Johan Fredrik Skomsvoll
Reproductive outcome in women with rheumatic disease
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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.

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Preface

The background of the thesis is the considerable research work by professor Monika Østensen on rheumatic diseases in pregnancy as well as her initiative to establish the Center for Mothers with Rheumatic Diseases in Trondheim. The question of how maternal rheumatic diseases influence obstetrical and perinatal outcome was raised. In an article by professor Lorentz M Irgens and professor Tor Bjerkeadal (1) the Medical Birth Registry of Norway (MBRN) was presented as an excellent and unique instrument for epidemiological studies of pregnancy and perinatal health. Consequently, the idea of using this database in solving our question was highlighted. At the Second International Conference on Sex hormones and Pregnancy in Rheumatic Diseases, organized by Monika Østensen (Trondheim 1998), I presented preliminary results. A lecture on MBRN and its potentials in epidemiological research on pregnancy and perinatal health was given by professor Irgens (MBRN).

The present investigations were carried out at the Department for Rheumatology, St. Olavs Hospital, Trondheim and the Medical Birth Registry of Norway (MBRN), at the University of Bergen from 1999 to 2002. The work has been financed and supported by the Norwegian Women’s Public Health Association (Norske Kvinners Sanitetsforening), the Norwegian Foundation for Health and Rehabilitation (Helse og Rehabilitering) and the Norwegian Society for Rheumatology (Norsk Revmatologisk Forening).

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I also thank Medical Statistician and coauthor Valborg Baste (MBRN) for providing data files from the MBRN and giving important and valuable help in the field of statistics, Steinar Nilssen (MBRN) for performing the linkage between the local database and the birth registry, Dr. Svein Rasmussen at the Department of Obstetrics and Gynecology, University Hospital of Bergen and MBRN, for taking time with me to discuss relevant matters and giving useful comments. Professor V Finsen at the Department of Orthopedic surgery, St. Olavs Hospital, for correcting the language in the manuscript and making adjustments in the text (during his stay at the monastery island of Solovki in the White Sea).

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And finally, to Åse Kristine, Hanne Kjersti and Randi for their patience, encouragement and support.

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Johan Fredrik Skønsvoll
1. List of papers


2. Abbreviations and definitions

2.1 Definitions

- **Apgar score** < 6 (after 1 and 5 minutes): moderate to severe hypoxia
- **Birth defects**: congenital tumors, metabolic diseases, cardiac diseases, different types of hemias, specific major anomalies in any organ system and chromosomal aberrations i.a. Down syndrome.
- **Cesarean section**: acute and elective forms.
- **Fecundity**: the ability to conceive
- **Fertility**: the actual production of live offspring
- **Induction of labor**: amniotomy, oxytocin, prostaglandin
- **Infant survival**: proportion of all births after 16 weeks of gestation surviving the first year of life.
- **Inflammatory arthritides**: The dominant clinical feature is symptoms from the joints.
- **Inflammatory rheumatic diseases**: Includes different types of inflammatory arthritides and other systemic rheumatic diseases characterised by inflammation.
- **Instrumental deliveries**: vacuum extraction, use of forceps
- **Interpregnancy 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**: < 2500g
- **PDS**: Placental dysfunction syndrome: recurrence of any adverse pregnancy outcome such as preeclampsia or preterm birth or SGA.
- **Perinatal mortality**: stillbirths after 16 weeks of gestation and early neonatal deaths (< 7 days)
• **Positive predictive value**: The probability that a person actually has the disease given that she tests positive.

• **Postperinatal mortality**: deaths between 7 days and 1 year after birth.

• **Preterm birth**: < 37 weeks of gestation

• **Sensitivity**: The probability of testing positive if the disease is truly present.

• **Specificity**: The probability of testing negative if the disease is truly absent.

• **SGA**: small for gestational age defined as birthweight < 10 percentile for the actual gestational age (≥ 28 weeks).

• **Subsequent pregnancy rate**: percentage of all women who continued from the first birth (birth order one) to a second birth.

• **Umbilical cord complications**: abnormal length, any pathology in the cord and its insertion into the placenta.

• **Validity**: An index of how well a test or procedure in fact measures what it is intended to measure; an objective index by which to describe how valid a test or procedure is. The index comprises sensitivity, specificity as well as positive and negative predictive value.

### 2.2 Abbreviations

• **aPL**: antiphospholipid antibodies

• **APS**: antiphospholipid syndrome

• **AS**: ankylosing spondylitis

• **CTD**: connective tissue disease

• **PM/DM**: Dermatomyositis

• **FGR**: fetal growth restriction
• **HLA**: human leucocyte-type-system A

• **ICD8**: international classification of diseases, eighth ed.

• **JCA**: juvenile chronic arthritis

• **JRA**: juvenile rheumatoid arthritis

• **MBRN**: the Medical Birth Registry of Norway

• **MCTD**: Mixed connective tissue disease

• **NSA**: non-specified inflammatory arthropides

• **NSAIDS**: non-steroidal antiinflammatory drugs

• **OR**: odds ratio

• **PROM**: premature rupture of membranes

• **PsA**: psoriatic arthritis

• **RA**: rheumatoid arthritis

• **RR**: risk ratio

• **SA**: specified inflammatory arthropides

• **SLE**: systemic lupus erythematosus

• **SS**: Sjögren’s syndrome

• **SSC**: Systemic sclerosis (scleroderma)
3. General introduction/background

3.1 Incidence of rheumatic disease

The incidences of rheumatic diseases like RA and SLE are higher than in men. The incidence of RA increases with age. The gender and age corrected incidence rates possibly reflect hormonal and immunological changes during fertile and postmenopausal years (2-3). Pregnancy also influences the time of disease onset as well as disease activity (4-9).

The mean annual incidence rate of RA in Norwegian women has been estimated to 36.0-36.7/100,000 (10-11). No statistically significant difference in incidence rates has been found between the periods 1987-91 and 1992-1996 (10). The age specific mean annual incidence rate in RA women of fertile age was 5.0/100,000 (20-29 years), 15.7/100,000 (30-39 years) (10). In another study of RA the mean annual incidence rate in women of fertile age was 11.7/100,000 (20-29 years) and 18.1/100,000 (30-39 years) (11). In these two studies the mean annual incidence rate of RA increases to 48.8/100,000 (10) or 57.4/100,000 (11) in women in the age of 50-59 years.

The mean annual incidence rate of juvenile chronic arthritis has been estimated to 22.6/100,000 (children under 16 year of age) with a female: male ratio of 1.7:1 (12). Only prevalence data of ankylosing spondylitis (AS) have been reported in Norway (Table 6). However, two studies from Finland show an incidence of AS in the adult population of 10/100,000 (13) and 6.9/100,000 (14). In a study of AS patients from Norway the mean age of onset in women was 26.2 years and the female to male ratio was 1:2 (15).
The mean annual incidence rate of SLE in northern Norway has been estimated to 5.2/100,000 in women between 16-29 years old and 5.6/100,000 in women aged between 30-49 years (16). A decrease in the incidence rate of SLE was found after the age of 50 to 3.2/100,000 (16). In a Swedish study the mean annual incidence of SLE was estimated to be 4.5/100,000 in women aged 15-44 years (17). However, this increased to 15.9/100,000 in women aged 45-64. A similar trend was found in another recent study from Sweden (18).

Data of the incidence of primary Sjögren’s syndrome (SS) in Norway have not been reported. However, the peak incidence is in the fourth and fifth decades with a female to male ratio of 9:1 (19). In a non-population based study of young-onset primary SS 9% of patients had disease onset before 35 years of age and all were female (20). Connective tissue diseases like dermatomyositis and systemic sclerosis are extremely rare in Norway. The annual incidence of systemic sclerosis in Norway has been estimated to 4.7/million (21) and 7.4/million (22). Mean age of onset was 54 years (21) and the female to male ratio was 14:1 (21) and 1.3:1 (22). A Swedish study found a female to male ratio of 2:1 and the mean age at onset of disease was 42.3 years (23). Data of annual incidence of dermatomyositis in Norway have not been published, but a Swedish study has found an annual incidence of 7.6 cases/million (24). The disease may occur at any age and the overall female: male ratio is 2.5:1, but during childbearing years (15-44 years) this ratio increased to greater than 5:1 (25).

3.2 The clinical pictures of rheumatic diseases

3.2.1 The inflammatory arthritides
The inflammatory arthropides are characterised by inflammation in the peripheral joints and the spine, but with less systemic features than the connective tissue diseases. An active disease may cause functional disability before and during pregnancy as well as post partum.

*Rheumatoid arthritis (RA)*

RA is a chronic, inflammatory, systemic disease characterised by persistent and progressive synovitis in peripheral joints. RA encompasses a wide spectrum of features, from self-limiting disease to progressively chronic disease with varying degrees of joint destruction to clinically evident extra-articular manifestations. The primary inflammatory joint lesion involves the synovium of the joints and tendon sheets.

*Ankylosing spondylitis (AS)*

AS is a chronic, systemic inflammatory disorder of the axial skeleton, affecting the sacroiliac joints and the spine. Peripheral joints and extraarticular structures may also be involved. The inflammation appears to originate in ligamentous and capsular sites of attachment to bones (enthesitis), juxtaarticular ligamentous structures, the synovium, articular cartilage, and subchondral bone of the involved joints. The inflammatory process frequently results in gradual fibrosis and bony ankylosis.

*Juvenile chronic arthritis (JCA)*

Inflammation may develop in articular structures as well as extraarticular organs. By definition the onset of disease is under the age of 16. A minor proportion of patients develop a systemic form of the disease. A polyarticular (≥ 5 joints) involvement or a pauciarticular (< 4 joints) involvement, also affecting the eyes, may develop. These two types of JCA most often cause inflammation in peripheral joints and to a lesser extent
affect the spine. Only 50% of JCA patients may have active disease that persists into adulthood (26).

3.2.2 The connective tissue diseases

The connective tissue diseases are characterised by systemic features which often involve many organs and frequently overlap as demonstrated by shared clinical and serological features.

*Systemic lupus erythematosus (SLE)*

SLE is an autoimmune disease characterised by the production of antibodies to components of the cell nucleus in association with a diverse array of clinical manifestations including multiorgan involvement. The pathologic findings of SLE occur throughout the body and are manifested by inflammation, blood vessel abnormalities that encompass both bland vasculopathy and vasculitis, and immune complex deposition.

*Sjögren’s syndrome (SS)*

Essential features of SS include focal lymphoid infiltrates in the lacrimal and salivary glands as well as the presence of autoantibodies. The most common clinical presentation is the combination of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia), but extraglandular organ manifestations may develop. It is divided into primary and secondary forms. The latter form affects patients with sicca symptoms who also have other autoimmune diseases, most commonly RA, SLE or systemic sclerosis.

*Systemic sclerosis (SSC)*

SSC is characterised by small-vessel vasculopathy and fibrosis in the setting of autoimmunity. SSC encompasses disease with skin and internal organ involvement. Subcategories of the disease are defined by the extent of skin involvement, which
predicts the clinical course. Patients with limited SSC have skin thickening below the elbows and the knees, and sometimes also have face and neck involvement. Patients with diffuse SSC have more extensive skin thickening that involves the upper extremities and the trunk. They also have a more rapid and severe development of the disease including internal organ involvement.

Polydermatomyositis (PM/DM)
PM/DM is characterised by a nonsuppurative inflammation of skeletal muscle and circulating myositis-specific autoantibodies may be present. The dominant clinical feature of PM is symmetric proximal muscle weakness. The weakness may be accompanied by systemic symptoms such as fatigue, morning stiffness and anorexia. Multiorgan involvement may occur. The clinical features of DM include those described for PM plus a variety of cutaneous manifestations.

3.3 Changes in the diagnostic criteria for rheumatic diseases

3.3.1 The inflammatory arthritides
The original purpose of the criteria was to establish guidelines for the classification of disease syndromes and a correct diagnosis for patients taking part in clinical investigations. However, the criteria have in fact also been used as guidelines for patient diagnoses in clinical practice. The diagnostic criteria will probably change as improved instruments for diagnosis become available and as concepts of pathophysiology change.

Rheumatoid arthritis (RA)
The following comments are based on Silman & Hochberg (27). The first criteria to be developed for RA were accepted in 1956 (28). The criteria were revised in 1958 and
subdivided RA into possible, probable, definite and classical forms and thereafter
achieved widespread acceptance. A simpler version of these criteria, "The Rome
Criteria", was adopted for epidemiological studies (29). However, the low specificity of
these criteria led to a revision, The New York criteria (30). In which no cut-off point was
given for a "positive" which caused higher specificity, but lower sensitivity. In 1987 the
American Rheumatism Association (ARA) produced a revised version of the original
criteria (31). These new criteria which separate RA from "non-RA" have a sensitivity and
specificity of approximately 90%.

Ankylosing spondylitis (AS)
The first criteria for AS were proposed at the Conference on Population studies of the
Rheumatic Diseases (Rome) (29). These criteria specified that a diagnosis could be made
either if bilateral radiographic sacroilitis was present together with any one of five
clinical criteria, or if any four of these five clinical criteria were detected. However, when
using the Rome criteria in population studies, the prevalence of AS varied substantially
(from 2%-8%). Therefore the presence of radiographic sacroilitis was mandatory in the
New York set of criteria for AS (30). These latter criteria have gained wide acceptance in
population surveys.

Juvenile rheumatoid arthritis (JRA) and juvenile chronic arthritis (JCA)
The JRA criteria were proposed in 1977 (32) and were reviewed by the JRA Criteria
Subcommittee in 1982. They recommended a division into 3 subtypes: systemic,
polyarticular and pauciarticular. The general criteria include persistent arthritis of at least
6 weeks duration and exclusion of other causes of arthritis. No specific laboratory or
other test can establish the diagnosis of JRA.
Juvenile chronic arthritis (JCA) is not equivalent to JRA and is described in more detail in a report from the European Conference on the Rheumatic Diseases of Children (33).

3.3.2 The connective tissue diseases

*Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS)*

In 1971, the American Rheumatism Association published preliminary criteria for the classification of SLE (34). In 1982 the revised criteria for SLE were presented and studies showed a sensitivity of 96% and specificity of 96% (≥4 of 11 criteria, serially or simultaneously) (35). None of these methods for classifying patients with SLE were designed for diagnostic purposes, and both lack the sensitivity for recognizing milder cases of SLE. Antiphospholipid antibodies were recognized towards the end of the 1970’s and APS in the beginning of 1980’s (36). Diagnostic criteria were established in 1987 (37).

*Sjögren’s syndrome (SS)*

The syndrome was first described by H Sjögren in 1933 (38). In the early 1970’s autoantibodies to SSA/Ro and SSB/La were described and the association with Sjögren’s syndrome (19,39). At least 6 sets of criteria for the diagnosis of SS have been suggested, but unfortunately none has obtained universal acceptance (40). A recent editorial statement concerning SS diagnostic criteria remarked on the mandatory combination of measurements of exocrine dysfunction, histological confirmation of inflammation, serological evidence of autoimmunity, and exclusion of diseases mimicking primary SS (40).

*Systemic Sclerosis (SSC)*
The diagnostic criteria for SSC are 97% sensitive and 98% specific (41). The single criterion for proximal SSC is 100% specific and 91% sensitive. However, in mild limited forms of SSC, proximal scleroderma may be absent, particular in early phases of the disease.

*Dermatomyositis (DM/PM)*

Five major criteria to define PM and DM were proposed primarily for purposes of clinical research (42). The authors qualified the criteria by stating that “the diagnosis of PM and DM is not necessarily excluded by failure to meet them”. They also mentioned several exclusion criteria.

### 3.4 Changes in the drug treatment of rheumatic diseases

Patients diagnosed with RA between 1988-1996 were treated more actively than patients diagnosed in the period 1979-1987. During 1988 to 1996 auranofin, sulphasalazine, methotrexate, and corticosteroids replaced gold salts, antimalarials and D-penicillamine (43). In 1977-1992, patients with early and serious RA were selected for disease modifying antirheumatic drugs (DMARDs) therapy, but the treatment duration was too short for modern requirement (44). Pharmaceutical and surgical treatment patterns were otherwise mainly consistent with the present guidelines.

*Aspirin and non steroidal antiinflammatory drugs (NSAIDs)*

In 1930 aspirin was introduced in Norway, and different formulations of the substance have been presented in the Norwegian market ever since. Indomethacin was introduced in 1965, ibuprofen in 1971 and naproxen in 1974. A number of other NSAIDs have later been introduced in Norway like ketoprofen and diclofenac in the 1980s and piroxicam.
and mecloxicam and several other substances in the 1990s (Norsk Medisinaldepot. Personal communication).

Corticosteroids

Metylprednisolone was introduced in Norway in 1963 and prednisone and prednisolone in 1980 (Norsk Medisinal Depot. Personal communication).

Disease modifying antirheumatic drugs (DMARDs)

In 1947 sodium aurothiomalate was introduced in Norway and was increasingly used until 1988 and thereafter a gradual decrease in the prescription rate has been registered (Norsk Medisinaldepot. Personal communication). Auranofin was introduced in 1985. Sulfasalazin was introduced as early as 1942, and different administration forms of the substance were presented in 1967 and 1969. From the 1970s it has been increasingly used in Norway. Hydroxychloroquine was introduced in 1964 and D-penicillamine in 1979.

Cytotoxic drugs

During the last decades antimetabolites like methotrexate (MTX) (introduced in 1971) and azathioprine (introduced in 1968) have been more frequently used in the treatment of rheumatic disease, particularly MTX. Alkylating agents like cyclophosphamide and chlorambucile were introduced in 1959 and have been primarily used in the therapy of connective tissue disease with secondary vasculitis and severe organ damage as well as in primary vasculitis disease.

3.5 Why pregnancy may influence rheumatic disease and vice versa

3.5.1 The inflammatory arthritides
Disease related factors as well as medication influence reproduction in mothers with rheumatic disease. Inflammation of peripheral joints or the spine causes stiffness and pain with subsequent functional disability. Although, several inflammatory arthritides like RA may ameliorate during pregnancy, an effect of a subclinical disease process on pregnancy outcome cannot be excluded. There is a lack of information on how inflammatory arthritides may affect pregnancy and pregnancy outcome.

3.5.2 The connective tissue diseases

Hormonal and immunological changes during pregnancy suppress the activity of RA, but aggravate the symptoms of SLE with a subsequent increased risk of lupusflare. A higher disease activity, particularly renal disease and hypertension, and the presence of antiphospholipid antibodies (aPL) may negatively affect the outcome of pregnancy.

The effect of aPL on pregnancy and pregnancy outcome have been well described as well as the associated placental pathological lesions. Before 1983 antiphospholipid syndrome (APS) was not recognized and it was unknown that the adverse pregnancy outcome found in SLE women could be associated with the presence of aPL (36). Furthermore, before 1983 there also was a lack of knowledge on autoantibodies like anti SSA/Ro and anti-SSB/La and the association with congenital heart block (45). Immunodiffusion tests detecting antibodies to extractable nuclear antigens were used in Norwegian hospitals from 1987 and ELISA tests detecting antibodies to extractable nuclear antigens as well as cardiolipins were used from 1990 (Torolf Moen, Dep of Immunology, St. Olavs Hospital. Personal communication).
The primary or secondary APS is characterised by the presence of anticardiolipin antibodies (aCL) and/or lupus anticoagulants (LAC) as well as increased risk of arterial or venous thrombosis, thrombocytopenia, recurrent fetal loss, fetal growth restriction (FGR) and preterm birth (46). Particularly, second and third trimester losses are typical in APS (47). Fetal loss rate in aPL positive pregnancies has been estimated to be from 20% to 90%. In primary and secondary APS elevated aPL at the first prenatal visit is associated with increased fetal loss. Placental pathology in human and experimental APS shows massive infarction, necrosis and thrombosis of placental and decidual vessels (48).

In SLE patients who are LAC and aCL double positive, the incidence of extensive infarction, decidual vasculopathy, decidual thrombosis and perivillous fibrinoid change has been found to be significantly higher than in patients without aPL (49). There is a highly significant correlation between clinical outcomes like preterm birth/ small for gestational age (SGA) and placental pathology like extensive infarction or decidual vasculopathy in SLE women (50). A study of women without rheumatic disease found that umbilical-chorionic vasculitis, decidual vascular abnormality and chronic villitis was related to preterm birth (51). However, there are few data regarding placental pathology associated with maternal connective tissue disease and adverse pregnancy outcome, other than SLE and APS. Decidual vasculopathy, similar to that seen in hypertension, is common in systemic sclerosis and is associated with poor perinatal outcome (52).

3.6 How may pregnancy influence inflammatory arthritides and vice versa
3.6.1 The effect of pregnancy on inflammatory arthritis

In 1938 the amelioration of the symptoms and signs of RA during pregnancy was described for the first time (53). Since then, the effect of pregnancy on inflammatory rheumatic disease has been described in several studies. In a retrospective survey of 308 pregnancies of patients with RA, 73% of the patients had an amelioration of their disease during pregnancy (54,55). Three prospective studies comprising 33 pregnancies of RA women found improvement or remission in 77% (56-59). Another prospective study of 65 pregnancies reported remission in only 60% of the cases (60). Recently, a prospective study found that RA women reported an improvement in joint pain or swelling, although more than one-third reported no such change (61). Pregnancy-induced remission of arthritis is not likely to be repeated in subsequent pregnancies. Retrospective studies (62) as well as prospective studies (56-59) have found that initial arthritis relief occurred most frequently in the first trimester. A retrospective review of 296 RA pregnancies found that 57% improved in the first trimester, 34% in the second trimester and 9% in the third trimester (63). Prognosis of RA was investigated in two studies. Except for a trend for patients with multiple pregnancies to have a better functional level (64), no significant difference was found between women with and without pregnancy regarding functional capacity and disease activity (65). Recent studies have demonstrated a significantly increased risk of RA onset in the first year postpartum (6-8), particularly in those who breast-fed (8). A study of patients with RA found that first-time breast feeders had an increased disease activity 6 months post partum (66). In a study of 69 patients, recurrence was found in 36% within the first month postpartum, 69% by 2 months, 85% by the end of
4 months (62). However, the increase of disease activity in RA patients was found to be unrelated to lactation or resumption of menstruation (53,56,57).

In women with AS disease activity during pregnancy did not change in 40%, increased in 30% and decreased in 30% (56,67). Most women with RA and AS experience a disease flare 6 months postpartum which may last 2–6 months. In JCA inactive disease did not flare during pregnancy, but active polyarticular or pauciarticular JCA was improved by pregnancy, particularly during the second half of gestation (68). An arthritis flare was experienced in most patients during the first 6 months.

3.6.2 The effect of inflammatory arthropides on pregnancy, delivery and the newborn

The effect of inflammatory rheumatic disease on pregnancy is less well investigated. Studies, particularly population based ones, focusing on pregnancy complications and perinatal outcome in women with inflammatory arthropides are lacking. In a retrospective study of RA women of more than 40 years of age, an increased rate of spontaneous abortions was reported, both before and after disease onset compared to the controls (69). A review concluded that there was no significant increase in pregnancy complications and adverse perinatal outcome in women with RA (70). The few studies of women with AS (71,72) and JCA found no significant increase of adverse pregnancy outcome, except for an increase in the cesarean section rate (68,73). However, a recent study of women with JCA has shown an increased rate of miscarriages (74). Recently, a case-control study of the effects of RA on mothers and babies during pregnancy found a modest negative effect on birth weight (75).
Medication may also influence pregnancy outcome, and a prospective study found a reduction in birth weight in women treated for active rheumatic disease (76).

3.6.3 The effect of inflammatory arthritides disease on fecundity, fertility and family size

Three studies of RA women, one of them population based (77), have shown a significant reduction in number of births (78,79) and one study has shown a reduced fecundity in RA women (80) (Table 1). In JCA the number of births has been found to be reduced compared to the national average (68), and in a recent study, reduced fecundity has been shown (74). However, in this last study (74) of JCA the mean number of births was equal in cases and controls and similar to the national average.
Table 1 Number of births (livebirths per person or 1000 woman years) in studies of women with inflammatory arthritides compared to controls or national average.

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Disease</th>
<th>Cases N</th>
<th>Controls N</th>
<th>Results</th>
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<td>RA</td>
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<td>68</td>
<td>NS</td>
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<td>Decreased compared to national average†</td>
</tr>
<tr>
<td>Østensen (98) [72]</td>
<td>AS</td>
<td>649</td>
<td>-</td>
<td>Similar to national average</td>
</tr>
<tr>
<td>Østensen (82) [71]</td>
<td>AS</td>
<td>72</td>
<td>-</td>
<td>Similar to national average</td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis, JCA: juvenile chronic arthritis, AS: ankylosing spondylitis. NS: non significant difference between cases and controls. [Ref.No]: Reference number.

*McHugh: Mean number of births. 2.5 (cases) versus 3.1 (controls), p<0.05.
**Del Junco: Fertility rate ratio (livebirths per 1000 woman years of experience between the ages of 15 and 49, cases versus controls): 0.77, 95% CI 0.62-0.95.
***Kay: Mean number of births 1.60 ± 0.21 (cases) versus 2.49 ±0.24 (controls), p<0.01.
†Østensen: Mean number of births: 1.5 versus national average 2.2 (MBRN)

3.6.4 The effect of inflammatory arthritides on the recurrence risk of adverse outcome in a subsequent pregnancy

Previously, no study has focused on the risk of adverse outcome in subsequent pregnancies of women with inflammatory arthritides.

3.7 How may pregnancy influence systemic lupus erythematosus and antiphospholipid antibody syndrome and vice versa
3.7.1 The effect of pregnancy on SLE

In several studies the effect of pregnancy on SLE has been described using different study designs, patient selection and definitions of lupus flare. Of 6 case-control studies of SLE women between 1984-96, three found an increased flare rate during pregnancy and three did not (81-86). In the John Hopkins Lupus Cohort 60% of the SLE patients had a flare and most of them a mild disease during pregnancy (87). In a more recent uncontrolled study of SLE women half of the patients had a flare, one third of the flares occurring the first 8 weeks postpartum, the remainder equally divided among trimesters (88). The risk for puerperal flare was highest in patients with a pregnancy longer than 27 weeks (89). Despite the inconsistent results, lupus flares during pregnancy are fairly common, with a frequency of more than 57% and flare rates ranging from 0.06 to 0.136 per patients per month, exceeding the flare rates in non pregnant SLE women by 0.4-0.7 in three studies (90,81,82). Renal, musculoskeletal and hematological flares are most likely to occur whereas arthritis is suppressed by pregnancy (84,86). In one of the studies renal involvement was found in 43% of all flares during pregnancy versus 12% in controls, but only 11% of flares were regarded as severe according to physicians' global assessment (84). It may be difficult to differentiate between active lupus nephritis and preeclampsia (91,92). SLE flares are no more severe during pregnancy (88) and only a minority of pregnant patients suffers from severe complications of SLE.

SLE patients who conceive in a period of remission have a low risk of nephritis flare (91, 93-95). Various studies have found that a higher flare rate is reported in SLE women during pregnancy with active nephritis at conception than those with inactive nephritis
In a metaanalysis, deterioration of renal function was found in 17% of 151 pregnancies and permanent impairment of renal function in 8% (95). Predictors for a flare of lupus nephritis are active renal disease at conception, hypertension, and a creatinine level of 140 micromol/l or more (91). A nephrotic syndrome with marked proteinuria, but without severe hypertension and normal renal function, predicts a more favorable outcome. Preeclampsia has been described in 30-50% of SLE patients with preexisting renal disease. Apart from the general risk factors such as primigravida, preexisting systolic hypertension, obesity and previous history of pre-eclampsia, miscarriage or abortions (99), the presence of aPL is an additional factor for early onset preeclampsia (100). In the John Hopkin's SLE cohort, hypertension was not present in most of the patients with relapse of nephritis while raised blood pressure occurred almost universally in patients with preeclampsia (101). Lupus nephritis and preeclampsia may occur in the same patient.

3.7.2 The effect of SLE and antiphospholipid syndrome on pregnancy, delivery and the newborn

Fetal loss
Pregnancies in SLE women are characterised by an increased incidence of fetal loss (abortion and stillbirth), prematurity and fetal growth restriction (FGR) (102). In retrospective studies, the proportion of fetal losses has varied between 8 and 41% with an average of 28% in the series from 1959-80 (47). Two case-control studies found fetal loss in patients with SLE 1.5-2.5 times than in non SLE pregnancies (103,104) (Table 2). Pregnancies after a diagnosis of SLE had a higher rate of fetal loss (27%) than prior to diagnosis (19%). The best outcomes are reported in patients with inactive SLE (105).

However, other prospective studies of SLE women have shown a rate of fetal loss in the range 11%-29% (106) (Table 3). A more favorable prognosis may be due to better monitoring and treatment of SLE pregnancies as well as better timed obstetrical intervention, but also study design and patient selection may influence the results.

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>Disease</th>
<th>Cases N</th>
<th>Controls N</th>
<th>Fetal loss †</th>
<th>Fetal loss rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petri (93) [163]</td>
<td>SLE</td>
<td>203</td>
<td>283</td>
<td>21</td>
<td>Increased (p&lt;0.01)</td>
</tr>
<tr>
<td>Julkunen (93) [106]</td>
<td>SLE</td>
<td>112</td>
<td>192</td>
<td>21</td>
<td>Increased (RR 2.5, 95%CI 1.4-4.5)</td>
</tr>
<tr>
<td>Georgiou (00) [221]</td>
<td>SLE</td>
<td>47</td>
<td>57</td>
<td>17</td>
<td>Increased (p&lt;0.01)</td>
</tr>
<tr>
<td>Steen (99) [156]</td>
<td>SSC</td>
<td>214</td>
<td>105</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Silman (88) [152]</td>
<td>SSC</td>
<td>115</td>
<td>115</td>
<td>29</td>
<td>Increased (RR 2.1, 95%CI 1.0-4.3)</td>
</tr>
<tr>
<td>Giordano (85) [226]</td>
<td>SSC</td>
<td>86</td>
<td>86</td>
<td>11</td>
<td>Increased (p&lt;0.05)</td>
</tr>
<tr>
<td>Julkunen (95) [160]</td>
<td>SS</td>
<td>51</td>
<td>42</td>
<td>20</td>
<td>Increased (RR 2.7, 95%CI 1.1-6.5)</td>
</tr>
<tr>
<td>Takaya (91) [225]</td>
<td>SS</td>
<td>40</td>
<td>129</td>
<td>5</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: non significant difference between cases and controls.
[Ref.No]: Reference number.
*Fetal loss including spontaneous abortions and fetal deaths (stillbirths)
†Percentage of pregnancies in cases with fetal loss
A recent population registry based study of women with SLE showed an increased risk of fetal loss (OR 5.1, 95%CI 2.4-10.7) as well as neonatal death (OR 6.8, 95%CI 3.9-11.8) (107). Active lupus nephritis, previous history of fetal death and the presence of aPL have been shown to be predictive factors for fetal loss in lupus pregnancies (91,92, 94-98,108-113). Active lupus nephritis and creatinine above 140 umol/l have been associated with a 50% pregnancy loss (91,92). Hypertension was statistically significantly associated with preterm birth and FGR in two studies (114,115).

The presence of aPL further increases the risk of fetal loss (104) and tends to occur after 10 weeks of gestation, most often in the second and third trimester (111,114). The aPLs have been found in 10%-40% of SLE women. Prospective studies (116-121) of patients have confirmed the association between aPL and fetal loss. The aPLs are shown to be the best predictor for spontaneous abortion and FGR, and a study found a fetal loss rate as high as 30% (122). A close correlation was also found between significant titres of aPL and fetal distress (113). Coexistence of both positive lupus anticoagulant and high titre IgG anticardiolipin antibodies has been found to be associated with the highest risk of fetal loss (123). On the other hand, decreasing titres or disappearance of aPL has been found to predict with improved fetal prognosis (124).
Table 3 Fetal outcome in prospective cohort studies of women with SLE after the diagnosis.

<table>
<thead>
<tr>
<th>Author (year of publication) [Ref No]</th>
<th>Preganacies N</th>
<th>Live births (%)</th>
<th>Therapeutic abortions (%)</th>
<th>Spontaneous abortions (%)</th>
<th>Fetal deaths (%)</th>
<th>Total losses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mintz (86) [81]</td>
<td>102</td>
<td>78</td>
<td>0</td>
<td>17</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Nosente (90) [113]</td>
<td>39</td>
<td>85</td>
<td>0</td>
<td>10</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Wong (91) [93]</td>
<td>24</td>
<td>71</td>
<td>21</td>
<td>8</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Huong (94) [117]</td>
<td>99</td>
<td>77</td>
<td>5</td>
<td>13</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Lima (95) [106]</td>
<td>108</td>
<td>82</td>
<td>2</td>
<td>7</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Huong (97) [128]</td>
<td>62</td>
<td>81</td>
<td>3</td>
<td>16</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Rahman (98) [114]</td>
<td>141</td>
<td>60</td>
<td>14</td>
<td>24</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>Carmona (99) [127]</td>
<td>60</td>
<td>80</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Cortes-Hernandez (02) [115]</td>
<td>103</td>
<td>66</td>
<td>7</td>
<td>15</td>
<td>12</td>
<td>34</td>
</tr>
</tbody>
</table>

SLE: systemic lupus erythematosus. [Ref No]: Reference number.

_Cesarean section and induction_

Rates of cesarean section or induction, between 11% and 65%, have been found in previous studies of SLE (81,106,114,125-128). In a recent population registry based study of SLE women, the rate of cesarean section was 38% vs 20% in controls (p<0.001) (107). Indications like fetal growth restriction, fetal distress, premature rupture of membranes (PROM), lupus activity and/or maternal hypertension have been the most common reasons for induction or cesarean section (81,91,106,107,127). Increased rates of adverse pregnancy outcomes like fetal distress in 41%, FGR in 32%, PROM in 36%, and preterm births in 43% have been found in SLE women (106). Reduced Apgar scores of infants born to SLE mothers have been reported (114). No increase in birth defects has been observed in infants born to mothers with SLE (106).

_Preterm birth_

The reported rate of preterm birth in older studies varied from 3% to 73% in SLE pregnancies (81,83,95,97,126,129-131). Several recent studies have also shown an
increased rate of preterm birth in SLE pregnancies varying from 24% to 63% (103,106-107,114,127-128, 132) (Table 4). Not only does the definition of preterm birth vary between studies, but also the obstetric policy regarding timing of delivery in order to reduce morbidity. In some retrospective reports a lack of obstetrical details concerning timing of delivery is a problem. Multiple risk factors for preterm birth have been found such as active lupus, treatment with high steroid doses (> 20-15 mg), renal disease, hypertension (particularly in the second trimester), preeclampsia, PROM, fetal compromise (e.g., abnormal fetal heart-rate recordings, FGR, or oligohydramnios) and Raynauds phenomenon (84,87,114,133). Higher rates of preeclampsia, FGR, and abnormal fetal heart rate recordings all contribute to preterm birth in APS women. Preterm birth has been reported in 12% to 35% of women with aPL (120,134,135)

Fetal growth restriction (FGR)

FGR is common in women with SLE and has been reported in 12% to 32% of pregnancies (83,126,136-138). In a case control study, FGR was found in 23% of SLE pregnancies progressing beyond 20 weeks gestation, compared to 4% of controls (81). In recent studies, the FGR rate has varied from 8% to 29% (91,106,93,114,127,128) (Table 4). A population registry based study found the risk of reduced birth weight (stratified by gestational age) to be increased (107). Factors like active disease, renal lupus and hypertension, preeclampsia and aPL may increase the risk of FGR. Also, hypocomplementemia seems to be associated with FGR. Different definitions of FGR have been used in studies and only a few have been well designed using healthy controls. The outcome measure small for gestational age (SGA) also has been been used in some studies of SLE women, demonstrating increased rates of SGA (81,91,94,130).
Neonatal lupus erythematosus (NLE)

NLE syndrome consists of congenital heart block (CHB), transient cutaneous lupus lesions, cytopenia, hepatic and other systemic manifestations in children born to mothers with SLE, SS or other rheumatic diseases with the presence of anti-SSA/Ro or anti-SSB/La antibodies. The Research Registry for Neonatal lupus (US) defines NLE by two criteria: (1) maternal antibodies to the 52 kD SSA/Ro, 60 kD SSA/Ro, or 48 kD SSB/La ribonucleoproteins and (2) heart block or transient skin rash. Transient cutaneous lupus lesion is the most common manifestation and CHB is the only permanent one (139). The population based estimated risk of having a CHB infant for a woman with antibodies to SSA/Ro or SSB/La is 0.5%, but the risk is higher (5%) in pregnancy of women with connective tissue disease (CTD) and antibodies to both SSA/Ro and SSB/La (139,140).

Heart block occurs most often in infants of mothers who have enzyme-linked immunosorbent assay (ELISA)-determined antibodies to both SSA/Ro and SSB/La antigens or immunoblot-identified antibody to both 48 kD SSB/La and 52 kD SSA/Ro, but not to the 60 kD SSA/Ro bands (141), possibly due to the maximal expression of the cardiac 52 beta antigen during development. The highest risk of CHB was observed with positive anti-52 kD SSA, OR 18.9 (95%CI 7.7-46.5) (139). A recent prospective study showed the prevalence of CHB in newborns of women (n=100) with CTD and anti SSA/Ro positive to be 2% (142). The risk might be higher in women with primary SS or undifferentiated CTD than in those with SLE. Also, sinus bradycardia and prolongation of Q-T intervals may be present. In mothers having a child with CHB the recurrence risk has been estimated to 12%-16% (139-141). CHB is be associated with a substantial mortality
(15-30%) (140,142). Mothers of children with CHB have a higher risk of fetal loss than healthy mothers and most losses are spontaneous first trimester abortions (139,140).

3.7.3 The effect of SLE on fertility and family size

Women with SLE have normal fertility, except in cases with lupus nephritis and high creatinin (> 300 micromol/l) and after treatment with alkylating agents (138, 143,144).

However, reduced family size in SLE women has been found in a population based study without detailed analysis of contributing factors (145). Another study found a reduced mean number of births in SLE women compared to controls (78).

3.7.4 The effect of SLE on the recurrence risk of adverse outcome in a subsequent pregnancy.

One study of SLE women has shown an increased risk of adverse outcome in subsequent pregnancies in aPL positive patients compared to aPL negative ones (146). The increased risk of recurrent pregnancy loss in women testing positive for aPL is well documented (147,148). However, no population based study of women with rheumatic disease using women without rheumatic disease as controls has addressed the risk of adverse outcome in a subsequent pregnancy.

3.8 How may pregnancy influence other connective tissue diseases and vice versa?

3.8.1 Systemic sclerosis (SSC)

In women with SSC, an increased number of miscarriages has been seen in several series (149,150) before (151,152) and after (153) onset of disease. In a retrospective study there was no increase in frequency of miscarriages (154). However, in a subset of women with
long-standing diffuse scleroderma, an increased rate of miscarriage was found (155-156).

In this case control study, a significantly increased risk of preterm birth (29%) was found in women with SSC compared to controls. An early retrospective study found a high frequency of full-term small infants (154), but in the latest study, only one preterm infant was small for date (155,156).

Some SSC patients may experience a temporary increase in skin thickening during pregnancy, but little overall change postpartum. In many cases of SSC, renal crises have been reported (157,158), but it has not been possible to demonstrate any significant effect of pregnancy on the development of that complication (154-156). However, most patients with renal crisis have early diffuse scleroderma. Raynaud phenomenon may improve during pregnancy, but esophageal reflux may become worse (155,156).

3.8.2 Sjögren’s syndrome (SS)

In early retrospective studies of patients with primary SS the fetal loss rate has varied between 7% and 24% and in two studies a significant increased risk has been found (159,160). One study has found increased levels of IgA-aCL in patients with primary SS (161), but this finding has not been confirm (160). No significant increase in the frequency of preterm births and FGR was found. Most primary SS patients have a mild course and may not even have been seen in centres treating systemic rheumatic diseases. In fact, the majority of pregnancies in primary SS occur before the onset of the disease. Primary SS, definite or subclinical, is the predominant autoimmune disease in mothers of children with isolated heart block (162).

3.8.3 Polydermatomyositis (PM/DM)
PM/DM may start during pregnancy, and onset of disease during pregnancy has been reported in 45% of cases (163). Exacerbations of the disease have been found in 15% of cases. Muscle fatigue and respiratory impairment are the greatest dangers to the pregnant patient with myositis. In late pregnancy, pulmonary fibrosis may compromise maternal respiratory reserve. Uterine contractions in labor usually proceed normally, but maternal weakness when “pushing” in the third stage may be a limiting factor. The risk to the fetus is dependent on the complications presenting during pregnancy and the therapy. Fetal loss rate has been reported to be 18% in inactive disease and 36% in active disease (163). Fetal loss occurred in 50% of mothers when the disease started during pregnancy. A high incidence of preterm birth (37%) was described.
Table 4 Fetal/Neonatal outcome in studies of women with connective tissue disease

<table>
<thead>
<tr>
<th>Author (year of publication) [Ref No]</th>
<th>Disease</th>
<th>Cases</th>
<th>Controls</th>
<th>Preterm birth †</th>
<th>Growth restriction †</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mintz (86) [81] *</td>
<td>SLE</td>
<td>75</td>
<td>114</td>
<td>49</td>
<td>20</td>
<td>S</td>
</tr>
<tr>
<td>Patzi (93) [103] **</td>
<td>SLE</td>
<td>203</td>
<td>283</td>
<td>24</td>
<td>NA</td>
<td>S</td>
</tr>
<tr>
<td>Julkunen (93) ***</td>
<td>SLE</td>
<td>112</td>
<td>192</td>
<td>16</td>
<td>9</td>
<td>S</td>
</tr>
<tr>
<td>Huong (94) [127]</td>
<td>SLE</td>
<td>103</td>
<td>-</td>
<td>63</td>
<td>29</td>
<td>-</td>
</tr>
<tr>
<td>Huong (97) [128]</td>
<td>SLE</td>
<td>38</td>
<td>-</td>
<td>60</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Camona (99)</td>
<td>SLE</td>
<td>46</td>
<td>-</td>
<td>21</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Georgiou (00) [221]</td>
<td>SLE</td>
<td>47</td>
<td>59</td>
<td>13</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>Yasmine (01) †† [107]</td>
<td>SLE</td>
<td>555</td>
<td>60 000</td>
<td>21</td>
<td>6.7</td>
<td>S</td>
</tr>
<tr>
<td>Cortes-Hernandez (02) [115]</td>
<td>SLE</td>
<td>60</td>
<td>-</td>
<td>27</td>
<td>35</td>
<td>-</td>
</tr>
<tr>
<td>Lima (96) [135]</td>
<td>APS</td>
<td>47</td>
<td>-</td>
<td>43</td>
<td>31</td>
<td>-</td>
</tr>
<tr>
<td>Steen (99) †† [156]</td>
<td>SSC</td>
<td>59</td>
<td>48</td>
<td>23</td>
<td>0</td>
<td>S</td>
</tr>
<tr>
<td>Steen (89) [154]</td>
<td>SSC</td>
<td>48</td>
<td>48</td>
<td>11</td>
<td>10</td>
<td>S</td>
</tr>
<tr>
<td>Julkunen (95) [160]</td>
<td>SS</td>
<td>21</td>
<td>42</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Talaya (91) [225]</td>
<td>SS</td>
<td>40</td>
<td>129</td>
<td>4</td>
<td>NA</td>
<td>NS</td>
</tr>
</tbody>
</table>

NA: data not available. S: Statistically significant difference between cases and controls. NS: not significant difference.
SSC: systemic sclerosis. SS: Sjögren’s syndrome. [Ref No]: Reference number
† Percentage of pregnancies in cases with preterm birth or fetal growth restriction (FGR).

* Case control study, preterm birth: p<0.0001; Small for gestational age: p<0.0001
** Case control study, preterm birth: Friends as controls OR 3.35 (95% CI 1.84-6.11); relatives as controls OR 3.56 (95% CI 2.13-5.96)
*** Case-control study, preterm birth: RR 5.8 (95% CI 3.2-10.5); FGR: RR 8.6 (95% CI 3.0-24.3)
†† Population based registry study: Preterm birth: OR 5.8 (95% CI 4.9-7.2); FGR: OR 5.6 (95% CI 4.1-7.8)
††† Case control study, preterm birth: RR 2.69 (95% CI 1.94-3.56).

3.9 Possible adverse effects of antirheumatic drugs on the pregnancy, the delivery, the fetus and the newborn
Therapy during pregnancy can influence fetal and neonatal health. Recent reviews have given comments on the possible adverse effects of antirheumatic drugs on the mother, the fetus and the newborn (164,165).

3.9.1 Non steroidal antiinflammatory drugs (NSAIDs)

NSAIDs may reduce inflammation of joints and may be indicated in active rheumatic disease during pregnancy. In a study of women with rheumatic disease treated with NSAIDs during pregnancy a reduction in birtweight was found, but no other significant increased risk of adverse pregnancy outcome was detected (166). In the mother, reported adverse effects of NSAID treatment in the third trimester are prolongation of pregnancy and labour as well as increased maternal blood loss at delivery (167,168). Prospective national surveillance drug studies (American Collaborative Perinatal Project, the Michigan Medicaid surveillance study, Swedish Registry for Drug use in Pregnancy) including several hundred thousand pregnancies have failed to demonstrate any increase in congenital abnormalities (169). A Swedish study found no increase in total birth defects in women using NSAID in the first trimester (170). However, in this study, increased risks of cardiac defects (n=36) and orofacial clefts (n=6) were found, but there was no drug specificity for cardiac defects and of six mothers of infants with orofacial clefts, five had used naproxen (170). These findings may be random, cardiac defects may be overreported and confounding by an underlying disease can not be excluded. The study has several limitations and e.g. that the exact exposure time and dosage are not known.

NSAIDs given in the latter part of gestation they can affect pregnancy and the fetus. NSAIDs inhibit prostaglandin synthesis, and may cause a reduction in renal blood flow.
and constriction of fetal ductus arteriosus. The risk of ductal constriction is markedly increased after 32 weeks of gestation. Thus, exposure to NSAIDs close to delivery may cause pulmonary hypertension in the newborn. An increased risk of blood clotting abnormalities or haemorrhage exists if maternal treatment with a non-selective COX-inhibitor or high dose aspirin continues until delivery (171). Low dose aspirin (60-80 mg daily) does not impair neonatal platelet aggregation nor does it impair renal or ductal blood flow (172,173).

A recent population based study found an increase in miscarriages in women using NSAIDs (174). Adjusted odd ratios for miscarriage decreased as the time between filling prescriptions and miscarriages increased. The results may be confounded by indication, they need confirmation before one can conclude that NSAIDs increase the risk of miscarriage.

3.9.2 Corticosteroids

A recent metaanalysis of epidemiological studies found a significantly increased risk of oral clefts after first trimester exposure to corticosteroids (175). Several studies of SLE pregnancies treated with 5 to 100 mg of prednisolone daily did not find any increased risk of birth defects or FGR (81,102,173). In some studies an increased incidence of low-birth-weight babies have been found in mothers on corticosteroids. PROM has been found in SLE pregnancies and during corticosteroid treatment (102,133).

3.9.3 Disease modifying antirheumatic drugs (DMARDs)

Except for two children with hip abnormality, no congenital malformations were observed in 102 children born to patients who had terminated gold therapy in early to mid pregnancy, or in the offspring of 26 patients treated with gold throughout pregnancy.
(176). One case of multiple fetal malformations in a mother who received 20 mg of aurothiomalate weekly during the first 20 weeks of pregnancy has been reported, but a relationship to gold therapy has been disputed (177). Information on the safety of gold during human pregnancy is insufficient.

The antimalarial drug chloroquine crosses the placenta and accumulates in the melanin-containing structures in the fetal uveal tract and inner ear. Abnormalities of the retina and the inner ear have been reported in five infants exposed to higher than recommended doses of chloroquine throughout pregnancy (178). More than 100 pregnancies treated with either chloroquine 250 mg or hydroxychloroquine 200-400 mg daily during the first trimester were not associated with an increase in congenital abnormalities (179-182).

Sulfasalazine use during pregnancy is mainly reported in literature concerning patients with inflammatory bowel disease. More than 300 pregnancies in patients with ulcerative colitis and nearly 800 in patients with Chron’s disease treated with either sulfasalazine alone or in combination with corticosteroids at some time during pregnancy have been reported (183). No increase in birth defects, or SGA babies was detected.

Accumulated data from renal transplant centers in North America and Europe on pregnancies in renal allograft recipients treated with corticosteroids and azathioprine found no predominant or frequent birth defect (184). Fetal growth restriction has sometimes been related to use of azathioprine and corticosteroids (185). However, the possible contribution of the underlying maternal disease is unclear. There is no indication
that azathioprine in doses 1.5 – 2 mg/kg/day is a strong teratogen or causes lasting
immunosupression in the neonate (164).

Cyclosporine is used primarily as an immunosuppressive drug to prevent rejection of
organ transplantation. The efficacy of cyclosporine has been demonstrated in RA and
SLE patients with lack of response on conventional therapy. More than 600 pregnancies
exposed to cyclosporine for several weeks, or throughout gestation, have been reported.
The observed rate of 3% congenital malformations does not exceed the rate reported in
the general population nor has any particular pattern of abnormalities emerged (186).

Major problems of cyclosporine-treated pregnancies were prematurity (< 37 weeks) in
40-46% and low birth weight (<2500g) in 44-65% of cases. To which extent the maternal
disease or drug treatment has contributed to these pregnancy outcomes is difficult to
decide.

3.9.4 Cytotoxic drugs

Methotrexate (MTX) is a folic acid antagonist which impairs dihydrofolate reductase and
interferes with the production of purines. Folic acid deficiency during early pregnancy
may lead to neural tube defects in the offspring. Closure of the neural tube takes place
during week 5, and therefore the embryo is probably most vulnerable to anti-folate drugs
at this time. The congenital anomalies observed in animals and humans exposed to MTX
in utero usually involved the central nervous system, cranial ossification, and the palate
(187). A total of 20 pregnancies exposed to MTX 20 mg or less once weekly has been
reported. Four pregnancies were terminated electively, four ended in miscarriage and of
the 12 proceeded to delivery, one child was born with the “aminopterin syndrome” (187).
The birthweights of the full-term infants were within the normal range.
Cyclophosphamide is an alkylating agent found to be teratogenic in all animal species studied. Birth defects have been reported in human fetuses after first-trimester exposure to cyclophosphamide with facial, skin, musculoskeletal and visceral organ anomalies, growth restriction and developmental delay (188). Intravenous cyclophosphamide given during the first trimester in seven pregnancies of six women with lupus nephritis resulted in 2 miscarriages, 1 elective termination of pregnancy, 2 children with multiple anomalies and 1 child with short arms and legs and only one healthy child.
4 Aims of the study

The general objective of the present study was to describe the effect of inflammatory arthritides and connective tissue disease on pregnancy, delivery and the newborn. This objective was attempted achieved by the following aims:

- To study possible associations between inflammatory arthritides or connective tissue disease and pregnancy complications as well as delivery practice in the period 1967-95 with emphasis on secular trends (Paper I).

  Specific aims:
  - To estimate the risk of pregnancy complications.
  - To estimate the risk of induction of labor and cesarean section.
  - To study the impact of inflammatory arthritides and connective tissue disease on perinatal outcome in the period 1967-95 with emphasis on secular trends (Paper II).

  Specific aims:
  - To estimate the risk of preterm birth.
  - To estimate the risk of SGA.
  - To estimate the risk of birth defects.
  - To estimate the proportion of infants with Apgar score <= 6 after 1 and 5 minutes.
  - To estimate perinatal and postperinatal mortality.

- To study the female reproduction after a diagnosis of inflammatory arthritides and connective tissue disease in the period 1967-95 (Paper III).

  Specific aims:
  - To estimate the mean number of births.
  - To estimate the maternal mean age at first and last birth.
- To estimate the subsequent pregnancy rate.
- To estimate the median interpregnancy interval.
- To study the recurrence risk of an adverse pregnancy outcome in subsequent pregnancies in women with inflammatory arthropides or connective tissue disease in the period 1967-95. (Paper IV).

Specific aims:
- To estimate the recurrence risk of preeclampsia, preterm birth, SGA, low birth weight, cesarean section and induction of labor in the second pregnancy (birth order two).
- To estimate the recurrence risk of markers of placental dysfunction in the second pregnancy.
- To assess the validity of a diagnosis of inflammatory arthropides and connective tissue disease in the Medical Birth Registry of Norway (MBRN) against a gold standard (local hospital databases) (Paper V).

Specific aims:
- To estimate the sensitivity of the MBRN, e.g. to ascertain a diagnosis of rheumatic disease.
- To estimate the correctness of type differentiation in the MBRN, e.g. to ascertain the correct diagnosis (type) of rheumatic disease.
5. Materials and methods

5.1 Data sources

5.1.1 The Medical Birth Registry of Norway (MBRN)

Established on the basis of compulsory notification introduced in Norway in 1967, MBRN comprises medical information on all live births and stillbirths at >= 16 weeks gestation. 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 (Fig 1). Until recently (1999), the notification form has not been changed since the start of the registration, except from the addition, in 1978, of Apgar scores. Midwives or physicians attending the birth complete a standardized form. The form contains demographic data on the child, the father and the mother, data on maternal health before and during pregnancy, complications and procedures during delivery, and the condition of the child at birth are available. The national person identification number makes it possible to link births into sibships.

5.1.2 The Center for Mothers with Rheumatic Disease,

Department of Rheumatology, University Hospital of Trondheim

In our Center, data on women with rheumatic disease who have given birth during the last two decades have been collected. Data have been collected on the basis of outpatient consultations, and the diagnoses have been verified on the basis of clinical examinations and hospital records (Ostensen M. Personal communication). The Center for Mothers with Rheumatic Disease gives information and advice to women with rheumatic disease who plan a pregnancy, during pregnancy and after delivery. Information about disease,
medication and prognosis is given. When necessary, clinical monitoring of maternal
disease and fetus is performed in collaboration with the National Center for Fetal
Medicine.
Fig 1 Notification form for the Medical Birth Registry of Norway in use 1967-1998.
5.2 Materials

5.2.1 Material: Papers I and II

We analyzed data on all single births in Norway during the period from 1967 to 1995, a total number of 1,546,325 there of 5,155 births in women with rheumatic disease. Cases were defined as all women for whom rheumatic disease was notified before or during pregnancy (n=3,403), while all women without such a diagnosis formed the reference group (n=6,712,221). Due to the small number of mothers with rare rheumatic diseases, cases were grouped into 3 categories according to ICD8:

1. Connective tissue diseases (CTD; ICD8:734 and 716; SLE, systemic sclerosis, Sjögren’s syndrome and polymyositis/dermatomyositis),

2. Specified inflammatory arthritides (SA; ICD8:712; rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis) and


To assess secular trends on the effects of rheumatic diseases possibly attributable to changes in disease expression, disease severity or medical practice, we compared data for three time periods: 1967-76, 1977-86 and 1987-1995. Secular trends in diagnosis and treatment of rheumatic diseases have been reported in several studies (10-12,15,16,43,44,189,190). Data regarding maternal rheumatic disease, pregnancy complications, delivery practice, and perinatal outcome were analysed in the present study.

5.2.2 Material: Papers III and IV

We analysed data for all single births in Norway in 1967 to 1995. By the mothers’ national identification number, all births were linked into sibships, which were used as
the unit of analysis. Sibships with multiple births and sibships in which the first birth occurred before 1967 were excluded. Cases were defined as all women with a rheumatic disease notified before the first birth (n=1933), all other women formed the reference group (n=672 691). The total number of births was 3,325 in women with rheumatic disease and 1,396,180 in references. All diseases were grouped into 3 categories according to the ICD8 as in paper I and II.

The following data was obtained: Number of births; maternal age at first and last birth, the subsequent pregnancy rate: the number of all women who continued from the first birth (birth order one) to a second birth (birth order two); interpregnancy interval: the time period from the date of the first birth to the first day of the last menstrual period of the subsequent pregnancy (second birth); infant survival: the proportion of all births after 16 weeks of gestation surviving the first year of life. The time periods 1967-76, 1977-86 and 1987-95 were used for some of the analyses.

Women with only one birth were excluded in paper IV. Cases were defined as all women for whom rheumatic disease was notified before the first birth (birth order one) (RD1, n=1065) or with a rheumatic disease notified after the first birth but before the second birth (birth order two) (RD2, n=919). Most had specified inflammatory arthritides: 85.3% of those who had a diagnosis before the first birth and 82.5% with a diagnosis before the second birth. Women with CTD represented only 5.4% (before first birth) – 7.8% (before second birth) of all women with rheumatic disease included in this study. All women without such a diagnosis formed the reference group (n = 487,432). Data regarding maternal rheumatic disease, pregnancy complications, delivery practice and perinatal outcome were analysed.
5.2.3 Material: Paper V

Data in hospital records were compared to the diagnoses notified to MBRN and coded by ICD8 in the MBRN. Patients included in the local databases were pregnant women with a diagnosis of rheumatic disease attending a pregnancy outpatient clinic and finally giving birth. Patients were selected from 3 areas of Norway according to changing affiliation of one of the authors (M Østensen). During the period 1979 - 1985 data on pregnant patients were derived from the University Hospital of Tromsø, Northern Norway, from 1986 to 90 patients from the University Hospital of Oslo, Southern Norway, and from 1991 to 95 from the University Hospital of Trondheim, Central Norway. A total of 217 patients were recorded. Altogether 48 patients were excluded due to either lack of year of diagnosis or delivery before the diagnosis was made. Name, identification number, diagnosis, time of diagnosis, number of births and birthdays of children were recorded. Data from the patient records were linked to the MBRN by the mother's national identification number. Diagnoses in the MBRN have been registered with the specific diagnosis (subtype) during pregnancy, and with the diagnostic category/ disease group (type) before pregnancy.

5.3 Study design

Papers I-IV are population registry based cohort studies. In papers I and II 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 papers III and IV a longitudinal cohort design within sibships, meaning all pregnancies or births to a woman (birth order 1-2) instead of pregnancy or birth per se, was used.
Table 5. Variables used in the various papers covering different domains, the outcome measure of effect, the statistical method and potential confounding factors adjusted or stratified for.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Domain</th>
<th>Outcome variable</th>
<th>Adjustment variable/stratification</th>
<th>Outcome measure of effect</th>
<th>Statistical method</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pregnancy complication</td>
<td>Abruptio placenta</td>
<td>1, 2, 3</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placenta previa</td>
<td>1, 2, 3</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Preclampsia</td>
<td>1, 2, STR</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td></td>
<td>Delivery practice</td>
<td>Induced labor</td>
<td>1, 2, STR</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cesarean section</td>
<td>1, 2, STR</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td>II</td>
<td>Perinatal health</td>
<td>Preterm birth</td>
<td>1, 2, STR</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SGA</td>
<td>1, 2, 3</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Birth defects</td>
<td>1, 2, 3</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stillbirth</td>
<td>1, 2, 3</td>
<td>OR</td>
<td>Log. Reg.</td>
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<tr>
<td></td>
<td></td>
<td>Early neonatal death</td>
<td>1, 2, 3</td>
<td>OR</td>
<td>Log. Reg.</td>
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<tr>
<td></td>
<td></td>
<td>Perinatal mortality</td>
<td>1, 2, 3</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postperinatal mortality</td>
<td>1, 2, 3</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td>III</td>
<td>Reproduction</td>
<td>Number of births</td>
<td>4, 5</td>
<td>N, mean</td>
<td>ANOVA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maternal age at first birth</td>
<td>-</td>
<td>Mean age</td>
<td>ANOVA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maternal age at last birth</td>
<td>4, 5</td>
<td>Mean age</td>
<td>ANOVA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subsequent pregnancy rate</td>
<td>4, 5, STR</td>
<td>RR</td>
<td>Cox</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interpregnancy interval</td>
<td>-</td>
<td>Median years</td>
<td>Kaplan</td>
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<tr>
<td></td>
<td></td>
<td>Probability of a second birth</td>
<td>4, 5</td>
<td>“Survival curves”</td>
<td>Meier</td>
</tr>
<tr>
<td>IV</td>
<td>Recurrence risk in second pregnancy</td>
<td>Preterm birth</td>
<td>6, 7, RD</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cesarean section</td>
<td>6, 3, RD</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induced labor</td>
<td>6, 3, RD</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SGA</td>
<td>6, RD</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low birth weight</td>
<td>6, RD</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placental dysfunction syndrome</td>
<td>6, RD</td>
<td>OR</td>
<td>Log. Reg.</td>
</tr>
</tbody>
</table>

Adjustment variables: 1=maternal age, 2=birth order, 3=time period, 4=infant survival, 5=maternal age at first birth, 6=maternal age at second birth, 7=interpregnancy interval, STR=stratified by time period, RD=variable dependent on the diagnosis of rheumatic disease before first or second birth and adverse event in first pregnancy. OR = odds ratio. Log. Reg. = Logistic regression, ANOVA= Analysis of variance, Cox = Cox regression.

5.4 Statistical analysis

5.4.1 Paper I and II
An overview of the statistical analyses is presented in table 5. Potential associations between rheumatic disease and pregnancy complications/delivery practice were examined in logistic regression models providing odds ratio estimates with adjustment for maternal age (< 19, 20-24, 25-29, 30-34, 35-39, 40+), birth order (one, two, three+) and time period (1967-76, 1977-86, 1987-95) (Paper I). The results were presented for each time period if a significant interaction between rheumatic disease and time period was found. Variance analysis was used to test for differences in mean maternal age and mean birth order between categories of rheumatic disease and the reference group. The analyses were performed by the statistical package SPSS for windows.

5.4.2 Paper III and IV

Differences between the disease groups and the reference group regarding mean number of births, and mean maternal age at first and last birth were tested by analysis of variance (Paper III). Analyses of mean number of births and maternal mean age at last birth were adjusted for infant survival and maternal age at first birth. Due to a higher proportion of women with rheumatic disease diagnosed in the last time period (CTD 73.1%, SA 59%) and the possibility of birth after the end of study (31st. December 1995), the analysis of the number of births and maternal age at last birth were also analysed with a restriction to at least 10 years follow up after last birth. Otherwise, an inclusion of these women would have caused a registration dependent reduction in the mean number of births and in the mean maternal age at last birth.

Interpregnancy intervals and subsequent pregnancy rate were estimated by Cox proportional hazards analysis, adjusted for maternal age at first birth and infant survival,
and due to an interaction between time period and rheumatic disease, specified for each
time period (Paper III). Women who did not have a subsequent pregnancy (second birth),
were treated as censored observations with censored time equal to the last data of
registration (31st. December 1995) or at the age of 50. The assumption of proportional
hazards was assessed by log-minus-log survival plots which give a visual inspection of
the proportional hazard assumption (191). Parallel curves in such a plot indicates that the
assumption is valid. Estimates from Cox analysis were used to calculate adjusted survival
curves.

To assess the recurrence risk of adverse outcomes in women with rheumatic disease, the
women were categorised into 6 groups according to whether the diagnosis was made
before the first birth (RD1), before the second birth (RD2) or no diagnosis (controls) and
whether the first pregnancy outcome was normal or adverse (Paper IV). The occurrence
of adverse outcomes in the second pregnancy in these 6 groups was compared by logistic
regression analysis. Odds ratios were adjusted for maternal age (<19, 20-24, 25-29, 30-
34, 35-39, 40+) at second birth. Due to secular trends in cesarean section and induction of
birth, the odds ratios were also adjusted for time period (1967-76, 1977-86, 1987-95).

Since an increased interpregnancy interval, as observed in women with rheumatic
disease, is associated with a higher risk of preeclampsia (192), odds ratios were also
adjusted for interpregnancy interval. We compared the recurrence rates in mothers with
rheumatic disease with rates among mothers without rheumatic disease with no adverse
outcome in the first pregnancy. Furthermore, we attempted to assess the excessive risk
attributable to rheumatic disease by comparing them to women without rheumatic disease.
with an adverse outcome in the first pregnancy. The analyses were performed with SPSS for windows 10.05.

5.4.3 Paper V

The sensitivity of MBRN was calculated as the proportion of all cases in the local databases that had a rheumatic diagnosis in MBRN. The correctness of type differentiation was calculated as the proportion of all cases notified to MBRN that was correct with respect to type of rheumatic disease in the local database. The diagnoses were defined as incorrect when the MBRN had registered a rheumatic disease not identical with the physician’s diagnosis. Since validity may vary with the year of delivery, we calculated sensitivity and correctness of type differentiation for each time period (1967-76, 1977-86 and 1987-95). The calculations were done with EpiCalc 2000 version 1.02.

6. Ethical considerations

The studies were approved by the local Ethical Review Committee.

7. Review of the results

7.1 Paper I

All together 0.5% of all women giving birth in Norway in 1967-95 had an inflammatory arthritis or connective tissue disease. The proportion of women with rheumatic disease giving birth increased from 0.1% in 1967-76 to 0.9% in 1987-95. Furthermore, the
proportion of women with SA was 0.43% and CTD 0.035% of all women giving birth in Norway 1967-95.

Mean age at delivery (CTD: 29.0 years, SA: 28.4 years) was statistically significantly higher (p<0.001) in women with rheumatic disease than in references (26.6 years). Mean birth order was highest in the NSA (2.3) and the SA (2.1) groups, which was higher (p<0.001) than in the CTD (1.9) and reference group (1.9).

Women with rheumatic disease had statistically significantly higher rates of preeclampsia and cesarean section. The risk of preeclampsia in the CTD group in 1967-75 was OR 2.80 (95%CI 1.92-4.09) and particularly high in 1977-86. In women with inflammatory arthritides, the risk of preeclampsia was slightly increased in 1987-95. The risk of cesarean section was high in all patient groups throughout the observation period and particularly in women with connective tissue disease (1977-86: OR 4.23, 95%CI 2.33-7.66 and 1986-95: OR 2.52, 95%CI 1.89-3.36). The rate of induction of labor was statistically significantly increased in the CTD group in 1987-95 (OR 2.16, 95%CI 1.62-2.89).

7.2 Paper II

Women with rheumatic disease had statistically significantly higher rates of preterm birth than references and this was only partly due to the increased occurrence of preeclampsia. The risk of preterm birth was highest in the CTD group in 1977-86 (OR 7.85, 95%CI 4.42-13.93). A larger proportion of infants with birth weight <2500g was found in all patient groups, the risk was particularly high in the CTD group (OR 5.82, 95%CI 4.43-7.65). The risk of SGA infants was statistically significantly higher
both in women CTD (OR 1.61, 95%CI 1.16-2.12) and inflammatory arthritides. The increased risk of low birth weight and SGA remained stable over time. The proportion of infants with Apgar score ≤ 6 after 1 minute and 5 minutes (OR 3.29, 95%CI 1.59-6.80) was statistically significantly increased in the CTD group. A slightly increased risk of birth defects was found in all patient groups, but the increase was statistically significantly only in the SA group (OR 1.21, 95%CI 1.03-1.41). The rate of perinatal mortality was high in the CTD group (OR 3.74, 95%CI 2.23-6.29) and postperinatal mortality was increased in infants born to mothers with rheumatic disease (CTD: OR 3.99, 95%CI 1.49-10.72 and SA: OR1.96, 95%CI 1.35-2.85).

7.3 Paper III

After the diagnosis was made, women with rheumatic disease (SA and CTD groups) had a statistically significantly lower mean number of births (CTD: mean 1.7, 95%CI 1.5-1.9) and a shorter time span of reproduction. Also, longer interpregnancy intervals (CTD: 1987-95; 4.0 years, 95%CI 2.4-5.6 and SA: 1987-95; 3.8 years, 95%CI 3.4-4.3) and reduced subsequent pregnancy rates (CTD: 1967-76; RR 0.22, 95%CI 0.07-0.69 and 1977-86; RR 0.53, 95%CI 0.31-0.89) were found in women with rheumatic disease. The subsequent pregnancy rates increased with time in the disease groups. Five years after the first birth 56.7% (95%CI 46.4-67.0) of CTD women, 61.6% (95%CI 58.9-64.4) of SA women and 57.1% (95%CI 49.2-65.1) of NSA women had their second birth compared to 69.1% (95%CI 68.0-70.3) of references (total period 1967-95).

7.4 Paper IV

Mainly women with specified inflammatory arthritides were included in this study which represented 85.3% of all women with a rheumatic disease with a diagnosis before first
birth and 82.5% with a diagnosis before second birth. Women with CTD represented only 5.4% (before first birth) – 7.8% (before second birth) of all women with rheumatic disease included in this study.

Women with rheumatic disease and adverse outcome in the first pregnancy had a statistically significantly higher recurrence risk of the same event in the second pregnancy than women without rheumatic disease (Preeclampsia: 25.9% vs 13.9%, OR 2.22, 95%CI 1.18-4.19; cesarean delivery: 61.2% vs 48.1%, OR 1.52, 95%CI 1.05-2.21; preterm birth: 26.0% vs 15.7%, OR 1.86, 95%CI 1.12-3.11). In women with rheumatic disease diagnosed between the first and the second birth, a statistically significantly increased recurrence risk of low birth weight occurred (29.5% vs 15.9%; OR 2.22, 95%CI 1.16-4.26). Women with rheumatic disease also had a higher occurrence of markers for placental dysfunction (preeclampsia, preterm birth or small for gestational age) in the second birth after any of these outcomes in the first birth (35.1% vs 29.2%; OR 1.35, 95%CI 1.02-1.78).

7.5 Paper V

After linkage of the MBRN and the local database, 149 of 169 mothers had a diagnosis of rheumatic disease notified to the MBRN, a sensitivity of 88.2%. Altogether 145 of these 149 diagnoses were correct with respect to type of rheumatic disease representing a correctness of type differentiation of 97.3%. Most of the mothers (57.3%) were registered in 1987-95 and only a small proportion (6.5%) in 1967-76. Also, most mothers were registered with a diagnosis of inflammatory arthritides. Connective tissue disease (CTD) mothers were only notified in 1987-95. The validity increased by year of birth.
8. Discussion

8.1 Methodological considerations

8.1.1 Random errors

Random error leads to loss of precision. Precision can be improved by increasing the sample size. In this study it was not possible to increase sample size because all births in Norway since 1967 have been recorded in the MBRN. Although the study population was large, small samples in the subgroups may represent a problem in some of the analyses.

8.1.2 Selection bias

Selection bias may occur if an exposed individual with an adverse outcome is more likely to be included. However, based on the entire Norwegian birth population, this cohort study was most likely not affected by selection bias.

8.1.3 Recall bias

Mothers may underreport rheumatic disease. If the association between an adverse pregnancy outcome and rheumatic disease is known to the mother, underreporting would particularly apply to women without an adverse pregnancy outcome. This may cause inflated relative risk estimates. However, such a recall bias would probably not apply to any extent since the data on maternal disease are registered prior to the birth. Furthermore, the high ascertainment of rheumatic disease in the registry is not compatible with such a recall bias.

8.1.4 Misclassification and ascertainment of diagnoses (Paper V)

Non-random or differential misclassification in a cohort study occurs when errors in the classification of individuals according to outcome are due to information on exposure in these individuals. Non random misclassification of rheumatic disease in the MBRN is
possible. Paper V reports the sensitivity of the MBRN data to ascertain a diagnosis of rheumatic disease and the correctness of type differentiation, reflecting one aspect of positive predictive value, e.g. to ascertain the correct diagnosis of rheumatic disease. By linking a smaller database to the MBRN, a high validity of diagnoses of rheumatic disease in the MBRN was found (sensitivity of 88.2% and a correctness of type differentiation of 97.3%). However, due to insufficient data and lack of sensitive and specific diagnostic tools, a lower validity is suspected for the period 1967-76. This is reflected by the decrease of the diagnosis “unspecified arthritis” found by us comparing the first to the last time period. A higher number of incorrect diagnoses may deflate the risk estimates. However, only a total of 2.7% of the diagnosis had an incorrect type differentiation in the present study. Furthermore, nearly all of these mothers had a diagnosis of rheumatic disease such as unspecified arthritis or rheumatism. Undefined arthritis was frequently registered at first birth and later on a more specified diagnosis like RA was recorded at a subsequent birth, perhaps because the development of the fullblown clinical picture was delayed. The statistical effects of these findings on the outcome measures are probably not important and are unlikely to change the relative risks observed in our previous studies. However, misclassification might influence the differences between disease groups, but only to some extent. There will be no effect at all on the outcome measures of the 11.8% of the mothers lacking a diagnosis.

Another way to validate MBRN diagnoses would have been to check the hospital records of all cases with rheumatic disease in MBRN to ascertain false positive cases, assessing the positive predictive value. This would have been timeconsuming and expensive.
Differences in pregnancy outcome between disease groups and references could be markedly disturbed only by a large increase in incorrect diagnoses (false positives) and not by lack of diagnoses (false negatives). However, our data do not indicate such a misclassification, particularly not for the periods 1977-86 and 1987-95. On the other hand, data from the first time period should be interpreted with caution due to a possibly higher misclassification.

The result in our study fits to some extent with the prevalence data of rheumatic disease in women of comparable age in some, but not in all epidemiological studies (10,16,17,193-196) (Table 6). However, different diagnostic criteria have been used in different time periods and the completeness of other registries and studies varies which make comparison with the MBRN even more difficult. Due to the small proportions of women with rheumatic disease, particularly in the first time period (1967-76) (Table 7), one might suspect an underreporting of rheumatic disease in this period. Although, rheumatic disease may be under-reported in the MBRN, the proportions of women with different types of rheumatic disease indicate approximately the prevalence rates of the types of the disease in the total cohort of mothers in the study period. Improved diagnostic, monitoring and treatment of women with rheumatic disease is reflected in a higher clinical attention and better health care of these women and may have contributed to the increase in the reported proportion of women with rheumatic disease in the Norwegian maternal population in 1967-95.

Due to the coding practice at the MBRN, most of the diagnoses were presented in broad diagnostic categories (type) (ICD 8 codes like 712) before pregnancy and with a more
specific diagnosis (subtype) (ICD8 codes like 712.3) during pregnancy. The linkage
between the local database and the MBRN was performed at the Locus of registry based
epidemiology, University of Bergen. To avoid the problems due to small numbers of
patients, we found it necessary to compare disease groups (inflammatory arthritides
versus CTD) rather than specific diseases. Consequently, we calculated the numbers of
women and births in the disease groups (types) of rheumatic disease (CTD, SA, NSA)
(Table 7).

<table>
<thead>
<tr>
<th>Reference [Ref No]</th>
<th>Population</th>
<th>Disease</th>
<th>Study period or year</th>
<th>Year (published)</th>
<th>Age</th>
<th>Prevalence % (females)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Aho et al [194]</td>
<td>Finland</td>
<td>RA</td>
<td>1978-80</td>
<td>1989</td>
<td>30-49</td>
<td>0.46</td>
</tr>
<tr>
<td>**Hochberg [195]</td>
<td>England, Wales</td>
<td>RA</td>
<td>1972</td>
<td>1990</td>
<td>15-44</td>
<td>0.25</td>
</tr>
<tr>
<td>***Kvien et al [193]</td>
<td>Norway</td>
<td>RA</td>
<td>1994</td>
<td>1997</td>
<td>20-39</td>
<td>0.15</td>
</tr>
<tr>
<td>†Riise [10]</td>
<td>Norway</td>
<td>RA</td>
<td>1994</td>
<td>2000</td>
<td>30-39</td>
<td>0.16</td>
</tr>
<tr>
<td>††Gran et al [196]</td>
<td>Norway</td>
<td>AS</td>
<td>1979-80</td>
<td>1984</td>
<td>20-49</td>
<td>0.60</td>
</tr>
<tr>
<td>Nived et al [17]</td>
<td>Sweden</td>
<td>SLE</td>
<td>1982</td>
<td>1985</td>
<td>15-44</td>
<td>0.059</td>
</tr>
<tr>
<td>†††Voss et al [210]</td>
<td>Denmark</td>
<td>SLE</td>
<td>1995</td>
<td>1998</td>
<td>39.2(mean)</td>
<td>0.038</td>
</tr>
<tr>
<td>††††Nossent et al [18]</td>
<td>Norway</td>
<td>SLE</td>
<td>1996</td>
<td>2001</td>
<td>30-49</td>
<td>0.10</td>
</tr>
</tbody>
</table>

[Ref No]: Reference number
*Aho: 30-39 years: 0.2% (seropositive RA).
**Hochberg: In 1982: 0.28 % period prevalence in the same age group.
***Kvien: 40-49 years: 0.43% prevalence
†Riise: 20-29 years: 0.03% prevalence
‡Gran: 30-39 years: 0.3% prevalence
††Voss: Point prevalence in 1995, Definite SLE, (incomplete SLE: 0.052% prevalence)
†††Nossent: Point prevalence in the arctic region of Norway in 1996.
Table 7. Number and proportions of women with rheumatic disease in MBRN, 1967-95.

<table>
<thead>
<tr>
<th>Time period</th>
<th>CTD* N (%)</th>
<th>SA** N (%)</th>
<th>NSA*** N (%)</th>
<th>Ref† N</th>
<th>Total N (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967-76</td>
<td>19 (0.008)</td>
<td>228 (0.091)</td>
<td>101 (0.041)</td>
<td>247554</td>
<td>247902</td>
</tr>
<tr>
<td>1977-86</td>
<td>40 (0.019)</td>
<td>884 (0.423)</td>
<td>125 (0.059)</td>
<td>207758</td>
<td>208807</td>
</tr>
<tr>
<td>1987-95</td>
<td>180 (0.082)</td>
<td>1759 (0.807)</td>
<td>67 (0.031)</td>
<td>215909</td>
<td>217915</td>
</tr>
<tr>
<td>1967-95</td>
<td>239 (0.035)</td>
<td>2871 (0.426)</td>
<td>293 (0.029)</td>
<td>671221</td>
<td>674624</td>
</tr>
</tbody>
</table>

*CTD: connective tissue disease, *SA: specified inflammatory arthritides, **NSA: non specified inflammatory arthritides, †Ref: Reference group.

8.1.5 Ascertainment of other data

At low gestational age, stillbirths might have been considered abortions and thus not notified (MBRN 1997). Still, routinely updated with the Central Population Registry and the Cause of Death Registry, both run by Statistics Norway, ascertainment of births as well as perinatal deaths is considered almost complete. Data from MBRN and a perinatal database at the University Hospital of Tromsø have been compared (197). The proportion of spontaneous onset of preterm birth was nearly identical in MBRN and in Tromsø. Ascertainment of birth defects varies according to the diagnoses with high ascertainment in diagnoses easily made at birth, like orofacial clefts and neural tube defects, while in non-overt diagnoses the ascertainment may be lower (198).

8.1.6 Preeclampsia

Data from MBRN and a perinatal database at the University Hospital of Tromsø were compared and the incidence of pregnancy induced hypertension and preeclampsia was of the same order of magnitude in MBRN and in Tromsø (197).

In the first time period of our study, not only cases with both hypertension and proteinuria were included in the clinical definition of preeclampsia, but also cases with
either hypertension or proteinuria without renal disease (199). The proportion of preeclampsia cases according to this definition in the MBRN has declined through the years from 34.7% (n=794) in 1967 to 2.3% (n=48) in 1995. As previously mentioned, most of the patients with rheumatic disease have been registered in the MBRN in the last time period. In recent years a more strict definition of preeclampsia has been used requiring both hypertension and proteinuria (200,201). One of the intentions of the study was to study secular trends and we therefore found it most correct to be consistent in all time periods and to include not only patients with both hypertension and proteinuria, but also those with only hypertension or proteinuria (without renal disease). If we had used only the updated criteria of preeclampsia in the first time period, we could have introduced a bias in the secular trend resulting in a false time trend.

However, we also intended to study the proportions of pregnancies with preeclampsia according to modern criteria. The results of this analysis showed that the risk of preeclampsia in the CTD group in 1967-95 was OR 2.54 (95%CI: 1.67-3.87) which is slightly lesser than OR 2.80 (95%CI: 1.92-4.09) (Paper I). In women with rheumatic disease the OR of preeclampsia, according to the revised definition, remained unchanged in the period 1987-1995. In 1977-86, a reduction in the risk of preeclampsia was found in the CTD group from OR 9.47 (95%CI: 5.19-17.28) to OR 7.48 (95%CI: 3.72-15.03). Only minor changes in the odd ratios were found in the other disease groups in 1967-76 and 1977-86. When using the revised definition of preeclampsia in estimating the recurrence risk of preeclampsia, a higher risk was found in women with rheumatic disease compared to women without rheumatic disease.

8.1.7 Confounders
In any study in which an outcome variable and exposure variable are associated with a third variable, adjustment may be necessary, provided that the association between the outcome variable and the third variable (a possible confounder) is independent of the exposure and not merely an intermediate link in the causation (202). In order to control for confounding factors, factors that distort the apparent effect of the exposure of interest, adjustment were made.

Due to lack of data on socioeconomic status and education, we could not adjust for these variables in the Cox regression analyses of mean number of births, subsequent pregnancy rate and interpregnancy intervals. However, there is no evident association between rheumatic diseases and these variables. The MBRN does not contain data on drugs, which may influence fertility and probably pregnancy outcome. Most rheumatic diseases are not life threatening disorders and are therefore not treated with potent immunosuppressive medication during pregnancy.

Where appropriate we have adjusted for maternal age, birth order, and time period in the logistic regression analyses of pregnancy outcome.

Due to different perinatal mortality in exposed and non-exposed, Cox regression analyses were adjusted for infant survival. In the analyses of mean number of births, subsequent pregnancy rate and interpregnancy interval we adjusted for maternal age at first birth. In the logistic regression of the recurrence risk of adverse pregnancy outcome in second pregnancy, we adjusted for maternal age at second birth and also interpregnancy interval in the estimation of recurrence risk of preeclampsia.

Other cofounders not measured, are environmental exposures such as alcohol and smoking, nutritional factors or viral disease may influence the results. However, there is
no reason to believe that these potential confounders should be differentially distributed between the disease group and the reference group. In fact, women with rheumatic disease often take vitamin supplements and eat healthy food from which they may benefit (203-205).

**Gestational age**

We did not adjust for gestational age in the logistic regression analyses since gestational age may be considered a variable. Thus, odd ratios or relative risks were only slightly reduced when we adjusted for gestational age in the logistic regression analyses. The reduction was highest in the CTD group. The higher proportion of pregnancies in the CTD group with gestational age from 28-36 weeks at birth may be due to the disease causing pregnancy complications with subsequent preterm birth and preterm labor. This assumption is supported by a statistically significantly higher proportion of women with rheumatic disease with cesarean section or induction in the gestational age 28-36 weeks at first and second birth compared to references. Due to insufficient registration, abortions before 16 weeks of gestation and births after 46 weeks of gestation were not included.

**8.1.8 Limitations and advantages**

The methodological limitations have been discussed with focus on several aspects, but particularly on possible reduced validity of diagnoses in the first time period (1967-76) and also the lack of drug data and other possible confounders which may influence the results. As a consequence of medical progress, the definition of preeclampsia has changed during the study period. Except for a slight decrease in the OR for preeclampsia in the CTD group in the middle period, no major impact has been found of this change in
definition on the preeclampsia risk. (In a prospective follow up study, a consistency in
definition would have to be a prerequisite.)

The major advantage of the present study is the nation wide population based design
including a large number of births with a follow up in a longitudinal cohort design.

Furthermore, the data can be reorganized in sibships allowing for analyses of subsequent
pregnancy rate, interpregnancy intervals as well as recurrence risks. To our knowledge,
this is the first study of women with rheumatic disease using such a study design.

8.2 Interpretation and comparison with other studies

8.2.1 Pregnancy complications

Preeclampsia

It has long been known that connective tissue diseases, particularly SLE and related
disorders, affect pregnancy outcome. The significantly increased rate of preeclampsia
(revised definition; 1967-1995: OR 2.54, 95%CI 1.67-3.87) is therefore not unexpected.
However, other studies have found a much higher occurrence of preeclampsia in SLE
pregnancies, varying between 30% and 50% (91,106,206,207). In a retrospective case
(n=203) control (n=192) study of lupus pregnancies the risk of preeclampsia was OR1.67
(95%CI 1.07-2.59) compared to best friends as controls and OR 5.85 (95%CI 3.35-10.23)
compared to relatives as controls (103). Pregnancies after a diagnosis of SLE were more
likely to have preeclampsia than pregnancies before a diagnosis of SLE (OR 4.81, 95%CI
2.81-8.20). However, these studies were not population based. A recent population based
study of SLE pregnancies showed an increased rate of maternal hypertensive
complications (OR 8.6,95%CI 5.2-14.1) compared to controls, but preeclampsia was not
defined (107). Patients with an increased activity of SLE, a history of lupus nephritis, hypertension and higher steroid doses are more susceptible to develop preeclampsia (87, 88, 91, 206-209). Furthermore, epidemiological studies of SLE in Norway, Sweden and Denmark have indicated less hematological, renal and cerebral complications in Scandinavian women with SLE than those in other countries (16-18,189,210-212).

The slight increased rate of preeclampsia (revised definition; 1967-1995: OR 1.20, 95%CI 1.02-1.42) in patients with inflammatory arthritides was unexpected, as this has not been reported in previous studies of RA, AS or JCA pregnancies (68,70,72,213). This may be due to the small number of patients in several of the previous studies and the lack of controls. In a recent prospective case control study of women with inflammatory polyarthritis (RA and undifferentiated polyarthritis) who had babies of lower birth weight, no instances of preeclampsia was found (75). In a study of normal women, an increased risk of preeclampsia was observed both for women who had HLA-DR4 and for mother-child pairs who shared HLA-DR4 (214). Another study found a significant association between HLA-DR4 and preeclampsia (215). However, the reported increase in HLA-DR4 in mothers and infants from preeclamptic pregnancies has not been confirmed for mothers (216).

Placental abruption

Except for some reports among aPL positive patients (217-219), an increased occurrence of placental abruption has not been reported in women with connective tissue disease (220) (Paper I, Table 1). Placental abruption may be regarded as part of a placental dysfunction syndrome, a cause of FGR and fetal loss (197). Another finding was the
increased rate of umbilical cord complications seen in women with inflammatory arthritis, particularly in 1967-76, for which we have no explanation (Paper I).

8.2.2 Delivery practice

We found a significantly higher rate of induction and cesarean section in all patient groups (Paper I, Table 3), whereas no such difference was found for other types of instrumental deliveries. Cesarean section was positively associated with maternal age and negatively with birth order in all three periods. Complications, which as a rule result in instrumental deliveries, were not more frequent in any of the rheumatic disease groups compared to references. In our present study, women with and without preeclampsia had similar cesarean section rates. Thus, since patients without preeclampsia also had an increased rate of cesarean section, there must have been additional indications. Indications for surgical delivery were not analyzed in our study, but we analysed the proportion of elective or emergency cesarean section in the period 1988-1995 (Table 8). The risk of elective cesarean section in CTD women fits with data in previous reports. However, in a recent case control study higher risk of emergency cesarean section in CTD women has been reported than in the present study (107). In this retrospective population based case (n=555) control (n=60 000) study a significant increase in non-elective cesarean section was found in SLE women. The most important indications were hypertensive complications (OR 15.8, 95%CI 10.0-24.7), fetal distress (OR 1.8, 95%CI 1.3-2.4), failed induction (OR 2.0, 95%CI 1.3-3.3) and antepartum hemorrhage (OR 1.7, 95%CI 1.1-2.8) (107). Increased rates of cesarean section have been reported in CTD (87,106,114,128), AS (72) and JCA (68,74).
We found an increased rate of mainly elective cesarean sections, particularly in the CTD group (Table 8), but also the rate of elective performed as emergency cesarean section and the rate of emergency cesarean section was slightly increased, both in women with CTD and inflammatory arthritides. Recently, a prospective case control study has also found an increased rate of cesarean sections of 23% in RA (11% emergency procedures) (75). The reasons for emergency cesarean section in this study were fetal distress or failure to progress in delivery. Except for this study of RA women (75), there is lack of data concerning the risk of elective versus emergency cesarean sections in women with inflammatory arthritides. All together 28% of AS women had cesarean sections and in 58% of the cesarean deliveries the reason was AS (72). Cesarean section was performed in 39% of the JCA women. The major indication was bilateral hip prosthesis (68).

Table 8. The proportions of elective or emergency cesarean sections in births of women with rheumatic disease and references, MBRN 1988-1995

<table>
<thead>
<tr>
<th>Type of CS**</th>
<th>Diagnostic groups</th>
<th>1988-1995</th>
<th>Total N</th>
<th>N</th>
<th>%</th>
<th>OR*</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective CS</td>
<td>CTD</td>
<td></td>
<td>232</td>
<td>32</td>
<td>13.8</td>
<td>3.48</td>
<td>2.39-5.07</td>
</tr>
<tr>
<td></td>
<td>SA</td>
<td></td>
<td>2412</td>
<td>183</td>
<td>7.6</td>
<td>1.76</td>
<td>1.51-2.05</td>
</tr>
<tr>
<td></td>
<td>NSA</td>
<td></td>
<td>95</td>
<td>4</td>
<td>4.2</td>
<td>0.93</td>
<td>0.34-2.53</td>
</tr>
<tr>
<td></td>
<td>Ref</td>
<td></td>
<td>423719</td>
<td>17565</td>
<td>4.1</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>EICS-EmCS***</td>
<td>CTD</td>
<td></td>
<td>232</td>
<td>3</td>
<td>1.3</td>
<td>2.36</td>
<td>0.76-7.40</td>
</tr>
<tr>
<td></td>
<td>SA</td>
<td></td>
<td>2412</td>
<td>32</td>
<td>1.3</td>
<td>2.38</td>
<td>1.67-3.38</td>
</tr>
<tr>
<td></td>
<td>NSA</td>
<td></td>
<td>95</td>
<td>2</td>
<td>2.1</td>
<td>3.67</td>
<td>0.90-14.93</td>
</tr>
<tr>
<td></td>
<td>Ref</td>
<td></td>
<td>423719</td>
<td>2261</td>
<td>0.5</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Emergency CS</td>
<td>CTD</td>
<td></td>
<td>232</td>
<td>26</td>
<td>11.2</td>
<td>1.86</td>
<td>1.23-2.81</td>
</tr>
<tr>
<td></td>
<td>SA</td>
<td></td>
<td>2412</td>
<td>179</td>
<td>7.4</td>
<td>1.20</td>
<td>1.03-1.40</td>
</tr>
<tr>
<td></td>
<td>NSA</td>
<td></td>
<td>95</td>
<td>4</td>
<td>4.2</td>
<td>0.80</td>
<td>0.29-2.19</td>
</tr>
<tr>
<td></td>
<td>Ref</td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OR (odds ratio) estimates calculated by logistic regression and adjusted for maternal age and birth order. **CS: cesarean section. ***EICS-EmCS: elective CS performed as emergency CS.

8.2.3 Perinatal outcome
Preterm birth

Our study shows that perinatal health in children of mothers with rheumatic disease was compromised in several ways including preterm birth, low birthweight and SGA. These complications have previously been observed in CTD, particularly in SLE and SSC (81,103,91,135,128,155), but not in inflammatory arthritides, except for preterm birth which was found increased (but not statistically significantly) in one study of RA pregnancies (154). In a recent case control study of SLE women, no significant increase in preterm birth was found (221). The wide variation in the risk of preterm birth in previous studies may be due to small numbers of pregnancies, but also different definition (< 36 week or < 37 weeks or < 38 weeks), and improvement in monitoring and treatment may influence the results. However, another recent retrospective population based case control study found a statistically significantly increased risk of preterm birth in SLE patients (OR 5.8, 95%CI 4.9-7.2) (107).

In SLE, there are several causes of preterm birth among which premature rupture of membranes (PROM) has been recognised as the most important (106,91,133), especially in patients taking prechisolone (114). In our study, the occurrence of PROM was not increased compared to references. Although, there was no significant interaction (p=0.3838) between rheumatic disease and time period regarding preterm birth, we found it necessary to show data for each time period (Paper II, Table 1). During 1977-95 preterm birth occurred statistically significantly more often in the CTD and SA groups, with the peak observed in 1977-86 for CTD. Also, a peak proportion of preeclampsia was found in CTD women in the same time period. Adjusted for preeclampsia, the risk of preterm birth was slightly reduced in the CTD group in 1977-86 from OR 7.85 (95%CI
4.42-13.93) to OR 6.01 (95%CI 3.33-10.98). Preeclampsia was probably a contributing factor for preterm birth in women with CTD, but was not the main factor since a statistically significantly increased rate of preterm birth also occurred in patients without preeclampsia. Other factors like active disease (103), decidual vasculopathy (50) and treatment with immunosuppressive drugs (164,165,222) may contribute, but were not analysed in our study.

SGA

The increased proportions of preterm births and low birthweight infants were not unexpected. However, the statistically significantly increased rate of SGA infants in all patients groups and not only in those with CTD (Paper II, Table 2), was unexpected and has not been reported previously (68,70,72).

Several studies have shown SGA infants in SLE pregnancies (81,91,103,105), particularly during active disease, renal lupus and hypertension, preeclampsia and when antiphospholipid antibodies (aPL) were present (81,91,105,135). A recent population based study of SLE women showed a statistically significantly lower mean birth weight, stratified by gestational age, compared to controls (107).

Previous studies on pregnancy outcome in patients with inflammatory arthritides have not reported an increase in SGA infants. However, in a recent prospective case (n=133) control (n=103) study women with RA or undifferentiated inflammatory polyarthritis had a higher rate of babies with a slightly lower birth weight than controls (75). Particularly, women with active disease during the last trimester of pregnancy had lighter babies than the minority whose disease was in complete remission, but there was no statistically significantly difference between these two subgroups when adjusted for
gestational age and birth order (75). Complete remission of arthritis during pregnancy is rare, and the question arises if there is sufficient continuing disease activity to have a modest effect on fetal growth in women with inflammatory polyarthritis. Since the polyarticular joint diseases tend to improve during pregnancy, immunosuppressive treatment is not likely to be a reason for SGA in these diseases. There is no evidence to suppose different smoking habits during pregnancy (155,223). Interestingly, in our study, the proportion of infants with low birthweight and SGA remained stable over time. This may suggest that neither improved monitoring nor treatment of high-risk pregnancies have influenced this aspect of neonatal health.

*Birth defects*

We found a modest, yet significant increase in birth defects in the children of women with inflammatory arthritides, an unexpected finding not easy to explain (Paper II, Table 3). Commonly used antirheumatic drugs including NSAIDS, prednisolone, azathioprine, sulphasalazine, antimalarials and gold have previously shown no effect on the malformation rate (164-165,224). Cytotoxic drugs are not given to pregnant rheumatic patients at least during the first trimester and can thus not be responsible for our observation (164-165). Also, there was no change with time suggesting that secular trends in medication are unlikely to have influenced the rate of birth defects. It is not possible to say if inflammatory rheumatic disease per se is a risk factor for birth defects or whether other factors are involved.

*Apgar score*

A reduced Apgar score in infants of women with CTD as found in our study has also been observed in infants of SLE women in a recent study (114). However, in this study
the mean Apgar score in neonates of SLE patients was 7.6 at 1 minute and 8.8 at 5 minutes and there were no controls. In the CTD group in our study, the increased perinatal mortality and the significant increased proportion of infants with Apgar score < 6 after 1 minute and 5 minutes may indicate SGA, intrauterine stress conditions or fetal hypoxia.

Perinatal and postperinatal mortality

Most studies of rheumatic diseases and pregnancy have focused on fetal loss (including both abortions and stillbirths)(104,160, 225,226), but few studies have addressed perinatal health. In our study, we found a statistically significantly higher rate of perinatal mortality in infants of women with CTD (Paper II, Table 4 and 5). Since definitions of stillbirth and early neonatal death are different in our study and other studies, we cannot make a direct comparison. In other studies of CTD the perinatal mortality rate varies from 0.5% to 8% (91,103,105,132,138,155,227,228). The increased postperinatal mortality rate (not reported in previous studies) in infants of women with rheumatic disease (Paper II, Table 5) may partly be due to the increased occurrence of SGA infants which have a higher mortality in the first year of life than appropriate for gestational age infants (229). However, after adjustment for SGA there still was a significant increase in postperinatal mortality indicating that also other factors may be relevant.

8.2.4 Family size

We found a statistically significantly lower mean number of births and a reduced period of reproduction in women with rheumatic disease compared to references (Paper III, Fig 1). In women with CTD, a higher risk of miscarriage before 16 weeks of gestation might
contribute to the lower number of children (103,132). However, our study did not include
data on first trimester pregnancy loss. Previous studies of SLE and systemic sclerosis
have reported slightly reduced numbers of births in patients compared to controls
(145,155). A prospective study of planned SLE pregnancies found no difference in the
birth rate in SLE patients compared to the normal population (128). Except for one
population based retrospective study (77) and two other studies of RA women (78,79), no
other studies of patients with RA have found a statistically significant reduction in
number of births (70,230-233). The discrepancy between our results and those previously
reported may partly be due to a different study design. Our study was population based
and included the total cohort of mothers giving birth between 1967-95, whereas several
other studies have had small sample sizes and also selection biases in both cases (only
cases who plan a pregnancy) and controls (friends, relatives, neighbourhood, newspaper
advertising) which may reduce or increase potential differences between cases and
controls.

8.2.5 Subsequent pregnancy rate and interpregnancy interval

We also found an increased interpregnancy interval and a reduced subsequent pregnancy
rate in women with rheumatic disease (Paper III, Table 2 and Fig 2). A secular trend was
observed with an increasing subsequent pregnancy rate from the first to the last time
period, possibly indicating better monitoring and treatment of women with rheumatic
disease in the last decades and improved ability to deal with high-risk pregnancies. In a
previous study of healthy women, the most important factors influencing the
interpregnancy interval were the outcome of the previous pregnancy, social class and
maternal age (234). In our study, the interpregnancy interval was significantly increased
in women with rheumatic disease corrected for maternal age. It is less likely that social
class or cultural differences have influenced our results. The Norwegian population
comprises 95% Caucasians and is socioeconomically fairly homogeneous. The country
has public health care and social security systems covering all citizens and particularly
beneficial for families with small children. Loss of income due to disease is almost
completely compensated for by social security. Previously, we have reported a higher
perinatal and postperinatal mortality in births of women with rheumatic disease (Paper
II). When the subsequent pregnancy rate was adjusted for infant survival, it remained
statistically significantly decreased.

Few studies have addressed interpregnancy interval in women with rheumatic disease
(235), but one study has found an increased interval to conception in RA cases prior to
the first, second and third pregnancies (77). A number of factors may cause an increased
interpregnancy interval and a reduced reproductive period. Miscarriage before 16 weeks
of gestation may cause increased interpregnancy interval. Adverse pregnancy or
postpartum experience may reduce the wish for a subsequent child. An increased
interpregnancy interval has been observed after cesarean section (236). However,
rheumatic disease may also reduce the ability to conceive either by hormonal
disturbances induced by the disease process or medications applied (237,238). Also, a
significantly reduced fecundity in RA patients before disease onset has been reported
(80). Recently, reduced fecundity has been found in JCA women (74). Some
antirheumatic drugs (like cytotoxics) are not compatible with pregnancy (164) or some
(like NSAIDs) can disturb ovulation (239). Unfortunately, drug data are not available in
the MBRN. Another factor influencing family size is the frequency of sexual intercourse
which has been found to be reduced in women with rheumatic disease, possibly due to impaired function and reduced sexual desire (240).

8.2.6 Recurrence risk of adverse outcome in the second pregnancy

In general, previous adverse outcomes predict subsequent adverse pregnancy outcomes, and rheumatic disease increased the risk of recurrence up to twofold. Thus, we found that the increased recurrence risk of pregnancy events like preeclampsia, preterm birth, low birth weight and SGA was even higher in women with rheumatic disease (Paper IV, Table 1-4). Furthermore, rheumatic disease increased the recurrence risk of an adverse pregnancy outcome independent of the time of diagnosis (before first or second birth).

No other population based study of inflammatory arthritis and CTD, exist for comparison.

Women with rheumatic disease, particularly with CTD, have an increased risk of preeclampsia and preterm birth. Both events tend to recur in a subsequent pregnancy even without a diagnosis of rheumatic disease. Two other population based studies (241, 242) have shown that previous preeclampsia predicts preeclampsia in a subsequent pregnancy with an estimated OR between 11.8 and 20. Our study confirmed this finding and showed that the recurrence risk of preeclampsia and preterm birth is even higher in women with rheumatic disease. In another population based study of women without rheumatic disease, previous low birth weight was associated with increased risk of preeclampsia (243). Possibly, a shared etiological factor or a recurrent pathophysiological mechanism may cause fetal growth restriction in the first pregnancy and preeclampsia in the next. Consistent with this, occlusive changes in spiral arteries caused by inadequate trophoblast invasion early in pregnancy have been found in preeclampsia as well as
normotensive FGR (244, 245). On the basis of our finding, one might speculate that an autoimmune mechanism may contribute as well (246,247).

In our present study, the risk of a second SGA infant was not significantly increased in a rheumatic mother compared to a reference mother, but the recurrence risk of low birth weight was significantly higher. Furthermore, the recurrence risk of cesarean section or induction in second birth was higher than in references which partly explains the higher risk of preterm birth and low birth weight, and may indicate that disease related conditions increase the propensity to undertake such obstetrical interventions (Paper IV, Table 5 and 7). The proportions of women with rheumatic disease having induction or cesarean section at the second birth were significantly higher in all the gestational age groups, particularly in 28-36 weeks (p<0.000), 37-41 weeks (p<0.000), than in references. Similar findings were present at first birth.

9. Conclusions and implications

- A slightly increased risk of preeclampsia was found in women with inflammatory arthritides. A higher risk was found in women with CTD.
- A higher risk of induction and cesarean section (both elective and emergency) was found in women with rheumatic disease. From 1977-86 to 1987-95 a reduction in the risk of cesarean section was found in the CTD group.
- The risk of preterm birth was higher in women with rheumatic disease, particularly in women with CTD.
- The risk of SGA was increased.
• The risk of birth defects was slightly increased in offspring of women with specified inflammatory arthritides.

• An increased proportion of offspring in CTD women had an Apgar score \( \leq 6 \) after 1 and 5 minutes.

• Perinatal mortality was higher in offspring of women with CTD.

• Postperinatal mortality was higher in offspring of women with rheumatic disease and particularly of CTD.

• After the diagnosis was made, a reduced family size (mean number of births) was found in women with rheumatic disease.

• Women with rheumatic disease had a higher maternal mean age at first birth and a lower maternal mean age at last birth than references, indicating a shorter time span of reproduction.

• The subsequent pregnancy rate was reduced in women with rheumatic disease compared to references. An increase in the subsequent pregnancy rate from the first to the last time period was found.

• The median interpregnancy interval was longer in women with rheumatic disease.

• Women with rheumatic disease and one of the adverse outcomes (preeclampsia or cesarean section or preterm birth) in the first pregnancy had a higher recurrence risk of the same event in the second pregnancy.

• Women with rheumatic disease diagnosed before second birth had an increased recurrence risk of low birth weight.

• In women with rheumatic disease a slightly higher occurrence of any adverse pregnancy outcome including preeclampsia, preterm birth or SGA in the second birth
after any of the same outcomes in the first birth (recurrent placental dysfunction) was
found.

- Taking into consideration the limitations in the study of validity, in terms of the
  small numbers of mothers and the lack of CTD diagnoses in 1967-76, the validity
  (sensitivity and correctness of type differentiation) of rheumatic disease diagnoses in
  the MBRN is assumed rather high in the period 1977-95.

Our population based study shed new light on different aspects of pregnancy
complications and delivery practice in these patients. We have shown that not only CTD,
but also inflammatory arthritides may affect pregnancy as shown by increased rates of
preeclampsia and surgical delivery. The mechanisms for these findings are unknown, but
warrant further research.

Furthermore, this study is the first population based study to show that perinatal outcome
is comprised in children born to mothers with rheumatic disease, including women with
inflammatory arthritides. Since this observation showed no time trend, it seems unrelated
to secular changes in treatment and monitoring of pregnant patients with rheumatic
disease. We hypothesise that the disease process of the mother has an impact on perinatal
health. Studies are needed to elucidate the factors responsible for a negative perinatal
outcome.

In spite of the fact that women with rheumatic disease do wish for children (248), our
study indicates that these women have a reduced family size. Many factors may be
involved and vary from one patient to another. To improve counselling, further studies of
possible factors involved are necessary.
Adverse pregnancy outcome and recurrent pregnancy complications are increased in women with rheumatic disease, particularly in women with connective tissue disease. As a consequence, we have established an interdisciplinary pregnancy clinic for women with rheumatic disease where patients are monitored and treated according to the risk calculated from individual disease characteristics and previous pregnancy experience. Counselling before a planned pregnancy by specialists in internal medicine and obstetrics is always offered as well as monitoring of placental function and fetal surveillance by a specialist in fetal medicine in case of any known risks.

As documented in our study, several aspects of reproductive life in women with rheumatic disease may be affected. However, except for women with CTD, there is no high risk of pregnancy complications in women with rheumatic disease compared to women without rheumatic disease. In fact, the risk of pregnancy complications is higher in diabetic women than in women with rheumatic disease when compared to references, particularly in the first time periods (249,250).

10. Errata

*Paper I*

P 491, Statistical analyses

The following sentence should be omitted:

The chi-square method was used to test for differences in proportions.

P 492, Table 1

The number of references with abruptio placentae now reads: n=90979.
The number of references with abruptio placentae should read: \( n = 9079 \).

P 492, Table 2.

The number of references with preeclampsia in 1987-95 now reads: \( n = 1593 \)
The number of references with preeclampsia in 1987-95 should read: \( n = 15930 \)

P 492, Table 2

The percentage of NSA with preeclampsia in 1987-95 now reads: 3.4%
The percentage of NSA with preeclampsia in 1987-95 should read: 0.8%

P 493, Table 3

The number of references with cesarean section in 1967-76 now reads: 1369
The number of references with cesarean section in 1967-76 should read: 13690

Paper II

P 353, Table 1

The footnote now reads: OR estimates provided by logistic regression and adjusted for maternal age, birth order and time period.
The footnote should read: OR estimates provided by logistic regression and adjusted for maternal age and birth order.

Paper III

P 2312, Table 2

The percentage of subsequent pregnancy in CTD women in 1987-95 now reads: 40%
The percentage of subsequent pregnancy in CTD women in 1987-95 should read: 43%.

Paper IV

The Table numbers in the previous version of the manuscript have been changed in the offprint: Table 1 has been numbered Table 8 (p 1200), Table 2 has been numbered
Table 1 (p1197), Table 3 has been numbered Table 2 (p1197), Table 4 has been numbered Table 3 (p 1198), Table 5 has been numbered Table 4 (1198), Table 6 has been numbered Table 5 (p 1199), Table 7 has been numbered Table 6 (p 1199) and Table 8 has been numbered Table 7 (p 1200).

P 1199, Table 5 (offprint)

The footnote in Table 4 in the previous version of the manuscript read: Estimates provided by logistic regression and adjusted for maternal age at second birth, and using controls with no cesarean delivery in first pregnancy as reference group.

The footnote in Table 5 in the offprint now reads: Estimates provided by logistic regression and adjusted for maternal age at second birth and time period, and using controls with no cesarean delivery in first pregnancy as reference group.
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