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Pregnancy related aspects of chronic inflammatory arthritides: disease onset postpartum, pregnancy outcomes and fertility

Data from a Norwegian patient registry linked to the Medical Birth Registry of Norway

Thesis for the degree of Philosophiae Doctor

Trondheim, February 2011

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ISBN 978-82-471-2574-8 (printed ver.)
ISBN 978-82-471-2575-5 (electronic ver.)
ISSN 1503-8181

Doctoral theses at NTNU, 2011:28

Printed by NTNU-trykk

Science never solves a problem without creating ten more (George Bernard Shaw)

Kronisk inflammatorisk artrittsykdom og svangerskapsrelaterte aspekter: debut av artrittsykdom etter fødsel, svangerskapsutfall og fertilitet.

Resultater fra en datakobling mellom et norsk pasientregister og Medisinsk Fødselsregister

Bakgrunn:
Tidligere studier har vist at revmatoid artritt (RA) ofte debuterer etter svangerskap, men om dette også gjelder andre artrittformer har vært lite studert. Generelt er første svangerskap assosiert med økt risiko for ulike typer komplikasjoner (for eksempel preeklampsi, keisersnitt, prematuritet, lav fødselsvekt) i forhold til påfølgende svangerskap. Autoimmun sykdom kan også påvirke ulike aspekter ved svangerskap som maternale og føtale komplikasjoner. Lite er kartlagt omkring fertilitet og potensiell risiko ved svangerskap hos kvinner med så aktiv inflammatorisk revmatisk sykdom at de må bruke sykdomsmodifiserende behandling, og det er tidligere ikke gjort separate analyser på utfall av første svangerskap og fødsel i denne pasientgruppen.

Det norske pasientregisteret NOR-DMARD (Norwegian Disease Modifying Antirheumatic Drug) inkluderer pasienter fra fylte 18 år med RA, psoriasisartritt (PsA), ankyloserende spondylitt (AS), uspesifisert artritt (UA) og voksne pasienter med juvenil idiopatisk artritt (JIA) som starter med sykdomsmodifiserende behandling. Registeret ga mulighet til å studere svangerskapsrelaterte aspekter i en pasientpopulasjon med høy grad av inflammatorisk aktiv sykdom.

Mål:
Artikkel 1:
Undersøke hvor stor andel av pasientpopulasjonen som hadde debut av artrittsykdom de første to år etter tidspunkt for fødsel for kvinner med RA versus andre artrittformer (OCA).
Undersøke andel av pasienter med debut av artrittsykdom 0-24 måneder versus 25-48 måneder etter fødsel for kvinner med henholdsvis RA og OCA.
(OCA = PsA, AS og UA samlet).

Artikkel 2:
Undersøke svangerskapsutfall for kvinner med inflammatorisk artrittsykdom, alle diagnoser samlet, versus referansepopulasjon fra Medisinsk fødselsregister (MFR) ved å studere utfall for både mor og barn og undersøke utfall for første og senere svangerskap separat (para 0, para 1+), før og etter diagnosetidspunkt.

Artikkel 3:
Undersøke fertilitetsrater for kvinner med henholdsvis RA, OCA og JIA versus referanser fra Det sentrale folkeregister matchet med pasientenes fødselsår.
Identifisere andel av kvinner uten barn blant pasientene versus referansepopulasjonene.
Studere intervallet mellom første og andre svangerskap hos pasientgruppene versus referansepopulasjonene.

Metode:
Data fra 631 kvinner i aldersgruppen 18-45 år fra NOR-DMARD registeret ble koblet med data fra MFR. Referansepopulasjoner var fødsler registrert i MFR (artikkel 2) og kvinner fra Det sentrale folkeregister matchet med pasientenes fødselsår og deretter koblet med data fra MFR (Artikkel 3).

Resultater:
Ved sammenligning av debut av RA versus OCA var det ingen statistisk signifikant forskjell i andelen av pasienter med debut av artrittsykdom de første to år etter fødsel, verken for debut av artritt etter alle svangerskap samlet eller etter første svangerskap. Kvinner med RA hadde en statistisk signifikant insidens topp 0-24 måneder etter fødsel sammenlignet med 25-48 måneder etter fødsel, både for alle svangerskap totalt og etter første fødsel. Kvinner med OCA hadde ikke noen signifikant insidens topp, men en trend ble observert etter første fødsel.

Pasientene hadde en høyere risiko for fødsler med keisersnitt, både totalt og elektivt, sammenlignet med referansegruppen. Denne risikoen var uavhengig av paritet. Alle andre observerte forskjeller mellom pasienter og referansepopulasjon var relatert til første svangerskap. Pasientene hadde en statistisk signifikant høyere risiko for blødning i svangerskapet og induserte fødsler. Barn av førstegangsfødende pasienter hadde statistisk signifikant høyere risiko for perinatal mortalitet, hadde en lavere gjennomsnittlig fødselsvekt, var oftere premature og var oftere små i forhold til gestasjonsalder (SGA). Svangerskapsutfall før diagnose var ikke forskjellig fra referansegruppen.

Alle pasientgrupper (RA, OCA, JIA)hadde statistisk signifikant lavere fertilitetsrater enn referansegruppene etter diagnose, men ikke før. Statistisk signifikant flere pasienter enn referanser var barnløse. Vi fant statistisk signifikant lengre intervall mellom første og andre svangerskap hos pasientene enn hos kontrollene når første svangerskap var før diagnostisert artrittsykdom og andre etter. Ingen signifikante forskjeller i intervallene ble observert når både første og andre svangerskap var etter diagnose.

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Finansieringskilde: Samarbeidsorganet mellom Helse Midt-Norge RHF og NTNU

Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden PhD i klinisk medisin.
Disputas finner sted i Auditoriet, Medisinsk teknisk forskningssenter, fredag 4.februar 2011 kl.12.15.

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Acknowledgement

This thesis emanates from The Norwegian University of Science and Technology (NTNU), the Medical Birth Registry of Norway (MBRN), and the rheumatology departments at St Olavs Hospital and Diakonhjemmet Hospital. Financially the actual work was supported by the Liaison Committee between the Central Norway Regional Health Authority (RHA) and NTNU.

The work with this thesis would never have been possible without the substantial contribution of a great number of people. Especially I am grateful to all the patients who have been willing to participate in the Norwegian Disease Modifying Antirheumatic Drug (NOR-DMARD) registry and who were willing to participate in the data linkage between NOR-DMARD and MBRN. I wish to express my gratitude to all of them.

My sincere appreciation to my supervisors:

- Medical in charge for Center of Pregnancy and Rheumatic Diseases, St Olavs Hospital and Associate Professor at NTNU, Johan Fredrik Skomsvoll, who was also Head of the Department of Rheumatology, St Olavs Hospital during two of the years I was working on the Ph.D. project. He had the idea to the data linkage between NOR-DMARD and the Medical Birth Registry of Norway (MBRN). I thank you for introducing me to research in the field of pregnancy and rheumatic diseases, for your strong believe in this project and all encouragement.

- Professor Lorentz M. Irgens, Medical Birth Registry of Norway (MBRN). I thank you for your contribution of important ideas, constructive criticism, wise advice and encouragement during the research period.

- Professor Tore Kristian Kvien, Head of the Department of Rheumatology, Diakonhjemmet Hospital and the "father" of the NORD-DMARD registry. Your enthusiasm, encouragement, knowledge and extensive experience with high quality clinical research have been invaluable for my project.

- Professor Kjell Åsmund Salvesen, NTNU was the obstetrical expert in the group. I thank you for participating in this research project with your obstetrical knowledge, interesting ideas, discussions, for your encouragement and positive attitude to my work.

The NOR-DMARD registry is a collaboration between the rheumatologic departments in Tromsø, Trondheim, Lillehammer, Drammen and Diakonhjemmet hospital in Oslo. Thanks to my other co-authors who have been responsible for the NOR-DMARD study at their respective Rheumatology Departments during the work with this thesis: Wenche Koldingsnes,

Tromsø, Bjørn-Yngvar Nordvåg, Trondheim, Knut Mikkelsen, Lillehammer and Cecilie Kaufmann, Drammen.

The NOR-DMARD nurses deserve special mentioning. Their conscientious work with the data collection has been of crucial importance for the study, and they have always been available for my questions. Further, I appreciate the help I got from the study nurses in sending out patient information to about 700 patients to ask about their consent to participate in the data linkage between NOR-DMARD and MBRN. I would like to thank them all, and in particular Sidsel Fekete (Tromsø), Anne Sofie Magnussen (Trondheim), Kari Hansen Berg and Eva Melbøe (Lillehammer), Tone B. Enersen, Drammen, Christin Lunner Olsen and Margareth Sveinsson, Diakonhjemmet Hospital.
Further, I want to thank Edel Kvam for helping me with organising the letters from Trondheim.

I would like to thank my contact person at MBRN, Jon Gunnar Tufta who was doing the linkage of data between NOR-DMARD and MBRN and between references from the Norwegian Population Registry and MBRN.

I owe my gratitude to all colleagues at the five NOR-DMARD departments who have been involved in recruiting patients and contributed to the data collection. I would also like to thank study nurse Hege Svean Koksvik at Center for Pregnancy and Rheumatic Diseases for encouragement and supporting words during my work.

Finally, I want to thank my family: my husband Per Eirik for statistical and professional advices, encouragement and patience and our sons Olav and Eimund for endless patience and support and for reminding me of what is most important in my life.
I also want to thank my parents Gerd and Edmund who have always encouraged me for education and contributed with practical support during the years.

List of papers

1. Wallenius M, Skomsvoll JF, Irgens LM, Salvesen KÅ, Koldingsnes W, Mikkelsen K, Kaufmann C, Kvien TK. Postpartum onset of rheumatoid arthritis and other chronic arthritides: results from a patient register linked to a medical birth registry. Ann Rheum Dis 2010;69:332-6.

2. Wallenius M, Skomsvoll JF, Irgens LM, Salvesen KÅ, Nordvåg BY, Koldingsnes W, Mikkelsen K, Kaufmann C, Kvien TK. Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth. ArthritisRheum.2010 Dec 28 (Epub ahead of print) PMID:21190298

3. Wallenius M, Skomsvoll JF, Irgens LM, Salvesen KÅ, Nordvåg BY, Koldingsnes W, Mikkelsen K, Kaufmann C, Kvien TK. Fertility in women with chronic inflammatory arthritides. Accepted for publication in Rheumatology (Oxford) Nov 2010.

Definitions and abbreviations

Definitions

Birth order one: first delivery in nulliparous women

Caesarean section total: acute, elective and unspecified forms

Chronic inflammatory arthritides: the dominant clinical feature are joint symptoms and signs reflecting inflammation

Fertility: the actual production of offspring

First delivery: first delivery in nulliparous women

Induction of labour: use of amniotomy, oxytocin or prostaglandin

Instrumental deliveries: use of vacuum extraction or forceps

Inter pregnancy interval: time period from the date of the first birth to the first day of the last menstrual period before the following pregnancy

Low birth weight: < 2500 gram

Nulliparous women: childless women

Other chronic arthritides: psoriatic arthritis, ankylosing spondylitis and unspecified arthritis combined

Perinatal mortality: stillbirths after 16 weeks of gestation and early neonatal deaths (< 7 days)

Preterm birth: < 37 weeks of gestation

SGA: small for gestational age defined as birth weight < 10 percentile for the actual gestational age

Validity: an index of how well a test or procedure measures what it is intended to measure or an objective index by which to describe how valid a test or procedure is

Abbreviations and definitions

ACR: American College of Rheumatology

Anti-CCP: anti-cyclic citrullinated peptide

AS: ankylosing spondylitis

CIA: chronic inflammatory arthritides

CNS: central nervous system

COX: cyclooxygenase

CRP: C reactive protein

CS: Caesarean section

DAS28: disease activity score by 28 joint count

DMARD: disease modifying antirheumatic drug

ESR: erythrocyte sedimentation rate

EULAR: European League Against Rheumatism

FDA: The United States Food and Drug Administration

HCQ: hydroxychloroquine

HLA: human leukocyte antigen

IBD: inflammatory bowel disease

IFN: interferon

IL: interleukin

ILAR: International League Association of Rheumatologists

IRF: interleukin regulatory factor

IRR: incidence rate ratio

JIA: juvenile idiopathic arthritis

MBRN: Medical birth registry of Norway

MFR: Medisinsk fødselsregister

MHAQ: modified health assessment questionnaire

MHC: major histocompatibility complex

MIF: macrophage inhibiting factor

MTX: methotrexate

NICU: neonatal intensive care unit

NOR-DMARD registry: The Norwegian Disease Modifying Antirheumatic Drug registry

NPR: The National Population Registry

NSAID: non-steroidal anti-inflammatory drug

OCA: other chronic arthritides

PsA: psoriatic arthritis

RA: rheumatoid arthritis

RF: rheumatoid factor

SF-36: The medical outcomes study 36-item short form

SGA: small for gestational age

SPSS: The Statistical Package for the Social Sciences

SSZ: sulphasalazine

STATA: Statistics / Data Analysis Programme

TGF: transforming growth factor

TNF: tumor necrosis factor

UA: unspecified arthritis

VAS: visual analogue scale

Summary

Pregnancy related aspects of chronic inflammatory arthritides: disease onset postpartum, pregnancy outcomes and fertility

Data from a Norwegian patient registry linked to the Medical Birth Registry of Norway

Background

It has been known for a long time that rheumatoid arthritis is commonly diagnosed post partum, but this issue has only been sparsely studied for other arthritides. It is increasingly recognized that autoimmunity can affect every aspect of pregnancy such as fertilization, maternal complications and adverse fetal outcomes. In general, first pregnancy is associated with higher risk of adverse outcomes than subsequent pregnancies, but outcomes of first pregnancy have not been examined separately in women diagnosed with chronic inflammatory arthritides (CIA) before. Previous studies have examined possibly heterogeneous patient populations. The Norwegian Disease Modifying Antirheumatic Drug (NOR-DMARD) registry gave access to study pregnancy related aspects in the most diseased women, all treated with synthetic and / or biological DMARDs. The registry includes patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA) and unspecified arthritis (UA).

Aims:

-To investigate the proportion of incident cases of RA compared with other chronic arthritides (OCA) during the first 24 months after delivery (OCA= PsA, AS and UA combined).

-To examine a possible peak of incident cases in the time period 0-24 months versus 25-48 months after delivery within each diagnostic group (RA and OCA).

-To examine possible different effects of CIA on pregnancy outcomes with separate analyses of outcomes in first birth and subsequent births

-To examine if a possible negative association with pregnancy outcomes was detectable before diagnosis of CIA.

-To compare fertility rates in women with RA, OCA and JIA with birth year matched references from the general population.

-To investigate the proportion of nulliparous women in each diagnostic group versus in birth year matched references

-To investigate a possible association between mean number of children and age of CIA diagnosis

-To examine inter pregnancy intervals in RA, OCA and JIA women versus birth year matched references

Material and methods:

Patients with inflammatory arthritides have been enrolled into the NOR-DMARD registry since 2001.The patients are included when they start treatment with synthetic and / biological DMARDs, but many of the patients have been diagnosed several years before the inclusion. Diagnosis and time of diagnosis was recorded from NOR-DMARD. Since 1967 medical data on all births in Norway have been recorded in the Medical Birth Registry of Norway (MBRN).

Data of 631 female patients aged 18-45 years and included in the NOR-DMARD registry in the period 2001-06 were linked with MBRN. Births until October 2007 were included in the linkage. In Paper 1 the time interval between the last child delivery before diagnosis and time of diagnosis was identified for each patient and used for analyses. In Paper 2 first births and subsequent births were analyzed separately, before and after diagnosis. In Paper 3 we analyzed fertility before and after diagnosis separately.

In Paper 2 reference deliveries were non-CIA deliveries selected from MBRN. Patient deliveries and reference deliveries were frequency sampled according to time periods of delivery. In Paper 3 references were selected from The Norwegian Population Registry. Each patient was birth year matched with 100 reference women, and data of each reference women was linked to the MBRN. Time of diagnosis of each patient was linked to the corresponding references to analyze fertility before and after diagnosis.

Results:

Paper 1 included 183 patients with RA and 110 patients with OCA, all diagnosed after delivery. The proportion of incident cases with onset 0-24 months post partum was not statistically significantly different between the diagnostic groups, neither in the analysis of all pregnancies, nor in the analysis of first pregnancy separately. A statistically significantly peak incidence during 0-24 months was seen in the RA group, both when considering all pregnancies and only the first pregnancy. A peak trend in onset of disease was observed after birth order one deliveries in the OCA group, but the result did not reach statistical significance.

Paper 2 included 128 first births (birth order one) and 151 subsequent births after diagnosis and corresponding 286 / 262 births before diagnosis. References were non-CIA deliveries from MBRN. A statistically significantly higher rate of Caesarean section, both total and elective, was related to all patient deliveries. All other excess risks were related to first birth in women diagnosed with CIA. The patients had statistically significantly higher risk of vaginal bleeding and labour induction than references. First born children of women diagnosed with CIA were statistically significantly more often preterm and small for gestational age. They also had statistically significantly lower mean birth weight and higher perinatal mortality. Pregnancy outcomes before diagnosis did not differ from the reference population.

Paper 3 included 631 patients with 849 children registered in MBRN. Of these, 289 children (34 %) were born after time of diagnosis versus 44 % in references. A statistically significantly higher proportion of CIA women were nulliparous compared with references, and relative fertility rates were statistically significantly reduced in all patient groups. The mean number of children in patients was associated with age at time of CIA diagnosis.
A statistically significantly increased inter pregnancy interval was observed in RA and OCA women diagnosed between first and second birth compared with references. No differences in intervals were observed in any of the diagnostic groups with both first and second birth after diagnosis.

Conclusions:

Our study has shown that not only RA but also other chronic arthritides may have frequent onset after delivery.
All negative diverging pregnancy outcomes in patients versus references were observed in relation to first birth after diagnosis of CIA. A higher risk of CS was related to all births in women diagnosed with CIA.
Fertility was reduced after time of diagnosis for all diagnostic groups compared with age matched references.

Background

Center for Pregnancy and Rheumatic Diseases was established in 1992 and is located at the Department of Rheumatology, St Olav's Hospital (Trondheim University Hospital). The Center is an interdisciplinary pregnancy clinic where patients are monitored and treated according to the risks of pregnancy related complications calculated from individual disease characteristics and previous pregnancy experience. The women are followed during pregnancy and after delivery. Before a planned pregnancy counselling by specialists in internal medicine and obstetrics is offered when necessary. During pregnancy monitoring of placental function and fetal surveillance by specialists in fetal medicine may also be necessary.

About 40 pregnant women with rheumatic diseases are monitored at the Center every year. Due to the important matter and sometimes complicated cases, the Center is also consulted about women with inflammatory rheumatic diseases planning pregnancies from other regions in Norway, which constitutes about 400 individual consultations per year. By the introduction of biological disease modifying anti-rheumatic drugs (DMARDs), evidence based knowledge about the impact on fertility, pregnancy and delivery has been increasingly demanded.

The background for this thesis is the special challenge I have met in counselling and monitoring women with inflammatory rheumatic diseases treated with synthetic and / or biological DMARDs and planning pregnancies. The patients regularly ask for our advice, which should build upon evidence based knowledge of our patient population. Thus, research is another main task for our Center. In a previous thesis, (Reproductive outcome in women with rheumatic diseases. Skomsvoll JF, NTNU, 2003) secular trends in pregnancy outcomes were studied in women with inflammatory rheumatic diseases during the years 1967-1995. Skomsvoll's studies were population based with data from the Medical Birth Registry of Norway. Although our Center previously has investigated different aspects on pregnancy and rheumatic diseases, unanswered questions have remained. Given the small number of patients with arthritides being pregnant per year, important research questions may not be answered by data from a single center. Therefore a multicenter approach was chosen. The Norwegian Disease Modifying Antirheumatic Drug (NOR-DMARD) registry gave access to study pregnancy related issues in the included women with chronic inflammatory arthritides. In contrast to the previous studies, we wanted to focus on the most seriously affected women

treated with synthetic or biological DMARDs. We have investigated pregnancy related aspects in this particular patient cohort by studying incident arthritis post partum, pregnancy outcomes and fertility.

1. Introduction

1.1 Diseases

According to the World Health Organisation, rheumatic diseases have been divided into four main categories: inflammatory rheumatic diseases (i.e. arthritides, connective tissue diseases, vasculitides), degenerative rheumatic diseases, soft tissue disorders and rheumatic manifestations of non-rheumatic diseases. The Norwegian Disease Modifying Antirheumatic Drug (NOR-DMARD) registry comprises inflammatory arthritides which have been focused in this thesis; i.e. rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA) in adult age and unspecified / undifferentiated arthritis (UA).

1.1.1 Rheumatoid arthritis (RA)

RA is a chronic, inflammatory, autoimmune disease characterised by destructive synovitis. Symmetric involvement of the small joints of the hands and feet is common. Additionally, RA may affect organs like lungs, kidneys, the vascular system, the bone marrow and the eyes (1). American College of Rheumatology (ACR) classification criteria for RA diagnosis are shown in Table 1. Traditionally, these criteria have been the most commonly used classification criteria for RA. However, new classification criteria for RA have recently been published (2).

The prevalence of RA is estimated to be about 0.5-1.0 % among Caucasians(3;4). The total annual incidence rate is 25-50 / 100000. Women are affected 2-3 times more frequently than men (5-7). In the Oslo RA registry the female : male ratio was found to be 4 : 1 in the premenopausal age (8). The peak onset of disease is about 60 years of age (6;7).

The etiology of RA is still unknown, but genetic and environmental factors are of importance for disease susceptibility. Among genes independently associated with RA, one located on chromosome 7 seems to have different genetic impact depending on gender, with a strong and apparently additive effect on disease status in females (9;10).

Environmental factors may both increase or reduce the risk of developing RA. Smoking, in the presence of human leukocyte antigen (HLA)-DR shared epitope, constitutes a major environmental risk factor for developing anti-cyclic citrullinated peptide antibody (CCP) positive RA (11). Several studies have investigated possible associations between reproductive factors and the risk of RA. While studies generally agree that abortions and

stillbirths are not related to the risk of RA (12-16), results for other reproductive factors like oral contraceptive use, parity, age at first pregnancy and lactation vary considerably (13-26).

The impaired physical function in RA patients is caused by a combination of inflammation and structural damage (27;28). Further, living with such a chronic, painful and disabling disease also has impairment of other dimensions of quality of life (7). In one study about one third of RA patients of working age were work disabled within one year after disease onset (29). In another study women were reported to have three times higher risk of work disability than men (30), and women of premenopausal age have been reported to have an even fourfold increased risk of work disability compared with men (31).

The disease is associated with substantial comorbidity and reduced life expectancy (32). The excess in deaths is attributable to infection, cardiovascular disease and respiratory disease, but also lung cancer and non-Hodgkin's lymphoma (33). Some studies suggest that the course of disease activity and health status in RA has improved during the last decades (34;35), which coincides with better treatment strategies. However, still increased mortality in RA patients compared with the general population has been reported (36).

The inflamed synovium in the rheumatoid joint is characterised by synovial lining hyperplasia, influx of inflammatory cells via adhesions molecules on activated endothelial cells, and neovascularisation on the synovial tissue (37). T cells, B cells, monocytes / macrophages and synoviocytes are cells that play important roles in a cascade of cell-to-cell interactions and cytokine mediated events. Tumour necrosis factor (TNF), interleukin (IL)-1, IL-6 and IL-17 are among the dominant proinflammtory cytokines which promote the breakdown of cartilage and bone-loss (37).

Table 1 Rheumatoid arthritis

1987 ACR criteria (38)

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

1.1.2 Psoriatic arthritis (PsA)

Psoriatic arthritis has been defined as an inflammatory, usually seronegative, arthritis associated with psoriasis (39). PsA is also classified into the group of seronegative spondylarthritides, which is a group of rheumatic diseases that share certain genetic and clinical features (inflammatory back pain, asymmetrical oligoarthritis, enthesitis, dactylitis and uveitis). Epidemiological, radiological and immunogenetic data support the existence of PsA as a specific entity (40;41). The exact prevalence of PsA is not known, but estimates vary from 0.1 % to 1 % (3;42;43). The female gender is overrepresented in polyarticular disease while oligoarticular and spinal disease is more prevalent in men (44-46). PsA may start at all ages (42;47). In a Finnish study the mean age at diagnosis was 46.8 years (48), and in a Norwegian study the mean age at onset of arthritis was 35 years (43).

Studies of environmental risk factors of PsA have focused on infection-related triggers and hormones. In a case-control study exposure to rubella vaccination substantially increased the risk of PsA as well as trauma (49). In a nested case-control study corticosteroid use moderately increased the risk of PsA, and pregnancy decreased the risk (50).

Various susceptibility genes to PsA have been identified. There is evidence that caspase recruitment domain 15 (CARD 15) has a role in PsA (9;51). Class I major histocompatibility complex (MHC) chain- related gene A (MICA) may confer additional susceptibility to PsA (9;52). Functional cytokine gene polymorphisms have also been associated with PsA, with tumour necrosis factor-alpha (TNF- α) -308 and TNF-β +252 polymorphism being significantly associated with age at onset of psoriatic skin disease, presence of joint erosions in PsA and progression of joint erosions in early PsA (9;53). HLA-B27 is strongly associated with axial disease, whereas HLA-B38 and HLA-B39 seem to be of more importance in peripheral disease (54).

Moll and Wright classified PsA into five subgroups; 1) Predominant involvement of DIP joints, 2) Arthritis mutilans, 3) Symmetrical polyarthritis (≥ 5joints), 4) Oligoarthritis (≤ 4 joints), 5) Predominantly spondylarthritis. Originally, oligoarthritis was believed to be the most frequent pattern (39), but recent studies indicate that more patients have polyarthritis and that joint pattern may change over time (42;55;56). The classical Moll and Wright criteria for diagnosis are shown in Table 2. A new set of criteria, the classification criteria for psoriatic arthritis (CASPAR) criteria, has now been developed (57).

Burden of disease in PsA is comparable with RA and AS (58). Despite higher disease activity and more structural damage in RA patients, patients with PsA report similar

impairment of physical functioning and psychosocial aspects of quality of life (58-60), which may be due to the additional burden of skin disease. Women diagnosed with PsA in premenopausal age have been reported to have a doubled increased risk of being work disabled compared with men (61). Radiological damage develop in up to 47 % of PsA patients within two years of disease (62). Mortality is increased in PsA patients, and active and severe disease are prognostic indicators for death (43;63).

Immunohistological studies of PsA have revealed that the synovitis in PsA resembles spondyloarthritis more than RA (64). Angiogenesis is a prominent feature in both skin and joints in PsA. The most common inflammatory cells are T-lymphocytes (65). High levels of TNF have been found in both skin lesions and inflamed synovium (66;67). In psoriatic skin disease TNF promotes proliferation of the keratinocytes (68).

Table 2 Psoriatic arthritis

Moll and Wright criteria (39)

1. An inflammatory arthritis (peripheral and / or sacroiliitis or spondylitis)
2. The presence of psoriasis
3. The absence of rheumatoid factor

1.1.3 Ankylosing spondylitis (AS)

Ankylosing spondylitis is the major subtype among the spondyloarthritides. AS affects 0.1-1.4 % of Caucasians (3;69;70), but the prevalence varies across ethnic groups and is correlated to the prevalence of HLA-B27 in the population (71). The estimated female: male ratio is 1: 2-3 (3;69). Disease onset is most frequent in the third decade of life (72), but a slightly higher age at onset of AS is reported in females than in males (44).

Sacroiliitis is a key feature of AS, and the presence of sacroiliitis is required to fulfil the 1984 modified New York classification criteria (73) (Table 3). Inflammation in spinal joints and ligament structures with subsequent structural damage results in pain and restricted spinal mobility (74;75). New classification criteria for spondyloarthritis have recently been published (76;77).

Epidemiological studies have focused on the genetics behind AS and the strong linkage of the major histocompatibility complex (MHC) with AS. Especially the relationship to HLA-B27 is well known (78). About 90-95 % of AS patients are HLA-B27 positive, as

compared to 7-8 % of the general population. The risk of developing AS is about 5 % in HLA-B27 positive individuals. However, HLA-B27 accounts for only a third of the total genetic effect (79;80). The search for an association between AS and non-MHC genes has gained much interest. Two new loci for AS have been identified; ARTS1 and IL-23R and another strong non -MHC linkage is located to chromosome 16q (9).

Few environmental risk factors and triggers have been studied in AS. Two studies support the hypothesis that bacterial antigens, especially from the gut flora, play a role in AS pathogenesis (81;82).

AS has impact on functional status, health related quality of life and work disability (83;84). Some studies also indicate an increased mortality, especially among men (85;86) With longstanding AS, men tend to have more severe radiographic abnormalities than women, but women report worse physical functioning than men (83). Women are also reported to have more peripheral arthritis than men (44;87).

The pathology in AS is characterised by bony formation with fusion of joints and intervertebral spaces. Inflammation located to enthesial sites causes bone destruction with subsequent repair and deposition of chondrogenic matrix that eventually remodel into bone (88). In sacroiliac joint biopsies in patients with AS, T cells, macrophages as well as abundant TNF messenger RNA have been found (89). TNF has proinflammatory properties, but it is also an inhibitor of bone formation. Thus, other pathways and cytokines may be of importance in AS structural changes, e.g. wingless (Wnt)-proteins, bone morphogenic proteins (BMP) and transforming growth factor beta (TGFβ)(88).

Table 3 Ankylosing spondylitis

1984 modified New York criteria (73)

1. Low back pain for at least three months duration improved by exercise and not relieved by rest.
2. Limitation of lumbar spine motion in sagittal and frontal planes
3. Chest expansion decreased relative to normal values for age and sex
4. Unilateral sacroiliitis grade 3-4
5. Bilateral sacroiliitis grade 2-4

Definite AS if criterion number 4 or 5 and any clinical criterion (1-3)

1.1.4 Juvenile idiopathic arthritis (JIA)

Juvenile idiopathic arthritis is the most frequent chronic inflammatory rheumatic disease during childhood. The criteria for diagnosis and classification have changed over the years (90). In 1972 the American College of Rheumatology (ACR) established criteria for juvenile rheumatoid arthritis (JRA), and the criteria was revised in 1977. In Europe the term juvenile chronic arthritis (JCA) was used. The European League Against Rheumatism (EULAR) established criteria for JCA in 1977. In 1997 the International League of Associations of Rheumatologists (ILAR) introduced the term juvenile idiopathic arthritis (JIA) which included seven different subgroups of the disease (91). Sets of classification criteria for JRA, JCA and JIA are shown in Table 4 (90). The main three groups are polyarticular, pauciarticular and systemic disease. In this thesis the term JIA is used.

Twin studies indicate a genetic component of JIA. In monozygotic twins both siblings were affected in 44 % compared to 4 % in dizygotic twins (92). HLA-DR 8 was associated with disease development in most of the JIA subgroups (enthesitis related arthritis, oligo- and polyarthritis) (93-95). HLA-B27 was associated to juvenile entesitis related arthritis (94;96). An association between JIA and genes coding for proinflammatory cytokines and cytokine receptors (IRF-1, TNF-α, IL-1Ra, IL-6, MIF) has been demonstrated (97).

Among the environmental risk factors studied, infection remains the most favoured of candidates. However, quite few studies have appeared.

The incidence of juvenile arthritis varies around the world. In Scandinavia an annual incidence of 11-23 / 100000 / year has been reported (98-101). The prevalence rates have varied from 86 in western Sweden to 148 / 100000 in northern Norway (98;100). About 17-20 % of children with incident arthritis have JIA (99;101), and about 60 % of the children who develop JIA are girls (99;101). A peak incidence is reported between 1 and 3 years of age and another peak between 10 and 13 years (101;102).

As many as 50 % of all JIA patients may still have active disease in grown-up life. In children with oligoarticular disease, about 50 % of patients will progress into polyarticular disease (5 or more affected joints) as adults (103;104). Children with polyarticular disease, regardless if they have rheumatoid factor or not, have the highest risk of a remaining active disease the rest of their lives. Many of these patients will need synthetic and / or biologic DMARD treatment in adult life. In children with systemic onset JIA 37 % may develop chronic destructive polyarthritis in adult life (105;106).

One study of JIA demonstrated a mortality of 2 % within 15 years of disease onset compared with less than 1 % in the general population (107;108). JIA related heart disease and amyloidosis were the most frequent causes of death, followed by infections and intoxications (109). Data from a national registry in Scotland have reported an increased life time mortality risk of 5 in women and 3 in men with JIA compared to the general population (110). The ratio between observed and expected mortality was higher for JIA than RA patients (110).

Table 4 Classification criteria for arthritis in childhood (90)

Criteria	ACR	EULAR	ILAR
Terminology	Juvenile rheumatoid arthritis (JRA)	Juvenile chronic arthritis (JCA)	Juvenile idiopathic arthritis (JIA)
Age at disease onset	<16 years	<16 years	<16 years
Duration of arthritis	≥6 weeks	≥3 months	≥6 weeks
Included subgroups	Systemic Polyarticular Pauciarticular	Systemic Polyarticular Pauciarticular Psoriatic arthritis Juvenile AS Arthritis associated with IBD	Systemic Polyarticular RF- Polyarticular RF+ Oligoarticular, persistent Oligoarticular, extended Psoriatic arthritis Enthesitis related arthritis Unspecified arthritis
Excluded subgroups	Juvenile AS Juvenile psoriatic arthritis Arthritis associated with IBD		

ACR = American College of Rheumatology, EULAR = European League Against Rheumatism, ILAR = International League Association of Rheumatologists, IBD = inflammatory bowel disease, RF = rheumatoid factor, AS = ankylosing spondylitis

1.1.5 Unspecified arthritis (UA)

Patients without a well-defined inflammatory arthropathy are labelled to have unspecified / undifferentiated arthritis. Some patients develop features to permit a later classification, whereas others remain undifferentiated, but with persistent joint inflammation, functional disability and development of radiographic joint damage. UA is common, with an estimated prevalence between 30 and 50 % of patients with arthritis presenting to rheumatologist (111-117). The patients fail to fulfil criteria for specific disorders such as PsA, RA or parvovirus B19 infections, and the diagnosis is usually one of exclusion. In patients with unspecified polyarthritis 13-60 % have a self-limited inflammatory joint disorder (112;116), however, unspecified polyarthritis is not always a benign disorder. In a Dutch study of undifferentiated arthritis, 60 % had a self -limited disease, 16 % developed a persistent, seronegative, non-erosive polyarthritis and 24 % an erosive, largely seropositive polyarthritis (118). In this study predictors for treatment with DMARD or the development of joint damage were presence of persistent synovitis at 3 months of disease, rheumatoid factor positivity, anti-CCP positivity, elevated erythrocyte sedimentation rate or C-reactive protein level ≥10 mg/l, female sex and the presence of early radiographic erosions.

Another study has compared MR imaging of the knees in patients with unspecified oligoarthritis, established RA or spondyloarthropathy. Patients with RA showed more destructive changes in terms of synovial thickening, bone marrow edema, cartilaginous and bone erosions compared with UA and spondylarthropathy (119).

1.2 Medications

1.2.1 Drug treatment of chronic inflammatory arthritides

The majority of patients included in this thesis had used or were using non steroidal anti-inflammatory drugs (NSAIDs) (including cyclooxygenase 2 inhibitors) and corticosteroids in addition to the use of synthetic and / or biological disease modifying anti rheumatic drugs (DMARDs).

NSAIDs inhibit prostaglandin synthesis by blocking cyclooxygenase enzymes. Prostaglandins are important mediators of pain and inflammation. Thus, the analgesic and

anti-inflammatory properties of NSAIDs make their use frequent in patients with all types of inflammatory arthritides. In AS therapy with NSAID is the first drug of choice (120).

Corticosteroids are potent anti-inflammatory medications and widely used in RA, JIA and UA, but more seldom in PsA and AS.

Synthetic disease modifying anti-rheumatic drugs (DMARDs)

In inflammatory active RA, PsA, JIA and UA treatment with synthetic DMARDs are commonly used and include methotrexate (MTX), sulphasalazine (SSZ), leflunomide, hydroxychloroquine (HCQ) and gold compounds. Gold compounds have been used for treatment of RA during several decades, but less common during the last decade because of new treatment options. The DMARDs azathioprine, D-penicillamine and cyclosporine are over the recent years infrequently used in the treatment of inflammatory arthritides and are not considered in this thesis.

Methotrexate (MTX) is a dihydrofolate reductase inhibitor that inhibits folic acid metabolism and purine synthesis (121). MTX is prescribed extensively in treatment of RA, both as monotherapy and in combination with other synthetic or biological DMARDs. MTX is also used in the treatment of PsA, JIA and UA. Oral MTX has a half life of 3 to 10 hours, but can persist in the liver for several months (122).

Sulphasalazine (SSZ) is a folic acid antagonist and is mainly used to treat patients with RA and inflammatory bowel disease (IBD). Its half-life is between 5 and 10 hours.

Leflunomide is an inhibitor of dihydroorotate dehydrogenase and thus inhibits pyrimidine synthesis (123). The medication is mainly used for treatment of RA, but also of PsA. Leflunomide has a half-life of 14 days, but its active metabolite undergoes extensive enterohepatic circulation and may persist in the body for up to 2 years (124).

Hydroxychloroquine (HCQ) is an antimalarial agent used to treat patients with lupus/ connective tissue disease or mild to moderate RA. Although its exact mechanism of action is unknown, it is thought to interfere with the presentation and processing of antigens (121). Its half-life is appro.ximately 8 weeks, and with this slow elimination the medication may persist in the body for months after discontinuing therapy.

Biological DMARDs

During the last decade treatments targeting specific cytokines or molecules involved in the inflammatory disease process have become available for use in clinical practice (125). Three anti- tumour necrosis factor-alpha inhibitors; infliximab, etanercept and adalimumab have

been commercially available during the time of inclusion of patients for the studies in this thesis. Infliximab is a chimeric anti-TNF-α monoclonal antibody (IgG1), etanercept is a TNF-α receptor p75 IgG1 construct, and adalimumab is a TNF receptor-IgG fusion protein (126). Infliximab, etanercept and adalimumab bind directly to TNF-α preventing activation of its receptor on targeting cells (127). Anti-TNF therapy is indicated for active inflammatory disease in RA, PsA and JIA when not responding on traditional DMARD therapy, and in AS if treatment with NSAIDs is without response (128). Recently, two new TNF-α-inhibitors have also been commercially available, certolizumab and golimumab. Certolizumab is a pegylated, humanized anti-TNF Fab fragment, and golimumab is a fully human monoclonal antibody (129).

Anakinra is a recombinant IL-1 receptor antagonist approved for treatment of moderate to severe RA. Its use in RA has been limited, given the poor efficacy of Anakinra on RA and availability of superior medications.

Other treatment options have also been commercially available in the treatment of RA during the last years. Rituximab is a chimeric murine / human monoclonal antibody directed against CD-20 antigen expressed on the surface of B-lymphocytes and induces lysis of CD20+ B lymphocytes. Tocilizumab is a humanized monoclonal antibody against interleukin 6 receptor, and abatacept is a human cytotoxic T-lymfocyte-associated antigen 4-IgG1 fusion protein, blocking T-cells by binding to costimulatory proteins present on antigen-presenting cells.

1.2.2 Drug treatment of chronic inflammatory arthritides (CIA) in pregnancy

To avoid destruction of joints, involvement of internal organs, severe disability and even increased mortality, disease control with medication is essential in patients with CIA.
In women with CIA who plan to become pregnant, a therapeutic regimen is required that quickly induces remission or maintains improvements. In addition, the regimen should be compatible with pregnancy. These requirements exclude several highly efficient immunosuppressive and biologic drugs and reduce the possibilities of combination therapies. However, in RA the disease course itself may improve during pregnancy. Retrospective and small prospective studies have reported improvement of disease activity in as many as 70-90 % of pregnant patients with RA (130). On the other side two large prospective studies have used validated measurements of disease activity and found improvements during pregnancy in

only 63 % and 48 % of the patients, respectively (131;132), and even less than 20 % of the patients reported complete remission (131). Consequently, some form of drug treatment will be necessary for 40-50 % of pregnant RA patients (130).

Generally, women with CIA are advised to plan their pregnancies in periods where the disease activity is low. Managements strategies and recommendations for prescribing antirheumatic drugs during pregnancy may differ by region depending on guidelines published by national specialist associations (130).

The United States Food and Drug Administration (FDA) safety category classification of pharmacotherapies for use during pregnancy have published recommendations and warnings about use of medications before conception and during pregnancy (Table 5). Although the FDA category classification is almost exclusively based on animal reproductive data, physicians and patients use it as an important resource. However, the FDA classification is limited in its ability to precisely predict the human risk (133).

Table 5 The United States (US) Food and Drug Administration safety category classification of pharmacotherapy for use during pregnancy (134)

Category	Description
A	Adequate and well-controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester and no evidence of a risk later in pregnancy
B	Animal studies fail to demonstrate a risk to the fetus and no adequate and well-controlled human data available
C	Animal studies have revealed no evidence of harm to fetus, however, there are no adequate and well-controlled studies in pregnant women Or Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus
D	Animal studies have shown an adverse effect, and there are no adequate and well-controlled studies in pregnant women or No animal studies have been conducted, and there are no adequate and well-controlled studies in pregnant women
X	Animal or human studies demonstrate fetal abnormalities, and there is evidence of human fetal risk based on investigational / marketing experience in humans / risks clearly outweigh any potential benefit

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1.2.2.1 NSAIDs

Effects on fertility

Prostaglandins are involved in ovulation and implantation. Several case reports and small series have described transient infertility following treatment with indomethacin, diclofenac, piroxicam and naproxen (135-137). Studies in animals and humans have shown that NSAIDs can inhibit rupture of the luteinized follicle and thereby cause infertility (136). Still, we lack epidemiological data about chronic users of NSAIDs are at increased risk of infertility. Cyclooxygenase (COX) 2 is expressed in preovulatory follicles and inducing the maturation of the ovum. In rats and mice inhibition of both COX 1 and COX 2 interfere with fertilisation, implantation and decidualisation (136;138).

Early and mid-pregnancy

NSAIDs cross the placenta and enter the fetal circulation (139). A few studies have found possible fetal lesions like oral cleft, cardiac and gastric defects related to NSAID use in early pregnancy (140;141), whereas others could not confirm these findings (142;143). Two population-based cohort studies have shown an association between use of NSAID early in pregnancy and miscarriages, but causal association was not established (142;143). Traditional NSAIDs are considered category B medications (Table 5). Thus, it is advisable to use NSAIDs with short half-life and at the lowest effective dosage in early and mid-pregnancy.

Late pregnancy

The use of NSAID in late pregnancy and a premature closure of ductus arteriosus is a well documented association (144). Renal dysgenesis and oligohydramnion have also been reported (145). Thus, NSAIDs are contraindicated beyond 32 weeks of gestation.

COX-2 inhibitors

There are not adequate safety data in human pregnancy concerning the use of COX-2 selective inhibitors, and they are classified as category C medications (Table 5). It is advisable to avoid these medications during pregnancy.

1.2.2.2 Corticosteroids

Maternal considerations

Corticosteroids such as hydrocortisone, cortisone and prednisone cross the placenta, but are rendered biologically inactive by placental enzymes. Thus, they can be used to treat maternal disease during pregnancy. Use of corticosteroids during pregnancy is associated with an increased risk of pregnancy-induced hypertension, preeclampsia and gestational diabetes (146;147). In addition, corticosteroid side effects in pregnant women include other well-known side effects like osteopenia, osteonecrosis and susceptibility to infections. Pregnancy specific complications like premature rupture of the membranes are also reported more frequently in patients using corticosteroids (148).

Corticosteroids are classified as category B medications (Table 5), and they can be used throughout pregnancy, either on a daily dosing or in a tapering schedule to manage flares. To avoid pregnancy complications, the cumulative amount should be minimized to the smallest dose required to control the symptoms.

Fetal considerations

One meta-analysis has reported increased risk of oral cleft defects with first-trimester exposure to corticosteroids like hydrocortisone and prednisone (149), however, two other large studies did not demonstrate increased risk of birth defects with use of these medications (150;151). A Dutch study in women with RA showed lower birth weight in infants of mothers using prednisone in pregnancy (152). Fetal adrenal suppression is rare (153).

Fluorinated corticosteroids (dexamethasone and betamethasone) cross the placenta and are used to prevent conditions such as respiratory distress syndrome and cerebral haemorrhage in the preterm newborn given as a single antenatal dose (154). However, animal studies suggest that repeated antenatal steroid doses can interfere with the growth and development of the immature brain (155;156). Human studies have also indicated that repeated antenatal steroid doses may have a negative effect on the neuropsychological development of the child (157-159). Possible negative effects seem linked more to dexamethasone than betamethasone, and it has been suggested that betamethasone should be preferred when available (154;160;161).

1.2.2.3 Synthetic DMARDs

Methotrexate (MTX)

MTX crosses the placenta. Experience with MTX in human pregnancy has been derived mainly from patients treated for cancer with multiagent therapy and MTX used in high doses (154). High-dose MTX exposure during pregnancy is associated with a specific pattern of cranial, central nervous system and limb defects referred to as the aminopterin / methotrexate syndrome (162). A fetal exposition of methotrexate therefore may lead to malformations of the skull, facial dysmorphism, CNS anomalies with lower intelligence and defects of the extremities as well as intrauterine growth restriction (163). The most vulnerable time for embryotoxicity has been suggested to be between 5 and 8 weeks of gestation (164). However, fetal malformations have also been observed before five weeks and after 11 weeks of gestation (165).

There are inadequate data to determine the outcomes of pregnancy exposed to low-dose MTX (5-20 mg weekly) as used in RA, JIA, PsA and UA. The malformation rate in the rheumatic diseases is difficult to calculate because only small retrospective case series on RA are reported, and they lack detailed information. However, a high rate of spontaneous abortion has been reported (166). MTX is labelled as a category X drug (Table 5). To avoid fetal exposition the use of MTX should be discontinued at least 3 months before conception.

Leflunomide

Leflunomide is reported to be embryo toxic in animal studies (167) and one case of blindness has been reported in a preterm born baby (168). Because of the long persistence of the active metabolite of leflunomide, the drug has to be discontinued and eliminated using cholestyramine before pregnancy. After cholestyramine chelating therapy, women should wait at least 3 menstrual cycles before attempting pregnancy. So far there is lack of data on the safety of leflunomide in human pregnancy, and it is labelled as a category X drug (Table 5).

Hydroxychloroquine (HCQ)

HCQ crosses the placenta. Concerns regarding its fetal toxicity were based on reports of retinal and ototoxicity in humans exposed to chloroquine, a related antimalarial agent (169;170). Although available data do not suggest increased fetal risk with exposure (171-173), HCQ is classified as a category C drug (Table 5), but it may be used in pregnancy when indicated.

Sulphasalazine (SSZ)

Both SSZ and its metabolite sulphapyridine cross the placenta, and equal concentrations of the drugs are found in the maternal serum and cord serum (174). No reports of teratogenicity exists for women with inflammatory bowel disease using SSZ (175;176). Two case-control studies have shown a possible increased risk of oral cleft, neural tube and cardiovascular defects in pregnancies exposed to different folic acid antagonists including SSZ (177;178), but another study could not confirm these findings (179). Thus, available data indicate that the potential risk of teratogenicity is low, and SSZ is classified as a category B drug (Table 5). SSZ may be used during pregnancy with folate supplementation.

Gold compounds

Gold compounds cross the placenta (180;181) and have been found in fetal liver and kidneys. There are few reports of pregnancy outcomes in women taking gold compounds, and no evidence of an increase in neonatal malformations in the small number of pregnancies reported (182). Gold sodium thiomalate is classified as a category C drug (Table 5).

1.2.2.4 Biological DMARDs

There are no available human data on the use of anakinra during pregnancy, but animal studies have not found any fetal malformations. Anakinra is classified as a category B medication (Table 5).

In animal studies using analogous anti-TNF antibody, no evidence of teratogenicity has been observed (183). However, experience with TNF-α inhibitors is still limited. Most concerns have been about the use of TNF-α inhibitors during first trimester of pregnancy. The MHC class I-related Fc receptor mediates the transmission of IgG1 across the placenta (184). Thus, all anti-TNF agents containing the Fc receptor will pass the placenta. Significant trans placental passage of the monoclonal antibodies infliximab and adalimumab takes place from the second trimester of pregnancy onwards, and their levels increase in cord blood to reach levels similar to or higher than maternal levels at term(130;185;186). Long-term effects of intrauterine exposure to TNF-α inhibitors have not been studied (187). The anti-TNF agents adalimumab, etanercept and infliximab, are classified as category B drugs by the FDA (Table 5) and continuation of anti-TNF treatment in pregnancy is an issue under debate. The current expert opinion is to avoid the drugs after a positive pregnancy test. In women with

very active inflammatory disease in pregnancy, the current expert opinion is that anti-TNF treatment may be continued until gestational week 30. Use of anti-TNF in pregnancy should always be in agreement with the pregnant women and depend on the severity of disease and judgement of risks versus benefits.

Certolizumab is the only of the present available anti-TNF agents without Fc receptor, and there is no active transport over the placenta. So far there has been only a few casuistic reports from human pregnancies and without any adverse effects. Due to limited experience, certolizumab is recommended to stop 5 months before planned pregnancy. No human pregnancy reports exist for the new anti-TNF agent golimumab, and so far discontinuation is recommended 6 months before conception.

Studies in pregnant animals have shown that abatacept crosses the placenta. No human pregnancy reports exist neither for abatacept nor tocilizumab, and discontinuation is recommended 3 months before conception for both agents.

Only a few casuistic reports exist on rituximab treatment in pregnancy. All of these pregnancies were in women treated with rituximab for malignant or haematological diseases. Lymphopenia was noted in one of two neonates after first-trimester exposure to rituximab (130;188;189). In three of six cases treated with rituximab during second and third trimester, serum levels of rituximab were similar in the mothers and their newborns, and the infants had greatly reduced or undetectable numbers of B cells (130;190-192). Rituximab is classified as a category C drug by the FDA (Table 5), and discontinuation 12 months before pregnancy is recommended.

2 Why pregnancy may influence chronic inflammatory arthritides (CIA) and vice versa

2.1 Immunology in relation to pregnancy in women with chronic inflammatory arthritides

Pregnancy induces physiological changes in the maternal immune system in order to protect the fetus from immunological attack by the mother. Research over the past decade has indicated that no general immunosuppression takes place in the maternal system. Rather, there is a shift from prevailing Th1 response to a type Th2 response (193;194). CD4+ T cells can be

divided into two subsets: one is the T helper 1 type characterized by production of interferon γ (IFN γ), interleukin (IL)-12, tumour necrosis factor- β (TNF- β) and IL-2 and involved in cell mediated immunity. The other T cell subset consists of Th2 committed cells, which mainly produce IL-4, IL-10 and IL-13, thereby enhancing humoral immunity. The immunological changes taking place during and after pregnancy may modulate disease symptoms according to the underlying pathophysiology of the disease in question.

IFNγ is a major contributor to a Th1 immune response, up regulating Th1 cell differentiation and inhibiting Th2 cell development. IL-1β and TNF-α are proinflammatory cytokines that contribute to synovitis and joint destruction in both RA and AS (195-197). The immune modulating activities of cytokines are also regulated by soluble cytokine receptors like TNF- receptor (TNFR) which can buffer the biological effects of TNF-α (198). Another natural inhibitory mechanism involves the blocking of receptor binding by cytokine receptor antagonists like IL-1Ra (199).

RA is regarded as a T-cell mediated and Th1 response-driven disease (200). The frequently reported ameliorating effect of pregnancy on RA (201-203), is possibly caused by the increased immune tolerance and shift from Th1 towards Th2 differentiations of T cells with increased secretion of the anti-inflammatory cytokines IL-4 and IL-10. IL-10 down-regulates production of proinflammatory cytokines by Th1 cells and macrophages. In pregnancy IL-10 counteracts pregnancy related disorders, such as fetal growth restriction, fetal death and preeclampsia (194-197;204;205). The increase in the anti-inflammatory cytokines is driven by high concentrations of circulating hormones, such as cortisol, oestrogen and progesterone as well as endogenous corticosteroids (203;206). RA disease development is mitigated by oestrogen, and pregnancy typically suppresses disease activity (207). In contrast, there is often a flare in the disease during the postpartum period, which is associated with a sudden fall in hormones after delivery, and a high concentration of prolactin during breastfeeding (208).

Amelioration of RA during pregnancy has also been associated with a disparity in HLA class II antigens between mother and fetus (202). These findings suggest that the maternal immune response to paternal HLA antigens may have a role in the pregnancy-induced remission of RA.

Recently, the role of galactosylation of IgG during pregnancy has been discussed as disease remitting factor in pregnant patients with RA, but so far the question remains whether the observed increase in galactosylation is an epiphenomenon or a true remission-inducing factor (209;210).

In difference to RA, AS often remains active and is mitigated only in late pregnancy (44;211), and an aggravation of disease symptoms is commonly seen within the first six months after delivery. In AS a Th0 or Th2 type immune response is predominant (205). A recent study has demonstrated that pregnancy influenced the expansion and cytokine secretion of T-regulator ($T_{reg)}$ cells in both patients with AS and controls without AS. However, in contrast to observations in the controls, the T_{reg} cells of pregnant patients with AS failed to support an anti-inflammatory cytokine milieu and thereby possibly contributing to the persistent disease activity of AS during pregnancy (212).

In PsA, JIA and UA no explicit studies on immunological changes during pregnancy exist.

2.2 The effect of pregnancy on inflammatory arthritides

Most studies have focused on RA and the frequently reported ameliorating effect of pregnancy (201;213-217). However, one study has demonstrated a widespread variability in the effect of pregnancy on the disease activity (131), and another found that remission during pregnancy was not as frequent as previously reported (132). Improvement of disease activity during pregnancy may not be associated with changes in levels of autoantibodies during pregnancy, but seems to occur more frequently in the absence of anti-CCP and RF (218). Post partum a disease flare is reported in 90 % of the women within 6 months (207;219).

Studies of pregnant women with AS have demonstrated unchanged or even worse disease activity during pregnancy. Remission has been confined to patients with accompanying diseases like psoriatic skin disease, inflammatory bowel disease and small joint arthritis (211;216;217;220). A flare during the first 3 months post partum was reported in about 90 % of the pregnancies (217).

In PsA one study has reported improvement or even remission in 80 % of the pregnancies and a postpartum flare within 3 months in 70 % (217). In the same study quiescent JIA was not reactivated by pregnancy, and active disease at conception ameliorated in about 60 % (217). A post partum flare was reported in about 50 % of the women with JIA (217). In a Polish study 52 % of patients with early onset pauciarticular juvenile chronic arthritis had a post partum flare after delivery (221). The flares were most frequent in women who had active disease before pregnancy, and in those who had experienced a flare after a previous pregnancy and / or were breast feeding.

2.3 Incident arthritis post partum

Onset of RA is found to be rare during pregnancy but more frequent after delivery, with a peak incidence during the first twelve months post partum (214;222;223). It is difficult to predict incidence rates of arthritides after delivery, but a prospective Japanese study found that the incidence of RA was 0.08 % during the first year after delivery (214). A British report from 1950 concluded that RA occurred in 19 % within 1 year after pregnancy, and in 29 % during the first two years among all patients with RA under the age of 45 (224). Oka found that 12.6 % of patients with RA had disease onset within 1 year after delivery (214).

Breast feeding has been reported both to increase the risk of RA onset (17), and to reduce the risk of RA onset post partum. (18;23;225). Particularly the risk was reduced if the breast feeding was long- term (18;23). Further, some studies have reported that oral contraceptive use may protect against the development of RA (17;25;26), but other studies have been unable to confirm this effect (17;22).

Whether this pattern of incident arthritis post partum occurs also in other types of chronic arthritides, including PsA, AS and UA, has only been sparsely studied. A few published results indicate increased onset of PsA (226) and AS (227) post partum.

2.4 The effect of inflammatory arthritides on pregnancy, delivery and the infant

Autoimmunity can affect every aspect of pregnancy including fertilisation, maternal complications and adverse fetal outcomes (228). Also, effects of subclinical disease processes on pregnancy outcomes can not be excluded since a status of preclinical RA may exist (229-231).

The impact of CIA on pregnancy and delivery have been addressed in several studies (152;232-241). In earlier studies published in 1969 (242) and in 1983 (243) unfavourable effects on the fetus were not observed, however, this contrasts results of later studies.

The rate of miscarriage / spontaneous abortion in women with RA differ between the studies. Higher (244), lower (16) or similar rates (235-237) compared with controls have been reported. Increased rates of caesarean section (CS) have been reported in patients with CIA

and in specific diagnostic groups as RA, AS and JIA (227;232-235;238;245). Additionally, preeclampsia seems to occur frequently in RA and in CIA (234;238;240;241).
Increased proportions of preterm delivery (235;238;239), small for gestational age (SGA) infants and low birth weight (<2500 g) (232;234;238;239) as well as lower mean birth weight (152;232) have been reported in CIA pregnancies compared with references. A Dutch study has reported that both a high disease activity and use of low doses of prednisone during pregnancy may influence birth weight negatively (152).

Very few studies have reported on birth defects, perinatal and neonatal deaths (237;239;246). One study concluded with a slightly increased rate of birth defects and a significantly higher rate of post perinatal mortality, but not perinatal mortality in infants of mothers with CIA (239).

Only a few studies have addressed pregnancy outcome in women before the diagnosis of CIA and without any adverse reports compared with controls (236;246), except for a report of increased perinatal deaths among infants of women who subsequently developed RA after delivery (237).

First births

Generally, pregnancy and delivery complications are more frequent in first pregnancy (247-249). The risk of CS in nulliparous women with spontaneous start of labour, cephalic fetus and no previous scar has been reported to be 2.5 times higher than for comparable parous women (250). The causes for this increased risk are not fully understood, although it has been known for more than 40 years (251;252). Separate analyses of outcomes of first delivery and subsequent deliveries in women with CIA have not been previously published.

2.5 Fertility in women with chronic inflammatory arthritides

CIA may influence the production of offspring (fertility), and different mechanisms may be involved: physical, psychological, hormonal or immunological as well as medical treatments (136). Significantly lower mean number of births, shorter time span in reproduction, longer inter pregnancy interval and reduced subsequent pregnancy rate have been reported in women with inflammatory arthritides compared with references in a Norwegian population based study (253).

Fertility has particularly been studied in RA. Some studies indicate reduced sexual desire and lower frequencies of intercourse in women with RA (254-256). In structured interviews with about 400 married women with RA, nearly one out of five answered that the arthritic disease influenced childbearing decisions, and especially in those diagnosed at young age (257). The overall percentage of women having children was not different from the general population, but women with RA were more likely to opt for a single child (257).

Data obtained in cross sectional surveys have suggested low ability to conceive a child and longer time to achieve pregnancy in women with RA both before and after disease onset (258;259). However, a case-control study did not find any differences in number of children between cases and age matched controls (260).

Normal fertility has been reported in women with AS (220;227;261), however, a longer time to achieve pregnancy (136;261) have been reported in women with AS.

Long term physical and psychosocial impairment found in adult patients diagnosed with JIA may explain the longer time to achieve pregnancy (245;262). Fertility do, however, not seem to be impaired (262). In PsA and UA no explicit reports on fertility exist.

3. Materials and Methods

3.1 Data sources

3.1.1 The Norwegian Disease Modifying Antirheumatic Drug (NOR-DMARD) registry (263)

The NOR-DMARD registry was established in December 2000. From the beginning, three Norwegian rheumatology departments (Diakonhjemmet Hospital in Oslo, Lillehammer Hospital for Rheumatic Diseases and University Hospital of Northern Norway in Tromsø) recruited patients. In 2002 the registry was expanded with two additional rheumatology departments (St Olav's Hospital in Trondheim and Buskerud Central Hospital in Drammen). The five NOR-DMARD centers cover about 1.4 million inhabitants. Adult patients (≥18 years) with inflammatory arthropathies are consecutively included in the registry when they start with a new DMARD treatment and are followed longitudinally. Each DMARD regimen

represents one case, and a patient will be included as a new case if there is a change in prescription of a DMARD regimen. By August 2006, 5811 cases were registered in about 3700 different patients. The completeness of the registry is about 85 % and has been quite stable over the years. The remaining cases have either been missed for inclusion, excluded due to language barriers, refused enrolment or been enrolled in ongoing randomised clinical trials. The registry has received an annual grant from the Norwegian Directorate of Health and Social Affairs. Otherwise the conduct of the registry has been financed through unrestricted research grants from different pharmaceutical companies (Abbott, Amgen, Aventis, MSD, Schering Plough / Centocor, Wyeth, BMS, Roche and UCB). The sponsors have no influence on data collection, analyses, manuscript preparation or publications.

3.1.2 The Medical Birth Registry of Norway (MBRN) (264;265)

The registry was established on the basis of compulsory notification introduced in Norway in 1967 and is since 2002 organised under the Norwegian Institute of Public Health. Surveillance and detection of secular changes in perinatal health as well as epidemiological research are the main objectives of the MBRN.

For each birth a notification form is sent within the ninth day post partum. A revised and more detailed notification form has been used since December 1, 1998 (Appendix). From 1967 to 1998 the registry collected data on all deliveries in Norway after 16 weeks of gestation. Since December 1, 1998, all deliveries after 12 weeks of gestation have been registered.

Complete ascertainment of the births is ensured through a record linkage with the National Population Registry. The birth attendant completes the standardized form with demographic data on the child, the father and the mother, data on maternal health during pregnancy, complications and procedures during delivery and the condition of the child at birth. The national identification number enables linkage of births into sibships.

3.1.3 The National Population Registry

The National Population Registry (Det Sentrale Folkeregisteret) was established in 1964 and includes data about everyone residing in Norway. Data about citizens living in Norway are gathered for tax, electoral and population analyses by local tax offices. The registry is run by the Directorate of Taxes (Skattedirektoratet). Data from the National Population Registry, i.e.

names, addresses, citizenship, identification numbers, position of employment and civil status of people, are only accessible to authorised public sector offices. However, members of the public may apply for data from the National Population Registry for legal purposes including research.

3.2 Classification of diagnoses in the NOR-DMARD registry

Patients in the NOR-DMARD registry are diagnosed by a treating rheumatologist and classified according to the WHO international classification of diseases (ICD-10). For further analyses patients are classified as follows:

1. RA (M05.0, M05.1, M05.2, M05.8, M05.9, M06.0, M06.8, M06.9)
2. PsA (L40.5, M07.0, M07.1, M07.2, M07.3)
3. AS (M45)
4. JIA (M08.0, M08.1, M08.2, M08.3, M08.4, M08.8, M08.9)
5. Unspecified arthritis (M13.0, M13.9, M13.1, M02.9, M79.0)

3.3 Data collection / logistics

All patients give written informed consent before enrolment in the NOR-DMARD. The data are collected at baseline and at follow-up visits after 3, 6 and 12 months, and yearly thereafter. Each center has a research nurse working on the project. The standard operating procedures are as follows: At each visit the patients are seen both by the research nurse and the treating physician. The patients fill in the self-assessment forms. The nurses collect data on demographics, previous treatment, education and life style and the utilisation of health care resources. They also register ESR and CRP, do joint counts and measure blood pressure. The physicians register all data related to medical history including time of diagnosis, disease manifestations, treatment adjustments and adverse events. The research nurses check the completeness of the registrations.

All the CRFs are handled and computerised centrally by Smerud Medical Research AS, who also request additional information when data are missing. Data files are returned to Diakonhjemmet hospital for quality check before analyses.

3.4 Assessments in NOR-DMARD

The following assessments are included in NOR-DMARD:

- Age and gender
- Diagnosis
- Patient history including educational level, working status, date of diagnosis of the inflammatory rheumatic disease, age at diagnosis and smoking habits
- 32 swollen and 32 tender joint counts (28 joint counts plus forefeet and ankles) and calculation of DAS-28
- Rheumatoid factor present or absent
- Anti-CCP present or absent (registered since 2006)
- Erosions present or absent
- ESR and CRP

- Investigator's global assessment of health status on a 100 mm visual analogue scale (VAS)
- Patient's assessment of pain, fatigue and global health status on 100 mm VAS
- MHAQ
- SF-36
- Comorbidities
- Utilisation of health care
- Previous treatment: DMARD / biologics, corticosteroids, NSAIDs / COXIBs
- Current medication, including start of DMARD and / or biologics

Adverse events and patient priorities for treatment are recorded at follow-up. Treatment terminations and reasons for stopping treatment are also registered.

From 2006 the Bath Ankylosis Spondylitis Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional index (BASFI) and a utility measure, EQ-5D, were added to the case report form.

The disease activity score-28 (DAS-28) is computed based on 28 tender- and swollen joint counts, patient's global assessment on a 100 mm VAS and the erythrocyte sedimentation rate (ESR). The formula is shown in the Appendix.

The MHAQ (0-4) is a modified version of HAQ and comprises one question within each of eight categories of functioning: dressing, rising, eating, walking, hygiene, reach, grip and usual activities (266). The score ranges from 0 (good functioning) to 4 (poor functioning). The questionnaire has been translated to Norwegian.

The Medical Outcome Study 36-item Short Form (SF-36) is a commonly used generic health status measure. It originated in the USA (267;268), and has been translated and validated for use in Norway (269;270). It contains 36 questions measuring health across eight different dimensions: physical functioning, role limitations due to physical health problems, bodily pain, vitality, social functioning, role limitation due to emotional problems, mental health and general health. A score is computed within each dimension with a value from 0 (worse possible health state) to 100 (best possible health state).

3.5 Assessments from the NORD-DMARD registry used in this thesis

Gender
Age at inclusion
Diagnosis
Date of diagnosis
Age at diagnosis
Date of inclusion in NOR-DMARD
28 joint counts and DAS-28
Rheumatoid factor present or absent
Erosions present or absent.

3.6 Study population: Data linkage of NOR-DMARD and MBRN

Data of female patients aged 18 – 45 years at the time of inclusion in the NOR-DMARD registry in the period 2001-2006 were included in this thesis. Eligible women received written information about the planned linkage of NOR-DMARD data and MBRN. Fourteen women

opted out, and data of 631 women from the NOR-DMARD registry were linked with the MBRN. The linkage included deliveries until October 2007. Indirectly, the linkage identified the proportion of women without children.

3.7 Reference population from the Medical Birth Registry of Norway (MBRN)

The reference deliveries were frequency sampled from non-CIA deliveries in MBRN. The proportion of deliveries was equal for each decade among CIA patients and references. This procedure created two reference groups comprising 800000 reference deliveries after diagnosis and 1000000 before (Paper 2).

3.8 Reference population from the Norwegian Population Registry

Each woman included in the NOR-DMARD study was birth-year- matched with 100 randomly selected women from the Norwegian Population Registry (n= 63100 references). Each of the references was linked to the MBRN (Paper 3).

4 Statistics

The Statistical Package for the Social Sciences for Windows software, versions 15.0, 16.0 and 17.0, (SPSS, Chicago, IL, USA) and Statistics / Data Analysis (STATA), version 10.1 and 11.0 (StataCorp, Lakeway Drive College Station, Texas, USA) were used for statistical analyses.

All hypothesis testing was conducted assuming a 0.05 significance level ($\alpha = 0.05$) and a two-sided alternative hypothesis.

4.1 Group comparisons

Group differences were explored using Pearson Chi-Square tests for categorical variables and Mann-Whitney U-test for continuous variables. In the tables, values are displayed as percentages for categorical variables and mean (standard deviation (SD)) for continuous variables.

4.2 Survival analysis

Kaplan Meier plots were used to visualise the proportion of patients without disease during the first 5 years after delivery. The curves start at time of delivery, and time to event is time to diagnosis in years (Paper 1).

4.3 Regression analyses

4.3.1 Multiple linear regression analysis

Analyses of birth weights and head circumferences were analysed in multiple linear regression analyses with covariates for gestational age, gender, maternal age and parity when relevant (Paper 2).

4.3.2 Logistic regression analysis

Associations between chronic inflammatory arthritides and adverse pregnancy outcomes (Paper 2) were assessed in logistic regression analyses with adjustments for maternal age. In addition, analyses on birth weight <2500 g and transfer to neonatal intensive care unit (NICU) were adjusted for gestational age.

4.3.3 Cox regression analysis

The proportions of incident cases of RA and OCA with diagnosis 0-24 months after delivery, were estimated by Cox multiple regression analyses with adjustments for potential confounding variables as maternal age at delivery and birth order (Paper 1).

Comparisons of inter pregnancy intervals between the first and second birth in patients and references were estimated by Cox multiple regression analyses with adjustment for maternal age at first delivery (Paper 3).

4.3.4 Poisson regression analysis

Poisson regression analysis with adjustment for population at risk was applied to estimate incidence rate ratio (IRR) of disease 0-24 versus 24-48 months post partum (Paper 1).

Poisson regression analysis was used to estimate relative fertility rates in women with RA, OCA and JIA before and after diagnosis versus references. Adjustment was done for parity at time of diagnosis when relevant (Paper 3).

4.3.5 Locally weighted Scatterplot Smoothing (Lowess Fit)

The regression analysis with Lowess Fit was used to calculate and visualise mean number of children by age of diagnosis (Paper 3).

5 Legal and ethical aspects

The NOR-DMARD study was conducted according to the ethical principles of the Declaration of Helsinki. All patients had signed a written informed consent form before enrolment in the NOR-DMARD registry.

Permission to use data from MBRN was given by the Publication Board of the MBRN. The eligible women for the data linkage received written information about the planned linkage of NOR-DMARD data with the MBRN, and they were given the opportunity to withdraw from the study. The Norwegian Data Inspectorate, the Regional Ethics Committee of Central Norway and the Norwegian Directorate of Health approved the study. Permission to use data from the Norwegian Population Registry was given by the Norwegian Tax Authorities and the Regional Ethics Committee of Central Norway.

6 General aim and specific research questions

6.1 General aim

The general aim of this thesis was to examine pregnancy related aspects of chronic inflammatory arthritides in women treated with synthetic and /or biological DMARDs.

6.1.1 Specific aims

Paper 1:

Incident cases post partum

-To investigate the proportion of incident cases of RA compared with other chronic inflammatory arthritides (OCA) during the first 24 months after delivery.

-To examine a possible peak of incident cases in the time period 0-24 months versus 25-48 months after delivery within each diagnostic group (RA and OCA).

Paper 2:

The impact of CIA on pregnancy outcomes in women treated with synthetic or biological DMARDs (Reference deliveries from the Medical Birth Registry)

-To examine possible different effects of CIA on pregnancy outcomes with separate analyses of outcomes in first birth and subsequent births in women treated with disease modifying antirheumatic drugs.

-To examine if a possible negative association with pregnancy outcomes was detectable before diagnosis of CIA.

Specific aims:

-to estimate proportion of assisted reproduction

-to estimate risk of pregnancy complications: vaginal bleeding, preeclampsia

-to estimate risk of delivery complications: induction of labour, caesarean section, excessive vaginal bleeding >500 ml during delivery

-to estimate the risk of adverse perinatal outcomes: preterm birth, SGA, mean birth weight and head circumference in relation to gestational age, major birth defects, transfer to neonatal intensive care unit (NICU) and perinatal mortality

Paper 3:

Fertility (Reference population from the Norwegian Population Registry)

To compare fertility rates in women with RA, other chronic arthritides (OCA) and JIA with birth year matched references from the general population.

To investigate the proportion of nulliparous women in each diagnostic group versus in birth year matched references

To investigate a possible association between mean number of children and age of CIA diagnosis

To examine inter pregnancy intervals in RA, OCA and JIA women versus birth year matched references

7 Summaries of results

7.1 Paper 1

Postpartum onset of rheumatoid arthritis and other chronic arthritides: results from a patient register linked to a medical birth registry

In all, 69 (37.7 %) of 183 patients with RA and 31 (28.2 %) of 110 patients with OCA developed arthritis within 2 years post partum versus 27 (14.8 %) and 20 (18.2 %), respectively, during the next two years. The relative risk (RR) (95 % CI) of incident RA versus OCA diagnosed 0-24 months post partum was 1.41 (0.92, 2.16) (p=0.10), unadjusted. Adjusted for maternal age at delivery and birth order RR (95 % CI) was 1.38 (0.89, 2.12) (p=0.14).

When we examined incident arthritis after first pregnancy separately, 30 (41.1 %) of 73 patients with RA and 14 (31.8 %) of 44 patients with OCA developed arthritis within 2 years post partum versus 9 (12.3 %) and 5 (11.3 %) during the next two years. Unadjusted, RR (95 % CI) of incident RA versus OCA diagnosed 0-24 months post partum after first delivery was 1.37 (0.73, 2.60) (p=0.32). Adjusted for maternal age at delivery RR (95 % CI) was 1.01 (0.52, 1.93) (p=0.97).

When considering all pregnancies, the Incidence Rate Ratio (IRR) (95% CI) for diagnosis 0-24 months versus 25-48 months was 1.73 (1.11, 2.70) (p=0.01) for RA and 1.05 (0.59, 1.84) (p=0.86) for OCA. The IRR was 2.23 (1.06, 4.70) (p=0.03) and 1.87 (0.67, 5.21) (p=0.22), respectively when only considering diagnosis after the first pregnancy.

The proportions of incident cases with onset 0-24 months after delivery did not reach statistically significantly difference in the comparison between RA and OCA. A statistically significantly peak incidence during 0-24 months was seen in the RA group, both when considering all pregnancies and only the first pregnancy. In the OCA group we did not observe a statistically significantly increased peak incidence, but a trend was observed after birth order one.

7.2 Paper 2

Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth

We analysed 128 first births and 151 subsequent births after diagnosis and corresponding 286 / 262 births before diagnosis and compared the results with the reference population.

Assisted reproduction was more frequent in patients with first birth compared with references, but did not reach statistically significance after adjustment for maternal age at delivery (OR 1.77 (0.69, 4.53) (p=0.23). Vaginal bleeding in pregnancy was more frequently observed in patients with first birth, adjusted OR 2.01 (1.00, 4.13) (p=0.05).

Caesarean section (CS) was observed more frequently in all patient deliveries compared to references. Adjusted OR for CS total in first birth was 1.51 (1.00, 2.29) (p=0.05) and in subsequent births 1.79 (1.19, 2.68) (0.004), and for elective CS 2.60 (1.43, 4.75) (p= 0.002) and 2.18 (1.33, 3.58) (p=0.002), respectively. A higher rate of labour induction was observed in women with first birth, adjusted OR 1.61 (1.08, 2.41) (p=0.02).

First born infants of women diagnosed with CIA were more often preterm (OR 1.85 (1.09, 3.13) (p=0.02) and small for gestational age (OR 1.60 (1.00, 2.56) (p=0.05), and they had higher perinatal mortality (OR 3.34 (1.06, 10.51) (p=0.04) compared with references. First born infants of women diagnosed with CIA also had lower mean birth weight and smaller head circumference than the references (p=0.01 and 0.05, respectively) when adjusted for gestational age, gender and maternal age at delivery.

No excess risks in pregnancies prior to CIA diagnosis were observed for any birth order compared with references, except for an increased risk of preeclampsia after adjustment for maternal age in women with subsequent births.

7.3 Paper 3

Fertility in women with chronic inflammatory arthritides

Among 631 patients 849 children were registered in MBRN. Of these, 289 children (34.0 %) were born after time of diagnosis versus 44.3 % in references. In the diagnostic groups 147 children were registered in the RA group, 89 in the OCA group and 53 in the JIA group after diagnosis.

Altogether 206 of 631 (32.6 %) patients were childless versus 26.4 % in references ($p<0.001$). Among RA patients 28.4 % (96 of 338) were nulliparous versus 24.5 % in references ($p=0.09$), 30.7 % (67 of 218) in OCA patients versus 24.5 % in references ($p=0.03$) and 57.3 % (43 of 75) in JIA patients versus 40.9 % in references ($p=0.004$).

Mean number of children was associated with age at diagnosis of CIA. Adjusted relative fertility rates in RA, OCA and JIA after diagnosis were 0.88, 0.84 and 0.84, respectively compared with references ($p<0.001$ for all diagnostic groups). Relative fertility rates in patients before diagnosis were not reduced.

We observed significantly increased inter pregnancy intervals in RA and OCA women diagnosed between first and second birth compared with references ($p=0.003$ and $p=0.002$, respectively). No differences in the inter pregnancy intervals were observed in any of the diagnostic groups compared with references when both first and second birth were after diagnosis.

8 General discussion

8.1 Study design

8.1.1 Linkage of data between the NOR-DMARD registry and MBRN

The five NOR-DMARD centers cover about 25% of the Norwegian population. Originally, the NOR-DMARD registry was designed to study effectiveness of medical treatment regimens. However, registries like NOR-DMARD may also be used for other purposes, i.e. the linkage of data to other types of registries. Data linkages between two or more registries obviously give access to more information than one single registry, but limitations have to be considered. In general, registry data are predefined in registries like NOR-DMARD and MBRN, and does not give researchers influence on data collection.

The strengths of the NOR-DMARD registry are the comprehensiveness of the data collection; all main diagnoses of inflammatory arthritides in adult patients are included as well as nearly all DMARD prescriptions. Only few patients in need of DMARDs were not

included in the NORD-DMARD registry, mostly because they refused or were considered not eligible.

A special strength of the data linkage was possibility to access information about perinatal mortality, which very few previous studies of pregnancy outcomes in CIA have had access to. Another advantage was that the data linkage indirectly revealed the proportion of nulliparous CIA women by lack of match in the MBRN.

The NOR-DMARD registry is not powered to detect rare adverse events. Thus, the linkage of NOR-DMARD and MBRN did not have power to evaluate specific birth defects or birth defects in relation to use of medication, and we could not examine pregnancy outcomes for each diagnostic group.

A crucial variable from the NOR-DMARD registry for this thesis was the information about time of diagnosis of CIA, which is not registered in the MBRN. This variable was used in all of the three publications in the thesis.

A limitation of the thesis was that NOR-DMARD lacks information about medication used during pregnancy. Most female patients planning pregnancies stop DMARDs incompatible with pregnancy several months before they attain pregnancy. In the NOR-DMARD registry patients were withdrawn when they stopped a DMARD regimen and reincluded when they started a new DMARD regimen, which means that registrations of disease activity scores were not available during pregnancy since most of the women stop DMARD medication. Another limitation was lack of variables which could have provided useful information in this work, i.e. information about marital /cohabitate status in paper 3.

In general, the use of linked data is restricted by governmental rules. Especially, information about rare outcomes must be carefully managed to avoid publishing potential identifiable data of the patient.

8.1.2 Patients

For the studies in this thesis we selected patients from the NOR-DMARD registry in the age group 18-45 years; the fertile period. Initiation of DMARD regimen was the main entry criterion for the NOR-DMARD registry, and all patients in the studies comprising this thesis had inflammatory disease treated with DMARD medication (synthetic or biologic). The parous status of the women was unknown until the data linkage between NOR-DMARD and MBRN was performed.

8.1.3 Reference populations

In Paper 2 the reference deliveries were population based, frequency sampled from non-CIA deliveries in MBRN. The proportion of deliveries was equal for each decade among CIA patients and references. By using this method we did not have to adjust for time periods of delivery in the logistic regression analyses.

In Paper 3 references were selected from the Norwegian Population Registry (NPR). Each patient (women) was birth year matched with 100 randomly selected women from NPR, and data from the NPR women were linked with data from MBRN. Date of diagnosis for each patient was linked to the corresponding references. By this method fertility rates before and after time of CIA diagnosis could be calculated in patients and references.

8.2 Methodological considerations

In Paper 1, the longitudinal case-case design made it possible to study the proportion of cases developing RA or OCA during a certain time period after delivery. It was possible to calculate incidence rate ratios, i.e. the relationship between incidence rates.

In Paper 2, we studied outcomes of pregnancies from a registry based patient cohort (NOR-DMARD) compared with reference pregnancies from a population registry based cohort (MBRN). Single births were the unit of analysis, and a cross sectional design was used. All variables pertaining to a birth were recorded during the same pregnancy.

In Paper 3, the study design was a cohort study, and for each patient 100 birth year matched references were randomly selected from the Norwegian Population Registry. We identified the number of children at a certain time point (October 2007), but with a longitudinal cohort design with sibships, meaning all pregnancies or births to a women (birth order 1, 2).

8.2.1 Role of chance

In order to quantify the degree of variability accounting for the observed results, we performed a test of statistical significance (p-value); $p \leq 0.05$, meaning that there was no more than a 5 % probability of observing a result as extreme as that observed due to chance. However, a p-value is a composite measure that reflects both the magnitude of the difference between the groups and the sample size. Consequently, even a small difference may be statistically significant if the sample size is sufficiently large. Confidence interval (CI) may also be used, which has been done in all three papers in this thesis: the analyses of incidence ratios (Paper 1), the logistic regression analyses of pregnancy outcomes (Paper 2) and the analyses of relative fertility rates (Paper 3). The CI provides the range where the true magnitude of effects is. The effect of the sample size can be ascertained from the width of the confidence interval itself. The narrower the confidence interval, the less variability is present in the estimate of effect, reflecting a larger sample size. The wider the confidence interval, the greater the variability in the estimate of effect, and the smaller the sample size (271).

8.2.2 Validity and reliability

Validity is divided into internal validity (the degree to which the results of an observation are representative for the particular group of people being studied) and external validity (the degree to which the results of a study apply to people not in it; generalisability).

8.2.2.1 Internal validity

Internal validity may be reduced by bias and confounding. Bias is the possibility that some aspects of the design of a study have introduced an error into the results (i.e. selection bias). Confounding can occur when mixing of effects between exposure, the disease and a third factor that is associated with the exposure and independently affects the risk of developing disease (271). Thus, a confounder must be associated to both the exposure and the disease. Confounding can lead to either the observation of apparent differences between study groups when they do not truly exist or, conversely, the observation of no difference when they do exist. A potential confounder will be an actual confounder if adjustment for the variable results in a change in the estimate of the association between the exposure and the disease.

In this thesis data were collected from two sources, the NOR-DMARD registry and the MBRN. The disease scores (SJC, DAS28), information about RF positivity, erosive disease and time of diagnosis were performed, obtained and filled in by trained study nurses or doctors. Midwives fill in reports for all deliveries in Norway and send them to MBRN. Overall, the internal validity of the data from NOR-DMARD and MBRN is considered as good.

8.2.2.2 External validity

The patients of interest were all treated with synthetic and/or biological DMARDs. Thus, the results and conclusions from Article 2 and 3 can not be extrapolated to a general population of CIA women, from the mildest to the most diseased women, in which only a proportion of the patients are using DMARDs.

8.2.3 Random errors

Random errors lead to loss of precision. Precision can be improved by increasing the sample size. Small samples in some of the subgroups may represent a problem in a few analyses, i.e. the analyses of inter pregnancy intervals in Paper 3, the estimate of IRR in the OCA group in Paper 1 and for some estimates of Odds Ratio of adverse pregnancy outcomes in Paper 2. However, in most analyses the sample sizes were of adequate size.

8.2.4 Selection bias

Selection bias may occur if an exposed individual with adverse outcome is more likely to be included and vice versa. However, a strength of the NOR-DMARD registry is the selective inclusion restricted to only DMARD prescriptions, i.e. conventional DMARDs as well as biologics.

Usually, DMARDs are more widely used in patients with RA than in other chronic arthritides. This possible bias may have contributed to fewer incident cases in the OCA group (Paper 1).

Eligible women received written information about the planned linkage of NOR-DMARD and MBRN data. Fourteen women opted out, and we do not know about these

women were childless or had experienced any serious pregnancy outcomes. Over all, these women constituted a small proportion (2 %) of all eligible women.

8.2.5 Recall bias

Some mothers may underreport their rheumatic disease. If a possible association between adverse pregnancy outcome and rheumatic disease is well known, underreporting would most likely apply to women without an adverse pregnancy outcome. This may cause inflated relative risk estimates. However, the data on maternal disease were registered independently of births and could not cause recall bias.

8.2.6 Confounders

A confounding variable is associated with exposure and not an intermediate link in causation (271). We have adjusted for possible confounders such as maternal age at delivery and gestational age.

Maternal age at delivery was a confounding factor for assisted reproduction (Paper 2). Gestational age and maternal age at delivery were confounding factors in the analyses of birth weight < 2500 gram in first born children of mothers diagnosed with CIA (Paper 2).

Due to lack of data on socioeconomic status and educational level in the reference groups (Paper 2 and Paper 3), we were unable to adjust for these variables in the logistic regression analyses. Norway is a socioeconomically quite homogenous nation compared with many other countries. All pregnant women in Norway are offered pregnancy care free of charge and with a participation rate close to 100 %. However, previous studies have shown that socioeconomic status influences the outcome of musculoskeletal disease, including RA, in Norway (272). Furthermore, it has been shown that fertility rates of unemployed women are lower than those of employed women in Norway (273).

It is known that lifestyle factors including smoking, are associated with infertility (274). Even in Norway smoking is associated with lower socioeconomic status (275). Smoking habits were not adjusted for due to incomplete data among patients and references (Paper 2) or lack of data among references (Paper 3). Smoking habits have been voluntary registered in MBRN since the new form from Dec 1 1998, but most of the examined pregnancies before diagnosis of CIA were from before 1998. The frequency of smoking

during pregnancy has been reduced substantially from 30 % in 1980ies to 10-15 % in 2000-05 (276-280).

8.2.7 Misclassification and ascertainment of diagnoses

The patients included in clinical trials should be true representatives of the population of interest. Thus, classification criteria in clinical trials, as opposed to diagnostic criteria, are characterised by high specificity. Some commonly used classification criteria are the 1987 ACR criteria for RA (38), the 1984 modified New York criteria for AS (73) and the Moll and Wright criteria for PsA (39). For PsA, the CASPAR criteria (57) have been developed to increase the specificity, and new diagnostic criteria for both RA and AS have been published (2;76;77). The purpose of the new classification criteria is to include and classify patients in an early phase of the disease.

The NOR-DMARD registry was originally designed with the main focus on patients with RA, and the date of fulfilling the ACR criteria was recorded. Specific information on fulfilment of the classification criteria for AS, PsA, JIA and UA were not recorded in the NOR-DMARD registry. However, all patients were classified according to the ICD-10 system, i.e. based on the diagnoses given by rheumatologists. Although the modified New York criteria and the Moll and Wright criteria were not formally used, all patients were diagnosed by experienced rheumatologists, and the diagnoses are usually based on these criteria.

Adult patients with JIA were classified as JRA or JCA according to the changing terms (Table 4).

The group of patients with UA was classified according to the ICD-10 system. All had active inflammatory arthritis and were starting synthetic and/or biological DMARDs, but some of these patients may have had arthritis secondarily to additional diseases; i.e. inflammatory bowel disease. We used the initial diagnosis at time of inclusion in the NOR-DMARD registry, but some of the patients may have developed characteristics for other disease groups later in life. In about 20 % of patients with PsA the rheumatological manifestation precede the onset of cutaneous lesions (281). The new classification criteria for PsA (CASPAR) include PsA without manifest psoriatic skin disease (PsA sine psoriasis), but patients may previously have been misclassified as UA. It is also known that a proportion of patients with UA will develop RA (282).

9 Interpretation and comparison with other studies

9.1 Post partum onset of rheumatoid arthritis and other chronic arthritides: results from a patient register linked to a medical birth registry (Paper 1)

It has been known for a long time that RA is commonly diagnosed post partum, but this issue has not been extensively studied for other arthritides (PsA, AS, UA). Due to the low incidence of RA, few cases occur simultaneously or just after pregnancy. Consequently, the previous studies were mainly of a matched case-control design (214;222;223). Every study design carries the risk of introducing its own type of bias, and a strength of our study is that we have confirmed the increased incidence of arthritis post partum in a different setting. In previous studies (214;222;223) it was demonstrated that the increased incidence of RA after delivery was accompanied by a lower incidence during pregnancy. This suggests that the increased incidence of RA after delivery may be due to delayed occurrence of RA until after delivery (283). Previous studies have estimated time of disease onset (first symptom), and demonstrated a peak incidence during the first year after delivery. We studied time of diagnosis, which is probably more precise compared to time of symptom onset due to the insidious start of disease. Usually, there will be a delay between disease onset and diagnosis. This methodological difference may explain why we found an excess of incident cases even in the second year after delivery. Our study was not able to determine whether the observed increased incidence after delivery is a true increased incidence or a consequence of delayed onset until after delivery.

When analysing all incident cases, we found that both RA and OCA were frequently diagnosed during the first two years after delivery, but a higher proportion of incident cases were observed in the RA group. However, the disease risk did not reach statistically significance between the groups. We found a statistically significantly higher incidence rate at 0-24 months versus 25-48 months post partum in the RA group, but not in the OCA group.

When analysing incident cases after birth order one separately, the disease risk did not reach statistically significance between RA and OCA. We found a statistically significantly more frequent onset of disease during 0-24 months versus 25-48 months post partum in RA. For OCA the point estimates of IRR were numerically higher after the first delivery than after the second and additional deliveries, but did not reach statistical significance. A similar trend

has been reported in two other studies of RA patients (13;223). The previous studies also indicated a higher risk of developing arthritis after first birth.

Hazes et al found a lower risk of RA in women who had ever been pregnant (13). Also, the earlier the first pregnancy occurred, the lower was the risk of developing RA (13). Adjustments for birth order and maternal age at delivery in the Cox regression analyses did not significantly influence the relative risks for developing disease 0-24 months post partum in our study.

Overall, our results indicate that a higher incidence of arthritis post partum may not be unique for RA. Although a trend was observed after birth order one, it remains to demonstrate that there is a peak incidence in OCA post partum.

9.2 Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth (Paper 2)

Previous studies of pregnancy outcomes in women with CIA versus a reference population have used different study designs and different methods for data collection, which make comparisons of the results difficult. Three studies were population based with retrospective designs (234;239;240). Another study was population based with a cross sectional design (233). Three studies have used case-control design (16;235;244), and three other studies were of a prospective design (152;232;246). Data collection has often been based on interviews of CIA women about pregnancy complications. This method may introduce recall bias. However, repeated observed similar findings in studies of different designs may strengthen the observations. In most studies the CIA disease status (i.e. level of disease activity, use of treatment) have been poorly defined, and the patient cohorts may have been heterogeneous, from the mildest to the most diseased women, including patients with and without use of DMARDs. Further, some studies have not defined deliveries before or after diagnosis of CIA.

It has been suggested that RA and other autoimmune diseases have a preclinical autoimmune activity and a long prodromal phase, which may be of importance for pregnancies (229-231;284-288). Thus, from this perspective it is of particular interest to examine pregnancy outcomes before clinical onset and diagnosis of CIA. An advantage of our study was the possibility to analyse separately deliveries before and after diagnosis. Separate analyses of pregnancy outcomes before diagnosis has, as far as we know, only been done in two previous studies (236;246). Both our current data and previous reports indicate that the disease effect on pregnancy outcomes does not occur before the disease has been diagnosed.

Anti-CCP was included among recorded variables in NOR-DMARD in 2006. The majority of the patients in the studies comprising this thesis were included before 2006, and we did not have information about anti-CCP status in our analyses. We can not exclude that preclinical autoimmune activity is different in subgroups of patients with antibodies predicting RA (285-287) with possible influence on pregnancy outcomes. This question remains to be examined for pregnancy outcomes before disease onset.

An advantage of our study was the possibility to do separate analyses on outcomes of first births before and after the diagnosis of a rheumatic disease. This approach has not been applied in CIA pregnancies previously. No differences in pregnancy outcomes were observed between cases and references in first births before diagnosis. The majority of the observed differences in outcomes between patients and references were related to first birth in women diagnosed with CIA. However, increased rates of CS, both total and elective, were related to all births after diagnosis of CIA compared with references.

Assisted reproduction

Nulliparous CIA women had significantly more assisted reproduction compared with references in the unadjusted analysis. Maternal age at delivery was a confounding factor for assisted reproduction. Thus, adjusted, the difference was no longer statistically significant. The frequency of assisted reproduction has not been reported in CIA women before. The patient group in our study was older than references at time of first delivery, which may reflect that these women had experienced problems with attaining pregnancy. Reduced fertility has been reported for CIA women (258;259). A limitation of our study is that we did not know how many women who had tried assisted reproduction and not attained pregnancy.

Vaginal bleeding

Patients had a twofold higher risk of vaginal bleeding compared with references in pregnancies related to first birth. Use of NSAIDs among the patients during pregnancy might be one cause of this observed increased risk. No previous reports exist on a possible relation between use of NSAIDs and bleeding in pregnancy. Such use is easy to underestimate because patients may limit their report to prescribed drugs and not include over-the counter purchases.

We did not observe any excess risk of bleeding during delivery. Patients are advised not to use NSAIDs after 32 gestational weeks, and this may explain why we did not observe higher risk of bleeding during delivery.

Unfortunately, our study had insufficient information about the use of medication during pregnancy since most women stopped DMARD medication before they achieved pregnancy and were withdrawn from the NOR-DMARD-registry.

Labour induction and Caesarean section (CS)

Increased use of labour induction was observed in nulliparous patients compared with references. Only one previous study has reported a higher rate of labour induction in CIA women, but not specifically in relation to first birth (240). Increased CS rates have been reported from several studies and from different geographic areas (233-235;240). Our study confirmed significantly increased rates of CS, both elective and total, related to all deliveries after a diagnosis of CIA. We found a doubled rate of elective CS, both in first and subsequent births after diagnosis. Placental dysfunction, cephalopelvic disproportion and combined causes constituted each one third of the indications. Arthritic women may have stiffness and pain indicating inflammation, and obstetricians may choose to do CS because they anticipate problems during delivery. Women with AS had the highest occurrence of elective CS (25 %) among the different diagnostic groups, which may be due to inflammation and / or ankylosis in the sacroiliac joints and the lumbal spine, and vaginal birth may be especially difficult to women with AS.

Interestingly, we found no increase in acute CS rate in patients with CIA. The two dominating reasons for acute CS in Norway are labour dystocia and fetal distress (289). We did not observe differences in labour dystocia between patients and references. In Norway, vaginal birth after one caesarean delivery (VBAC) has been the rule for many years. We do not think this rule is different for women diagnosed with CIA, but we were not able to adjust for this possibility since we lacked information about sibships among the references.

The newborn

The risks of preterm delivery and SGA were higher for first born infants of mothers diagnosed with CIA compared with references, but not for infants of patients with subsequent births. Previous studies have reported increased risks of both preterm delivery and SGA without relating this to birth order (234;235;238).

The proportion of infants with birth weight less than 2500 gram was similar between patients and references, both for first born children and subsequent birth orders. However, we observed small, but statistically significantly differences, crude and adjusted, in mean birth weights and head circumferences in first born infants of women diagnosed with CIA, but not

in infants of subsequent births after diagnosis. Birth weight and head circumference may be related to placental function (290-292), but also to other factors, i.e. genetically. One previous study has reported that both high level of disease activity and use of low doses of prednisone during pregnancy may reduce birth weight (152). Unfortunately we did not have data of disease activity scores during pregnancy since most women were withdrawn from the NOR-DMARD registry during pregnancy.

We found no differences with regard to major congenital malformations between cases and references in contrast to previous reports (237;239). We did not have power to examine specific birth defects, post perinatal mortality or outcomes in each diagnostic group separately. Three of four children reported with perinatal deaths were first born children of mothers diagnosed with CIA. The perinatal mortality rate was 3 times higher in the children of CIA women compared with references. The result was statistically significant, but with wide confidence intervals and should be interpreted with caution. In a retrospective study of RA women, excess of perinatal deaths were reported in infants of mothers who subsequently developed RA after delivery (237), but has not been reported among infants of mothers diagnosed before delivery.

The observed higher frequency of events in first births may be accounted for by selective fertility after a CIA diagnosis, since women with the highest disease activity would most likely have only one child. However, all women in this study had active disease treated with synthetic or biological DMARDs, and were presumable among CIA women with highest disease activity. Another hypothesis is that immunological processes of the inflammatory disease influence first birth more than later pregnancies. Further studies on outcomes of first births in women diagnosed with CIA are needed to confirm our findings.

9.3 Fertility in women with chronic inflammatory arthritides (Paper 3)

In our study of fertility in women diagnosed with CIA, fertility was defined as the actual production of offspring. Previous studies have reported inconsistent observations about fertility in CIA women compared with references. There may be several reasons for this. Most studies have been restricted to women with RA and the patient cohorts have often been poorly defined and possibly heterogeneous. Other studies have small sample sizes (260). Further, selection bias in both cases (only cases who plan pregnancy) and controls (friends, neighbours, relatives, newspaper advertising) may have influenced the results.

An advantage of the present study was the birth year matched references from the National Population Registry. We did not have information about educational level of the references, but educational level was similar in nulliparous (childless) and parous (para 1+) patients. The Norwegian population comprises about 95 % Caucasians and is socioeconomically a rather homogenous population compared with many other countries. The country has public health care and social security systems covering all citizens and which are particularly beneficial to families with small children. However, we can not exclude possible socioeconomic differences between patients and references biasing our results.

Another advantage of our study was that we examined a defined patient cohort constituting the most severely diseased women treated with synthetic and / or biological DMARD. However, our results should be interpreted with caution and may not be generalized to all CIA women.

Nulliparity

Four previous studies of RA patients, one also including AS patients, have estimated fertility by including nulliparous patients (258;260;261;293). Nulliparity was in our study defined as lack of match in MBRN. We can not exclude that some of these women might have delivered in another country, but this possibility is probably minimal. Inclusion of nulliparous patients and references is therefore a strength of our study. A higher proportion of women diagnosed with CIA were nulliparous compared with age matched references. When we examined each diagnostic group separately, the proportion of nulliparity reached statistical significance for patients diagnosed with OCA and JIA, but not for RA women. Only one of the previous publications of nulliparity in RA women showed a statistically significantly higher rate compared with references, but three studies showed an increased trend among the patients (258;260;293). The study including patients with RA and AS showed no difference in nulliparity between patients and references (261). The very high proportion of nulliparous women among both JIA patients and their references in our study was most probably due to the younger age of this group (mean age of about 30 years at time of data linkage). Nulliparity has been discussed as a risk factor for RA (13;25;223;258;293;294), but to our knowledge nulliparity has not been discussed as a possible risk factor for OCA.

In the present study we did not know how many of the nulliparous women who had tried to become pregnant, which is a limitation of the study. We also lacked information about use of contraceptives among patients and references. All patients were using DMARDs. Since

many DMARDs are incompatible with pregnancy, the patients are advised to use contraceptives regularly, which might have introduced a bias in our results.

Previous studies have discussed several causes of nulliparity in women diagnosed with CIA. Non-remitting disease and functional impairment have been reported to reduce the wish for children in women with CIA (245;257). Health status may influence sexual activity and increased levels of fatigue, pain and mental distress have been reported among factors with negative impact on sexual activity in patients with RA (295-297). Also, severe disease flares have been reported to lower sexual activity more than physical handicap (298;299). Further, some patients have expressed concern about risk of arthritic disease in offspring, which may contribute to reduced fertility rates (300). Women with arthritis may also be concerned about their ability to physically take care of a child (300). Previous population based studies have reported an overrepresentation of various gynaecological disorders and surgery of the genital tract in women with rheumatic diseases (301;302) which could also contribute to a higher proportion of nulliparous women. In the present study we did not have data of associated gynaecological disorders.

Fertility rates

Overall, we observed that the patients mean number of children was associated with age at time of CIA diagnosis. This observation is also in accordance with another study (257). Women diagnosed after 30 years of age had a mean number of children comparable to the reference group, most probably because women diagnosed in the fourth decade have delivered the desired number of children before disease onset. We did not observe any differences in relative fertility rates in RA and OCA women compared with references before disease onset. Our findings contrasts two previous publication where a lower fertility rate was reported prior to disease onset in RA (258;293). Especially, a lower fertility rate was concentrated in a rheumatoid factor subgroup of patients (258). We did not examine rheumatoid factor positive subgroups due to small numbers. Additionally, the proportion of rheumatoid factor positive patients was low in the OCA group. In the two previous studies, selection of controls from the same geographical area as the patients may have biased the results.

RA, OCA and JIA women had significantly lower relative fertility rates after diagnosis. These observations are in agreement with previous studies (253;257;258;293). A possible contributing explanation to the reduced relative fertility rates we observed may be a heavy disease burden of the study population. The JIA group might be even more selected as

JIA patients in need of DMARDs constitutes about 50 % of the patient population diagnosed in childhood, and most of them have polyarticular disease (104).

We observed a higher proportion of CS in patients compared with references (Article 2), and this is also reported in previous studies (233-235;240). A Norwegian study has reported that women with CS at first delivery will have fewer children than a woman who starts with a vaginal birth (303). This may also contribute to the observed reduced number of children in the patient group.

Inter pregnancy interval

We observed an increased inter pregnancy interval for RA and OCA women diagnosed between first and second birth, which indicate that women diagnosed after first birth may postpone a second pregnancy until the disease is better controlled. To our knowledge no previous studies have reported this interval before.

No differences in inter pregnancy intervals were observed for women with all births after diagnosis. This is in contrast to another study where an increased interval after diagnosis was reported (253). These findings may indicate that improved treatment options during the last decade give better disease control and opportunities to continue to a second pregnancy. Our findings could also indicate that women with all births after diagnosis want to have their children within a shorter time period. Additionally, RA patients continuing to a second pregnancy were significantly older than the references at time of first delivery, giving a shorter reproduction period. This observation is in accordance with a Norwegian population based cohort study (253), but in contrast to observations in a Canadian case-control study of women with recent onset RA (260). Different study populations and study designs might explain the different results. The Canadian study examined women with new onset RA (within 3 years) and had a small sample size.

10 Conclusions and implications

10.1 Answers to research questions

10.1.1 Paper 1

- The proportions of incident cases with onset 0-24 months after delivery were not statistically significantly different between RA and OCA

- A statistically significant peak in incident cases 0-24 months versus 25-48 months post partum was seen in the RA group, both when considering all deliveries and only the first delivery

- A peak incidence was also observed in the OCA group after the first pregnancy 0-24 months versus 25-48 months post partum, but the result did not reach statistically significance.

10.1.2 Paper 2

- All negative diverging pregnancy outcomes in patients versus references were observed in relation to first birth after diagnosis:

    - A statistically significant excess of vaginal bleeding was observed

    - A statistically significantly higher risk of labour induction was observed.

    - Statistically significantly lower mean birth weight and smaller head circumference were observed.

- Statistically significantly higher rates of preterm deliveries and SGA children were observed.

- A statistically significantly higher rate of perinatal mortality was observed.

- A statistically significantly higher risk of CS (total and elective) was related to all births in women diagnosed with CIA.

- Pregnancy outcomes before diagnosis did not differ from the reference population.

10.1.3 Paper 3

- A statistically significantly higher proportion of nulliparous women were observed for all CIA women compared with birth year matched references.

- The proportion of nulliparous women reached statistical significance within the diagnostic groups for OCA and JIA, but not for RA compared with age matched references.

- The mean number of children was associated with age at time of CIA diagnosis.

- Relative fertility rates were statistically significantly reduced for all diagnostic groups after diagnosis,

- Relative fertility rates were not statistically significantly different between cases and references before diagnosis for any of the diagnostic groups.

- Inter pregnancy interval was statistically significantly increased in women with first birth before and second birth after diagnosis of CIA.

- Inter pregnancy interval was not statistically significantly different between patients and references when first and second birth were after diagnosis of CIA.

10.2 Clinical implications

Our study of women with CIA aged 18-45 years and treated with synthetic or biological DMARDs has shown that not only RA, but also other chronic arthritides frequently are diagnosed the first two years after delivery. Our study indicates that serious rheumatic diseases needing treatment with DMARDs, may start post partum. Doctors should pay special attention to women with onset of all kinds of arthritic symptoms in this period of life.

First births were associated with more negative outcomes for women diagnosed with CIA and their infants compared with references. For clinician this finding indicates particular awareness and regular controls when monitoring CIA women in their first pregnancy. No previous studies have examined outcomes of first births in women diagnosed with CIA separately, and our study needs confirmation. Our study indicated an increased risk of perinatal mortality in first born children of women diagnosed with CIA. However, we did not find other serious adverse outcomes for the children of the patients. Overall, our findings indicate that women with CIA should not be advised against having children because of possible risks of serious adverse outcomes. The recurrent observations of a higher rate of CS in CIA women after diagnosis should lead to obstetric attention to indications of CS in these women.

Our observation that most negative outcomes were associated with first births, also generate a new hypothesis that immunological processes of the inflammatory disease may influence first birth more than later births. Pregnancy outcomes were not affected for any birth order before onset of CIA, but we could not exclude that specific subgroups of patients may be affected in pregnancies. Future studies should focus on subgroups of patients i.e. anti-CCP positive / negative women versus references to examine if certain subgroups have higher risks for adverse pregnancy outcomes before manifest clinical disease.

Starting a family is of central importance in many people's life, also in CIA patients (300), however, our study indicates that women with CIA have reduced family size. We also observed a higher proportion of childless women in each of the diagnostic groups compared

with birth year matched references. We were not able to answer how many of the childless women had tried to become pregnant, and future studies should also take childbearing choices into account. We examined patients with high disease activity scores and reduced functional status. Thus, our results of pregnancy outcomes and reproduction can not be generalised to all women with CIA. However, we think that more women with CIA would profit from professional, individual advice before pregnancies.

Several aspects of reproduction concern women with CIA, and evidence based knowledge is necessary to counsel patients in these questions. After the introduction of biological DMARDs, clinicians are frequently asked about the impact of these medications on pregnancy. Improvements in the medical treatment of arthritides may not immediately lead to increasing fertility rates, but future trends will be of interest. Another aspect of future attention may be that women in Western countries more frequently postpone their first pregnancy until the fourth decade of life. Consequently, the proportion of patients with CIA becoming pregnant after disease onset will increase, which will have impact on the need for counselling and monitoring of these patients.

11. Erratum

Paper 1: Patients, Materials and Methods: Setting (page 332): data of women from the NOR-DMARD registry linked with MBRN should read 631

12. References

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Appendix

Formula DAS28 (0-9,4) ((304)0.56√28TJC + 0.28√28SJC + 0.70 LnESR +0.014PGA

DAS28 ≤ 2,6 = remission

Notification forms for the Medical Birth Registry of Norway in use from 1967-1998 and from Dec 1, 1998

Registreringsskjema fra 1967-1998

STATENS HELSETILSYN
Postboks 8128 Dep.
0032 OSLO

Medisinsk registrering av fødsel

Sendes 9. dag etter fødselen til fylkeslegen (stadsfysikus) i det fylket der moren er bosatt.

Merk: Det skal fylles ut blankett for hvert barn (foster). Dør barnet etter fødselen, skal det også fylles ut legeerklæring om dødsfall, og/eller dødsfallet meldes til skifteretten (lensmannen).

Barnet

Barnet var: 1 ☐ Levende født 2 ☐ Dødfødt foster | Født dag, mnd., år | Klokkeslett | Personnr. | Skriv ikke her

1 ☐ Enkel 2 ☐ Tvilling 3 ☐ Trilling 4 ☐ Firling | Kjønn: 1 ☐ Gutt 2 ☐ Pike

Etternavn, alle fornavn (bare for levendefødte)

Fødested. Navn og adresse på sykehuset/fødehjemmet | Kommune

Faren

Etternavn, alle fornavn | Født dag, mnd., år | Bostedskommune

Moren

Etternavn, alle fornavn. Pikenavn | Født dag, mnd., år

Bosted. Adresse | Kommune

Ekteskapelig status: 1 ☐ Ugift 6 ☐ Samboende 2 ☐ Gift 3 ☐ Enke 4 ☐ Separert 5 ☐ Skilt | Ekteskapsår (gifte)

Antall tidligere fødte (før denne fødselen)	Levende fødte	Av disse i live	Dødfødte

Er moren i slekt med faren? 1 ☐ Nei 2 ☐ Ja. Hvilket slektskapsforhold:

Morens helse før svangerskapet

1 ☐ Normal 2 ☐ Sykdom (spesifiser):

Siste menstruasjons første blødningsdag

Morens helse under svangerskapet

1 ☐ Normal 2 ☐ Komplikasjoner (spesifiser):

Ble fødselen provosert

1 ☐ Nei 2 ☐ Ja

Inngrep under fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Inngrepet utført av: 1 ☐ Lege 2 ☐ Jordmor

Komplikasjoner i forbindelse med fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Fostervann, placenta og navlesnor

1 ☐ Normalt 2 ☐ Patologisk (spesifiser):

Barnets tilstand

Bare for levende fødte. Tegn på asfyksi? 1 ☐ Nei 2 ☐ Ja | Apgarscore etter 1 min. | etter 5 min.

For levende fødte og dødfødte. Tegn på medfødt anomali, på skade eller sykdom? 1 ☐ Nei 2 ☐ Ja. Hvilke:

Lengde (i cm)	Hode-omkr. (i cm)	Vekt (i g)	For døde innen 24 timer Livet varte i	Timer	Min

For dødfødte. Døden inntrådte 1 ☐ Før fødselen 2 ☐ Under fødselen
Dødsårsak:

Seksjon? 1 ☐ Nei 2 ☐ Ja

Alvorlige arvelige lidelser i slekten

1 ☐ Nei 2 ☐ Ja Sykdommens art og hos hvilke slektninger:

Sted (sykehusets stempel) _____ Dato _____ Jordmor _____ Lege _____

IK - 1002.

50 000. 5.96. SSM GRAFISK

Melding om avsluttet svangerskap etter 12. uke – Fødsel, dødfødsel, spontanabort

Se utfyllingsinstruks for blanketten på baksiden

MFR

Sosial- og helsedirektoratet

A – Sivile opplysninger

Institusjonsnr: | Institusjonsnavn

Fødsel utenfor institusjon: ☐ Hjemme, planlagt ☐ Hjemme, ikke planlagt ☐ Under transport ☐ Annet sted

Mors fulle navn og adresse

Pikenavn (etternavn):

Mors sivilstatus ☐ Gift ☐ Ugift/enslig ☐ Annet ☐ Samboer ☐ Skilt/separert/enke

Slektskap mellom barnets foreldre? ☐ Nei ☐ Ja Hvis ja, hvorledes:

Mors bokommune

Fars fødselsdato | Fars fulle navn

Mors fødselsnr:

B – Om svangerskap og mors helse

Siste menstr. 1. blødn.dag ☐ Sikker ☐ Usikker

Mors tidligere svangerskap/fødte Levende-fødte | Dødfødte (24. uke og over) | Spontanabort/Død-fødte (12.–23. uke) | Spontanaborter (under 12. uke)

Ultralyd utført? ☐ Nei ☐ Ja UL termin:

Annen prenatal diagnostikk? ☐ Nei ☐ Ja, angi type:

Patologiske funn ved prenatal diagnostikk? ☐ Nei ☐ Ja, hvis bekreftet – spesifiser

Spesielle forhold før svangerskapet: ☐ Intet spesielt
☐ Astma ☐ Allergi ☐ Tidligere sectio ☐ Res. urinveisinfeksjon ☐ Kronisk nyresykdom ☐ Kronisk hypertensjon ☐ Reumatoid artritt ☐ Hjertesykom ☐ Epilepsi ☐ Diabetes type 1 ☐ Diabetes type 2 ☐ Annet, spesifiser i «B»

Regelmessig kosttilskudd: ☐ Nei Før sv.sk. I sv.sk.
Multivitaminer ☐ ☐
Folat/Folsyre ☐ ☐

Spesifikasjon av forhold før eller under svangerskapet:

Spesielle forhold under svangerskapet: ☐ Intet spesielt
☐ Blødning < 13 uke ☐ Blødning 13–28 uke ☐ Blødning > 28 uke ☐ Glukosuri ☐ Svangerskapsdiabetes ☐ Hypertensjon alene ☐ Preeklampsi lett ☐ Preeklampsi alvorlig ☐ Preeklampsi før 34. uke ☐ HELLP syndrom ☐ Eklampsi ☐ Hb < 9.0 g/dl ☐ Hb > 13.5 g/dl ☐ Trombose, beh. ☐ Infeksjon, spes. i «B»

Legemidler i svangerskapet: ☐ Nei ☐ Ja – spesifiser i «B»
☐ Annet, spesifiser i «B»

Røyking og yrke
Forutsetter mors samtykke – se rettledning på baksiden
☐ Skriftlig orientering gitt til mor ☐ Samtykker ikke for røykeoppl.

Røykte mor ved sv.sk. begynnelse? ☐ Nei ☐ Daglig ☐ Av og til Ant. sig. dagl.:

- ved sv.sk. avslutning? ☐ Nei ☐ Daglig ☐ Av og til Ant. sig. dagl.:

Mors yrke ☐ Samtykker ikke for yrkesoppl. ☐ Ikke yrkesaktiv ☐ Yrkesaktiv heltid ☐ Yrkesaktiv deltid

Mors yrke

Bransje:

C – Om fødselen

Leie/presentasjon: ☐ Normal bakhode ☐ Sete ☐ Tverrleie ☐ Avvikende hodefødsel ☐ Annet, spesifiser i «C»

Fødselstart: ☐ Spontan ☐ Indusert ☐ Sectio

Ev. induksjons-metode: ☐ Prostaglandin ☐ Oxytocin ☐ Amniotomi ☐ Annet, spesifiser i «C»

Indikasjon for inngrep og/eller induksjon ☐ Komplikasjoner som beskrevet nedenfor ☐ Fostermisdannelser ☐ Overtid ☐ Annet, spesifiser i «C»

Inngrep/tiltak ☐ Ingen ☐ Utskj. tang, hodeleie ☐ Annen tang, hodeleie ☐ Vakuumekstraktor ☐ Episitomi

Fremhj. ved setefødsel: ☐ Vanlig fremhjelp ☐ Uttrekning ☐ Tang på etterk. hode

Sectio: Var sectio planlagt før fødsel? ☐ Nei ☐ Ja
☐ Utført som elektiv sectio ☐ Utført som akutt sectio

Spesifikasjon av forhold ved fødselen/andre komplikasjoner

Komplikasjoner ☐ Ingen ☐ Vannavg. 12–24 timer ☐ Vannavg. > 24 timer ☐ Mekaniske misforhold ☐ Vanskelig skulderforløsning ☐ Placenta previa ☐ Abruptio placentae ☐ Perinealruptur (grad 1-2) ☐ Sphincterruptur (gr. 3-4) ☐ Blødn.> 1500 ml, transf. ☐ Blødning 500–1500 ml ☐ Eklampsi under fødsel ☐ Navlesnorfremfall ☐ Truende intrauterin asfyksi ☐ Risvekkelse, stimulert ☐ Langsom fremgang ☐ Uterus atoni ☐ Annet:

Anestesi/analgesi: ☐ Ingen ☐ Lystgass ☐ Petidin ☐ Epidural ☐ Spinal ☐ Pudendal ☐ Infiltrasjon ☐ Paracervical blokk ☐ Narkose ☐ Annet:

Placenta: ☐ Normal ☐ Hinnerester ☐ Ufullstendig ☐ Infarkter ☐ Koagler ☐ Utskrapning ☐ Manuell uthenting Placenta-vekt

Navlesnor ☐ Normal ☐ Velamentøst feste ☐ Marginalt feste ☐ Karanomalier ☐ Omslyng rundt hals ☐ Annet omslyng ☐ Ekte knute Navlesnor-lengde:

Fostervann ☐ Normal ☐ Polyhydramnion ☐ Oligohydramnion ☐ Misfarget ☐ Stinkende, infisert ☐ Blodtilblandet

Komplikasjoner hos mor etter fødsel ☐ Intet spesielt ☐ Feber > 38.5° ☐ Trombose ☐ Eklampsi post partum ☐ Mor overflyttet ☐ Mor intensivbeh. ☐ Sepsis ☐ Annet, spesifiser

D – Om barnet

Fødselsdato **Klokken**

Pluralitet ☐ Enkeltfødsel ☐ Flerfødsel For flerfødsel: Nr. Av totalt

Kjønn ☐ Gutt ☐ Pike Ved tvil spesifiser i «D»
For dødfødte: ☐ Usikkert kjønn

Barnets vekt: Hode-omkrets:

Total lengde: Eventuelt sete–issemål:

Apgar score: 1 min 5 min

Barnet var: ☐ Levendefødt ☐ Dødfødt/sp.abort Oppgi dødsårsak i «D»

For dødfødte: ☐ Død før fødsel ☐ Død under fødselen ☐ Ukjent dødstidspunkt

For dødfødte, oppgi også ☐ Død før innkomst ☐ Død etter innkomst

Levendefødt, død innen 24 timer Livet varte: Timer Min.

Død senere (dato): **Klokken**

Overfl. barneavd. ☐ Nei ☐ Ja Dato:

Overfl. til

Indikasjon for overflytting: ☐ Respirasjonsproblem ☐ Prematur ☐ Medfødte misd. ☐ Perinatale infeksjoner ☐ Annet, spesifiser

Neonatale diagn.: (Fylles ut av lege/pediater) ☐ Intet spesielt
☐ Hypoglyk. (< 2 mmol/l) ☐ Medf. anemi (Hb < 13.5 g/dl) ☐ Hofteleddsdyspl. beh. m/pute ☐ Transit. tachypnoe ☐ Resp. distress syndr. ☐ Aspirasjonssyndrom ☐ Intrakraniell blødning ☐ Cerebral irritasjon ☐ Cerebral depresjon ☐ Abstinens ☐ Neonatale kramper ☐ Konjunktivitt beh. ☐ Navle./hudinf. beh. ☐ Perinat. inf. bakterielle ☐ Perinat. inf. andre ☐ Fract. claviculae ☐ Annen fraktur ☐ Facialisparese ☐ Plexusskade

Behandlingskoder: ☐ Systemisk antibiotika ☐ Respiratorbeh. ☐ CPAP beh.

Icterus behandlet: ☐ Lysbehandlet ☐ Utskifting

Årsak:
☐ ABO uforlik.
☐ RH immunisering
☐ Fysiologisk
☐ Annen årsak

Tegn til medfødte misdannelser: ☐ Nei ☐ Ja

Spesifikasjon av skader, neonatale diagnoser og medfødte misdannelser – utfylles av lege

☐ **Kryss av hvis skjema er oppfølgingsskjema**

Jordmor v/fødsel:

Jordmor v/utskrivning:

Lege:

Lege barsel/barneavd:

Utskrivningsdato

Mor:

Barn:

Protokollnr.: /

IS-1002 23011. 07.06. Andvord Grafisk.

Paper I

Is not included due to copyright

Paper II

Full-length article

Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth

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Keywords: pregnancy, arthritis, first birth, outcomes

Word count abstract: 249

Word count (excluding abstract, tables and references): 2894

Funding

Research grants for the NOR-DMARD registry have been received from Abbott, Amgen, Aventis, BMS, MSD, Roche, Schering-Plough / Centocor, Wyeth and the Norwegian Directorate for Health and Social Affairs. This actual work was supported by the Liaison Committee between the Central Norwegian Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU).

Abstract

Objective: To examine possible associations between chronic inflammatory arthritides (CIA) and pregnancy outcomes with separate analyses of first and subsequent births before and after diagnosis.

Methods: Linkage of data from a CIA patient registry and the Medical Birth Registry of Norway enabled a comparison of pregnancy outcomes in CIA- and non CIA-women. Outcomes of first birth and subsequent births before and after diagnosis were analysed separately. Associations between CIA and the women's health during pregnancy and delivery as well as perinatal outcomes were assessed in logistic regression analyses with adjustments for maternal age at delivery and gestational age.

Results: We analysed 128 first births and 151 subsequent births after diagnosis and corresponding 286 /262 births before diagnosis versus references. First born children of women diagnosed with CIA were more often preterm (OR 1.85 (1.09, 3.13)) and small for gestational age (OR 1.60 (1.00, 2.56)). They also had lower mean birth weight (p= 0.01) and higher perinatal mortality (OR 3.26 (1.04, 10.24)). Birth by caesarean section (CS) (all classifications) was more frequent in patients than references, and elective CS was twofold more frequent in patients, both in first birth (OR 2.60 (1.43, 4.75)) and subsequent births (OR 2.18 (1.33, 3.58)). No excess risks were observed prior to CIA diagnosis.

Conclusion: Excess risks were related to first birth in women diagnosed with CIA, including a higher rate of perinatal mortality. A higher CS rate was related to all patient deliveries. Pregnancy outcomes before diagnosis did not differ from the reference population.

It is increasingly recognised that autoimmunity can affect every aspect of pregnancy such as fertilisation, maternal complications and adverse fetal outcomes (1). Also, pregnancy may influence autoimmune diseases. An ameliorating effect of pregnancy on chronic inflammatory arthritides (CIA) has been reported (2-8). Several studies have addressed possible effects of CIA on pregnancy and delivery (9-22). Excess rates of caesarean section (CS) have been reported in patients with CIA (9;10;12;15-17;21). Furthermore, excess rates of preeclampsia (12;19;21;22), preterm delivery (17;19;20), infants small for gestational age (SGA) and low birth weight < 2500 g (9;12;19;20) have been reported. One study found a slightly increased rate of birth defects in infants of mothers with CIA (20). Two studies found no differences in perinatal, neonatal or infant death (20;23), but one study found increased perinatal mortality in infants of mothers diagnosed with rheumatoid arthritis (RA) after delivery (18). However, further studies of CIA and pregnancy outcomes are necessary because effects may change over time (20;21) due to improvements of diagnostic tools and medical treatments as well as changes in routines of registration of obstetric practice.

Another relevant issue is that effects of subclinical disease processes on pregnancy outcomes can not be excluded since a status of preclinical RA may exist (24-26). Two previous studies have reported specifically on pregnancy outcomes in women before a diagnosis of CIA without any observed differences between patients and references (23;27).

Pregnancy and delivery complications are more frequent in first pregnancy and delivery (28-30). The risk of CS in nulliparous women with spontaneous start

of labour, cephalic fetus and no previous scar has been reported to be 2.5 times higher than for comparable parous women (31). The causes for this increased risk are not fully understood, although it has been known for more than 40 years (32;33). Separate analyses of outcomes of first birth and subsequent births in women with CIA have not been previously published.

The aim of the present study was to examine possible different effects of CIA on pregnancy outcomes with separate analyses of outcomes in first and subsequent births in women treated with disease modifying antirheumatic drugs (DMARDs). Further, we wanted to examine if a possible negative association with pregnancy outcomes was detectable before diagnosis of CIA.

Material and methods:

Setting

The Medical Birth Registry of Norway (MBRN) (34;35) comprising more than 2.2 million births 1967 – 2008, used the same notification form 1967 - 1998. This form comprised data on all live births as well as stillbirths after 16 weeks of gestation. A more detailed form was introduced December 1, 1998 which comprises data on all births after 12 weeks of gestation (35). Data on complications, maternal disease and mode of delivery were entered into the notification form as free text until 1998 and in checkboxes or as free text from 1999 onward. The forms are filled in by birth attendants within one week of delivery. The record includes data on the mother's health at birth, before and during pregnancy and characteristics of the newborn within the first week after delivery. Data from the MBRN are routinely linked to the Cause of Death

Registry by the national identification number to obtain information on infant mortality.

Since 2001 patients with CIA have been enrolled into the Norwegian Disease Modifying Antirheumatic Drug (NOR-DMARD) registry. Patients are included when they start with a synthetic or biological DMARD and withdrawn when they discontinue DMARD medication. Several patients in the registry were diagnosed before 2001 and may or may not have used DMARDs before inclusion. The NOR-DMARD registry has previously been described in detail (36).

Data of female patients aged 18 – 45 years at the time of inclusion in the NOR-DMARD registry in the period 2001-2006 were included in the present study. All patients had signed a written informed consent form before enrolment in the NOR-DMARD registry. In addition, eligible women received written information about the planned linkage of NOR-DMARD and MBRN data. Fourteen women opted out, and data of 631 women from the NOR-DMARD registry were linked with the MBRN. The linkage included deliveries from 1970 until October 2007. The study was carried out in compliance with the Helsinki Declaration, and was approved by the Norwegian Data Inspectorate, the Regional Ethics Committee of Central Norway and the Norwegian Directorate of Health.

Exposure

The study population included women with RA, psoriatic arthritis (PsA), ankylosing spondylitis (AS) and unspecified arthritis (UA) diagnosed before 45 years of age, and adult patients with juvenile idiopathic arthritis (JIA) (diagnosed before 16 years of age). UA comprised patients without fulfilment of criteria of a specified arthritis. In the analyses all diagnoses were combined into a group called

chronic inflammatory arthritides (CIA). All patients were diagnosed by rheumatologists before or at enrolment in the NOR-DMARD registry, and the time of diagnosis was recorded during enrolment. Only data for single births were analysed. Data were stratified for births before and after time of diagnosis of CIA.

The reference deliveries were frequency sampled from non-CIA deliveries in MBRN. The proportion of deliveries were equal for each decade among CIA patients and references. This procedure created two reference groups comprising a total of 800000 reference deliveries after diagnosis and 1000000 before (Table 1).

Outcome

Data on parity and gestational age from week 16 were retrieved from MBRN. First birth was defined as the first delivery of nulliparous women. We also collected data from MBRN on maternal characteristics, assisted reproduction (all methods combined) and pregnancy complications (i.e. all reported vaginal bleeding in pregnancy (all trimesters combined), preeclampsia (preeclampsia and eclampsia)(37;38), induction of labour (amniotomy, oxytocin and prostaglandin), preterm delivery (<37 weeks of gestation), instrument-assisted deliveries (vacuum extraction or the use of forceps), excessive bleeding during delivery (> 500 ml), labour dystocia (prolonged delivery >24 hours, mechanical disproportion or uterine dysfunction /atony), caesarean section (CS) (total, elective and acute).

MBRN also provided data on the newborn (gender, head circumference, birth weight) and transfer to the neonatal intensive care unit (NICU). Birth defects included serious (major) malformations in any organ system and were defined according to a definition by MBRN based on International Classification of

Diseases (ICD)-8 (1967-1998) and ICD-10 (1999 and onwards). Perinatal mortality included stillbirths (≥ 22 weeks of gestation) and early neonatal deaths (0-6 days in live born children).

Analyses

Data were analysed in strata comprising first births and subsequent births. Group comparisons were performed with Mann-Whitney U test for continuous variables and chi-square tests for categorical variables. Associations between CIA and adverse perinatal outcomes were assessed in logistic regression analyses with adjustments for maternal age. In addition, the analyses of transfer to NICU and birth weight < 2500 g as dependent variable were adjusted for gestational age. Mean birth weights and mean head circumferences were analysed in multiple linear regression analyses with covariates for gestational age, gender, maternal age and parity. Data were analysed using the Statistical Package of Social Sciences, version 16.0 (SPSS Inc., Chicago, Illinois, USA) and Statistics / Data Analysis (STATA), version 10.1 (StataCorp, Lakeway drive College Station, Texas, USA).

Results

Of 631 eligible women from the NOR-DMARD registry, 393 (62 %) were also registered in the MBRN. Table 1 shows patient characteristics stratified for deliveries after and before diagnosis as well as reference characteristics. CIA women with first delivery after diagnosis were significantly older than the references at time of delivery ($p<0.001$). Opposite, cases with first delivery before diagnosis were significantly younger than the references ($p<0.001$). Deliveries

(first birth / subsequent births (%)) after diagnosis of CIA across main diagnostic groups in NOR-DMARD were as follows: RA (45.3 / 54.3), PsA (14.1 / 13.2), AS (8.6 / 8.6), UA (7.8 / 10.6) and JIA (24.2 / 13.2).

First birth after diagnosis (Table 2)

Assisted reproduction was significantly more frequent in CIA women compared to references in the crude analysis. The statistically significant difference disappeared after adjustment. Vaginal bleeding in pregnancy was more frequently reported in CIA women, both for crude and adjusted comparisons.

We found increased risk of CS, (both total and elective) in CIA women compared to the reference population. There was no difference in acute CS. A statistically significantly higher rate of labour induction was also observed among the patients.

We observed more preterm deliveries and small for gestational age infants among CIA women. Infants of CIA women also had lower mean birth weight and smaller head circumference than infants of references. (Table 4). Unadjusted, more children of CIA women had birth weight < 2500 gram, but adjusted the difference was not statistically significant.

We found statistically significantly increased perinatal mortality among infants of CIA women compared to references.

Subsequent births after diagnosis (Table 3)

We observed excess CS rates, (both total and elective) in patients compared to references. We did not observe any other differences between patients and references.

Births before diagnosis (Online supplementary Tables S1, S2 and S3)

No differences were observed in outcomes between cases and references in first birth before receiving CIA diagnosis. Except for an increased risk of preeclampsia after adjustment for maternal age at delivery, we did not find other worse outcomes for cases compared to references in subsequent births.

Discussion

In this first study with separate analyses of outcomes of first birth and subsequent births in women with CIA, the observed differences between patients and references were related to first birth after diagnosis of CIA and not to subsequent births, except for CS.

We observed a higher frequency of assisted reproduction for nulliparous CIA women compared to references unadjusted, but not adjusted (Table 2). We have not found any previous studies reporting the frequency of assisted reproduction in CIA women. Age was a confounding factor for assisted reproduction (Table 2). This patient group was older at the time of first delivery (Table 1), which may reflect that these women had experienced more problems with attaining pregnancy. Reduced fertility has previously been reported for women with CIA (39;40), but we do not know how many women who had tried assisted reproduction and not attained pregnancy.

Patients had a twofold higher risk of vaginal bleeding compared to references in pregnancies related to first birth (Table 2). Use of non steroidal anti-inflammatory drugs (NSAIDs) among the patients may be the cause of this observed increased risk. No previous reports exist on a possible relation between use of NSAIDs and bleeding in pregnancy. Unfortunately, we did not have registrations of use of NSAIDs during the pregnancy. Such use is easy to underestimate because patients may limit their report to prescribed drugs and not include over-the-counter purchases. We did not observe any excess risk of bleeding during delivery. Patients are advised not to use NSAIDs after 32 gestational weeks, and this may explain why we did not observe higher risk of bleeding during delivery.

A higher rate of labour induction was observed for women with first birth, but not for subsequent births (Table 2, Table 3). Only one previous study has reported a higher rate of labour induction, but not specifically in relation to first birth (21). We found an increased CS rate (total and elective) both in first and subsequent births (Table 2, Table 3). Higher CS rate in patients with CIA has been reported in several previous studies and from different countries (9;12;15-17;19;21), but the causes of high CS rates have been less explored. We found a doubled rate of elective CS; both in first and subsequent births. We did not find any specific obstetric diagnoses or indications responsible for the increased rate of CS. Placental dysfunction, cephalo-pelvic disproportion and combined causes constituted each one third of the indications for CS. Women diagnosed with AS had the highest occurrence of CS (25 %) among the different diagnostic groups. The high occurrence of elective CS could be attributed to stiffness and pain in CIA patients and especially in the pelvic region of AS women. Furthermore,

obstetricians may choose to do an elective CS because they anticipate problems during delivery. Interestingly, we found no increase in acute CS rate. The two dominating reasons for acute CS in Norway are labour dystocia and fetal distress (41). We did not observe differences in risks of labour dystocia between patients and references (Table 2, Table 3). In Norway, vaginal birth after caesarean delivery (VBAC) has been the rule after one CS for many years. We do not think this rule is different for CIA women, but we were not able to adjust for this possibility since we lacked information about sibships among the references.

Birth weight was analysed in three ways: mean birth weight (Table 4), the number of children born small for gestational age (SGA) and the number of children with birth weight less than 2500 gram. All observed differences were related to first birth after diagnosis. The risks of both SGA and preterm delivery were increased for first birth (Table 2). This finding is in accordance with previous reports of CIA birth outcomes (12;17;19;20), but has not been examined separately for first born children before .

Unadjusted, more infants of the patients had birth weight less than 2500 gram compared to children of the references, but after adjustment the difference disappeared. Taking into consideration gestational age, gender and maternal age at delivery in the multiple linear regression analysis, we observed small, but statistically significantly differences in both mean birth weight and head circumference in the first- born children after diagnosis compared to references (Table 4). Both birth weight and head circumference are related to the placental function (42-45). One previous study has reported that a high level of disease activity and also the use of low doses of prednisone during pregnancy may influence birth weight negatively (11). Most female CIA patients who are

planning pregnancies, stop DMARDs incompatible with pregnancy several months before they attain pregnancy. In the NOR-DMARD registry patients are withdrawn when they stop a DMARD regimen, which unfortunately leads to lack of scores and current medication during pregnancy and often immediately before.

We found improved outcomes for infants compared with other reports, as we found no differences in birth defects or the need of transfer to neonatal intensive care unit (18;20). However, we observed a higher perinatal mortality related to first birth (Table 2). The rate was 3 times higher in the children of CIA women compared to references, but the result should be interpreted with caution because of the wide confidence intervals. Increased risk of perinatal deaths in infants of mothers who subsequently developed RA after delivery has been reported (18), but not in infants of mothers diagnosed before delivery. The current study did not have power to examine differences in specific birth defects or to do separate analyses within each diagnostic group.

A strength of this study was the possibility to analyse separately deliveries before time of diagnosis (online supplementary Tables S1, S2 and S3). This has only been done in two previous studies without observing any harmful effects on pregnancy outcomes (23;27). Some studies have suggested preclinical autoimmunity and a long prodromal phase in RA and other autoimmune diseases (24-26;46-49). From this perspective it is of particular interest also to examine pregnancy outcomes before clinical evident CIA. Except for a higher risk of preeclampsia in cases compared to references in subsequent pregnancies, we did not find any associations with poor pregnancy outcomes before diagnosis, indicating that the disease effect on pregnancy outcomes does not occur before the disease has been diagnosed. However, we cannot exclude that this is different in

subgroups of patients, for example in subgroups with antibodies predicting RA (25;49).

Our focus in the analyses was deliveries, not women. To account for the possibility of carrying on adverse events from one delivery to another involving dependence, adjustment by using mixed models could have been done. We were not able to do this adjustment because we lacked information about sibships among the references. However, most differences were observed in first births in which this bias does not exist.

Adjustment for smoking habits during pregnancy was not done because of insufficient information. This is a limitation of the study and of potential importance when studying birth weight. Another limitation was lack of information on educational level of the references since socioeconomic status may influence the level of pregnancy care. However, all pregnant women in Norway are offered pregnancy care free of charge with a participation rate close to 100 %, and we do not think lack of this information has biased the results.

The observed higher frequency of events in first births may be accounted for by selective fertility after a diagnosis of CIA, since women with the highest disease activity would most likely have only one child. However, all women in this study had active disease treated with synthetic or biological DMARDs, and were presumably among CIA women with highest disease activity. Another hypothesis is that immunological processes of the inflammatory disease may influence the first birth more than later births. Further studies on outcomes of first births after diagnosis are needed to confirm our findings.

In summary, the observed differences in pregnancy outcomes between CIA patients and references were related to first birth after diagnosis, including an

increased rate of perinatal mortality in the infants of the patients. An increased CS rate was related to all pregnancies after diagnosis. Pregnancy outcomes before diagnosis did not differ from the references. Overall, our findings indicate that special attention should be given to the first birth in women diagnosed with CIA.

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Table 1 Patient and reference characteristics, first birth and subsequent births, after and before diagnosis of CIA (mean (SD) for continuous variables, n (%) for counts).

	Deliveries after diagnosis	References	p-value	Deliveries before diagnosis	References	p-value
Total number of deliveries	279	800000		548	1000000	
First birth	128 (45.9)	335249 (41.9)		286 (52.2)	423532 (42.3)	
Age at delivery (years)	28.8 (4.7)	26.9 (4.8)	<0.001	24.9 (4.5)	25.9 (4.7)	<0.001
Gestational age (days)	276.6 (18.7)	278.7 (19.4)	0.17	280.7 (14.3)	280.0 (18.3)	0.82
Subsequent births	151 (54.1)	464751 (58.1)		262 (47.8)	576468 (57.7)	
Age at delivery (years)	31.5 (4.1)	30.8 (4.6)	0.04	28.6 (4.4)	30.1 (4.7)	<0.001
Gestational age (days)	276.9 (18.0)	278.9 (16.9)	0.16	279.7 (13.4)	280.0 (17.1)	0.14

CIA= chronic inflammatory arthritides, SD= standard deviation

Table 2 Crude and adjusted odds ratios of pregnancy outcomes in first births after CIA diagnosis versus reference deliveries

	Cases n=128 n (%)	References n=335249 n (%)		OR	CI	p-value
Assisted reproduction	5 (3.9)	5224 (1.6)	C	2.63	1.05, 6.28	0.04
			A*	1.77	0.69, 4.53	0.23
Pregnancy complications						
Vaginal bleeding in pregnancy	8 (6.3)	10216 (3.0)	C	2.12	1.04, 4.34	0.04
			A*	2.01	1.00, 4.13	0.05
Preeclampsia	4 (3.1)	17095 (5.1)	C	0.60	0.22, 1.62	0.31
			A*	0.59	0.22, 1.61	0.31
Delivery						
CS, total	29 (22.7)	48955 (14.6)	C	1.71	1.13, 2.59	0.01
			A*	1.51	1.00, 2.29	0.05
CS, elective	12 (9.4)	10917 (3.3)	C	3.07	1.70, 5.57	<0.001
			A*	2.60	1.43, 4.75	0.002
CS, acute	16 (12.5)	33262 (9.9)	C	1.30	0.77, 2.19	0.33
			A*	1.16	0.69, 1.97	0.57
Labour induction, total	32 (25.0)	55483 (16.5)	C	1.68	1.13, 2.51	0.01
			A*	1.61	1.08, 2.41	0.02
Labour dystocia	43 (33.6)	103922 (31.0)	C	1.12	0.78, 1.62	0.53
			A*	1.03	0.71, 1.48	0.89
Instrument-assisted deliveries	22 (17.2)	48197 (14.4)	C	1.27	0.80, 2.01	0.31
			A*	1.18	0.74, 1.87	0.48
Bleeding>500 ml during delivery	11 (8.6)	40690 (12.1)	C	0.68	0.37, 1.26	0.22
			A*	0.62	0.33, 1.16	0.13
Infant						

Birth weight< 2500 gram	12 (9.4)	16714 (5.0)	C	1.96	1.08, 3.55	0.03
			A**	1.94	0.87, 4.34	0.10
Preterm delivery	16 (12.5)	23119 (6.9)	C	1.91	1.13, 3.24	0.01
			A*	1.85	1.09, 3.13	0.02
SGA (<10 percentile)	21 (16.4)	36451 (10.9)	C	1.59	0.99, 2.54	0.05
			A*	1.60	1.00, 2.56	0.05
Transfer to NICU	10 (7.8)	18747 (5.6)	C	1.48	0.75, 2.92	0.26
			A**	1.19	0.56, 2.51	0.65
Major congenital malformations	4 (3.1)	10186 (3.0)	C	1.03	0.38, 2.79	0.95
			A	0.96	0.35, 2.60	0.93
Perinatal mortality	3 (2.3)	2427 (0.7)	C	3.29	1.05, 10.35	0.04
			A*	3.26	1.04, 10.24	0.04

C=crude, A=adjusted, OR= Odds ratio, CI= confidence interval, CS= caesarean section, SGA= small for gestational age, NICU= neonatal intensive care unit

* adjusted for maternal age at delivery

** adjusted for maternal age at delivery and gestational age

Table 3 Crude and adjusted odds ratios of pregnancy outcomes of CIA deliveries after diagnosis versus reference deliveries, subsequent births

	Cases n=151 n (%)	References n=464751 n (%)		OR	95% CI	p-value
Assisted reproduction	1 (0.7)	2504 (0.5)	C	1.23	0.17, 8.79	0.84
			A*	1.16	0.16, 8.31	0.88
Pregnancy complications						
Vaginal bleeding in pregnancy	7 (4.6)	14461 (3.1)	C	1.51	0.71, 3.23	0.28
			A*	1.50	0.70, 3.19	0.30
Preeclampsia	3 (2.0)	10924 (2.4)	C	0.84	0.27, 2.64	0.77
			A*	0.82	0.26, 2.58	0.74
Delivery						
CS, total	30 (19.9)	54792 (11.8)	C	1.85	1.24, 2.77	0.002
			A*	1.79	1.19, 2.68	0.004
CS, elective	18 (11.9)	26176 (5.6)	C	2.27	1.39, 3.71	0.001
			A*	2.18	1.33, 3.58	0.002
CS, acute	12 (7.9)	25015 (5.4)	C	1.52	0.84, 2.74	0.17
			A*	1.47	0.81, 2.66	0.19
Labour induction , total	19 (12.6)	61017 (13.1)	C	0.95	0.59, 1.54	0.84
			A*	0.94	0.58, 1.51	0.79
Labour dystocia	24 (15.9)	62515 (13.5)	C	1.21	0.78, 1.88	0.38
			A*	1.19	0.77, 1.84	0.43
Instrument-assisted deliveries	3 (2.0)	14062 (3.0)	C	0.67	0.21, 2.09	0.49
			A*	0.65	0.21, 2.04	0.46
Bleeding >500 ml during delivery	15 (9,9)	40904 (8.8)	C	1.14	0.67, 1.95	0.62
			A*	1.12	0.66, 1.91	0.67
Infant						
Birth weight < 2500 gram	3 (2.0)	15998 (3.4)	C	0.57	0.18, 1.78	0.33

			A**	0.23	0.03, 1.76	0.16
Preterm delivery	8 (5.3)	23762 (5.1)	C	1.05	0.51, 2.15	0.89
			A*	1.03	0.51, 2.11	0.93
SGA (<10 percentile)	11 (7.3)	29986 (6.5)	C	1.15	0.62, 2.13	0.65
			A*	1.17	0.63, 2.16	0.62
Transfer to NICU	0	18272 (3.9)				
Major congenital malformations	3 (2.0)	11047 (2.4)	C	0.83	0.26, 2.61	0.75
			A*	0.82	0.26, 2.57	0.73
Perinatal mortality	1 (0.7)	3173 (0.7)	C	0.97	0.14, 6.93	0.97
			A*	0.95	0.13, 6.79	0.96

C= crude, A= adjusted, OR= odds ratio, CI= confidence interval, CS= caesarean section, SGA= small for gestational age, NICU= neonatal intensive care unit

* Adjusted for maternal age at delivery

** Adjusted for maternal age at delivery, parity and gestational age

Table 4 Multiple linear regression analysis of birth weight and head circumference in offspring of CIA patients, first birth and subsequent births after diagnosis (mean (SD))

First birth				
		Patients (n=128)	References (n=335249)	p-value
	Birth weight* (gram)	3287.7 (647.3)	3454.7 (614.4)	0.01
	Head circumference* (cm)	34.7 (2.0)	35.0 (1.9)	0.05
Subsequent births				
		Patients (n=151)	References (n=464751)	p-value
	Birth weight** (gram)	3548.7 (597.2)	3610.1 (624.4)	0.52
	Head circumference** (cm)	35.1 (2.2)	35.3 (1.8)	0.15

SD=standard deviation, cm=centimeter

* Analyses with covariates for gestational age, gender of child and maternal age at delivery

** Analyses with covariates for gestational age, gender of child, maternal age at delivery and parity

Supplementary Table S1 Crude and adjusted odds ratios of pregnancy related outcomes in first births before CIA diagnosis versus reference deliveries

	Cases n=286 n (%)	References n=423532 n (%)		OR	CI	p-value
Assisted reproduction	3 (1.0)	3395 (0.8)	C	1.31	0.42, 4.09	0.64
			A*	1.95	0.61, 6.16	0.26
Pregnancy complications						
Vaginal bleeding in pregnancy	2 (0.7)	10886 (2.6)	C	0.27	0.07, 1.07	0.06
			A*	0.27	0.07, 1.10	0.07
Preeclampsia	14 (4.9)	19738 (4.7)	C	1.05	0.61, 1.80	0.85
			A*	1.06	0.62, 1.82	0.82
Delivery						
CS, total	43 (15.0)	54958 (13.0)	C	1.19	0.86, 1.64	0.30
			A*	1.29	0.93, 1.79	0.13
CS, elective	3 (1.0)	9757 (2.3)	C	0.45	0.14, 1.40	0.17
			A*	0.51	0.16, 1.60	0.25
CS, acute	27 (9.4)	30251 (7.1)	C	1.35	0.91, 2.01	0.13
			A*	1.59	0.99, 2.19	0.06
Labour induction, total	55 (19.2)	76982 (18.2)	C	1.07	0.80, 1.44	0.64
			A*	1.10	0.82, 1.48	0.53
Labour dystocia	53 (18.5)	83602 (19.7)	C	0.92	0.69, 1.25	0.61
			A*	0.98	0.73, 1.33	0.92
Instrument assisted deliveries	31 (10.8)	58181 (13.7)	C	0.77	0.53, 1.12	0.18
			A*	0.81	0.56, 1.18	0.28
Bleeding >500 ml during delivery	23 (8.0)	33055 (7.8)	C	1.03	0.67, 1.58	0.88
			A*	1.08	0.70, 1.65	0.73

Infant						
Birth weight< 2500 gram	13 (4.5)	21523 (5.1)	C	0.89	0.51, 1.55	0.68
			A**	1.02	0.51, 2.04	0.95
Preterm delivery	20 (7.0)	26687 (6.3)	C	1.10	0.70, 1.74	0.67
			A*	1.11	0.71, 1.76	0.64
SGA (<10 percentile)	36 (12.6)	51399 (12.1)	C	1.03	0.72, 1.46	0.89
			A*	1.02	0.72, 1.44	0.92
Transfer to NICU	5 (1.7)	7128 (1.7)	C	1.76	0.66, 4.67	0.25
			A**	1.68	0.58, 4.85	0.34
Major congenital malformations	6 (2.1)	10995 (2.6)	C	0.80	0.36, 1.80	0.60
			A	0.83	0.37, 1.86	0.65
Perinatal mortality	2 (0.7)	3845 (0.9)	C	0.77	0.19, 3.09	0.71
			A*	0.77	0.19, 3.08	0.71

CIA= chronic inflammatory arthritides, C= crude, A= adjusted, OR= Odds ratio, CI= confidence interval, CS= caesarean section, SGA= small for gestational age, NICU= neonatal intensive care unit

* adjusted for maternal age at delivery

**adjusted for maternal age at delivery and gestational age

Supplementary Table S2 Crude and adjusted odds ratios of pregnancy related outcomes of CIA deliveries before diagnosis versus reference deliveries, subsequent births

	Cases n=262 n (%)	References n=576468 n (%)		OR	CI	p-value
Assisted reproduction	0	1432 (0.2)	C			
			A*			
Pregnancy complications						
Vaginal bleeding in pregnancy	1 (0.4)	15919 (2.8)	C	0.13	0.02, 0.96	0.05
			A*	0.14	0.02, 0.98	0.05
Preeclampsia	10 (3.8)	12315 (2.1)	C	1.81	0.96, 3.42	0.06
			A*	1.93	1.03, 3.64	0.04
Delivery						
CS, total	25 (9.5)	59242 (10.3)	C	0.92	0.61, 1.39	0.69
			A*	1.01	0.67, 1.53	0.95
CS, elective	10 (3.8)	22117 (3.8)	C	0.99	0.53, 1.87	0.99
			A*	1.15	0.61, 2.16	0.67
CS, acute	12 (4.6)	22924 (4.0)	C	1.16	0.65, 2.07	0.62
			A*	1.27	0.71, 2.26	0.42
Labor induction, total	44 (16.8)	84775 (14.7)	C	1.17	0.85, 1.62	0.34
			A*	1.21	0.87, 1.67	0.25
Labor dystocia	20 (7.6)	47514 (8.2)	C	0.92	0.58, 1.45	0.72
			A*	0.96	0.61, 1.52	0.87
Instrument assisted deliveries	4 (1.5)	15800 (2.7)	C	0.56	0.21, 1.49	0.24
			A*	0.59	0.22, 1.60	0.30
Bleeding >500 ml during delivery	21 (8.0)	33320 (5.8)	C	1.42	0.91, 2.21	0.12

			A*	1.46	0.94, 2.29	0.09
Infant						
Birth weight < 2500 gram	9 (3.4)	20148 (3.5)	C	0.99	0.51, 1.93	0.99
			A**	1.27	0.57, 2.84	0.56
Preterm delivery	12 (4.6)	28218 (4.9)	C	0.94	0.53, 1.69	0.85
			A*	0.98	0.55, 1.75	0.94
SGA (<10 percentile)	14 (5.3)	43085 (7.5)	C	0.71	0.41, 1.22	0.21
			A*	0.69	0.40, 1.19	0.18
Transfer to NICU	4 (1.5)	7068 (1.2)	C	1.04	0.37, 2.90	0.94
			A**	0.73	0.21, 2.51	0.62
Major congenital malformations	5 (1.9)	12232 (2.1)	C	0.90	0.37, 2.17	0.81
			A*	0.93	0.38, 2.25	0.87
Perinatal mortality	3 (1.1)	4883 (0.8)	C	1.35	0.43, 4.23	0.60
			A*	1.39	0.44, 4.35	0.57

CIA= chronic inflammatory arthritides, C= crude, A= adjusted, OR= odds ratio,

CI= confidence interval, CS= caesarean section, SG= small for gestational age,

NICU= neonatal intensive care unit

* Adjusted for maternal age at delivery and parity

**Adjusted for maternal age at delivery, parity and gestational age

Supplementary Table S3 Multiple linear regression analysis of birth weight and head circumference in offspring of cases versus references, first birth and subsequent births before CIA diagnosis (mean (SD))

First birth				
		Patients (n=286)	References (n=423532)	p-value
	Birth weight* (gram)	3489.3 (540.8)	3440.5 (610.2)	0.23
	Head circumference* (cm)	34.9 (2.5)	35.0 (1.8)	0.50
Subsequent births				
		Patients (n=262)	References (n=576468)	p-value
	Birth weight** (gram)	3644.5 (591.9)	3593.3 (618.0)	0.18
	Head circumference (cm)**	35.4 (1.6)	35.3 (1.7)	0.08

CIA= chronic inflammatory arthritides, SD=standard deviation, cm=centimeter

* Analyses with covariates for gestational age, gender of child and maternal age at delivery

** Analyses with covariates for gestational age, gender of child, maternal age at delivery and parity

Paper III

Original article

FERTILITY IN WOMEN WITH CHRONIC INFLAMMATORY ARTHRITIDES

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Keywords: national registry, fertility rate, number of births, inflammatory rheumatic disease

Word count abstract: 245
Word count article (not including tables, figures and references): 2187

Abstract

Objective: To compare fertility rates in women with rheumatoid arthritis (RA), other chronic arthritides (OCA) and juvenile idiopathic arthritis (JIA) with reference women from the general population.

Methods: Each woman from a Norwegian patient registry was matched by year of birth with 100 reference women randomly selected from the National Population Registry. Data linkage of patients and references with the Medical Birth Registry of Norway (MBRN) identified all offspring in patients and references until October 2007, and indirectly also nulliparous (childless) women. Groups were compared with Mann-Whitney U-test for continuous variables and chi-square tests for categorical variables. Poisson regression analysis was applied to calculate relative fertility rates in the diagnostic groups versus references.

Results Among 631 patients 849 children were registered in MBRN. Of these, 289 children (34.0 %) were born after time of diagnosis versus 44.3 % in references. Altogether 206 of 631 patients (32.6 %) were nulliparous versus 26.4 % in references ($p<0.001$). Among RA patients 28.4 % (96 of 338) were nulliparous versus 24.5 % in references ($p=0.09$), 30.7 % (67 of 218) in OCA patients versus 24.5 % in references ($p=0.03$) and 57.3 % (43 of 75) in JIA patients versus 40.9 % in references ($p=0.004$). Adjusted relative fertility rates in RA, OCA and JIA after diagnosis were 0.88, 0.84 and 0.84, respectively, compared with references.

Conclusion: A higher proportion of women with chronic inflammatory arthritides were nulliparous compared with references, and relative fertility rates were reduced in all patient groups.

Introduction

Chronic inflammatory arthritides (CIA) may influence the production of offspring (fertility) due to different mechanisms: physical, psychological, hormonal or immunological as well as medical treatments [1].

Fertility has particularly been studied in rheumatoid arthritis (RA). Some studies have indicated reduced sexual desire and lower frequencies of intercourse in women with RA [2-4]. In a report with structured interviews of about 400 married women with RA, nearly one in five patients answered that RA influenced childbearing decisions, and especially in women diagnosed at a young age [5]. The overall percentage of women having children was not different from the general population, but women with RA were more likely to opt for a single child.

Data obtained in cross-sectional surveys have suggested low ability to conceive a child and longer time to achieve pregnancy in RA patients both before and after disease onset [6, 7]. However, a case- control study with age matched controls did not find any association between RA and low fertility [8].

Few publications exist on fertility in other chronic arthritides. In ankylosing spondylitis (AS) three studies have reported normal fertility [9-11], but longer time to achieve pregnancy has been reported in one study [11].

Women diagnosed with juvenile idiopathic arthritis (JIA) may experience long-term physical and psychosocial impairment [12]. In one study fertility was not impaired in JIA women [13], but longer time to achieve pregnancy has been reported [13, 14].

Previous studies have examined fertility in heterogeneous patient groups, from the worst to the mildest affected women. We wanted to study fertility among

the most severely affected patients, i.e. women treated with synthetic or biological disease modifying antirheumatic drugs (DMARDs). The aim of the study was to compare fertility rates in women with RA, other chronic arthritides (OCA) and JIA with birth year matched references from the general population.

Material and Methods:

Setting

Since 2001 data of patients with CIA have been recorded in the Norwegian Disease Modifying Antirheumatic Drug (NOR-DMARD) registry. Patients are enrolled when they start with a synthetic or biological DMARD, but many of the patients have been diagnosed and have used DMARDs several years before enrolment. The NOR-DMARD registry has previously been described in detail [15].

Since 1967 medical data on all births in Norway have been recorded in the Medical Birth Registry of Norway (MBRN)[16, 17]. From 1967 to 1998 the registry collected data on all births in Norway after 16 weeks of gestation. Since 1999 all births after 12 weeks of gestation have been registered. The records include demographic data on the parents and their reproductive history.

The study was performed in accordance with the Helsinki declaration and approved by the Norwegian Data Inspectorate, the Regional Ethics Committee of Central Norway and the Norwegian Directorate of Health. Permission to use references from the Norwegian Population Registry was approved by The Norwegian Tax Authorities and the Regional Ethics Committee of Central Norway.

Patients

Patients from the NOR-DMARD registry enrolled 2001- 2006 were included in the present cohort study. All patients had signed a written informed consent form before enrolment. In addition, eligible women received written information about the planned linkage of NOR-DMARD data and MBRN. Fourteen women opted out, and data of 631 women from the NOR-DMARD registry were linked with the MBRN including deliveries until October 2007. All patients were diagnosed by a rheumatologist before or at enrolment in the NOR-DMARD registry.

Due to low numbers, the women with psoriatic arthritis (PsA), AS and unspecified arthritis (UA) were analysed as an entity labelled other chronic arthritides (OCA). UA comprised patients without fulfilment of criteria of a specified arthritis. Thus, the study population included 338 women with RA, 218 with OCA and 75 adult patients with JIA, all diagnosed before 45 years of age, (JIA before 16 years of age).

Time of diagnosis was recorded by a rheumatologist when the patient was enrolled in the NOR-DMARD registry. Data on maternal age at delivery, birth order, date of last menstrual period, date of birth and gestational age were retrieved from MBRN. Nulliparous (childless) women were identified by lack of match in MBRN. Inter pregnancy interval was defined as the time period from the date of the first birth to the first day of the last menstrual period preceding the second birth.

Reference population

Each patient was matched by year of birth with 100 reference women randomly selected from the Norwegian Population Registry, totally 63100 references. All references were linked to the MBRN to identify all offspring.

Analysis

For group comparisons, Mann-Whitney U test was used for continuous variables and chi-square test for categorical variables**.** Date of diagnosis for each patient was linked to the corresponding references to analyse pre- and post diagnosis parity.

Poisson regression analysis was applied to estimate relative fertility rates in women with RA, OCA and JIA before and after diagnosis versus birth-year matched references with adjustment for parity at time of diagnosis when relevant.

Regression analysis by Locally Weighted Scatterplot Smoothing (LOWESS fit) was used to calculate and visualise mean number of children by age of diagnosis (Figure 1).

Cox regression analysis with adjustment for maternal age at first delivery was used to compare the interval between first and second birth in patients and references.

Two-sided p values of <0.05 were interpreted as significant. Data were analysed using the Statistical Package of Social Sciences, version 17.0 (SPSS Inc., Chicago, Illinois, USA) and Statistics / Data Analysis (STATA), version 11.0 (StataCorp, Lakeway Drive College Station, Texas, USA).

Results

Among the 631 patients 849 children were registered in MBRN. Of these, 289 children (34.0 %) were born after time of diagnosis versus 44.3 % in references. In the diagnostic groups 147 children were registered in the RA group, 89 in the OCA group and 53 in the JIA group after diagnosis (Table 1).

Altogether 206 of 631 (32.6 %) patients were nulliparous versus 26.4 % in references ($p<0.001$) at time of censoring (October 2007). Among RA patients 28.4% (96 of 338) were nulliparous versus 24.5 % in references ($p=0.09$), 30.7 % (67 of 218) in OCA patients versus 24.5 % in references ($p=0.03$) and 57.3 % (43 of 75) in JIA patients versus 40.9 % in references ($p=0.004$) (Table 1).

Mean number of children was lower in patients than references (Figure 1). Especially, this difference was marked in women diagnosed before 30 years of age. In women diagnosed after age 30 years, mean number of children approached that of the age matched references.

Adjusted relative fertility rates in RA, OCA and JIA after diagnosis were 0.88, 0.84 and 0.84, respectively (Table 2). Relative fertility rates in patients before diagnosis were not reduced (Table 2).

In the analyses of inter pregnancy interval 38 patients had their first delivery before they received a diagnosis of CIA and the second delivery after diagnosis (Table 3). Further, 70 patients had all deliveries after time of diagnosis. We observed significantly increased inter pregnancy intervals in RA and OCA women diagnosed between first and second birth. No differences in the intervals were observed in any of the diagnostic groups with both first and second birth after diagnosis (Table 3).

Discussion

In this study of CIA patients treated with synthetic or biological DMARDs, a higher proportion of patients were nulliparous compared to age matched references ($p<0.001$). When examining each diagnostic group separately, the proportion of nulliparity reached statistical significance for patients diagnosed with OCA and JIA, but not for RA women. The high proportion of nulliparous women among JIA patients and references was probably due to the younger age of this group with a mean age of about 30 years at time of data linkage (Table 1). Only three previous studies of RA patients have reported the proportion of nulliparous women [6, 8, 18], and all with an excess of nulliparity among patients. Nulliparity has been discussed as a risk factor for RA [6, 18-22], but to our knowledge nulliparity has not been discussed as a risk factor for OCA.

More likely, our observation of a higher proportion of nulliparity among CIA patients may be caused by non remitting disease and functional impairment, which have previously been reported to reduce the wish for children in women with CIA [5, 14]. Also, severe disease flares have been reported to lower sexual activity [23, 24]. Further, some patients have expressed concern about risk of arthritic disease in offspring, which may contribute to reduced fertility rates [25], and two previous studies have reported that women with RA and JIA sometimes are advised against having offspring [12, 25].

Previous population based studies have reported an overrepresentation of various gynaecological disorders and surgery of the genital tract in women with rheumatic diseases [26, 27], which could also contribute to a higher proportion of nulliparity. In the present study we did not have data of associated gynaecological

disorders, and we did not know how many of the nulliparous women had tried to become pregnant. We also lacked information about use of contraceptives among patients and references. In the present study all patients were using DMARDs. Since many DMARDs are incompatible with pregnancy, the patients are advised to use contraceptives regularly.

RA, OCA and JIA women had significantly lower relative fertility rates after diagnosis (Table 2). The results are in accordance with two previous studies [5, 28]. One possible contributing explanation to the reduced fertility rates may be the heavy disease burden of the study population. JIA women in the study were probably even more highly selected. Adult JIA patients treated with synthetic and / or biological DMARDs constitutes about 50 % of all patients diagnosed in childhood, and many of them have or will develop polyarticular disease [29].

Several studies of women with CIA have reported an increased frequency in Caesarean deliveries (CS) compared to references [10, 14, 30-34]. Unpublished data from the present patient population has also shown an increased risk of CS among the patients compared to references (data under review). A Norwegian study has reported that a woman with CS as her first delivery will have fewer children than a woman who starts with a vaginal birth [35]. This may also contribute to the observed reduced number of children in the patient group.

Overall, we observed that the mean number of children was associated with age at time of CIA diagnosis (Figure 1), which is in accordance with previous reports of RA [5, 28]. Women diagnosed after 30 years of age had a mean number of children comparable to the reference group.

We did not observe any differences in the relative fertility rates in RA and OCA women versus references before disease onset (Table 2). Our finding

contrasts a previous publication where lower fertility rate was reported prior to disease onset in RA, and especially lower fertility rate was concentrated in a rheumatoid factor positive subgroup of patients [6]. We did not examine rheumatoid factor positive subgroups due to small numbers. Especially, the proportion of rheumatoid factor positive patients was low in the OCA group.

We observed an increased inter pregnancy interval for RA and OCA women diagnosed between first and second birth. The increased interval indicates that women diagnosed after first birth may postpone a second pregnancy until the disease is better controlled. To our knowledge no other studies have reported this interval specifically before. No differences in inter pregnancy intervals were observed for women with first and second birth after diagnosis (Table 3). This contrasts another study reporting an increased interval after diagnosis [28]. The different findings may be explained by improved treatment options during the last decade giving better disease control and opportunities to continue to a second pregnancy. Further, our findings indicate that women giving birth after diagnosis have their children within a shorter time frame. RA women with their first birth after diagnosis were older than references at the time of first delivery, and had less time left of their reproductive age (Table 3).

A strength of the present study was the use of references randomly selected from the general population. Some previous studies have used controls which might bias the results (i.e. friends, newspaper advertisements or controls living in same geographical area as the patients). We did not have information about educational level of the references which is a limitation of the study, but we did not observe significantly differences in educational level between nulliparous and parous patients for any of the diagnostic groups (results not shown).

Starting a family is of central importance in many people's life, also in CIA patients [25]. More knowledge around different aspects of fertility, both physical and psychological, is necessary to counsel CIA patients in this regard. After the introduction of biological DMARDs, clinicians are frequently asked about fertility aspects of CIA. Improvements in the medical treatment of arthritides may not immediately lead to increased fertility rates, but future studies of fertility rates will be of interest, including factors taking personal childbearing choices into account.

We summarise that a higher proportion of CIA women treated with DMARDs were childless compared with references. Reduced relative fertility rates were observed for all diagnostic groups, which add to the burden of CIA in general.

Key messages:

A higher proportion of women with chronic inflammatory arthritides were childless compared with birth year matched references.

Relative fertility rates were reduced in women with RA, OCA and JIA compared with references.

Disclosure statement: The authors have declared no conflicts of interest.

Funding

Research grants for the NOR-DMARD registry have been received from Abbott, Amgen, Aventis, BMS, MSD, Roche, Schering-Plough / Centocor, Wyeth and the Norwegian Directorate for Health and Social Affairs. This actual work was supported by the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU).

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Table 1 CIA patients with references in diagnostic subgroups with numbers of nulliparous women and numbers of deliveries total and per woman

			Deliveries total and number per woman			Mean age at time of data linkage (years)	
	Patients	Nullipara n (%)	Total	Before diagnosis	After diagnosis	Para 1+	Nullipara
Total patients	631	206 (32.6)	849 1.35	560 0.89	289 0.46	NS	NS
Total references	63100	16658 (26.4)	101728 1.61	56670 0.90	45058 0.71	NS	NS
RA patients	338	96 (28.4)	501 1.48	354 1.05	147 0.43	41.1	36.7
RA references	33800	8281 (24.5)	56870 1.68	35656 1.05	21214 0.63	41.0	36.3
OCA patients	218	67 (30.7)	295 1.35	206 0.94	89 0.41	40.7	35.2
OCA references	21800	5341 (24.5)	35928 1.65	21013 0.96	14915 0.68	39.9	36.1
JIA patients	75	43 (57.3)	53 0.71	0	53 0.71	38.2	29.9
JIA references	7500	3067 (40.9)	8930 1.19	0	8930 1.19	36.1	29.5

CIA= chronic inflammatory arthritides, RA= rheumatoid arthritis, OCA= other chronic arthritides, JIA= juvenile idiopathic arthritis, NS= not stated

Table 2 Relative fertility rates (RFR) in patients from the NOR-DMARD registry versus references, before and after diagnosis

Group	Diagnosis		RFR	95% CI	p-value
After diagnosis	RA	Crude	0.88	0.83, 0.93	<0.001
		Adjusted*	0.88	0.84, 0.93	<0.001
	OCA	Crude	0.84	0.78, 0.90	<0.001
		Adjusted*	0.84	0.78, 0.90	<0.001
	JIA		0.84	0.77, 0.92	<0.001
Before diagnosis	RA		0.99	0.96, 1.03	0.89
	OCA		0.99	0.95, 1.04	0.78

*Adjusted for parity

RA=rheumatoid arthritis OCA=other chronic arthritides JIA=juvenile idiopathic arthritis

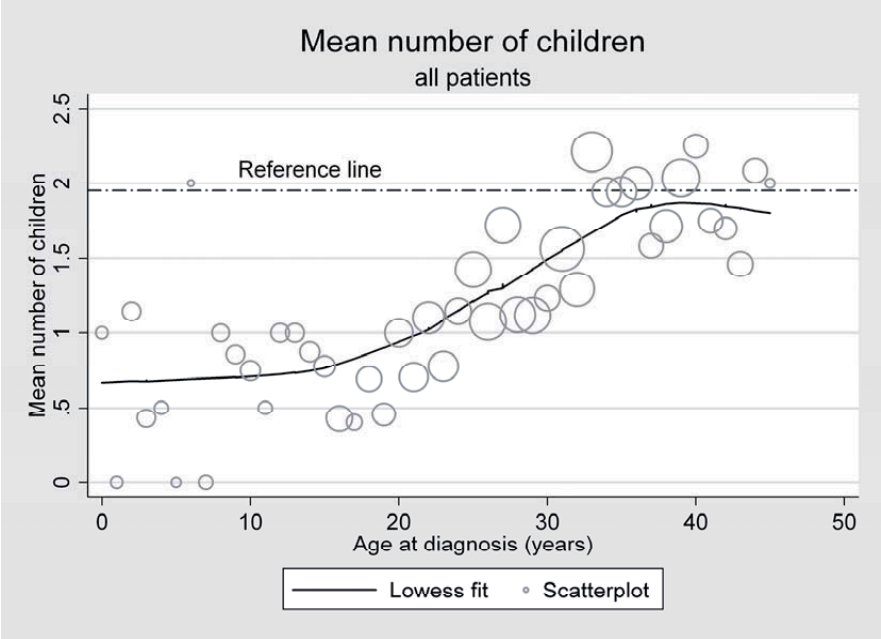
Table 3 Inter pregnancy interval[a] in relation to time of diagnosis, crude * and adjusted for maternal age at first delivery **

Group	Diagnosis	Age at first delivery patients (mean)	Age at first delivery references (mean)	p-value	Median interval patients (years)	Median interval references (years)	p-value
First birth before diagnosis, second birth after diagnosis	RA (n=22)	25.3	25.3	0.90	3.5	2.3	0.004* 0.003**
	OCA (n=16)	25.3	25.3	0.91	4.6	2.1	0.001* 0.002**
First and second birth after diagnosis	RA (n=36)	28.1	25.2	<0.001	2.6	2.2	0.33* 0.82**
	OCA (n=17)	26.9	25.2	0.09	1.9	2.2	0.64* 0.74**
	JIA (n=17)	25.0	25.2	0.94	2.5	2.3	0.56* 0.39**

[a] Analysis on single births

RA= rheumatoid arthritis, OCA= other chronic arthritides (psoriatic arthritis, ankylosing spondylitis and unspecified arthritis combined), JIA= juvenile idiopathic arthritis

Figure 1 Mean number of children in all patients with chronic inflammatory arthritides (CIA) by age at diagnosis



Lowess fit = regression line
Scatterplot = mean number of children, size weighted for the number of patients diagnosed per year

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109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
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112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
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116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
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126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
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130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
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137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
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143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
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154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
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157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.

161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
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169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
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186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
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188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97

191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
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193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
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225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
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229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
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239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
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243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
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246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
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254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
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267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE

271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
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274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
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284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
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286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OF PATHOLOGICAL GAMBLING IN NORWAY
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289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
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