijd geen adequate behandelmogelijkheden voor RA. Er werden percentages tot 90% gerapporteerd van vrouwen die spontaan verbeterden tijdens de zwangerschap. Echter na de bevalling (postpartum) keerde de ziekteactiviteit in een even zo groot percentage vrouwen weer terug. Het fenomeen van de spontane verbetering en verslechtering van RA spreekt tot de verbeelding van vele onderzoekers. Tot nu toe ontbrak het echter aan een studie waarin een groot aantal vrouwen vóór, tijdens en na de zwangerschap is gevolgd. Een dergelijke studie is nodig om goed onderzoek te kunnen doen naar de oorzaak van de verbetering, en naar factoren die hiermee geassocieerd zouden kunnen zijn. Deze factoren zouden op immunologisch, biochemisch en/of hormonaal gebied kunnen liggen. Of het eerder gerapporteerde hoge percentage vrouwen dat verbetert tijdens de zwangerschap nog reëel is, in een tijdperk met veel meer therapeutische mogelijkheden voor RA, is één van de belangrijkste onderzoeksvragen die als eerste beantwoord moet worden alvorens dieper op de oorzaak (etiologie) van de verbetering in te kunnen gaan. De PARA-studie (acroniem voor Pregnancy-induced Amelioration of Rheumatoid Arthritis) werd derhalve in 2002 gestart, en kan het beste omschreven worden als een landelijke observationele prospectieve cohort studie. (hoofdstuk twee)

Dit proefschrift is gebaseerd op de PARA-studie en beschrijft:

I A) het beloop van ziekteactiviteit van RA vóór, tijdens een zwangerschap en tot zes maanden postpartum.
B) welke kenmerken van de RA patiënte verband houden met het beloop van de ziekteactiviteit tijdens en na de zwangerschap.

II wat de invloed van ziekteactiviteit van RA en medicijngebruik (prednison) tijdens de zwangerschap is op de zwangerschapsuitkomst; in het bijzonder de invloed op zwangerschapsduur en geboortegewicht.

III welke problemen vrouwen met RA ervaren tijdens de zorg voor hun kind(eren) na de geboorte, als de ziekteactiviteit van RA meestal weer toeneemt.

METEN VAN ZIEKTEACTIVITEIT TIJDENS DE ZWANGERSCHAP

De ziekteactiviteit van RA kan alleen goed vastgelegd worden als er objectieve maten voor het meten van ziekteactiviteit tijdens de zwangerschap gedefinieerd zijn. Daarna kunnen ziekteactiviteit en functionaliteit in de tijd gemeten worden en kan er gezocht worden naar associaties met kenmerken van de patiënten

met RA. In het eerste deel van dit proefschrift worden hiertoe drie vraagstellingen beantwoord:

I a Hoe beïnvloedt een zwangerschap de score voor ziekteactiviteit gemeten met een 'disease activity score voor 28 gewrichten' (DAS28), en hoe de score voor functionaliteit gemeten met de 'health assessment questionnaire' (HAQ)?
b Hoe betrouwbaar kunnen deze scores de veranderingen in ziekteactiviteit en functionaliteit tijdens de zwangerschap vastleggen? (hoofdstuk twee)

II Verbetert de ziekteactiviteit van RA tijdens de zwangerschap, en verslechtert deze postpartum, ook in een tijd dat er meer therapeutische mogelijkheden zijn om RA te behandelen? (hoofdstuk drie sectie één)

III a Veranderen de concentraties autoantistoffen (anti-cyclisch citrulline peptide antistoffen (anti-CCP) en subklassen reumafactoren (RF; IgM-RF, IgG-RF en IgA-RF)) tijdens de zwangerschap en postpartum?
b Is een verandering in concentraties geassocieerd met de spontane verbetering in ziekteactiviteit van RA tijdens de zwangerschap en met de verslechtering postpartum? (hoofdstuk drie sectie twee)

Objectieve en gevalideerde meetmethoden

In hoofdstuk twee werd vastgesteld dat een zwangerschap zowel de meetmethode om ziekteactiviteit te meten (DAS28), als die om de functionaliteit te meten (HAQ) beïnvloedt. De invloed op de DAS28 was het meest uitgesproken als die berekend werd met de bezinking (BSE) en visuele analoge schaal voor algemene gezondheid (VAS-GH). De invloed op de DAS28 was het minst uitgesproken als die berekend werd met C-reactive protein (CRP) en zonder VAS-GH. Deze DAS28 kan kortweg worden aangegeven als DAS28-CRP-3. De invloed van zwangerschap op de HAQ was in het algemeen groot. Door het opstellen van zogenaamde HAQ-varianten, allemaal gedefinieerd binnen de regels om een valide HAQ te berekenen, verminderde de invloed van zwangerschap op de functionaliteitscore aanzienlijk. Het resultaat van dit onderzoek was dan ook dat de twee meest valide maten om ziekteactiviteit en functionaliteit tijdens de zwangerschap te meten zijn: de DAS28-CRP-3 en de HAQ-variant berekend zonder de 6 specifieke vragen, die het meest door een zwangerschap worden beïnvloed. Hoewel daardoor de invloed van zwangerschap op deze HAQ-score aanzienlijk werd gereduceerd, bleef enige invloed op de score aanwezig. Zodra de meetmethoden voor ziekteactiviteit en functionaliteit tijdens de zwangerschap en postpartum goed beschreven waren, konden ze gebruikt worden in de PARA-studie en zullen mogelijk ook hun meerwaarde bewijzen in toekomstig onderzoek.

Ziekteactiviteit tijdens en na de zwangerschap

In hoofdstuk drie sectie één werd de veronderstelling van reumatologen dat bijna alle vrouwen met RA een verbetering van ziekteactiviteit zullen ervaren tijdens de zwangerschap ontkracht. Dat lagere percentages gevonden werden dan in eerder onderzoek werd vermeld, moet geplaatst worden in de context dat er vele (nieuwe) therapeutische mogelijkheden voor RA zijn gekomen sinds de voorgaande studies. In de PARA-studie was een percentage van 25% van vrouwen in remissie (DAS28 <2.6) in het derde trimester van de zwangerschap. Dit percentage moet wel gezien worden in het licht dat medicatiegebruik tijdens zwangerschap reeds aanzienlijk was gereduceerd vergeleken met het gebruik vóór de zwangerschap, omdat het gebruik van de meeste medicatie tijdens de zwangerschap en het geven van borstvoeding (lactatie) wordt ontraden. Het percentage vrouwen dat verbeterde tijdens de zwangerschap werd berekend aan de hand van de vrouwen die in het eerste trimester tenminste matige ziekteactiviteit (DAS28 > 3.2) hadden. Alleen op deze vrouwen konden de gestandaardiseerde criteria voor verbetering, als gedefinieerd door de European League Against Rheumatism (EULAR), toegepast worden. Van deze vrouwen verbeterde 50% spontaan en zij werden geclassificeerd als hebbende tenminste een matige verbetering tijdens de zwangerschap. Postpartum konden alle vrouwen geclassificeerd worden naar de in dit proefschrift nieuw opgestelde criteria voor verslechtering (‘reversed’ EULAR criteria voor verbetering). In totaal verslechterde ruim één derde van alle vrouwen met RA postpartum, geclassificeerd als tenminste een matige verslechtering. Dit aantal zal een onderschatting zijn omdat de hoeveelheid medicatie die vrouwen postpartum gebruikten, aanzienlijk was toegenomen. In dit hoofdstuk konden geen kenmerken gedefinieerd worden die geassocieerd waren met een verbetering tijdens de zwangerschap of met een verslechtering postpartum (bijv. aan- of afwezigheid van alleen anti-CCP, of alleen RF, of erosies). Tenslotte was het opvallend dat vrouwen met een lage ziekteactiviteit vóór de zwangerschap, de zwangerschap met relatief gelijkblijvende ziekteactiviteit doorstonden.

Associatie met autoantistoffen

In hoofdstuk drie sectie twee werd een eerste poging gedaan om de spontane verbetering van RA tijdens de zwangerschap en de verslechtering postpartum te associëren met autoantistoffen. Het is bekend dat anti-CCP en RF een belangrijke rol spelen in de pathofysiologie van RA. In huidig onderzoek veranderden de concentraties autoantistoffen (anti-CCP en subklassen RF (IgM-RF, IgG-RF, IgA-RF)) tijdens de zwangerschap statistisch niet significant. Er werd zowel tussen de verandering in concentraties van een specifieke autoantistof en de spontane verbetering van de RA tijdens zwangerschap, als tussen verandering in concentraties en de verslechtering postpartum geen associatie gevonden. Postpartum lijkt meest waarschijnlijk dat het starten van

medicatie verantwoordelijk is voor de daling van alle concentraties autoantistoffen, behalve van IgG-RF. Uiteindelijk is er nog een opvallende conclusie uit dit onderzoek te trekken, namelijk dat vrouwen zonder beide autoantistoffen (afwezigheid van anti-CCP en RF) significant vaker een verbetering van de RA tijdens zwangerschap hadden, dan vrouwen met één of beide autoantistoffen in het bloed. Deze bevinding zou de hypothese kunnen onderschrijven dat RA een heterogene ziekte is waarbij verschillende pathogenetische mechanismen betrokken zijn.

BEPALEN VAN DE ZWANGERSCHAPSUITKOMST IN PATIËNTEN MET RA

In hoofdstuk vier worden de resultaten beschreven van het onderzoek naar de zwangerschapsuitkomsten van het cohort. Het doel van dit deelonderzoek was tweeledig:

I het bepalen van de invloed van ziekteactiviteit van RA tijdens de zwangerschap op de zwangerschapsuitkomst van de vrouwen in de PARA-studie (met name geboortegewicht en zwangerschapsduur)
II het bepalen van de relatie tussen prednisongebruik en zwangerschapsuitkomst.

De PARA-studie is ’s werelds grootste cohort van zwangere vrouwen met RA dat prospectief gevolgd is. Nooit tevoren kon de relatie tussen ziekteactiviteit en zwangerschapsuitkomsten in dit onderzoek gelegd worden. Het gebruik van geboortegewichten en geboortegewicht SDS (standaarddeviatie score), waarin gecorrigeerd wordt voor zwangerschapsduur en sekse van het kind, leverden nieuwe inzichten op. Het gemiddelde geboortegewicht van kinderen van vrouwen met RA is vergelijkbaar met de algemene Nederlandse obstetrische populatie. Ook het optreden van het aantal zwangerschapscomplicaties in de PARA-studie zijn grotendeels vergelijkbaar met die optreden in de Nederlandse obstetrische populatie.

Twee opvallende conclusies ten aanzien van ziekteactiviteit en zwangerschapsuitkomst zijn:

I vrouwen met hoge ziekteactiviteit in het derde trimester bevielen frequenter met een keizersnede
II zowel de kinderen van vrouwen met hoge ziekteactiviteit als van vrouwen met prednisongebruik hadden een lager geboortegewicht vergeleken met de kinderen van vrouwen met een lage ziekteactiviteit en zonder prednisongebruik.

III Met aanvullende analyses is in dit onderzoek aannemelijk gemaakt dat hogere ziekteactiviteit een direct negatief effect heeft op het geboortegewicht, terwijl prednisongebruik het geboortegewicht verlaagt door het verkorten van de zwangerschapsduur.

OUDERSCHAP POSTPARTUM

In hoofdstuk vijf worden resultaten getoond van een observationele studie naar de functionele moeilijkheden die vrouwen met RA in het ouderschap postpartum ervaren. Dit kon in kaart worden gebracht middels het uitdrukken van het functioneren met betrekking tot het ouderschap in 'Parenting Disability Indices' (PDI-scores). Tegelijkertijd werd de functionaliteit ook met standaard HAQ-scores gemeten en de ziekteactiviteit met DAS28-CRP-3. Op basis van veranderingen in PDI-scores tussen twee meetmomenten postpartum werden associaties gezocht met (veranderbare) factoren. PDI-scores bleken geschikt om de veranderingen met betrekking tot het functioneren in het ouderschap te registreren, en de score was sterk gecorreleerd aan de HAQ.

Twee (veranderbare) factoren konden worden aangewezen:
I erosieve schade
II hogere ziekteactiviteit

Het ligt in de lijn der verwachting dat met goede gewrichtsbeschermende instructies met betrekking tot de zorg voor baby's aan vrouwen met reeds beschadigde gewrichten, als mede met het verlagen van ziekteactiviteit postpartum, het functioneren in het ouderschap postpartum verlicht kan worden. De drie activiteiten waarmee de meeste problemen werden ervaren zijn: het dragen van de baby, de lichamelijke verzorging van de baby en het doen van het huishouden.

TOEKOMSTIG ONDERZOEK

De studies die in dit proefschrift werden beschreven leverden diverse nieuwe inzichten en aanbevelingen op voor toekomstige projecten op het gebied van klinisch en laboratoriumonderzoek met gegevens van de PARA-studie. (hoofdstuk zes)

Klinisch onderzoek

Een eerste voorstel voor toekomstig onderzoek zou kunnen zijn de ontwikkeling van kinderen van vrouwen met RA te volgen, met als doel het effect van de ziekteactiviteit van de moeder tijdens zwangerschap te relateren aan het bij kinderen optreden van risicofactoren voor metabool syndroom (o.a. verhoogde

aanleg voor hart- en vaatziekten). Het vinden van een toegenomen frequentie van deze risicofactoren onder de kinderen van vrouwen met hoge ziekteactiviteit tijdens de zwangerschap, zou een extra argument kunnen vormen om ook tijdens de zwangerschap ziekteactiviteit van RA zo optimaal mogelijk te controleren.

Een tweede voorstel zou gericht kunnen zijn op de specifieke karakteristieken van vrouwen die een niet-vervulde kinderwens hielden tijdens de PARA-studie. Associatiestudies naar (veranderbare) ziektekenmerken tussen vrouwen met RA die wel en niet zwanger geworden zijn, maar ook tussen ziektekenmerken en de tijd tot conceptie in de groep vrouwen die wel zwanger zijn geworden, zouden hier een antwoord op kunnen geven.

Een derde voorstel kan zijn het toetsen van de hypothese of het geven van gewrichtsbeschermende adviezen tot behoud van het functioneren postpartum als ouder, zinvol is bij patiënten met reeds schade aan de gewrichten en of dit leidt tot lagere PDI-scores. Wanneer dit inderdaad bijdraagt aan beter functioneren als ouder, kan dit aanleiding zijn om gewrichtsbeschermende adviezen op te nemen in de standaardzorg voor vrouwen met RA tijdens de zwangerschap, ter voorbereiding op de fysieke zorg voor een baby postpartum.

Laboratorium onderzoek

Dit proefschrift beschrijft de gevalideerde meetmethoden om ziekteactiviteit en het beloop ervan tijdens zwangerschap en postpartum vast te leggen. Hiermee kunnen toekomstige vergelijkingen tussen klinische gegevens en laboratorium bevindingen eenvoudig worden gemaakt. Niet alleen immunologisch onderzoek naar de reden waarom de aanwezigheid van autoantistoffen de kans op een spontane verbetering van RA tijdens de zwangerschap vermindert, maar ook biochemisch onderzoek naar glycosylering van deze autoantistoffen kan in dit verband zinvol zijn. Dit mechanisme kan bijdragen aan een verandering in de gevoeligheid van autoantistoffen voor antigenen, en zo het pathogene effect van autoantistoffen tijdens de zwangerschap moduleren. Een volgende te toetsen hypothese is of de verandering van het immuunsysteem naar een meer Th2 gestuurde respons op antigenen tijdens de zwangerschap een belangrijke bijdrage aan de spontane verbetering kan leveren. Of deze tijdelijke verandering in het functioneren van het immuunsysteem hormonaal, placentair, danwel door foetale kenmerken gestuurd is, levert vele mogelijkheden voor toekomstig laboratorium onderzoek.

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Secondly, dear Mary, what good things family from overseas can bring! Your love for linguistic and family affairs brought us together. I cannot thank you enough.

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Lieve papa en mama, dank voor jullie onuitputtelijke steun, eindeloze hulp en onvoorwaardelijke liefde. Jullie bijdrage aan dit boekje is groter dan jullie kunnen beseffen. Ik bewonder jullie om jullie inzet voor anderen, om jullie altijd harde werken, maar bovenal omdat jullie Amy en mij op jullie eigen wijze altijd gestimuleerd hebben 'verder te leren'.

ABOUT THE AUTHOR

CURRICULUM VITAE

Yaël Antonia de Man was born on July 22, 1974 in Brielle, The Netherlands. She attended grammar school at the Rijksscholengemeenschap in Brielle, from which she graduated athenaeum in 1992. That year she moved to Delft for attending Hoger Laboratorium Onderwijs and graduated her propaedeutic examination in 1993 and completed her first year of bachelor degree in biomedical laboratory sciences in 1994. In that same year she moved to Rotterdam for her medical studies. In 1998 she obtained her master degree in Medicine at the Erasmus University Rotterdam, with honourable mention as one of the twenty-five best students of the curriculum. In 2001 she received her medical degree cum laude from the Erasmus University Rotterdam.

Her graduate research project for her master degree was on Peptidoglycanes in Rheumatoid Arthritis, and was conducted at the Department of Immunology, Erasmus University Rotterdam, (head, Prof.dr. R. Benner) under guidance of Mrs. dr. I.A. Schrijver and Prof.dr. J.D. Laman.

During her medical training, Yaël took an elective clerkship in Rheumatology for four months in 2000 at Johns Hopkins Medical Institutions, Department of Medicine, Division of Rheumatology, (head, A. Rosen, M.D., Professor of Medicine) Baltimore, Maryland, U.S.A., under guidance of Mrs. J.M. Bathon, M.D., Associate Professor of Medicine.

From January 2002 onwards, she conducted the work described in this thesis at the Department of Rheumatology under the supervision of Mrs. Prof.dr. J.M.W. Hazes and dr. R.J.E.M. Dolhain. From January 2004 onwards, she combined this work with her residency in Internal Medicine at Erasmus MC, University Medical Center Rotterdam (head, Prof.dr. E.J. Kuipers) under guidance of Prof.dr. J.L.C.M. van Saase and dr. P.L.A. van Daele. As of January 2009, she combines her residency in Internal Medicine with a residency in Rheumatology at Erasmus MC, University Medical Center Rotterdam (head, Mrs. Prof.dr. J.M.W. Hazes).

LIST OF PUBLICATIONS

van de Geijn FE, de Man YA, Wuhrer M, Willemsen SP, Deelder AM, Hazes JMW, Dolhain RJEM. Can mannose binding lectin explain course and outcome of pregnancy in rheumatoid arthritis? 2009; *Submitted*.

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de Man YA, Bakker – Jonges LE, Dufour - van den Goorbergh BCM, Tillemans SPR, Hooijkaas H, Hazes JMW, Dolhain RJEM. Women with rheumatoid arthritis negative for anti-CCP and rheumatoid factor are more likely to improve during pregnancy, whereas in autoantibody positive women autoantibody levels are not influenced by pregnancy. *Annals of the Rheumatic Diseases*. 2009; First-online since 11/03/2009; *in press*.

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PhD Portfolio

Summary of PhD training and teaching activities

General academic and Research skills	YEAR
Medical Ethics, Erasmus MC, Rotterdam, NL.	2008
Biomedical English Writing and Communication, Rotterdam, NL.	2006
Principles of Research in Medicine and Epidemiology, Erasmus Summer Programme, Rotterdam, NL.	2006
Introduction to Data-analysis, Erasmus Summer Programme, Rotterdam, NL.	2006
Regression Analysis, Erasmus Summer Programme, Rotterdam, NL.	2006
In-depth courses (e.g. Research school, Medical Training)	
Rheumatology, residency, Erasmus MC, Rotterdam, NL.	2009 -current
Internal Medicine, residency, Erasmus MC, Rotterdam, NL.	2004 -current
Immunobiology course, Dept. of Immunology, Erasmus MC, Rotterdam, NL.	2002
Invited lecture	
Reumapatiëntenbond, Wapenveld, NL; lecture 'Kinderen, kun je ze krijgen en krijgen zij het ook? Erfelijkheid en zwangerschap bij verschillende reumatische ziekten'.	2002
(Inter)national conference presentations	
American College of Rheumatology (ACR), 2008 annual scientific meeting, San Francisco, CA, U.S.A.. Poster presentation; 'No association between levels of auto-antibodies and the improvement of RA during pregnancy'.	2008
Najaarsdagen, Nederlandse Vereniging van Reumatologie (NVR), annual scientific meeting Veldhoven, NL. Oral presentation; 'Geen verband tussen autoantistoffen en de verbetering van RA tijdens de zwangerschap'.	2008
European League Against Rheumatism (EULAR), 2007, annual scientific meeting, Barcelona, Spain. Poster presentation; 'No association between levels of auto-antibodies and the	

improvement of RA during pregnancy'. Oral presentations; 'Does rheumatoid arthritis ameliorate during pregnancy? Results from a prospective Nationwide Cohort study (the PARA-study)', 'Disease activity and prednisone use influences birth weight in RA pregnancies', and press conference.	2007
Internistendagen, Nederlandsche Internisten Vereeniging (NIV), annual scientific meeting, Maastricht, NL. 'Verbetert reumatoïde artritis tijdens de zwangerschap? Resultaten van de PARA-studie'.	2007
American College of Rheumatology (ACR), 2006, annual scientific meeting, Washington D.C., U.S.A. Poster presentation; 'How to measure functionality and disease activity during pregnancy in rheumatoid arthritis'. Oral presentations; 'Does rheumatoid arthritis ameliorate during pregnancy? Results from a prospective Nationwide Cohort study (the PARA-study)' and 'Disease activity and prednisone use influences birth weight in RA pregnancies'.	2006
Najaarsdagen, Nederlandse Vereniging van Reumatologie (NVR), annual scientific meeting, Veldhoven, NL. Oral presenation; 'Verbetert reumatoïde artritis tijdens de zwangerschap? Resultaten van de PARA-studie'.	2006
Najaarsdagen, Nederlandse Vereniging van Reumatologie (NVR), annual scientific meeting, Veldhoven, NL. Oral presentation; 'Functionaliteit en ziekteactiviteit van patiënten met reumatoïde artritis tijdens de zwangerschap; hoe kunnen we die het beste meten?'.	2004
European League Against Rheumatism (EULAR), 2004, annual scientific meeting, Vienna, Austria. Poster presentation; 'How to measure functionality and disease activity during pregnancy in rheumatoid arthritis (RA)-patients'.	2004

Teaching

Supervising and teaching MSc students, Department of Internal Medicine and Rheumatology, Erasmus MC, Rotterdam, NL.	2004 -current
First year Medical students: Erasmus MC, Rotterdam, NL; 'Leren studeren'.	2006

Other

Referee activities for international scientific journals (Arthritis Care and Research, Annals of Rheumatic Diseases).	2006 -current

All rheumatologists working in the Netherlands were contacted by mail twice a year from the start in May, 2002, till May, 2008. They were asked to recruit patients with RA who had a wish to conceive or who were already pregnant (preferably in their first trimester). Patients were eligible for the study if they fulfilled the 1987 revised criteria of the American College of Rheumatology (ACR) for RA and had a good understanding of the Dutch language. During the study the patients' own rheumatologists provided patient care. Patients were visited six or seven times at their home address. They were visited before conception (if possible), at each trimester (8-12 weeks of gestation, 18-22 weeks, and 28-32 weeks) and three times postpartum (4-6 weeks, 12 weeks and 26 weeks) (see Figure 2.1.1). The visit before conception took place if the woman had a wish to conceive, i.e. she and her partner did not use any contraceptives. If a woman did not conceive within a year after the first visit, another visit took place. Data collected before conception was classed as 'before pregnancy'. Medical and obstetrical history were taken at the first visit by interview. Erosions were ascertained from the patients' medical records. Pregnancy outcome was ascertained, only if complicated, from patients' medical records. All

In this PhD thesis, embedded in the PARA-study, several clinical aspects of the spontaneously occurring pregnancy-induced improvement of rheumatoid arthritis (RA) are addressed. An overview is given of all rheumatic diseases and the current knowledge about their disease courses and treatment options during pregnancy and postpartum. This thesis focuses firstly on the description of tools to objectively measure the disease activity and functionality of RA before, during, and after pregnancy. Associations with the disease course and patient's characteristics are subsequently made. The influence on the pregnancy outcome of both disease activity and treatment of RA with prednisone, are assessed regarding pregnancy duration and birth weight. Postpartum however RA tends to flare again. The problems which patients with RA will encounter in parental function, while nursing their babies, are addressed.

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