Health Related Quality of Life before, during and after pregnancy in Norwegian women with Rheumatoid Arthritis and Juvenile Idiopathic Arthritis.

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Abstract

Background: There is a known interaction between pregnancy and rheumatic disease. Women with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) are concerned about the potential impact of a pregnancy. Therefore, it is important to get more knowledge on how pregnancy affects these womens health related quality of life (HRQL).

Purpose: To study changes in HRQL in Norwegian women with RA and JIA before, during and after pregnancy.

Methods: A total 35 patients with RA and 27 patients with JIA were assessed up to six times (before pregnancy, once in each trimester, and at six weeks and six months postpartum) using the short form 36 (SF-36). In addition, these women were compared to a group of non-pregnant reference women in the same age group, 66 women with RA and 33 women with JIA.

Results: In the study group RA women had better HRQL than the JIA patients at baseline in the aspects of mental health, vitality and role physical. Independent of disease group the womens, experience of vitality was lower in 1st, 2nd and 3rd trimester compared to baseline. Six months postpartum, the RA women in the study group scored better in the aspects of social function, physical function, role physical and role emotional than the non-pregnant reference women with RA.

Conclusion: HRQL was lower during pregnancy for both RA and JIA women. However, despite a wide range, the women seemed to reach the same level as pre-pregnancy at the time of six months postpartum.

Relevance

There are few studies done to assess health related quality of life (HRQL) in women with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) related to pregnancy. There are a small number of women with RA and JIA giving birth each year in Norway, and planning a family is a big issue for these women. Getting more knowledge on how a pregnancy affects these women's health related quality life from before pregnancy and to six months postpartum is valuable when consulting these women in the rheumatology unit.

List of abbreviations

ACR:	American College of Rheumatology
ADL:	Activities of daily living
BP:	Bodily pain (SF-36 aspect)
CI:	Confidence Interval
CRP:	C-reactive protein value
DAS-28:	Disease activity score by 28
DMARD:	Disease modifying anti rheumatic drug
ESR:	Sedimention rate
EULAR:	European League against Rheumatism
GH:	General Health (SF-36 aspect)
HAQ:	Health Assessment Questionnaire
HRQL:	Health related quality of life
ILAR:	International League Association of Rheumatologists
JIA:	Juvenile Idiopathic Arthritis
MH:	Mental Health (SF-36 aspect)
MHAQ:	Modified Health Assessment Questionnaire
NOR-DMARD:	The Norwegian Disease Modifying Anti rheumatic Drug register
PF:	Physical Functioning (SF-36 aspect)
PP:	Postpartum
QOL:	Quality of Life
RA:	Rheumatoid Arthritis
RE:	Role-Emotional (SF-36 aspect)
RF:	Role-Physical (SF-36 aspect)
SF:	Social Functioning (SF-36 aspect)
SF-36:	The medical outcomes study 36-item short form
SPSS:	The Statistical Package for the Social Sciences
VT:	Vitality (SF-36 aspect)

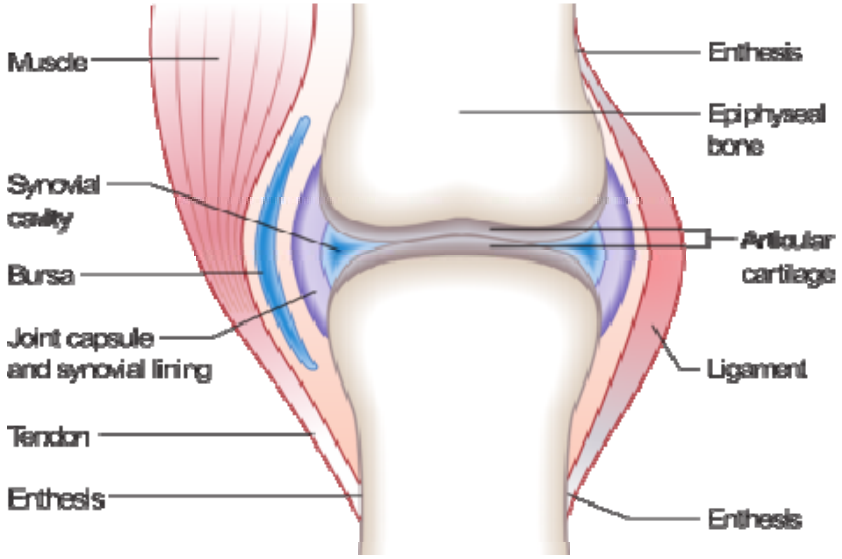
Introduction

This is a study about health related quality of life (HRQL) before, during and after pregnancy in Norwegian women with Rheumatoid Arthritis (RA) and Juvenile Idiopathic Arthritis (JIA).

Disease characteristics

RA and JIA are chronic, inflammatory autoimmune diseases characterised by destructive synovitis (Figure 1). Systematic involvement of joints of the hands and feet is common (1, 2), but all joints surrounded with synovia can be involved (3). Inflammation in joints can be very painful, and ongoing disease activity can lead to major destruction and erosions in the joints if not treated (3). Pain and stiffness in these diseases occurs because of inflammation in the synovial cavity and tenosynovitis. The synovial lining is the soft tissue around the joint capsule. Tenosynovitis involves inflammation in the tendons and the tendon sheath. The inflammation often debuts in smaller joints, like the wrist and hands (3).

Figur 1. Joint model.



http://images.rheumatology.org/ (4)

A flare in RA and JIA means an increase in disease activity. Living with RA or JIA can mean living with pain, stiffness, fatigue and reduced functioning (5). Both RA and JIA can lead to problems in the daily life, and especially when having small children (6).

Rheumatoid Arthritis (RA)

RA usually debuts during 20-30 years of age, and is about 3 times more common in women than men (7). The prevalence of RA around the world is 0.5-1 % (8, 9). The incidence of RA in Norway is around 25 per 100000 (10). RA often occurs with a general feeling of sickness. The different symptoms can be fatigue, mild fever, pain and stiffness in the joints, and morning stiffness (3).

In 2/3 of those diagnosed with RA, the disease develops slowly, whereas 1/3 have an acute debut (3). In some people, RA also affects organs such as heart, lungs, kidneys, eyes, the vascular system and the bone marrow (11). There are two serum tests that can be taken to set the RA diagnosis. The oldest one is the serum rheumatoid factor. In the latest years the anti-CCP (anti-cyclic citrullinated peptide antibodies) is more used (12).

RA is diagnosed with the 1987 American College of Rheumatology (ACR) criteria.

The ACR criteria

1. Morning stiffness for at least 6 weeks
2. Arthritis for three or more joint areas for at least 6 weeks
3. Arthritis of hand joints for at least 6 weeks
4. Symmetric arthritis for at least 6 weeks
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes.

RA is diagnosed if 4 of 7 items are present (13).

Juvenile Idiopathic Arthritis (JIA)

The most common of chronic rheumatic diseases that debuts in childhood is JIA. The debut of JIA is present in all years of childhood (8). Approximately 60 % of the children diagnosed with JIA are girls (8). About 50 % of the patients diagnosed with JIA in childhood, have an active disease in adulthood, and 50 % of them develop a polyarticular disease with five or more joints affected (14).

The prevalence of JIA is difficult to estimate, since large population studies are using different diagnostic criteria around the world, and there is a lack of a joint definition of an

active JIA. Due to this, the incidence worldwide is estimated to be 86-148/100000 children each year. The annual incidence of JIA in Norway is 14-23/100000 children, an estimate based on epidemiological studies (15). JIA is a disease that can affect smaller and larger joints, and other organs such as eyes. As a consequence, this can lead to reduced function, pain and stiffness. JIA can also affect growth in childhood (16).

JIA is diagnosed differently over the years with The American College of Rheumatology (ACR) have criteria's from 1977, the European League against Rheumatism (EULAR) criteria's from 1977, and the International League of Associations of Rheumatologists (ILAR) criteria's from 1997 (15).

The ACR criteria`s for juvenile rheumatoid arthritis (JRA) is used for patients included in this study. The ACR criteria are set at debut < 16 years of age, duration of arthritis at ≥ 6 weeks, and include systematic polyarticular disease and pauciarticular disease. Excluded subgroups are juvenile ankylosing spondylitis, juvenile psoriatic arthritis and arthritis associated with inflammatory bowel disease (15). Since 1997 the name JIA has been used, also on the patients diagnosed before 1997.

Disease modifying anti-rheumatic drugs (DMARDs)

Many of the patients with RA and JIA are in need of drugs to keep their disease in remission. DMARDs are frequently used in treating arthritis in Norway. There are two different types of DMARDs, synthetic DMARDs and biological DMARDs. Not all drugs are consistent with conception, pregnancy and lactation. Because of this it is important to adjust the drugs in a period of planning a pregnancy (17).

Fertility and pregnancy

RA and JIA can influence fertility due to different mechanisms like physical, psychological, hormonal and immunological as well as medical treatments (2, 18). According to two Norwegian studies of fertility and parity, women with arthritis have a higher proportion of nullparous compared to the normal population (19). In addition, women with RA have a lower parity than women with JIA (20).

Pregnancy is in general a big change both organic and hormonally (1). There is a well-known interaction between pregnancy and inflammatory rheumatic disease (2, 21, 22). Pregnancy affects the rheumatic disease, and the rheumatic disease affects the pregnancy (23). According to Forger and Østensen (2005) the negative symptoms during pregnancy are often dominating in healthy women. In woman with chronic inflammatory diseases a focus on the positive sides of becoming a mother is more often seen (1).

Most of the women with RA experience a decreased disease activity during pregnancy (24, 25). Most frequently a decreased disease activity is seen during pregnancy in women that are rheumatoid factor negative or anti-CCP negative (26). Around 40 % of all women with RA experience a flare postpartum within 3-6 months after delivery (22).

For women with JIA that have been in remission during the early adulthood, a flare related to pregnancy is not expected (16). About 50 % of the women with JIA with active disease in adulthood can expect the disease activity to be the same, or better during pregnancy (16, 27). Around 50 % of women with JIA can expect a flare within 3-6 months postpartum (16, 24).

Health Related Quality of Life (HRQL)

The term quality of life (QOL) has over the years become an important part of medical research (28, 29). There are a lot of different definitions of QOL that reflects the origin they were developed for (28, 29). Researchers have agreed that the term QOL is subjective and involves different aspects of life (28).

In line with this agreement, the World Health Organisation (WHO) has defined quality of life as: “individual’s perception of their position in life in the context of the culture and the value systems in which they live, and in relation to their goals, expectations, standards and concerns” (30).

QOL is a broader concept than HRQL. Distinguished from QOL, HRQL include those aspects of life that are most related to health status, instead of living standards and environment (31).

Ware et al (1995) have defined eight HRQL aspects of importance i.e. physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health (31).

Living with a chronic rheumatic disease leads to challenges on different levels, and may have a major impact on physical and mental health (32). Measurements of disease activity and disease related function does not always cover what is most important in the everyday life in people with RA and JIA. HRQL is an important aspect of the women living with chronic rheumatic disease (1). Previous studies have shown that RA and JIA have a negative effect on HRQL in women (33, 34). A study of young females with JIA have shown that they have lower HRQL, and also achieved less milestones in life compared to healthy women (35). During pregnancy, the hormonal and organ specific changes may alter not only the physical functioning, but also mental wellbeing (1, 21).

Only one small study has prospectively evaluated the impact of pregnancy on HRQL in pregnant women with a rheumatic disease with the SF-36 (1). This study had a small number of subjects, only 10 with each rheumatic disease, RA and ankylosing spondylitis. Even so, the study concluded with that pregnancy had no impact on mental and emotional health. No studies have assessed HRQL before, during and after pregnancy in Norwegian women with RA and JIA.

Aim of the study

The aim of this study is to assess women with RA and JIA before, during and after pregnancy in order to explore if the pregnancy influence HRQL.

The specific aims of this study are to:

- Compare the RA and JIA patients pre-pregnancy to non-pregnant reference women with RA and JIA in the same age at baseline and six months postpartum
- Explore the differences in HRQL between the RA and JIA patients in pregnancy, compared to non-pregnant reference women with RA and JIA in the same age
- Explore the longitudinal changes in HRQL in woman with RA and JIA from before pregnancy, during pregnancy and up to six months postpartum
- Explore the longitudinal changes in disease activity and function score, scored by DAS-28 and MHAQ in women with RA and JIA from before pregnancy, during pregnancy and to six months postpartum

Methods

Design

This is a longitudinally observational study. Women were included if they were diagnosed with RA or JIA, assessed before, during and after pregnancy and enrolled in the RevNatus registry. A reference group of non-pregnant women with RA and JIA in the same age group was included from the NOR-DMARD (The Norwegian Disease Modifying Anti Rheumatic Drug Register).

Subjects

RevNatus sample

Women in fertile age ≥18 years diagnosed with RA or JIA after the ACR criteria were included (36, 37). RevNatus is administrated at the National Service for Pregnancy and Rheumatic Diseases in Trondheim, Norway (Appendix 1). There are 12 rheumatology units in Norway that are including patients in RevNatus. The number of rheumatology units involved has increased since the register was established at St. Olavs Hospital in 2006. Registrations are done pre-pregnancy, in the 1st trimester (0-12 weeks), 2nd trimester (13-27 weeks), 3rd trimester (28-40 weeks), six weeks after delivery, six months and 12 months postpartum. Patients are also included during pregnancy. All women included in this study from RevNatus had live births. The data from RevNatus available for this study are collected from 2006-2012. For the present study, data for visits up to six months postpartum were available. This group will be referred to as the study group in this thesis.

NOR-DMARD reference sample

A reference group of non-pregnant women, in the same age group as the RevNatus sample, with RA and JIA in the NOR-DMARD registry was used for comparison. In this study, the patients from the Trondheim population of NOR-DMARD were available. All reference patients from the NOR-DMARD registry are expected to have their disease activity in control after six months of treatment with the same regime. Each person in the NOR-DMARD registry is evaluated three months after starting a new drug regime, and drug treatment is changed if disease activity is not changed to the better at that point of time. The data from

NOR-DMARD available for this study was collected from 2000-2010. This group of patients will be referred to as non-pregnant reference women in this thesis.

Measures

Both the pregnant and the non-pregnant reference women with RA and JIA have been assessed with SF-36 for HRQL, disease activity with disease activity score 28 (DAS-28-CRP(3)), and disease related function with Modified Health Assessment Questionnaire (MHAQ).

The Short Form 36 (SF-36)

The Short Form SF-36 (version 1.2) is a generic self-reported instrument used in health care and in clinical trials to measure HRQL and, normally, it takes approximately 5 minutes to complete (38).

The 36 short form questions are grouped into eight multi-item subscales covering eight HRQL aspects, i.e. physical functioning including 10 items, role physical with four items, role emotional with three items, bodily pain with two items, social functioning with two items, mental health with five items, vitality with four items and general health with five items (See table X for more information) (31, 38).

Each item has two to six response categories and each aspect is calculated, using the SF-36 manual. The score are ranging from 0-100, where 0 is the worst possible situation, and 100 is the best possible situation (38) (Table 1).

The SF-36 has been translated into Norwegian and been validated in people living with RA (39, 40) and has been used in studies of pregnant women with RA (1, 41).

Table 1. Aspects of SF-36 (31).

Aspects	Lowest possible Score	Highest possible Score
Physical Functioning PF	Very limited in performing all physical activities, including bathing or dressing	Performs all types of physical activities including the most vigorous without limitations due to health
Role- Physical RF	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities
Bodily pain BP	Very severe and extremely limiting pain	No pain or limitations due to pain
General Health GH	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent
Vitality VT	Feels tires and worn out all of the time	Feels full of pep and energy all of the time
Social Functioning	Extreme and frequent interference with normal social activities due to physical and emotional problems	Performs normal social activities without interference due to physical or emotional problems
Role-Emotional RE	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities
Mental Health MH	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time

Disease activity score 28 (DAS-28)

DAS-28(Appendix 3) is a validated measurement for disease activity in patients with RA (22), and is widely used on JIA. It contains of joint count, 28 joints are assessed for swollen and tenderness. In addition, a c-reactive protein value (CRP) or sedimention rate (ESR) value is included in making a score. The physician's or patient's measurement of general health on a visual analogue scale (VAS) can be included in the DAS-28. The DAS-28 comes in four different versions depending on the number of measurements, and if CRP or ESR is chosen. The DAS-28(4), DAS-28(3), DAS-28-CRP(4), DAS-28-CRP(3).

Because the pregnancy itself can influence the scoring with a natural elevation of ESR during pregnancy, the DAS-28-CRP(3) with three different measurements and CRP is considered the most reliable (42). The score is ranging from 0 to 9.1, whereas < 2.6 is considered as remission, < 3.2 is low disease activity, and > 5.1 is considered as high disease activity (43). DAS-28-CRP(3) has previously been used for rheumatic patients during pregnancy (22, 42).

Modified health assessment questionnaire (MHAQ)

MHAQ measures disease related function in patients with arthritis (44) (Appendix 4). MHAQ has previously been used to measure disease related function in patients with RA and JIA (40), and has been used in rheumatic pregnant women (22). MHAQ has been translated and validated into Norwegian (39). MHAQ includes eight questions on disease related function with patients ticking a 4-point Likert scale from 0 to 3, where 0 means no problem, 3 means unable to perform (44, 45). The eight scores are summarized and divided with eight to get the total MHAQ score wich is ranging from 0 to 3 (45).

Additional measures

Baseline characteristics on disease duration, age and work status from both the study group and the non-pregnant reference women with RA and JIA were available. Age and disease duration in the study group were registered in RevNatus at the first visit when pregnant, and for the non-pregnant reference women at time of inclusion in NOR-DMARD. Disease duration was set at years and months. Work status was defined as working or not working. Working was defined as more than five hours a week and students were categorized as working. The number of DMARDs was registered at each visit.

Procedures and ethics

Women included in RevNatus and NOR-DMARD were invited with written and oral information. All women included in this study have given their written confirmed content (Appendix 1 and Appendix 2) to be registered in RevNatus or NOR-DMARD, and were informed that the data would be used in research. The study was approved by the Regional Committee for Medical and Health Research (REK) (2012/447/REKmidt).

Statistical Methods

To analyse this dataset we used the Statistical Package for Social Sciences (SPSS) version 18. The data from the study group was manually put into the SPSS. All data was controlled twice. The data from the non-pregnant reference women was scanned into the SPSS file and was delivered in a data file to this study. All the results were controlled by two persons after doing the analysis twice.

The descriptive statistics was done with Chi-square test or Fisher exact test (depending on the sample size and distribution under study) for categorical data. Continuous data are presented with mean scores and 95 % confidence intervals (CI).

When comparing the scores of eight aspects of SF-36, the DAS-28-CRP(3) and MHAQ in the RA and JIA women in the study group to the non-pregnant reference women with RA and JIA, the Mann-Whitney U test was used. Using the conservative non-parametric Mann-Whitney U test was chosen since the numbers of observations were relatively few, the normality of the distribution could be questioned and this method was regarded as equally good as the two sample t-test. The test looks for differences in independent groups of samples in order to find if one of the groups have larger values than the other (46).

Changes in the eight aspects of HRQL were measured by the SF-36, DAS-28 and MHAQ were explored in the study group from pre-pregnancy and through six months postpartum, using the generalized mixed effect model for incomplete dataset in order to explore change by time point and rheumatic disease. This model is normally used for normal distributed data, and there is no good alternative for this type of tests for non-normal distributed data. When looking at the distribution of the data, there were no severe deviations from normal distribution, and using this test was considered as relevant. The reference level in the generalized mixed effect model was JIA women and the pre-pregnancy scores.

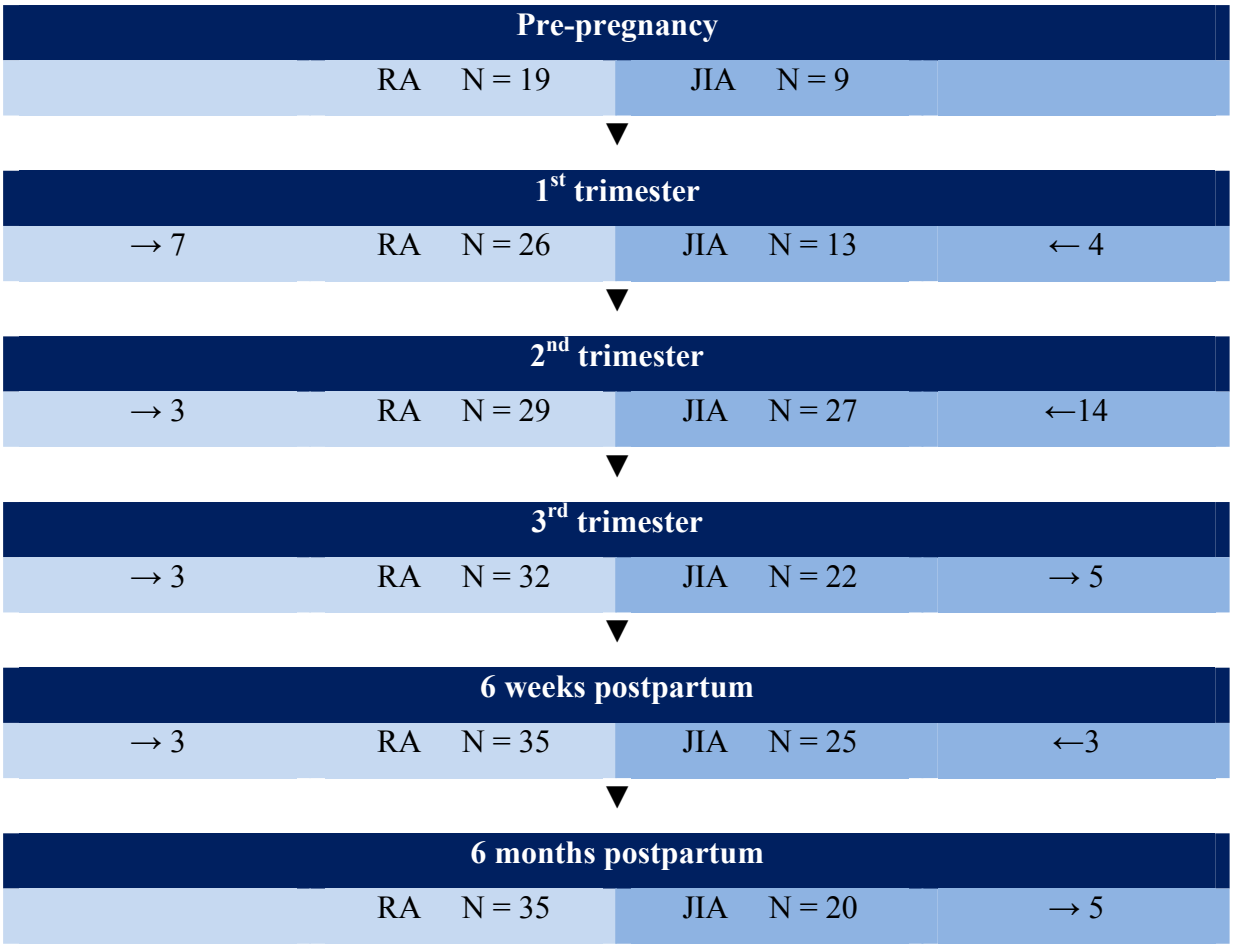
In addition to the generalized mixed effect model analysis of incomplete dataset of change in HRQL, DAS-28 and MHAQ in the study group, change in each of the RA and JIA women in the study group from pre-pregnancy throughout the pregnancy and up to six months postpartum was studied using the Wilcoxon test for related samples.

In this study the significance level was set to <0.05. All findings were looked at not only for p-value, but also for the relevance in this patient group.

Results

The flowchart (Figure 2) describes the slightly increasing number of RA women in the study group from before, during and after pregnancy, and the somewhat inconsistent number of JIA women in the study group throughout the pregnancy and postpartum. All available patients in the study group were included in this study, but between 2nd and 3rd trimester, and between six weeks and six months postpartum some JIA women were lost to follow-up. All of the women in the study group with both RA and JIA with a pre-pregnancy visit were also assessed at six months postpartum.

Figure 2. Flowchart of the study group.



Women meeting the inclusion criteria for the non-pregnant reference women were 66 non-pregnant women with RA and 33 non-pregnant women with JIA, all from the 3rd visit in the NOR-DMARD registry.

Patient characteristics

The RA and JIA women in the study group were comparable to the non-pregnant RA and JIA reference women in baseline characteristics, except that the study group used less DMARDs and the JIA women in the study group had lower score on DAS-28-CRP(3) compared to the non-pregnant reference women with JIA(Table 2). The study group women used less DMARDs compared to the non-pregnant reference women six months postpartum.

Table 2. Patient characteristics for the study group and non-pregnant reference women with Rheumatoid Arthritis (RA) and Juvenile Idiopatic Arthritis (JIA).

		Study group[a]		Non-pregnant reference women	
		RA	**JIA**	**RA**	**JIA**
Age [b]	Mean	**31.4**	**27.8**	**32.7**	**27.6**
	(95% CI)	(29.9-32.4)	(25.9-29.7)	(31.7-33.7)	(25.8-29.3)
Disease duration	Mean	**6.4**	**20.5**	**6.7**	**15.4**
	(95% CI)	(4.9-7.9)	(18.0-23.0)	(5.6-7.8)	(13.2-17.7)
DAS-28-CRP(3)					
Baseline	Mean	**3.0**	**2.1**[c]	**3.1**	**3.2**
	(95% CI)	(2.4-3.5)	(1.7-2.6)	(2.8-3.4)	(2.7-3.7)
6 months p.p	Mean	**2.5**	**3.0**		
	(95% CI)	(2.2-2.8)	(2.5-3.6)		
MHAQ					
Baseline	Mean	**0.28**	**0.06**	**0.39**	**0.48**
	(95% CI)	(0.10-0.45)	(0.007-0.12)	(0.28-0.49)	(0.29-0.67)
6 months p.p	Mean	**0.24**	**0.47**		
	(95% CI)	(0.11-0.37)	(0.25-0.70)		
DMARDs					
Baseline	Mean	**0.44**[d]	**0.53**[e]	**1.48**	**1.45**
	(95% CI)	(0.15-0.73)	(0.20-0.86)	(1.34-1.62)	(1.24-1.67)
6 months p.p.	Mean	**0.91**[f]	**0.57**[g]		
	(95% CI)	(0.65-1.17)	(0.31-0.82)		
Work status[h]					
In work					
Baseline	(N) %	**(13) 70 %**	**(5) 71.4 %**	**(31) 60.4 %**	**(11) 46.2 %**

[a] All statistical comparisons between the RA and JIA women in the study group and the non-pregnant reference women with RA and JIA were performed with the Mann-Whitney U test

[b] Age is taken from the first RevNatus visit that the patient is pregnant, and the first NOR-DMARD visit.

[c] The study group of JIA women scored lower in DAS-28-CRP(3) at baseline compared to the non-pregnant reference women, p=0.03

[d] The study group of RA women used less DMARDs at baseline compared to the non-pregnant reference women, p<0.01

[e] The study group of JIA women used less DMARDs at baseline compared to the non-pregnant reference women , p<0.01

[f] The study group of RA women used less DMARDs at 6 months postpartum compared to the non-pregnant reference women, p<0.01

[g] The study group of JIA women used less DMARDs at 6 months postpartum compared to the non-pregnant reference women, p<0.01

[h] There are some missing data in the dataset for work status. The percentage in work is calculated from them with registered with work status, and N is the number in each group working.

Eventually differences in work status between the study group and non-pregnant reference women with RA and JIA were tested with Fisher exact test

p.p = postpartum

C.I. = confidence interval

Health Related Quality of Life

HRQL in the study group compared to the non-pregnant reference women

The scores of HRQL from SF-36 for the study group are presented with mean and 95% CI in Table 3 and 4.

At baseline (pre-pregnancy), the RA women in the study group had better physical function than the non-pregnant reference women with RA ($p=0.03$) and the JIA women in the study group had higher vitality ($p=0.04$) and general health ($p=0.02$) score than the non-pregnant reference women ($p=0.02$), but otherwise they did not differ significantly. The women with JIA in the study group did not differ from the non-pregnant reference women at any other points.

The RA women in the study group had at 1st trimester a better score in the aspect of role emotional than the non-pregnant reference women ($p=0.05$). In the 3rd trimester the RA women in the study group scored lower in the aspect of role physical than the non-pregnant reference women ($p<0.01$).

At six months postpartum the RA women in the study group scored better in the aspects of social function, physical function, role physical and role emotional than the non-pregnant reference women ($p<0.05$).

Table 3. Mean scores and 95 % confidence interval (CI) of each SF-36 dimension in the study group women and non-pregnant reference women with Rheumatoid Arthritis (RA).

		Study group RA[a]						Non-pregnant reference women RA
		Pre-pregnancy	1st trimester	2nd trimester	3rd trimester	6 weeks postpartum	6 months postpartum	3rd visit
N		19	26	29	32	35	35	63
Mental Health	Mean	**81**	**84**	**80**	**82**	**83**	**86**	**79**
	95% CI	(74-87)	(80-88)	(75-86)	(78-86)	(79-87)	(83-89)	(75-83)
Vitality	Mean	**52**	**41**	**42**	**44**	**51**	**57**	**47**
	95% CI	(74-87)	(32-50)	(33-50)	(36-53)	(44-58)	(50-64)	(42-53)
Social Function	Mean	**84**	**75**	**76**	**76**	**75**	**86[b]**	**75**
	95% CI	(75-93)	(66-84)	(68-85)	(68-83)	(66-84)	(78-94)	(69-81)
Role Emotional	Mean	**84**	**95[c]**	**80**	**84**	**88**	**92[d]**	**81**
	95% CI	(70-99)	(89-101)	(66-93)	(73-94)	(78-98)	(84-101)	(74-89)
Bodily Pain	Mean	**62**	**61**	**54**	**59**	**60**	**62**	**54**
	95% CI	(51-72)	(51-72)	(43-65)	(49-70)	(51-69)	(53-71)	(47-60)
General Health	Mean	**60**	**60**	**57**	**59**	**61**	**67**	**62**
	95% CI	(51-69)	(51-68)	(49-66)	(52-66)	(53-68)	(60-74)	(57-68)
Physical Function	Mean	**80[e]**	**73**	**69**	**60**	**71**	**78[f]**	**67**
	95% CI	(68-91)	(63-83)	(59-79)	(51-70)	(61-82)	(69-87)	(60-73)
Role Physical	Mean	**62**	**51**	**41**	**23[g]**	**53**	**69[h]**	**51**
	95% CI	(44-80)	(34-67)	(25-58)	(10-35)	(36-69)	(54-84)	(41-62)

The score is ranging from 0-100 where 0 is worst possible health is, 100 is best possible health.

[a] All statistical comparisons between the RA and JIA women in the study group and the non-pregnant reference women with RA and JIA were performed with the Mann-Whitney U test

[b] The study group of RA women scored better in the aspect of social function at 6 months postpartum compared to the non-pregnant reference women, p=0.027

[c] The study group of RA women scored better in the aspect of role emotional at 1st trimester compared to the non-pregnant reference women, p=0.045

[d] The study group of RA women scored better in the aspect of role emotional at 6 months postpartum compared to the non-pregnant reference women, p=0.04

[e] The study group of RA women scored better in the aspect of physical function at pre-pregnancy compared to the non-pregnant reference women, p=0.03

[f] The study group of RA women scored better in the aspect of physical function at 6 months postpartum compared to the non-pregnant reference women, p=0.015

[g] The study group of RA women scored lower in the aspect of role physical at 3rd trimester compared to the non-pregnant reference women, p=0.001

[h] The study group of RA women scored better in the aspect of role physical at 6 months postpartum compared to the non-pregnant reference women, p=0.04

Table 4. Mean scores and 95 % confidence interval (CI) of each SF-36 dimension in the study group women and non-pregnant reference women with Juvenile Idiopathic Arthritis (JIA).

		Study group JIA[a]						Non-pregnant reference women JIA
		Prepregnancy	**1st trimester**	**2nd trimester**	**3rd trimester**	**6 weeks postpartum**	**6 months postpartum**	**3rd visit**
N		9	13	27	22	25	20	30
Mental Health	Mean	**80**	**82**	**74**	**79**	**73**	**76**	**76**
	95% CI	(70-90)	(73-90)	(66-82)	(73-85)	(66-81)	(71-82)	(69-90)
Vitality	Mean	**57**[b]	**40**	**39**	**39**	**36**	**40**	**41**
	95% CI	(42-72)	(25-55)	(29-48)	(30-49)	(29-43)	(30-50)	(32-50)
Social Function	Mean	**89**	**79**	**74**	**73**	**65**	**66**	**73**
	95% CI	(75-103)	(67-91)	(64-83)	(63-82)	(55-75)	(53-79)	(63-83)
Role Emotional	Mean	**100**	**93**	**68**	**80**	**60**	**60**	**72**
	95% CI		(85-101)	(51-85)	(66-95)	(43-77)	(40-80)	(57-88)
Bodily Pain	Mean	**66**	**54**	**54**	**51**	**45**	**41**	**52**
	95% CI	(46-86)	(43-65)	(44-64)	(41-62)	(51-69)	(31-51)	(41-63)
General Health	Mean	**75**[c]	**63**	**58**	**61**	**52**	**45**	**54**
	95% CI	(57-92)	(47-80)	(48-67)	(52-69)	(42-61)	(35-56)	(45-64)
Physical Function	Mean	**81**	**70**	**66**	**59**	**63**	**64**	**65**
	95% CI	(68-93)	(57-83)	(56-77)	(51-67)	(53-74)	(53-76)	(55-75)
Role Physical	Mean	**64**	**54**	**43**	**35**	**30**	**35**	**47**
	95% CI	(32-96)	(31-77)	(26-59)	(18-52)	(15-45)	(16-54)	(30-63)

The score is ranging from 0-100 where 0 is worst possible health is, 100 is best possible health.

[a] All statistical comparisons between the RA and JIA women in the study group and the non-pregnant reference women with RA and JIA were performed with the Mann-Whitney U test

[b] The study group of JIA women scored better in the aspect of vitality at pre-pregnancy compared to the non-pregnant reference women, p=0.043

[c] The study group of JIA women scored better in the aspect of general health pre-pregnancy compared to the non-pregnant reference women, p=0.045

HRQL in the RA and JIA study group women

Using the generalized mixed effect model analysis for incomplete dataset, we found that RA women had better HRQL than the JIA women in some aspects at baseline, i.e. the mental health, vitality and role physical aspects of SF-36 (Table 5). The RA women seems to have somewhat higher scores on social function than the JIA women, although not significantly higher (p=0.07). Independent of the disease group the women belonged to (RA or JIA), their experience of vitality was lower at 1st trimester, 2nd trimester and 3rd trimester, compared to pre-pregnancy. Furthermore, independently of disease group they experienced more bodily pain (lower score) six weeks postpartum, and poorer general health and lower physical functioning at the 3rd trimester, compared to pre-pregnancy. In addition, the general health, tended to be lower in the 2nd trimester and six weeks postpartum (p=0.07 and p=0.06, respectively). Lastly, independent of the disease group the pregnant women belonged to, they experienced a lower role physical in the 1st trimester. The Wilcoxon test for two related samples performed in the RA and JIA women in the study group separately could partly confirm the generalized mixed effect model results, i.e. women with RA had lower physical function and role physical in 3rd trimester, and women with JIA had lower for physical health in 3rd trimester and lower general health six months postpartum.

Table 5. Generalized mixed effect model presented with ß-coefficient and 95 % confidence interval (CI) of eight aspects of HRQL by SF-36 in the study group women.

		RA	1st trimester	2nd trimester	3rd trimester	6 weeks postpartum	6 months postpartum
Mental Health	ß-coeffisient	**7.03**[a]	**4.00**	**-0.59**	**2.02**	**0.66**	**2.78**
	95% CI	(2.06 - 11.99)	(-1.52 - 9.52)	(-5.77 - 4.60)	(-3.20 - 7.43)	(-4.53 - 5.85)	(-2.42 - 7.99)
Vitality	ß-coeffisient	**9.08**[b]	**-9.44**[c]	**-9.60**[c]	**-8.00**[c]	**-5.73**	**-1.84**
	95% CI	(0.69 - 17.46)	(-17.38 - -1.50)	(-17.06 - -2.14)	(-15.52 - -0.47)	(-13.20 - 1.75)	(-9.33 - 5.66)
Social Function	ß-coeffisient	**9.05**	**0.05**	**-3.41**	**-2.54**	**-5.27**	**-3.93**
	95% CI	(-0.97 - 19.08)	(-9.22 - 9.32)	(-12.12 - 5.30)	(-11.33 - 6.25)	(-13.98 - 3.44)	(-12.70 - 4.84)
Role Emotional	ß-coeffisient	**5.17**	**-0.72**	**-2.69**	**-0.78**	**-4.77**	**-2.34**
	95% CI	(-3.90 – 14.25)	(-8.15 - 6.73)	(-9.68 - 4.30)	(-7.84 - 6.27)	(-11.78 - 2.25)	(-9.37 - 4.68)
Bodily Pain	ß-coeffisient	**6.42**	**-4.73**	**-5.01**	**-5.99**	**-9.97**[d]	**-2.81**
	95% CI	(-2.79 - 15.63)	(-13.54 - 4.07)	(-13.28 - 3.26)	(-14.33 - 2.36)	(-18.22 - -1.72)	(-11.12 - 5.50)
General Health	ß-coeffisient	**5.09**	**-1.64**	**-6.90**	**-15.58**[e]	**-7.12**	**-1.80**
	95% CI	(-5.58 - 15.77)	(-9.67 - 6.40)	(-14.45 - 0.65)	(-23.20 - -7.95)	(-14.66 - 0.43)	(-9.39 - 5.79)
Physical Function	ß-coeffisient	**8.25**	**-3.85**	**-13.94**	**-29.96**[f]	**-13.16**	**0.61**
	95% CI	(-6.47 - 22.98)	(-20.86 - 13.16)	(-29.93 - 2.04)	(-45.99 - -13.93)	(-29.09 - 2.76)	(-15.43 - 16.64)
Role Physical	ß-coeffisient	**16.48**[g]	**13.01**[h]	**-4.32**	**1.91**	**-3.36**	**-1.48**
	95% CI	(4.66 - 28.30)	(-0.02 - 26.04)	(-16.64 - 7.99)	(-10.54 - 14.35)	(-15.64 - 8.92)	(-13.88 -10.91)

The reference level in the generalized mixed effect model was JIA women, and the pre-pregnancy scores.

[a] The mental health aspect of SF-36 was significantly better in women with RA at baseline compared to women with JIA, p=0.005

[b] In the aspect of vitality the women with RA in the study group is significantly better than the JIA women, p=0.031

[c] The vitality aspect of SF-36 was reduced at 1st, 2nd and 3rd trimester compared to prior pregnancy, p=0.02, 0.012 and 0.037

[d] The women in the study group had lower scores in the aspect of bodily pain at six weeks postpartum, p=0.018

[e] The women in the study group had lower scores in the aspect of general health at 3rd trimester, p<0.01

[f] The women in the study group had lower scores in the aspect of physical health at 3rd trimester, p<0.01

[g] In the aspect of role physical the women with RA in the study group is significantly better than the JIA women, p=0.006

[h] The women in the study group had better scores in the aspect of physical health at 1st trimester, p=0.0

Disease activity during and after pregnancy

In the generalized mixed effect model for disease activity (DAS-28-CRP(3)) (See table 6) there was no difference in disease activity between the women with RA and JIA in the study group at baseline, and the disease activity during and after pregnancy did not change compared to pre-pregnancy (Table 6). The nonparametric test for dependent samples (Wilcoxon test) was performed separately for the study group women with participating at both time points confirms these results ($p>0.05$).

Changes in disease related function during and after pregnancy

In the generalized mixed effect model for disease related function (MHAQ) there was no difference between the women in the study group with RA and JIA at baseline (Table 6). Independent of disease in the study group the disease related function was poorer (higher score) at 3rd trimester and at six weeks postpartum. The separate nonparametric analysis for dependent samples (Wilcoxon test) of RA and JIA women in the study group mainly confirmed the results from the generalized linear mixed model finding that the MHAQ score in the 3rd trimester was higher compared to pre-pregnancy, but the result concerning six weeks postpartum found in generalized linear mixed model was not confirmed.

Table 6. Generalized mixed effect model presented with ß-coefficient and 95 % confidence interval (CI) of DAS-28-CRP(3) and MHAQ in the study group women.

		RA	1st trimester	2nd trimester	3rd trimester	6 weeks postpartum	6 months postpartum
DAS-28-	ß-coeffisient	**0.03**	**0.23**	**<-0.01**	**-0.21**	**0.35**	**0.68**
CRP(3)	95% CI	(-0.88 - 0.94)	(-1.33 - 1.78)	(-1.48 - 1.47)	(-1.67 - 1.26)	(-1.08 - 1.79)	(0.76 - 2.12)
MHAQ	ß-coeffisient	**-0.08**	**-0.02**	**0.09**	**0.24**[a]	**0.16**[a]	**0.05**
	95% CI	(-0.25 - 0.10)	(-0.18 - 0.14)	(-0.05 - 0.24)	(0.10 - 0.39)	(0.01 - 0.30)	(-0.10 - 0.20)

The reference level in the generalized mixed effect model was JIA women, and the pre-pregnancy scores.

[a] The women in the study group had higher scores in MHAQ at 3rd trimester and six weeks postpartum compared to prior pregnancy

Discussion

Six months postpartum the RA women in the study group scores better in the aspects of social function, physical function, role physical and role emotional than the non-pregnant reference women.
HRQL declined during pregnancy in the RA and JIA women in the study group. However the RA women in the study group scored better in the HRQL aspects of mental health, vitality and role physical than the JIA women. The RA and JIA women in the study group had lower scores in the HRQL aspects of vitality, general health and physical function at 3rd trimester compared to baseline.
Despite the wide range in scores, the women in the study group seemed to reach the same level in HRQL, DAS-28-CRP(3) and MHAQ as pre-pregnancy at the time of six months postpartum.

Strengths and limitations

Strengths of the present study are the use of prospectively collected data from two registers, frequently visits and high adherence. Unfortunately, the number of patients with pre-pregnancy visit was limited. There is a challenge for the rheumatology units to get the patients to come in contact prior to pregnancy and many of the patients take contact with the rheumatology unit at the time their pregnancy is established (Figure 2). Pregnancy in women with chronic rheumatic diseases are considered risk pregnancy (47). Among women with chronic arthritis 50-60 % deliver children small for gestational age, and 30-50 % deliver before pregnancy week 37 (48). Not all women with RA and JIA are referred to the rheumatology units when pregnant, despite that related to pregnancy these women are supposed to be assessed once prior to pregnancy, and during pregnancy at the specialist care unit according to the National Service for Pregnancy and Rheumatic Disease (47).

The number of rheumatic women giving birth each year in Norway is small. In the women with specified arthritis, including RA, JIA, psoriatic arthritis and ankylosing spondylitis 2736 births were registered in the time period from 2000-2009 in the Norwegian Birth registry (Unpublished number given to this paper with content, 29th of October 2012 from Marianne Wallenius). Therefore, the number of participants available was quite restricted during a seven year perspective with recruiting patients to RevNatus.

The transition from childhood and adolescent into adult life involves challenges in coping strategies and adjustment processes for patients with JIA (49). It is known that patients with JIA often have challenging transfers to adult rheumatology (50). One study have shown that 29 % fail to meet to their first appointment at the adult rheumatology unit (50). Moreover, 52 % failed to come in contact with the rheumatology unit within the first two years after transfer (50). Corresponding to the known dropout difficulties of JIA patients, five of the women with JIA in the study group with a six weeks visit failed to come to the visit six months postpartum (Figure 2).

As a consequence of the inconsistent number of participants throughout the study period and several repeated measures, the linear mixed model analysis for incomplete dataset was regarded as a relevant method in order to study change in HRQL, disease activity and disease related function from pre-pregnancy, during pregnancy and postpartum. The distribution of the outcome variables was checked initially and we found no severe deviations from normal distribution. Therefore, using the generalized mixed effect model analysis for incomplete dataset was considered relevant, especially since there are no good alternative nonparametric tests. However, in order to inspect the results of change over time for the study group women, nonparametric analysis (Wilcoxon test for related samples) were used for the eight aspects of HRQL, disease activity and the disease related function. When using this nonparametric analysis, each disease specific study group were analysed separately (RA and JIA), thus inconsistent number of participants throughout the study period and consequently increasing risk of type II error (finding no significant differences even if there is one). However, the results from generalized mixed effect model were partly confirmed.

One the other hand, there is a strength that we used more than one statistical approach in the present study and the statistical level of 0.05 seems adequate in the context of the clinical relevance for these women. Even so, a previous small study of HRQL in pregnant women with RA using only nonparametric analysis chose a lower significant level, due to multiple comparison (1).

Due to the low number of participants the statistical power was restricted and all potential relevant variables influencing the HRQL could not be included in one integrated model. For example, it is known that age and work status may influence HRQL as well as disease activity (51). Futhermore, we could not study change in HRQL in the RA study group versus the JIA

study group throughout the pregnancy due to low number of data and restricted statistical power.

Most of the patients with an active RA and JIA are in contact with the specialist care, however not all rheumatology units in Norway are linked to the RevNatus and NOR-DMARD register. Continuing collecting data is important to increase the number of women to the study; however, due to the low number of women with rheumatic disease giving birth each year enrolling women from other rheumatology units in Norway seems reasonably. In addition, multinational studies including countries that are comparable with Norway in rheumatology care enables larger number of patients, and thus more statistical power.

Furthermore, the use of SF-36 to measure HRQL is a strength to the study. In rheumatology the SF-36 is most frequently used tools to measure health outcome (28, 32). There are no disease specific measurements for HRQL translated and validated into Norwegian. The SF-36 has been validated on people living with RA after translation into Norwegian (40). However, the physical functioning measured with the SF-36 has shown not to cover all aspects of physical HRQL (39), therefore the MHAQ modified from HAQ (Health Assessment Questionnaire) (44) as a disease specific supplement to measure physical function was added in this study. The SF-36 was used in both the study group women and the non-pregnant reference women who made it possible to compare HRQL between the two groups. Furthermore, since SF-36 is a generic instrument frequently used in health care and in clinical trials to measure HRQL (28), enables us to compare these women to healthy controls in future studies.

It is a strength that we used the DAS-28-CRP(3) for measuring disease activity which is regarded the most suitable version for use during pregnancy (22). However, the challenge with this instrument it is the inter-rater reliability in the joint count, since two different persons may score different in the same patient at the same time, depending on investigators technique in performing joint count (52). However, most of the patients included were measured by the same rheumatologist or nurse throughout the study period. This makes the measurements more reliable for change.

A major limitation in the present study is the lack of a reference group of healthy women going through a pregnancy. Following a group of healthy women through pregnancy would

give valuable information on how rheumatic pregnant women differ from healthy pregnant women in HRQL before, during and after pregnancy. We had two groups of non-pregnant reference women (one with RA and one with JIA), but they were at baseline not quite comparable with the study group since the RA women in the study group used less DMARDs at baseline compared to the non-pregnant reference women and the JIA women in the study group scored better in DAS-28-CRP(3) and used less DMARDs at baseline compared to the JIA non-pregnant reference women.

Another limitation in this study is the lack of information on gestational age and possible obstetric complications which may influence HRQL postpartum. All the women in the study group gave live births. Futhermore, marital status and parity of the non-pregnant women are unknown.

Health related quality of life

HRQL is influenced by the problems of daily life (32). Participating in life roles, such as motherhood, makes an important contribution on QOL, and illness in form of chronic inflammatory arthritis may influence participation in these roles (53).Pregnancy may influence the perception of HRQL, also in healthy women (54).

It is expected that HRQL is experienced differently in women with chronic rheumatic diseases compared to healthy women, since the disease can have major impact on both physical and psychological health (1, 32). When comparing HRQL in the study group at baseline and six months postpartum to the non-pregnant reference women we found that especially the RA women in the study group scored better six months postpartum in the aspects of social function, physical function, role physical and role emotional. The JIA women in the study group scored better in the aspects of vitality and general health pre-pregnancy compared to the non-pregnant reference women. Another study of HRQL in healthy women confirms the positive effect of becoming a mother, with increased scores on physical function postpartum (1). In the present study, RA women in the study group had better HRQL than the JIA women in the study group in some aspects, i.e. the mental health, vitality and role physical aspects of SF-36 independent of time of study. A study of young adults with JIA found that the unpredictability of the disease development and possible reduced function affected their life (49). Another study has shown that pregnancy and raising children are important issue for

women with JIA (55). Women with JIA have had their chronic rheumatic disease longer than the RA women, therefore they may have experienced more impact on their life (14).

Early pregnancy symptoms, such as nausea and fatigue are most common in the 1st trimester among pregnant women in general (54). Although these symptoms are expected to decline after the 12 first pregnancy weeks (56), other physical problems, such as pelvic pain, leg cramps, heartburn, constipation and weight gain often occur in the 2nd and 3rd trimester of pregnancy (54). One study has shown that healthy women have reported lower physical health in the 2nd and 3rd trimester (1). Another study on HRQL on healthy women showed declined scores on physical health and vitality aspects throughout the pregnancy (57). Women with RA and JIA experiences the same negative symptoms during pregnancy as the normal population (54), which is reflected in the present study i.e. the study group reported lower vitality and role physical in the study group for both RA and JIA women. The study group reported lower general health and physical function in the 3rd trimester.

Function may be naturally influenced by pregnancy, and this is reflected in the results from the generalized mixed effect model of MHAQ which found higher scores (poorer) in 3rd trimester. Some of the activities included in the MHAQ, are more challenging as the pregnancy progress, also in healthy women, such as bending down to the floor to pick up clothes, and getting out of bed (Appendix 4).

In 40-50 % of women RA and JIA, a postpartum flare is expected within three to six months after delivery (16, 22). This is a time when the newborn is small, and need a lot of care from their mother. Feeding, changing diapers, carrying the baby and getting up in the middle of the night to feed the baby is challenging with morning stiffness, swollen and tender joints and fatigue (6, 58, 59). In the study group, both women with RA and JIA reported lower scores (more pain) in the aspect of bodily pain six weeks postpartum. This is in accordance with one other study assessing RA patients 12 weeks postpartum (1).

Planned pregnancies give the rheumatologist the opportunity to optimize the medical treatment before the pregnancy occurs, and also to help the women to reflect about their life situation before getting pregnant (47). The women are also able to think about the support they can receive from their network if a flare occurs postpartum. Having a partner have positive impact on HRQL (6). Patients with RA and JIA that comes in contact with their

rheumatologist in 1st and 2nd trimester, have less chance to get their medications adjusted, because there are medications that take up to 12 weeks to be effective (60). Since planning of pregnancy is the major success factor for women with chronic rheumatic diseases like RA and JIA (47), this is frequently addressed during rheumatology consultations for women in fertile age.

Despite this we may assume that not all pregnancies included in the present study was planned with the rheumatology unit as shown by increasing number of women in the RevNatus registry during pregnancy (Figure 2).

Disease activity during pregnancy

In the present study, the study group of RA and JIA women differed from the non-pregnant reference women with RA and JIA in use of DMARDs. This may be explained by the fact that some DMARDs are not compatible with pregnancy and lactation (60). Patients with RA and JIA that come in contact with their rheumatologist in 1st and 2nd trimester, have less chance to get their medication adjusted, because there are medications that take up to 12 weeks to be effective (60).

The last larger studies on disease activity in patients with RA and JIA during and after pregnancy were published before it was known that it was safe to use some biological drugs up until pregnancy is established, and during lactation (16, 22, 47). This is a big advantage in treating these women the last 10 years. Today, women can start the biological treatment regimen 14 days after giving birth (47). In the present study this is reflected in the mean scores of DAS-28, which did not change from pre-pregnancy to six months postpartum (Table 6).

Practical implications

This study have shown that the JIA women in the study group scored lower in the HRQL aspects than the RA women in the study group at baseline. This result supports what is already known about JIA patients and their difficult transfers to adult life and follow up their controls at the rheumatology unit. Our work in the transfer from child rheumatology unit to adult rheumatology units is an area we need to give more attention, to give these women the best possible opportunity to have control of disease, and to give the best possible tools to live with their disease in adulthood. This study also shows that going through a pregnancy not necessarily have a negative effect on HRQL, disease activity or disease related function, when

comparing pre-pregnancy scores to scores six months postpartum. The mean score for disease activity in the study group showed that they were in remission (low disease activity) pre-pregnancy. This is a well-known success factor for pregnancies in women with chronic rheumatic diseases (47). This knowledge is confirmed in this study and we need to address this to these patients. Since we know that planning a pregnancy is a big issue for these women, this is valuable information for these women when deciding whether they should go through a pregnancy or not.

Future recommendations for research

In the future, a similar study on HRQL in RA and JIA patients should be done including a group of healthy women followed through a pregnancy. This would give us more information on how rheumatic women are differs from the normal population. Furthermore, information on the factors that may influence HRQL such as marital status, parity and pregnancy outcome should be included in future research. Extended follow-up time with visits 12 and 24 months postpartum will give more knowledge on the long-term effect of a pregnancy on HRQL.

Conclusion

In the study group, the SF-36 scores for women with RA were better than the JIA patients in the HRQL aspects of mental health, vitality and role physical at baseline. Despite a wide range in scores, the women in the study group seemed to reach the same level in HRQL, DAS-28-CRP(3) and MHAQ as pre-pregnancy at the time of six months postpartum. HRQL is an important aspect of living with a chronic rheumatic disease, and planning a family is an important concern for these women. The women in the study group had a low mean score in DAS-28-CRP(3) pre-pregnancy reflecting that their disease was well controlled and in remission when the pregnancy occurred. This may be the reason the mean score of DAS-28-CRP(3) remained low six months postpartum. This knowledge is valuable when consulting these women.

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Appendix 1

Forespørsel om å bli registrert i en database for forskning på svangerskap og revmatiske sykdommer.

Ved revmatologisk avdeling, St.Olavs Hospital er det et kompetansesenter innen svangerskap og revmatiske sykdommer. Formålet med kompetansesenteret er å gi råd og veiledning til pasienter og helsepersonell om problemstillinger knyttet til svangerskap og revmatiske sykdommer. Samtidig skal senteret drive forskning for å bedre kvaliteten på tilbudet til kvinner med en revmatisk sykdom som planlegger å bli gravid eller som er gravide. I forbindelse med denne studien samarbeider vi med Rikshospitalet/Radiumhospitalet om utarbeidelse av variabler og inkludering av pasienter.

Ved å samle opplysninger om deg og din sykdom under svangerskapet i en database, vil vi kunne bruke disse dataene for å forske på ulike problemstillinger knyttet til svangerskap og revmatisk sykdom. Deltagelse vil medføre at du må fylle ut et spørreskjema om sykdomstilstanden din under svangerskapet og frem til ett år etter fødselen. Dette vil gjøres samtidig som du er til kontroll hos revmatolog. Det vil bli gjort opptil 7 registreringer i tiden før, under og fram til 1 år etter svangerskapet.

Aktuelle data om svangerskapsutfall fra din pasientjournal vil bli overført til denne databasen. Databasen vil være permanent. Det vil ikke være personidentifiserbare data (personnummer, adresse, telefonnummer etc) i databasen.

Vi spør deg herved om du kan tenke deg å delta i denne undersøkelsen, og dermed la dine medisinske data bli registrert i denne databasen. Ved å skrive din signatur på baksiden av dette arket (samtykkeerklæringen) gir du oss tillatelse til å registrere data fra spørreskjemaet og data om din sykdomsaktivitet og fødsel fra pasientjournalen. Dersom du på nytt blir gravid, vil du få en ny forespørsel om deltagelse.

Det er helt frivillig å være registrert i databasen og du kan på hvilket som helst tidspunkt trekke deg fra videre deltagelse, eller kreve at opplysningene du har gitt blir slettet uten å måtte begrunne dette. Hvorvidt du velger å delta i dette prosjektet eller ikke, har ingen betydning for den behandling du vil få ved avdelingen.

Alle opplysninger vil bli behandlet konfidensielt, og alle personer tilknyttet prosjektet har taushetsplikt. Dataene hentet ut fra databasen vil bli publisert som gruppedata, uten at den enkelte kan gjenkjennes.

Prosjektet er meldt til Personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste AS og tilrådet av Regional komite for medisinsk forskningsetikk, Region Midt-Norge.

Ved behov for mer utfyllende informasjon kan du ta kontakt med oss.

Forskningssykepleier, Hege Svean Koksvik St. Olavs Hospital tlf. 72 82 64 00
Revmatolog, overlege Marianne Wallenius tlf. 72 82 64 00

Samtykkeerklæring:
Jeg har mottatt informasjon og sier meg villig til å delta i prosjektet.

…… …… ……..……..
(sted) (dato) (signatur)

Appendix 2

Informasjon og forespørsel om deltakelse i forskningsprosjektet NOR-DMARD:
Overvåking av sykdomsmodifiserende legemidler i behandlingen av revmatoid artritt (kronisk leddgikt) og beslektede sykdommer: Effekt, bivirkninger og kostnader.

Lege eller sykepleier har nettopp gitt deg beskjed om at det er grunn til å starte behandling med et nytt sykdomsmodifiserende legemiddel eller en ny kombinasjon av flere slike midler. Vi spør deg derfor om du er villig til å delta i en undersøkelse med tanke på kartlegging av effekt, bivirkninger og kostnader for deg og samfunnet under slik behandling. Den offisielle norske tittelen på denne undersøkelsen er: *Undersøkelse av langtidseffekt og bivirkninger av sykdomsmodifiserende legemidler ved leddgikt og beslektede sykdommer. En sammenliknende, multisenter, fase IV-, longitudinell observasjonsstudie.* Sykdomsmodifiserende legemidler kalles DMARD (disease-modifying antirheumatic drugs) – i kortversjon går dette forskningsprosjektet under navnet NOR-DMARD.

Bakgrunn
Flere kontrollerte kliniske undersøkelser har vist at sykdomsmodifiserende legemidler som brukes i behandling av leddgikt og beslektede sykdommer, har effekt på sykdomsaktivitet og sykdomsforløp. Man mangler imidlertid resultater fra gode sammenlignende undersøkelser av slik behandling i vanlig praksis. Tidligere undersøkelser har vist at det for enkelte sykdomsmodifiserende midler kan være forskjeller i de behandlingsresultater man oppnår i klinisk praksis og i kontrollerte kliniske undersøkelser. Dette kan ha sammenheng med blant annet forskjeller i pasientutvelgelse, hvilket betyr at resultatene fra kontrollerte kliniske studier ikke alltid har full overføringsverdi til klinisk praksis.

I de senere år har det kommet nye muligheter for behandling av leddgikt og beslektede sykdommer. Dette dreier seg blant annet om kombinasjoner av flere sykdomsmodifiserende legemidler og om nye biologiske legemidler (bl.a. etanercept, infliximab, adalimumab, rituximab, abatacept). For slike behandlingsopplegg finnes få resultater når det gjelder oppfølging av behandlingseffekt og bivirkninger utenom kontrollerte kliniske legemiddelutprøvninger.

Hensikt
Undersøkelsen sammenligner ulike behandlingsopplegg med sykdomsmodifiserende legemidler med hensyn på effekt, bivirkninger og kostnader i vanlig klinisk praksis. Man vil også forsøke å påvise om det er bestemte sykdomsfaktorer som kan forutsi om enkelte pasienter vil få effekt eller bivirkninger av de enkelte legemidlene.

Undersøkelsen gjennomføres ved revmatologiske avdelinger ved 5 sykehus i Norge. Hensikten er at alle pasienter som starter ny behandling med sykdomsmodifiserende midler eller kombinasjoner av flere slike midler skal ha en systematisk oppfølging eller overvåking av behandlingen. Undersøkelsen startet i desember 2000 og per januar 2008 er over 7000 behandlingsregimer inkludert.

Gjennomføring av prosjektet
I forbindelse med oppstart av medisinene vil du bli bedt om å fylle ut spørreskjemaer, og det gjøres en leddundersøkelse. Hvis sykdomsforløpet er tilfredsstillende vil det etter 3, 6, 12 og 24 måneder - og senere årlig bli foretatt en kontrollundersøkelse ved sykehuspoliklinikken eller i avdelingen, og hvor det på nytt vil bli tatt blodprøver og bli gjort en klinisk undersøkelse. Du vil ved hver undersøkelse også bli bedt om å fylle ut spørreskjemaer angående din egen helse. I mange tilfeller vil en prosjektsykepleier organisere undersøkelsene og sammen med legen gjøre leddundersøkelsene. Det kan også være aktuelt å ta andre prøver og undersøkelser i forbindelse med klinisk rutine, men som ikke nødvendigvis er en del av dette prosjektet.

Dersom det skulle komme alvorlige bivirkninger eller andre forhold som gjør det nødvendig å avslutte behandlingen, vil du bli bedt om å komme tilbake til en ny undersøkelse så snart som mulig.

Fordeler for deg
Denne oppfølgingen vil sikre en god kvalitet på vurderingen av bivirkninger og behandlingseffekt. Derved vil behandlende lege ha et bedre utgangspunkt for å ta stilling til om behandlingen hjelper og om du skal fortsette med legemidlene.

Ulemper for deg
Ulempene er først og fremst at du fyller ut noe mer skjemaer og gjennomgår litt mer nøyaktig undersøkelser enn man vanligvis gjør i klinisk rutine. Undersøkelsen vil imidlertid vanligvis bli organisert med spesielle prosjektsykepleiere og man vil tilstrebe så lite unødig tidsbruk som mulig.

Andre opplysninger
Denne undersøkelsen gjennomføres av en gruppe revmatologer i Norge, som i denne undersøkelsen også samarbeider med helseøkonomer. Undersøkelsen gjennomføres uavhengig av farmasøytisk industri, men flere farmasøytiske firmaer og helsemyndighetene bidrar med økonomisk støtte. Ingen av de involverte parter mottar særskilte honorarer for gjennomføringen av prosjektet, men prosjektmidler brukes til å lønne prosjektsykepleier ved de fem revmatologiske avdelingene som er involvert.

Resultatene publiseres fortløpende på fagmøter og i internasjonale medisinske tidsskrift. Doktorgradsstipendiater som arbeider med data fra forskningsdelen av dette prosjektet er lønnet av forskningsmidler fra ulike helseregioner i Norge.

Siden dette dreier seg om en registrering av opplysninger i vanlig praksis tegnes ingen spesielle forsikringer. Du er beskyttet etter gjeldende bestemmelser i Norge knyttet til vanlig klinisk virksomhet i sykehus.

Alle opplysninger som nedtegnes i registreringsskjemaene blir en del av din fremtidige journal. Opplysningene vil også bli brukt til forskningsformål, men vil da være avidentifisert, det vil si at personer som analyser data vil ikke knytte resultater til din identitet. Dataene vil bli oppbevart i avidentifisert form frem til 31. desember 2025. Alle som er involvert i forskningsprosjektet har taushetsplikt. Vi gjør oppmerksom på at kontrollmyndigheter vil kunne ha behov for å sjekke at opplysninger gitt i studien stemmer med opplysninger i din journal for å kontrollere studiens kvalitet. Alle opplysninger vil bli behandlet konfidensielt.

Undersøkelsen er vurdert av Regional Etisk Komité og lagring og tillatelse til analysering og lagring av data for forskningsformål er gitt av Datatilsynet. Det er frivillig å være med i denne undersøkelsen og du står fritt til å trekke deg når du måtte ønske, og du behøver ikke å oppgi noen grunn for dette.

Samtykke
Undertegnede har informert pasient om undersøkelsen

Dato:_____

Navn:_____
Jeg har mottatt skriftlig og muntlig informasjon og er villig til å delta i studien.

Dato:_____

Navn:_____ Sign.:_____

Appendix 3

DAS-28 formula

DAS28(4) = (0.56*sqrt(t28) + 0.28*sqrt(sw28) + 0.70*Ln(ESR) + 0.014*GH

DAS28(3) = [0.56*sqrt(t28) + 0.28*sqrt(sw28) + 0.70*Ln(ESR)]*1.08 + 0.16

DAS28-CRP(4) = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP+1) + 0.014*GH + 0.96

DAS28-CRP(3) = [0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP+1)] * 1.10 + 1.15

High disease activity >5.1, low disease activity <3.2, remission <2.6

Appendix 4

MHAQ – Modified Health Assesment Questionnaire

MHAQ

Navn: ..... nr. ..... Dato: .....

SPØRRESKJEMA – UTDELES OG UTFYLLES VED KLINISK UNDERSØKELSE

SPØRSMÅL OM FUNKSJON, SMERTE, TRETTHET OG LEDDPLAGER

I LØPET AV SISTE UKEN, KUNNE DU:	UTEN problemer	med VISSE problemer	med STORE problemer	kunne IKKE
Kle på deg selv, inkl. å knytte skolisser og å kneppe knapper?	☐	☐	☐	☐
Komme opp i og ut av sengen?	☐	☐	☐	☐
Løfte en full kopp eller et fullt glass til munnen?	☐	☐	☐	☐
Gå utendørs på flat mark?	☐	☐	☐	☐
Vaske og tørke deg over hele kroppen?	☐	☐	☐	☐
Bøye deg for å ta opp klær fra gulvet?	☐	☐	☐	☐
Skru vanlige kraner opp og igjen?	☐	☐	☐	☐
Komme inn og ut av en bil?	☐	☐	☐	☐