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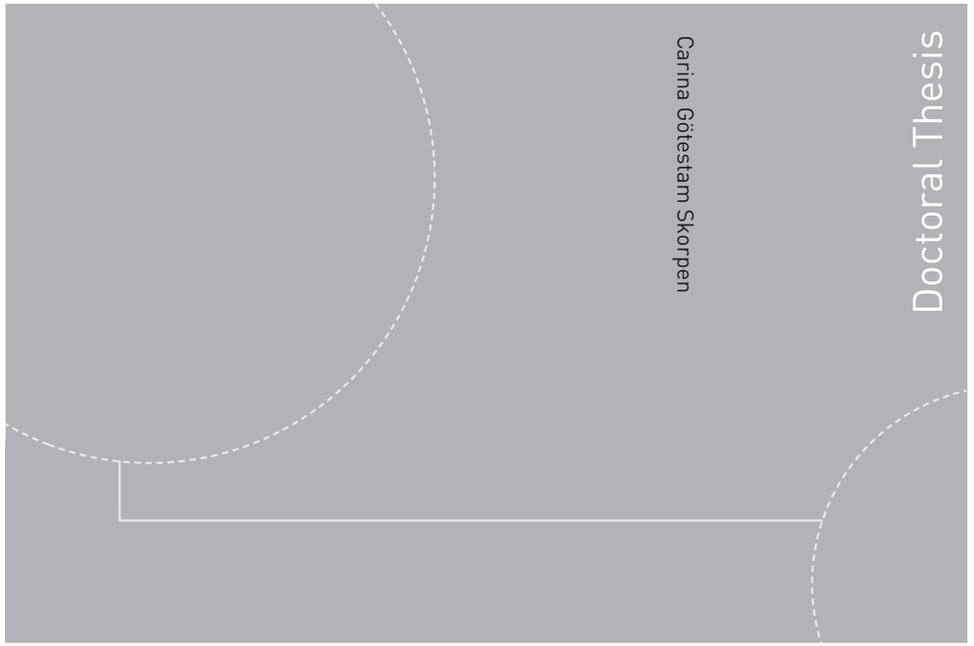

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Results from a prospective multicenter study

Thesis for the degree of Philosophiae Doctor

Trondheim, June 2018

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Interaksjonen mellom svangerskap og systemisk lupus erythematosus – resultat fra en prospektiv multisenter studie.

Systemisk Lupus Erythematosus (SLE) er en kronisk revmatisk sykdom som oftest rammer unge kvinner. Kvinner med SLE har økt risiko for komplikasjoner relatert til svangerskap og fødsel, inkludert svangerskapsforgiftning, for tidlig fødsel (før svangerskapsuke 37) og veksthemning hos barnet.

Høy sykdomsaktivitet i månedene før og i svangerskapet er en kjent risikofaktor, mens inaktiv sykdom eller lav sykdomsaktivitet er et godt utgangspunkt for et minst mulig komplisert svangerskap når det ikke foreligger andre risikofaktorer. SLE er en sykdom hvor symptombildet varierer over tid, i form av perioder med inaktiv sykdom eller lav sykdomsaktivitet alternerende med perioder med symptom økning (oppbluss). Tidligere studier har vist at rundt halvparten av gravide kvinner med SLE har målbar sykdomsaktivitet, og at en like stor andel har ett eller flere oppbluss i løpet av svangerskapet.

RevNatus er et landsdekkende norsk svangerskaps-register som ble etablert i 2006. Kvinner med revmatisk sykdom inkluderes ideelt sett når de planlegger svangerskap (visitt 0), og følges opp i hvert trimester i svangerskapet (visitt 1-3) og 6 uker, 6 og 12 måneder etter fødsel (visitt 4-6). Medisinsk fødselsregister (MFR) er et helseregister som har eksistert siden 1967, hvor alle svangerskapsutfall i Norge etter svangerskapsuke 12 er meldepliktige (spontane aborter, dødfødsler og levende fødsler).

Denne avhandlingen inneholder tre artikler som handler om hvordan svangerskapet påvirker SLE og hvordan sykdommen påvirker svangerskapet og svangerskapsutfall. Data ble hentet fra RevNatus for perioden 2006 til 2016 (artikkel 1, 2 og 3), og fra medisinsk fødselsregister for perioden 2006 – 2015 (artikkel 2).

Målsettingen for den første artikkelen var å beskrive sykdomsaktivitet gjennom svangerskapet og det første året etter fødsel hos kvinner med SLE inkludert i RevNatus. Sykdomsaktiviteten ble registrert på hver visitt, med et mål som er validert for bruk hos gravide med SLE. Over halvparten av sykdomsaktivitetsmålingene (51.6%) registrert i svangerskap og året etter fødsel (visitt 1-6) indikerte at sykdommen var inaktiv, 42.1 % indikerte lav sykdomsaktivitet og bare 6.3% indikerte moderat aktiv sykdom. Modellen viste en statistisk signifikant og klinisk betydningsfull endring i sykdomsaktivitet over tid, og illustrerer variasjonen i sykdommen. Vi fant også at kvinnene hadde høyere sykdomsaktivitet 6 og 12 måneder etter fødsel sammenlignet med i 3. trimester og 6 uker etter fødsel.

I artikkel to ønsket vi å beregne og sammenligne forekomsten av svangerskapsforgiftning og for tidlig fødsel hos kvinner med inaktiv SLE, kvinner med aktiv SLE og populasjonskontroller, og å beregne og sammenligne barnets fødselsvekt (uttrykt gjennom z-score) i de samme gruppene. Data fra RevNatus ble koblet med data fra medisinsk fødselsregister. Vi fant at forekomsten av svangerskapsforgiftning og for tidlig fødsel var høyere hos kvinner med inaktiv SLE og kvinner med aktiv SLE enn hos populasjonskontroller, og at den var høyest hos kvinnene med aktiv SLE. Vi fant ingen økt sannsynlighet for svangerskapsforgiftning hos kvinner med inaktiv SLE sammenlignet med populasjonskontroller, men derimot hos kvinner med aktiv sykdom sammenlignet både med populasjonskontroller og kvinner med inaktiv SLE. Det var økt sannsynlighet for fødsel før

svangerskapsuke 37 hos kvinner med inaktiv SLE sammenlignet med populasjonskontroller, og for kvinner med aktiv SLE sammenlignet både med populasjonskontroller og kvinner med inaktiv SLE. Fødselsvekt justert for svangerskaps-alder og kjønn (z-score) var lavere hos barn av kvinner med inaktiv og aktiv SLE sammenlignet med hos barn av populasjonskontroller, og det var økt forekomst av barn små for gestasjonsalder (SGA) hos kvinnene med SLE.

I den tredje artikkelen ville vi undersøke om det er forskjeller mellom kvinner med SLE og kvinner med leddgikt (RA) med barneønske, når det gjelder andel som blir gravide i en gitt oppfølgingsperiode, og hvor mange måneder det tar før de blir gravide. Vi ønsket å kartlegge helserelatert livskvalitet og sammenligne denne hos de som ble gravide og de som ikke oppnådde graviditet. Vi sammenlignet derfor kvinner med SLE og kvinner med RA som var inkludert i RevNatus før de ble gravide (visitt 0). Det var en større andel kvinner med SLE enn kvinner med RA som ble gravide i oppfølgingsperioden, og de brukte kortere tid på å oppnå graviditet. Kvinner med SLE som ikke ble gravide, hadde lavere livskvalitetsmål i enkelte domener enn de som ble gravide. Kvinner med RA som ikke ble gravide hadde høyere gjennomsnittsalder og brukte NSAIDs i større grad enn de som oppnådde graviditet, mens alle kvinner med RA hadde livskvalitets-målinger som tydet på lav helserelatert livskvalitet.

Resultatene fra den første artikkelen viser at de fleste gravide kvinner med SLE i Norge har inaktiv sykdom eller lav sykdomsaktivitet i svangerskapet og året etter fødsel, noe som tyder på velbehandlet sykdom og god oppfølging. Høyere sykdomsaktivitet 6 og 12 måneder etter fødsel indikerer at oppfølgingen i relasjon til svangerskap bør inkludere det første året etter fødsel for å fange opp og behandle økende sykdomsaktivitet i denne perioden.
Selv om kvinnene i vår studie hadde lav sykdomsaktivitet, viste resultatene fra den andre artikkelen at det å ha aktiv sykdom utgjør en betydelig risiko for komplikasjoner sammenlignet med inaktiv sykdom. Den kliniske betydningen er å tilstrebe inaktiv sykdom før og i svangerskap, for å motvirke komplikasjoner hos flere kvinner med SLE. Det betyr også at oppfølgingen kan differensieres på bakgrunn av om pasienten har inaktiv eller aktiv sykdom. Resultatene i den siste artikkelen peker på viktigheten av å ta opp familieplanlegging tidlig i sykdomsprosessen for å identifisere begrensende faktorer for å oppnå graviditet hos kvinner med revmatisk inflammatorisk sykdom.

Cand. med. Carina Götestam Skorpen
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Hovedveileder: Marianne Wallenius
Biveiledere: Stian Lydersen, Inge-Margrethe Gilboe, Kjell Åsmund Salvesen og Johan Skomsvoll
Finansieringskilde: Regionalt samarbeidsorgan for utdanning, forskning og innovasjon, Forskningsutvalget Helse Møre og Romsdal.
Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden PhD i klinisk medisin.
Disputas finner sted i Auditoriet, Ålesund sykehus, torsdag 7. juni 2018 kl 12.15.

Learn from yesterday, live for today, hope for tomorrow.

The important thing is not to stop questioning.

Albert Einstein

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Without the participants of RevNatus, this thesis could never have been written. I am very grateful, and thank you all for your unique contribution.

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*Betanien hospital, Skien; Diakonhjemmet hospital, Oslo; Haugesund Sanitetsforenings Rheumatism Hospital, Haugesund; Haukeland University Hospital, Bergen; Helse Førde, Førde hospital, Førde; Helse Møre og Romsdal, Ålesund Hospital, Ålesund; Lillehammer Hospital for Rheumatic diseases, Lillehammer; Nordland hospital, Bodø; Oslo University Hospital Rikshospitalet, Oslo; Private practice Anne N Bendvold, Kristiansand; St Olavs hospital, Trondheim University Hospital; Trondheim; Sørlandet Hospital Kristiansand, Kristiansand; University Hospital of North Norway, Tromsø; Vestre Viken Hospital, Drammen; Østfold hospital,Moss; Helgeland Hospital, Mo i Rana and Private practice Cybele Kristo;Oslo.

SUMMARY

The interaction of pregnancy and systemic lupus erythematosus - results from a prospective multicenter study

Systemic Lupus Erythematosus (SLE) is a chronic rheumatic disease affecting young women. Pregnancy in these women entails increased risk of preeclampsia, preterm birth (< 37 weeks) and growth retardation of the child.

High disease activity before conception and during pregnancy is a well-known risk factor, while inactive disease or low disease activity is a good basis for the least complicated course if there are no other risk factors present.

SLE is a fluctuating disease, with inactive disease alternating with flares. Earlier studies have found that one of two pregnant women with SLE has measurable disease activity, with a similar proportion experiencing flares during pregnancy.

RevNatus is a nationwide Norwegian pregnancy register established in 2006. Women with rheumatic diseases are ideally included before conception (visit 0), and have follow-up each trimester (visit 1-3) and at 6 weeks, 6 and 12 months after birth (visit 4-6).

The Medical Birth Registry of Norway (MBRN) is a registry with mandatory notification of all pregnancy outcomes after week 12 (miscarriages, fetal deaths and live births), existing since 1967.

This thesis includes three papers focusing on the influence of pregnancy on SLE and how SLE affects pregnancy and pregnancy outcomes. Data was extracted from RevNatus during 2006 to 2016 (paper 1, 2 and 3) and from MBRN during 2006 to 2015 (paper 2).

The aim of the first paper was to describe disease activity during pregnancy and the first year after birth in women with SLE included in RevNatus, applying a disease activity score validated for use in pregnancy. Disease activity was registered longitudinally at visit 1 through 6. The disease activity scores indicated inactive disease in 51.6%, low disease activity in 42.1% and only 6.3% indicated moderate disease activity. The model showed a

statistically significant and clinically meaningful change over time, illustrating the relapsing and remitting course of the disease. The women had higher disease activity 6 and 12 months after birth compared to 3rd trimester and 6 weeks after birth.

In the second paper we wanted to estimate and compare the occurrence of preeclampsia and preterm birth in women with inactive SLE, women with active SLE and population controls, and to estimate and compare birthweight (expressed as z-score) in offspring of these three groups. Data from RevNatus were linked with data from MBRN. We found that the occurrence of preeclampsia and preterm birth was higher in women with SLE than population controls, and highest in women with active SLE. We found no increased odds for preeclampsia in women with inactive disease compared to population controls, while women with active SLE had increased odds compared to both population controls and women with inactive SLE. Preterm birth had higher odds in women with inactive SLE than population controls, and higher odds in women with active SLE compared to both population controls and inactive SLE. Birthweight adjusted for gestational age and gender (z-score) was lower in offspring of women with inactive and active SLE compared to offspring of population controls, with an associated higher occurrence of small for gestational age (SGA) in offspring of women with SLE.

In the third paper we sought to investigate possible differences in women with SLE and women with rheumatoid arthritis (RA) concerning the ability to get pregnant and time to pregnancy, and to register and compare health-related quality of life (HRQoL) in women achieving and not achieving pregnancy. We compared women with SLE and women with RA included in RevNatus before pregnancy (visit 0). There was a higher percentage of women with SLE achieving pregnancy during follow-up as compared to women with RA, and they had a substantially shorter time to pregnancy. Women with SLE not achieving pregnancy had lower HRQoL than women achieving pregnancy. Women with RA not achieving pregnancy

were older and used NSAIDs more frequently compared to women achieving pregnancy. Women with RA had generally low HRQoL-scores whether or not achieving pregnancy.

The results from the first paper demonstrate that most pregnant women with SLE in Norway have inactive disease or low disease activity during pregnancy and the first year after birth. This indicates satisfactory treatment and follow-up. Higher disease activity 6 and 12 months after birth substantiates the need for follow-up to include the first year after birth, to detect and treat flares and increased disease activity. Even though the women in our population had low disease activity, the results from the second paper demonstrates that active disease represents a considerable risk for complications compared to inactive disease. The clinical implication is to strive for inactive disease before and during pregnancy, to diminish the risk in more women with SLE. It also allows for a differentiated follow-up according to disease activity status. The results in the third paper points to the importance to discuss and reveal issues of family planning in women with rheumatic inflammatory disease early in the course of the disease.

TABLE OF CONTENTS

DEFINITIONS AND ABBREVIATIONS

Definitions

Fecundity: the capacity to have a live birth

Fertility: the capacity to establish a pregnancy

Low birthweight (LBW): < 2500 gram

Preterm birth: < 37 weeks of gestation

Small for gestational age (SGA): < 10 percentile for the gestational age

Subfertility: time to pregnancy exceeding 12 months

Time to pregnancy (TTT): time taken to establish a pregnancy, measured in months

Total fertility rate: the average number of live births per woman

Very preterm birth: < 34 weeks of gestation

Abbreviations

ABA: abatacept

ACR: American College of Rheumatology

ACPA: anti-citrullinated protein antibody

AMH: Anti- Müllerian hormone

Anti-CCP: anti-cyclic citrullinated peptide

AIR: annual incidence rate

aPL: antiphospholipid antibody

APS: antiphospholipid syndrome

APO: adverse pregnancy outcome

AZA: azathioprine

BEL: belimumab

bDMARD: biologic DMARD

BMI: body mass index

CA: chronic active

CNS: central nervous system

CRP: c-reactive protein

csDMARD: conventional synthetic DMARD

CYC: cyclophosphamide

CZP: certolizumab

DAS28: disease activity score by 28 joint count

DMARD: disease-modifying antirheumatic drug

EULAR: European League Against Rheumatism

ESR: erythrocyte sedimentation rate

ETA: etanercept

GH: global health

HCQ: hydroxychloroquine

HRQoL: health-related quality of life

ICD-10: the International Statistical Classification of Diseases and Related Health Problems, 10th Revision

IFN: interferon

IL: interleukin

LAI: Lupus Activity Index

LAI-P: Lupus Activity Index in Pregnancy

LQ: long quiescent

MBRN: The medical birth registry of Norway

MAR: missing at random

MCAR: missing completely at random

MMF: mycophenolate mofetil

MNAR: missing not at random

m-LAI: modified Lupus Activity Index

MTX: methotrexate

NKSR: The Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases

NSAID: non-steroidal anti-inflammatory drug

PGA: physician global assessment

PP: point prevalence

RA: rheumatoid arthritis

RAND 36: 36-item, patient-reported survey of patient health

REC: Regional ethics committee

RF: rheumatoid factor

RR: remitting relapsing

SGA: small for gestational age

SLE: systemic lupus erythematosus

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

SLEPDAI: Systemic Lupus Erythematosus Pregnancy Disease Activity Index

SLICC: Systemic Lupus International Collaborating Clinics criteria for classification of systemic lupus erythematosus

SSZ: sulphasalazine

SPSS: The Statistical Package for the Social Sciences

STATA: statistics and data analysis program

T2T: treat to target

TFR: total fertility rate

TLR: toll-like receptor

TNFi: tumor necrosis factor inhibitor

TOF: tofacitinib

TOZ: tocilizumab

Tregs: regulatory T-cells

tsDMARD: targeted synthetic DMARD

TTP: time to pregnancy

LIST OF PAPERS

1. Götestam Skorpen C, Lydersen S, Gilboe IM, Skomsvoll JF, Salvesen KÅ, Palm Ø, Koksvik HSS, Jakobsen B, Wallenius M.
   Disease Activity During Pregnancy and the First Year Postpartum in Women With Systemic Lupus Erythematosus.
   Arthritis Care Res (Hoboken). 2017 Aug;69(8):1201-1208. doi: 10.1002/acr.23102. Epub 2017 Jul 10.

2. Götestam Skorpen C, Lydersen S, Gilboe IM, Skomsvoll JF, Salvesen KÅ, Palm Ø, Koksvik HSS, Jakobsen B, Wallenius M.
   Influence of disease activity and medications on offspring birth weight, pre-eclampsia and preterm birth in systemic lupus erythematosus: a population-based study.
   Ann Rheum Dis. 2018 Feb;77(2):264-269. doi: 10.1136/annrheumdis-2017-211641. Epub 2017 Nov 1.

3. Götestam Skorpen C, Lydersen S, Gilboe IM, Skomsvoll JF, Salvesen KÅ, Palm Ø, Koksvik HSS, Jakobsen B, Wallenius M.
   Women with SLE get pregnant more easily than women with RA.
   Rheumatology (Oxford). 2018 Mar 14. doi: 10.1093/rheumatology/key049. [Epub ahead of print]

BACKGROUND

My motivation for pursuing this project is threefold.

I was brought up in a home with focus on scientific thinking, and even before medical school I attended the first research-training course in Trondheim, founded by my father. All his professional life he promoted research as an important and necessary resource for improving health care. He performed research, taught students and supervised PhD-candidates, eager to obtain new insights to serve his patients.

In my work as a rheumatologist I have met many women with rheumatic diseases. Having a family affects all aspects of life and acquiring a chronic disease implicates that an extra piece needs to be fitted in the puzzle of daily living. As a mother I experience happiness, worry, pride, concern and the love that defines parenthood, and I cherish these feelings every day of my life. For me, treating a woman with a rheumatic disease has to include caring for her when childbearing is an issue.

I completed my speciality as a Rheumatologist at St Olavs Hospital in 2007. The pregnancy register RevNatus was established in 2006, and when I moved back to Ålesund, I brought RevNatus with me. This initiated my commitment to the follow-up of pregnant women with rheumatic diseases in Møre og Romsdal. As a professional, I wish to provide the best possible care to women with rheumatic diseases before, during and after pregnancy and contribute with knowledge to improve treatment, counselling and monitoring in this important and at times challenging setting.

1 INTRODUCTION

The Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases (NKSR) is located at the department of Rheumatology at St Olavs hospital in Trondheim. The predecessor was the Center for Pregnancy and Rheumatic Diseases, established in 1992. The main task of NKSR is to hold competence about subjects related to pregnancy and the puerperium in all rheumatic diseases, and to convey this knowledge to rheumatologic departments, other health care providers and patients. Conducting this task promotes equality in treatment and follow-up in pregnant women with rheumatic diseases in Norway. NKSR is available to answer questions from patients and health professionals, and organizes seminars and lectures regionally and nationally. The other important task is to perform research, aiming at contribution of empirical evidence to improve knowledge in this field.

RevNatus is a nationwide Norwegian observational register including women with different rheumatic diseases when they plan pregnancy or early in pregnancy, with follow-up in each trimester and the first year after birth. It was established as a research register in 2006 and evolved into a quality register in 2015. RevNatus is administered by NKSR. It serves two main functions, parallel to the tasks of NKSR. Primarily, it promotes equal quality of treatment and follow-up in pregnant women with rheumatic diseases throughout Norway. Secondarily, the registered information is available for research purposes. The professional milieu constituting NKSR and the existence of RevNatus are the two prerequisites for this project. This thesis is based on data gathered in RevNatus from its establishment in 2006 through 2016, and it is the first time the register has been applied to answer research questions.

Rheumatic inflammatory diseases

The inflammatory rheumatic diseases include arthritic diseases, connective tissue diseases and vasculitides, and are heterogenic regarding symptoms, damage potential, treatment options and long-term outcome (1, 2). In RevNatus a woman with any inflammatory rheumatic disease who plans pregnancy or is pregnant may be included, after written informed consent. In my thesis, the focus is women with systemic lupus erythematosus (SLE) and pregnancy. The comparison of women with SLE to women with rheumatoid arthritis (RA) in the last paper requires a less extensive presentation of RA and pregnancy.

Systemic lupus erythematosus (SLE)

SLE is a chronic rheumatic disease that may affect any organ in the body. It is a heterogenic disease regarding clinical course and severity, with geographical variations and change over time (3, 4). The clinical expression differs between ethnicities (5). Incidence and prevalence is higher in women compared to men regardless of age and ethnicity (4). The etiology involves genetic predisposition, influence of gender and environmental factors, and there are multiple pathways involving the innate and adaptive immunity (6). One important pathway for SLE is chronic activation of the type 1 interferon (IFN) (7) resulting in inappropriate stimulation of the immune system and a subsequent development of autoimmunity (6). The response is sexually dimorphic, probably associated to differential effects of estrogen and testosterone on type 1 IFN responses and may explain differences in risk and disease activity in males and females (8).

The American College of Rheumatology (ACR) classification criteria for SLE, revised in 1982 and 1997 (9, 10), are shown in Table 1. The criteria were developed for scientific reasons, but are commonly used in the diagnosis of SLE. Presence of any four or more of the

11 criteria, serially or simultaneously and during any interval of observation, indicates a diagnosis of SLE. The 1997 revised ACR-criteria are applied in RevNatus.

Table 1. The 1997 revised ACR-criteria for classification of SLE*(9, 10)

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3.Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis-convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion *OR* b) Pericarditis-documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not peformed *OR* b) Cellular casts-may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	a) Seizures-in the absence of offending drugs or knownmetabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance *OR* b) Psychosis-in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	a) Hemolytic anemia-with reticulocytosis *OR* Leukopenia-less than 4,000/mm3 total on 2 or more occasions *OR* Lymphopenia-less than 1 ,500/mm3 on 2 or more occasions *OR* Thrombocytopenia-less than 100,000/mm3 in the absence of offending drugs
10. Immunologic disorder	a) Anti-DNA: antibody to native DNA in abnormal titer *OR* b) Anti-Sm: presence of antibody to Sm nuclear antigen *OR* c) Positive finding of antiphospholipid antibodies based on 1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2) a positive test result for lupus anticoagulant using a standard method, or 3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test.
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with “drug-induced lupus” syndrome

* The proposed classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation

In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) criteria were developed. According to the SLICC rule for classification of SLE, the patient must satisfy at least four of 17 criteria, including one clinical and one immunologic criterion or the patient must have biopsy-proven lupus nephritis in the presence of antinuclear antibodies (ANA) or anti-double-stranded DNA antibodies (anti-dsDNA) (11). In the validation of the two criteria

sets, SLICC had improved sensitivity, but lower specificity than the 1997 revised ACR criteria (11). The classification criteria sets were similar in classifying SLE in an uncontrolled real-life scenario (12), with a sensitivity of 97% and 92% respectively, and an equal specificity of 99%. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) collaborate to develop new ACR/EULAR criteria, with the objective to increase sensitivity, maintain specificity and improve performance of the criteria in early disease (13).

A cohort of Caucasian patients with newly diagnosed SLE from 11 European countries, found few regional differences in disease presentation and management. The most frequently reported symptoms were arthritis (69%), leukocytopenia (54%) and malar rash (53%), and clinical signs of lupus nephritis (LN) in 39%. Despite early reduction in disease activity, the risk for disease flare and damage accrual was substantial during follow-up (14). Commonly described patterns of disease in SLE are long quiescent (LQ), relapsing-remitting (RR) and chronic active (CA) disease (15, 16). In a prospective lupus-cohort of Scandinavian ancestry patients LQ and RR of almost equal size was identified, with the RR pattern most common in younger patients (17). In a retrospective observational study of patients with SLE in five European countries, patients with black African descent had higher disease activity, more severe disease and more annual flares compared to white European patients (3). Ethnic differences in the expression and severity of disease were also pointed out in the LUMINA-cohort, concluding with higher disease activity and more damage accrual in non-Caucasian populations (Hispanics, African descendants and Asians) (18).

In Scandinavia, the lowest incidence and prevalence is in Denmark (19), while prevalence is similarly higher in Sweden and Norway (20, 21). In a northern Norwegian cohort, the annual incidence rate (AIR) and point prevalence (PP) per 100 000 at risk were 2.6 (4.6 in women and 0.6 in men) and 49.7 (89.3 in women and 9.7 in men) in the period 1978 to 1996 (22). A

gradually increasing PP overall was most prominent in women aged 30 – 49 years (PP 101.5 in 1996). Similarly, annual incidence rate and point prevalence were 3.0 (5.0 in women and 0.8 in men) and 51.8 (91.0 in women and 10.7 in men) in a southern Norwegian cohort in the period 1999 to 2008 (20). The annual incidence rate had a bimodal age peak in women at 16 to 29 (8.1) and 50 to 59 (5.9) years.

Persons with SLE have increased mortality, and carry an increased risk of cardiovascular disease, osteoporosis, malignancy and infectious disease (23) compared to the general population. In a Norwegian population-based study, a statistically significantly reduced 5- and 10-year survival of 95% and 90% in patients with SLE was demonstrated (24). Active disease, disease damage, toxicity of medication and comorbidities are predisposing factors, and makes the follow-up of SLE demanding. Recent recommendations help specialists in their decisions (23). A treat to target approach (T2T) was undertaken by the T2T/SLE international task force (25) involving targeting remission, preventing damage and improving quality of life. This initiated a process to reach consensus on definitions for remission in SLE, based on clinical disease, serological activity, duration and received treatment (26). In applying these definitions median duration of remission was short, prolonged remission was rarely achieved (27, 28) and two consecutive years was the shortest duration of remission associated with a decrease in damage progression (29).

The health-related quality of life (HRQoL) in patients with SLE is consistently lower than in matched healthy controls (30-33). Identified predictors of poor HRQoL in patients with SLE include older age, fatigue and the presence of neurological or psychiatric disorders, particularly depression or anxiety. High levels of pain seem to increase the presence of fatigue, anxiety and depression in women with SLE (34). There is diverging evidence of the relationship between HRQoL and disease activity and damage, encompassing weak or absent

association (32, 35-38) contrasting with the observed correlation of lower HRQoL with active disease and damage accrual (30, 33, 39, 40).

SLE and pregnancy

Pregnancy levels of estradiol stimulate the expression of anti-inflammatory cytokines (41), and it is expected that a B-cell and antibody driven disease like SLE exacerbate, while a T-cell driven disease with cytotoxic and innate immune response like RA improves (42). However, SLE is a complex disease, with involvement of both adaptive and innate immune alterations (6, 7). The crosstalk between SLE and pregnancy is intricate, and emerging understanding delineates a more complicated picture (8, 43, 44).

Establishment and maintenance of pregnancy represents a challenge for the maternal immune system. The regulatory T-cells (Tregs) have an important function in protecting the fetus by preventing immune and autoimmune responses against self-antigens (44). In SLE, Tregs are dysfunctional. In inactive disease during pregnancy, Tregs might ensure maternal-fetal tolerance because functional Tregs predominate. In active SLE, inactive or deficient Tregs may impair maintenance of fetal immune tolerance and result in adverse pregnancy outcomes (APOs) such as miscarriage, preterm birth or preeclampsia (43). A recent study showed that complement pathway activation triggers or amplifies inflammation at the maternal–fetal interface and is associated with APOs in patients with SLE and/or aPL (45).

It is generally accepted that the risk for flare in pregnancy is dependent on the disease activity state 6 – 12 months before conception (46). Remission or stable low disease activity is recommended to minimize the risk (47). There seems to be a weak hormonal impact on inducing flares when disease activity is low, as opposed to more active disease (8). The estradiol level does not rise as high in the 2nd and 3rd trimester in women with SLE as in healthy controls (43), and this may explain why disease does not always exacerbate.

Fertility in SLE

Fertility is the capacity to establish a pregnancy, subfertility is time to pregnancy (TTP) exceeding one year and fecundity is the capacity to have a live birth (48). Total fertility rate (TFR) is the average number of live births per woman (48). There has been an increasing number of children born to mothers with SLE during the last decades (49). Still, they have lower TFR than the general obstetric population (50, 51). The subfertility rate in women with SLE is similar to healthy women (46), and does not explain this finding. Known reasons for subfertility in SLE are severe and active disease as well as medication use (50, 52-54). Antiphospholipid antibodies (aPL) are detected in up to 40% of patients with SLE (55). The relationship of aPL with fertility remains to be clarified (55), but their negative impact on fecundity due to the association with pregnancy loss is well documented (46, 47). A higher rate of miscarriage is considered the main reason for a reduced total fertility rate in women with SLE (56, 57). The personal choice of limiting family size due to the disease and fear of complications contributes to fewer births (51).

Treatment of SLE

Treatment options of SLE include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional synthetic disease-modifying antirheumatic drug (csDMARDs) and biologic DMARDs (bDMARDs).

NSAIDs are used intermittently to relieve pain and inflammatory symptoms. Glucocorticoids are preferred as part of induction therapy and to control severe flares. In cases where long-term treatment is necessary, the lowest possible dose is advocated (25). In a recent observational study, lower doses prevented damage due to side effects without worsening long-term disease control (58).

Hydroxychloroquine (HCQ) is a csDMARD, and a cornerstone in the treatment of SLE. The main clinical effect is prevention of flares, while secondary favorable effects include reduced platelet aggregation, improved glycemic control and a beneficial effect on the lipid profile (59). HCQ is cheap and widely available, with the opportunity to treat patients with SLE worldwide (59). The T2T/SLE task force suggests using HCQ in all patients with SLE, assuming no contraindications (25). In more severe disease, and as maintenance treatment in SLE with internal organ manifestations the advice is to add csDMARDs including azathioprine (AZA), mycophenolate mofetil (MMF) or methotrexate (MTX). MMF is often first line treatment as induction and maintenance treatment of lupus nephritis (LN) (60). Cytotoxic treatment with cyclophosphamide (CYC) may also be appropriate as induction therapy in LN and other severe internal organ manifestations. bDMARDs including rituximab (RTX) and belimumab (BEL) are used in non-responders. The importance of treating comorbidities with relevant therapies is emphasized (25).

Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease of unclear etiology manifested by a progressive and destructive polyarthritis in association with serological evidence of auto reactivity (61). In 2015 the global age-standardized prevalence was 0.35%, with a higher prevalence of 0.44% in the Nordic countries, affecting at least twice as many women as men (62).

The classification criteria of RA proposed by the American College of Rheumatology in 1987 differentiated established RA from other rheumatic diseases (63). These criteria are used in RevNatus to classify RA (Table 2).

Table 2. The 1987 revised criteria for the classification of RA *(63)

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

* For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is *not* to be made. See Table 3 for definitions of abbreviations.

The new criteria proposed by the ACR/EULAR in 2010 (64) allow to classify RA at earlier stages (65). A score ≥ 6 is indicative of presence of definite RA (Table 3).

Table 3. The 2010 ACR/EULAR classification criteria for RA (64)

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)#	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

Several risk factors for developing RA are identified, and the strongest associations are seen with female sex, a family history of RA, the genetic factor the "shared epitope," and exposure to tobacco smoke (66).

In a northern Norwegian cohort, the total annual incidence rate was 28.7/100 000 (36.0/100 000 women and 21.4/100 000 men), with a prevalence in 1994 of 0.47% (0.63% in women and 0.30% in men) (67). The Oslo RA register study found that the gender ratio was above four in the premenopausal age (68). RA entails an increased morbidity and mortality, and the risk of cardiovascular disease is elevated compared to the general population, with the need for risk assessment and treatment (69). Other associated comorbidities are respiratory conditions, infectious disease, osteoporosis, periodontal disease and malignancy (70).

Patients with RA have a substantially reduced HRQoL compared to healthy controls and other physical illnesses (31, 71), and especially in the physical domains (72).

RA and pregnancy

An amelioration of symptoms is reported in approximately 50% of women with RA during pregnancy (73-75). The Th2-shift of pregnancy induces an anti-inflammatory milieu (76), stimulating anti-inflammatory molecules (as the IL-1 receptor antagonist), suppressing inflammatory cytokines and modulating T-cell responses (8, 77). Further, it has been shown that glycosylation of IgG and other key effector molecules contribute to the observed improvement (78). A more aggressive treatment before pregnancy contributes to controlled disease (79), and remission early in pregnancy is the main predictor of continued remission (75). Risk factors for active disease or flare in pregnancy are active disease before conception, erosive disease, RF positive or ACPA positive disease (73) and tumor necrosis factor inhibitor (TNFi) discontinuation in early pregnancy (79).

Fertility in RA

Women with RA have fewer children than their peers (51, 80, 81). A higher occurrence of subfertility of 36 – 42% (51, 82, 83) is perceived the main cause of reduced total fertility rate (TFR) in this group, although lower fecundity may also play a role (84). Increasing age is an

important reason for impaired fertility (85). Active disease, disease damage and treatment cause ovulatory disturbances (82), reduced ovarian reserve (86, 87) and impaired sexual function (88, 89). Coinciding with SLE, an additional factor in reducing TFR is the personal choice of limiting family size due to the disease and fear of complications (51, 90).

Treatment of RA

The repertoire of medical treatment for RA is comprehensive, including NSAIDs, glucocorticoids, csDMARDs, targeted synthetic DMARD (tsDMARDs) and a wider range of bDMARDs including tumor necrosis factor inhibitors (TNFi), rituximab (RTX), tocilizumab (TOC) and abatacept (ABA). Treatment regimens depend on the seriousness of the disease. Unfavorable factors include high disease activity and acute phase reactant levels, many swollen joints, presence of rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA) and erosions. EULAR recommends the use of a csDMARD, preferably methotrexate (MTX), combined with short-term glucocorticoids as primary treatment (91). The aim is remission or low disease activity. If treatment fails and there are favorable prognostic factors, it is recommended to switch to or add another csDMARD. With unsatisfactory effect and unfavorable prognostic factors, adding a bDMARD or tsDMARD is advocated. If the effect is still unsatisfactory, a switch to another bDMARD or tsDMARD is advised. As for SLE, the importance of treating comorbidities is accentuated (91).

Medications during pregnancy and breastfeeding

The evidence concerning safety of medications in pregnancy and during breastfeeding is insufficient (92, 93). Nevertheless, it is paramount to evaluate and adjust medication before a planned pregnancy (47, 92). Discontinuation of medication before or in pregnancy increase the risk of active disease and adverse pregnancy outcomes (46, 47, 77, 79, 94), and when medications are considered safe for the child this should be avoided.

NSAIDs are compatible with use in 1st and 2nd trimester. Population based studies are reassuring presenting no increased risk of congenital malformations or miscarriages (95-99), while one study found an increased risk of miscarriage in women using NSAIDs early in pregnancy (100). Prednisolone is the drug of choice to control flares throughout pregnancy when indicated. The lowest dose to control disease is recommended (92), to diminish the risk of maternal diabetes, infection and premature rupture of membranes. There are reassuring data concerning congenital malformations (101, 102).

In SLE, HCQ is mandatory before and throughout pregnancy to prevent flares and reduce pregnancy complications (59, 103-108). There is emerging evidence for a beneficial effect of HCQ on pregnancy outcomes in women with aPL (109). HCQ may be accompanied by AZA if needed (110, 111). HCQ and AZA have solid evidence for not harming the fetus/child (103, 104, 106, 112-124). MTX, MMF and CYC are proven teratogens (112, 114, 125-130) and must be withdrawn before intended pregnancy (92), at different times depending on the half-life of the drug. Replacing MMF with AZA before pregnancy may protect against renal flares and negative outcomes (111). In life-threatening disease, the use of CYC may be justified in 2nd and 3rd trimester (92). There is limited evidence concerning the use of rituximab (131-137) and belimumab (138-140). Current knowledge indicates no increased rate of congenital malformations after exposure. In exceptional cases rituximab may be considered used early in gestation, after informed consent. If used at later stages of pregnancy, there is a risk of B cell depletion and other cytopenia in the child. Belimumab should be replaced by other medication (92).

Low dose anticoagulants are recommended in all pregnant women with SLE to reduce the risk of adverse events (46, 47), and in combination with low-molecular-weight-heparin (LMWH) in women with earlier pregnancy complications associated to aPL or APS.

In RA, HCQ and/or Salazopyrin EN (SSZ) are csDMARDs compatible with pregnancy and may replace methotrexate. There are no indications of teratogenicity of SSZ (73, 114, 115, 141), provided daily folic acid supplement. In severe disease, TNFi may be used until confirmed pregnancy and in exceptional cases continued (92). The difference in placental transfer related to molecule structure and half-life needs to be taken into account, and inhibitors with a low placental passage, like certolizumab (142) and etanercept (143-145) are preferred. There is limited data concerning the other bDMARDs (146-149) and tsDMARDs (150). Consequently, withdrawal before an intended pregnancy is recommended and treatment during pregnancy is discouraged (92).

Medications compatible with breastfeeding are congruent with medications compatible with pregnancy (92). Based on their physiological properties, bDMARDs should not be discouraged during breastfeeding if no other treatment is available (92).

Table 4 shows medications used to treat SLE and RA relevant to our population, and their compatibility before conception, in pregnancy and during breastfeeding.

Table 4. Medications before conception and during pregnancy and breastfeeding

	SLE treatment	RA treatment	Compatible conception	Compatible pregnancy	Comment	Compatible breastfeeding	Comment
NSAIDs	√	√	√	√	1st and 2nd trimester only	√	Weight adjusted dose <0.1% (minimal)
Glucocorticoids	√	√	√	√	Lowest effective dose	√	Weight adjusted dose < 1.5% (minimal)
csDMARDs							
HCQ	√	√	√	√		√	Weight adjusted dose <2.0 % (minimal)
AZA	√		√	√	Up to 2 mg/kg daily	√	Weight adjusted dose < 1.0 % (minimal)
SSZ		√	√	√	Up to 2 g daily, With folic acid	√	With folic acid, Caution preterm and hyperblirubinemia
MMF	√		X	X	Teratogenic	X	No data, Long half-life
MTX	√	√	X	X	Teratogenic	X	Limited data
bDMARDs							
BEL	√		X	X	Limited data	X	Limited data, Large protein, absorption unlikely
RTX	√	√	X	X	Limited data	X	Limited data, Large protein, absorption unlikely
TNFi		√	√	√	CZP and ETA preferred	√	Limited data, Large protein, absorption unlikely
ABA		√	X	X	Limited data	X	No data, Large protein, absorption unlikely
TOZ		√	X	X	Limited data	X	No data, Large protein, absorption unlikely
tsDMARDs							
TOF		√	X	X	Limited data	X	No data, Low molecular weight might facilitate passage

HCQ= hydroxochloroquine AZA= azathioprine SSZ=sulfasalazine MMF=mycophenolate mofetil MTX=methotrexate BEL=belimumab RTX=rituximab TNFi=tumor necrosis factor inhibitor ABA=abatacept TOZ=tocilizumab TOF=tofacitinib
Weight adjusted dose is child dose (mg/kg in child) relative to maternal dose (mg/kg in mother) < 2% = minimal, 2-5% = low, 5-10% = moderate, 10-50% = high (151)

2 AIMS OF THE THESIS

General aims

- To assess the importance of disease activity status in pregnant women with SLE concerning outcome
- To provide evidence for the counselling, monitoring and treatment of women with SLE before, during and after pregnancy.

Specific aims

- To describe disease activity longitudinally during pregnancy and the first year postpartum in women with SLE using a score validated for pregnancy (paper 1).
- To explore the possible associations of disease activity and medications with offspring birthweight and the occurrence of preeclampsia and preterm birth in women with SLE (paper 2).
    - To estimate mean birthweight z-score in offspring of women with inactive SLE, women with active SLE and population controls with no rheumatic disease
    - To estimate incidence of preeclampsia and preterm birth in women with inactive SLE, women with active SLE and population controls with no rheumatic disease
    - To compare mean birth weight z-score in offspring and incidence of preeclampsia and preterm birth in women with inactive SLE, women with active SLE and population controls with no rheumatic disease
- To compare the frequency of achieving pregnancy and time to pregnancy among women with SLE and women with RA (paper 3).
    - To identify possible predisposing factors in women with SLE and RA not achieving pregnancy, including the assessment of HRQoL

3 MATERIAL AND METHODS

Data sources

RevNatus

RevNatus is a nationwide multicenter, prospective observational register including women with an inflammatory rheumatic disease when they plan pregnancy or are pregnant. Specialists in rheumatology across Norway recruit patients during ordinary follow-up of the rheumatic disease, and at present 15 of 18 departments of rheumatology and 2 private practices participate. Women at least 18 years old are included after informed consent. There is follow-up in each trimester of pregnancy and at 6 weeks, 6 months and 12 months after birth (152). Inclusion before pregnancy is desirable, totaling seven time points of registry of data (visits 0 – 6). However, inclusion at any visit is possible, in order to provide the standardized follow-up that RevNatus offers in the remaining course of the pregnancy and the postpartum period. At inclusion demographic data, information on concomitant diseases and history of medical use including NSAIDs, glucocorticoids, csDMARDs, bDMARDs, tsDMARDs and anticoagulants are registered. Parity and obstetric history including pregnancy loss, term and preterm births, mode of delivery and pregnancy complications (e.g. preeclampsia) are documented. All visits include a general clinical examination, present use and changes of medication, blood tests and urine sample. Disease activity is assessed according to a score validated for the rheumatic disease in question. Pregnancy outcomes, mode of delivery and complications during the present pregnancy are recorded at the visit 6 weeks postpartum. Breastfeeding status is documented on all postpartum visits.

The medical birth registry of Norway (MBRN)

MBRN is a national health registry with mandatory registration of variables on all births in Norway. The variables were selected after consensus among obstetricians, neonatologists and epidemiologists. It was established in 1967, and since 2002 it has been organized under the Norwegian Institute of Public Health. Following December 1998 all deliveries after gestational week 12 are registered, and include live births, stillbirths and miscarriages. Notifications are sent continuously, and at the latest one week after discharge from the maternity unit. One form is submitted per child. It includes demographics, information about maternal health before and during pregnancy as well as maternal and neonatal complications during pregnancy and birth. The task of the registry is to clarify the causes and consequences of health problems related to pregnancy and birth, and to monitor the incidence of congenital abnormalities (153).

Classification of diagnosis in RevNatus and MBRN

Patients in RevNatus are diagnosed by the treating specialist in rheumatology before inclusion, according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), and this determines the diagnosis in the registry. Additionally, it is recorded whether the classification criteria for the disease are fulfilled. In MBRN, pre pregnant maternal diseases have been coded according to ICD-10 since December 1998(153). The ICD-10 codes M32.1, M32.8, and M32.9 designate SLE and the ICD-codes M05.0, M05.1, M05.2, M05.8, M05.9, M06.0, M06.8, and M06.9 designate RA in the two registers.

Study population

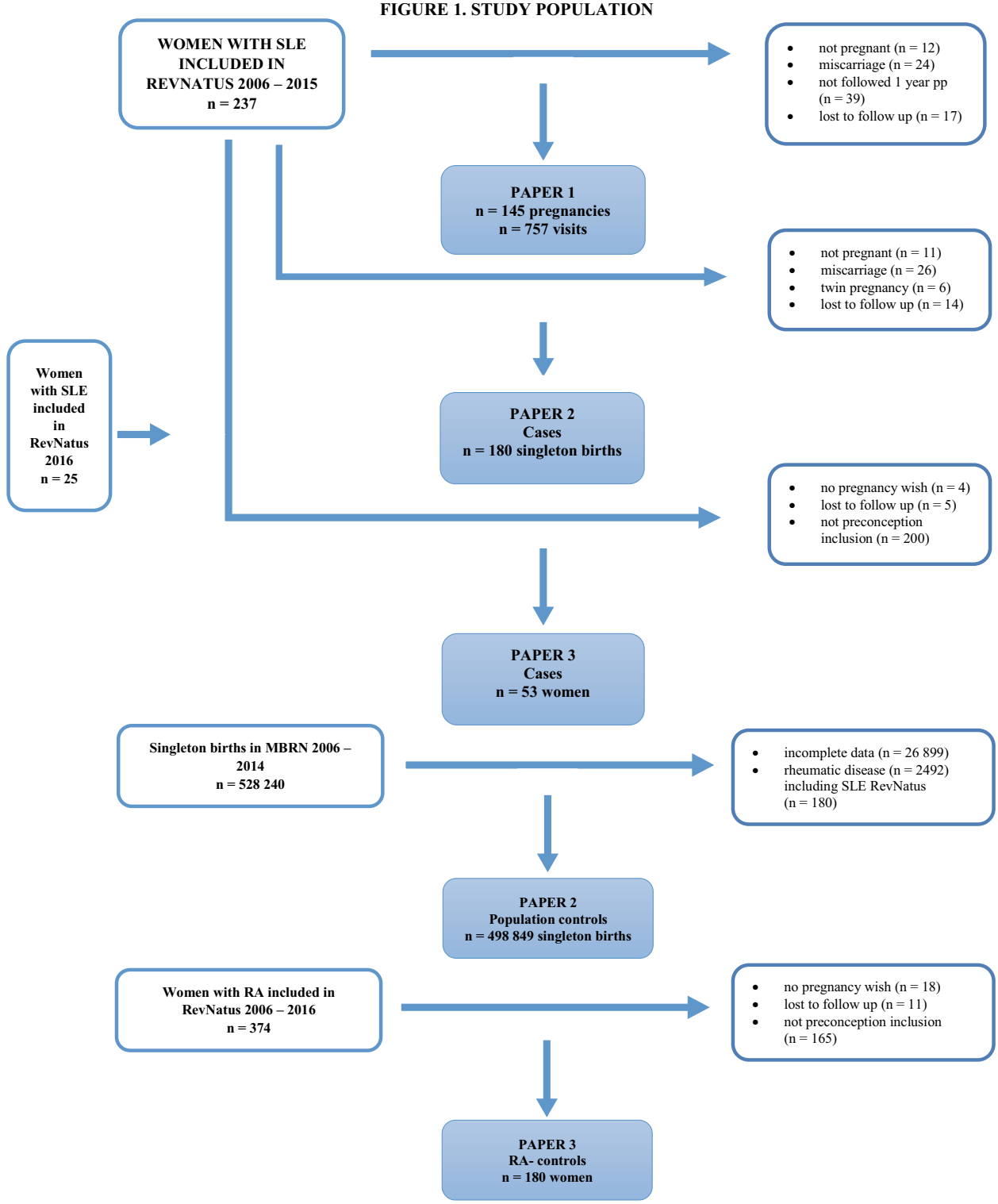
In paper 1 and 3 the data-source was RevNatus, while in paper 2 data was gathered from RevNatus and MBRN. For paper 1 and 2, data from RevNatus collected during 2006 – 2015, and for paper 3 during 2006 – 2016 was utilized. For paper 2, data from MBRN for the period 2006 – 2015 was extracted.

During the period 2006 to 2015 there were 237 inclusions of women with SLE in RevNatus, increasing to 262 inclusions for the period 2006 to 2016.

In the second paper, RevNatus was linked with MBRN. Singleton births recorded in MBRN 2006 – 15 were eligible for inclusion, totaling 528 240 births.

Figure 1 displays the selection of patient populations for the three papers, followed by the control populations from MBRN (paper 2) and RevNatus (paper 3).

FIGURE 1. STUDY POPULATION



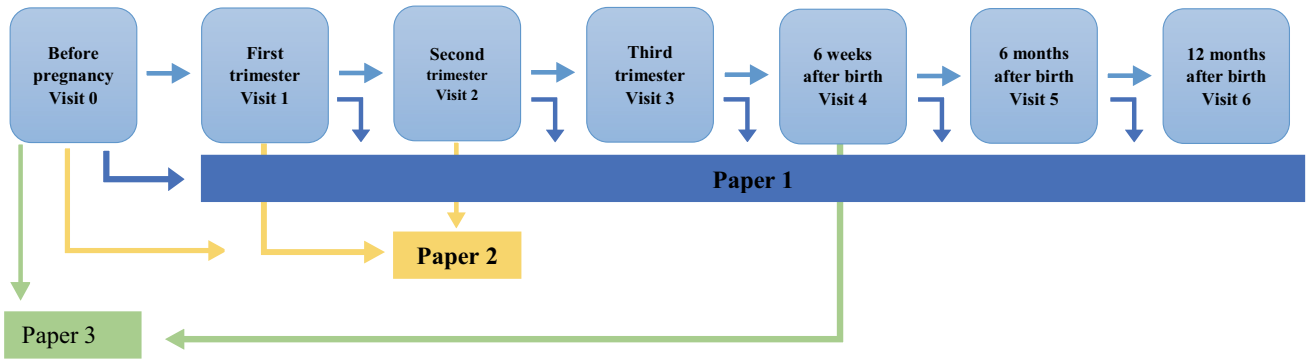
Variables assessed in RevNatus

In paper 1 demographic data, obstetric history and disease specific information reported at inclusion were used in the descriptive analysis. Disease activity scores, csDMARDs and prednisolone use reported on visit 1 to 6 were applied in the ordinal logistic mixed model analysis.

In paper 2 educational status, obstetric history and disease specific information reported at inclusion were used in the descriptive analysis. Disease activity scores and medication in 2nd trimester were retrieved from RevNatus for the patient group and used in the main analysis.

In paper 3, variables were obtained from data collected at the visit before pregnancy and included demographic data, obstetric history, disease specific characteristics, medication use and health-related quality of life (HRQoL) variables in women with SLE and RA. The outcomes live birth and miscarriage were retrieved from visit 4. Figure 2 illustrates the longitudinal follow-up in RevNatus, and the data sources for the three papers.

Figure 2. Visits in RevNatus



Disease activity in SLE

SLE disease activity was scored according to the Lupus Activity Index in Pregnancy (LAI-P) during pregnancy and at 6 weeks after birth, and according to a modified Lupus Activity Index (m-LAI) at 6 and 12 months after birth. Lupus activity index (LAI) is a global score assessing overall disease activity in SLE over the previous two weeks. It consists of five sections and includes a Physician Global Assessment (PGA), and items describing general and organ specific clinical manifestations, current medication and certain laboratory findings, scored on a visual analogue scale to indicate presence and severity (154, 155). The index allows comparisons of patients with different disease manifestations, and is appropriate for detecting change in disease activity over time (154). LAI-P is a modified version of LAI, with a good ability to measure disease activity and detect disease flares in pregnancy and the puerperium in women with SLE (156, 157). In LAI-P, the PGA is excluded to decrease the degree of subjectivity to the scale, leaving four groups of items. The original visual scale is replaced with a graded scale, and asthenia is excluded to avoid pregnancy related symptoms to be scored as disease activity (157).

LAI-P scores disease activity on a continuous scale from 0 to 2.6. Zero indicates no disease activity, while a score ≥ 2 is considered high disease activity (158). A change in disease activity score ≥ 0.25 is perceived a clinically relevant change indicating worsening (flare) or improvement of disease (156, 157). To have comparable scales, we modified the original LAI (m-LAI) excluding PGA and using the same items as in LAI-P except fever, graded similarly and giving the same continuous scale. Table 2 shows the items in each group and the score calculation algorithm.

Table 2. Lupus Activity Index in Pregnancy (LAI-P) and modified Lupus Activity Index (m-LAI)

Group 1	Fever (LAI-P)/Fatigue (m-LAI)	0	1			
	Rash	0		2		
	Arthritis	0		2	3	
	Serositis	0	1	2	3	
						a: Mean
Group 2	Neurologic	0			3	
	Renal	0		2	3	
	Lung	0			3	
	Hematologic	0	1	2	3	
	Vasculitis	0			3	
						b: Maximum
Group 3	Prednisone, NSAIDs, HCQ	0	1	2	3	
	Immunosuppressor	0			3	
						c: Mean
Group 4	Proteinuria	0	1	2	3	
	Anti-DNA	0	1	2		
	C3, C4	0	1	2		
						d: Mean

LAI-P score/m-LAI score = $\frac{a+b+c+d}{4}$

Disease activity in RA

DAS28 is a modified version of disease activity score (DAS) validated for use in RA (159), and is the most used assessment in evaluating disease activity. It was scored according to DAS28 calculated with c-reactive protein (CRP) instead of erythrocyte sedimentation rate (ESR), and without global health (GH) assessment, as this performs best in pregnant women, with little influence due to pregnancy itself (74).

Antiphospholipid antibodies

Antiphospholipid antibodies (aPL) are in some populations of SLE present in up to 40%, and are associated with adverse pregnancy outcomes including fetal death, recurrent early miscarriages, preeclampsia and placental insufficiency (160). Positive aPL in conjunction with clinical manifestations constitute antiphospholipid syndrome (APS), and was first defined in the preliminary Sapporo classification criteria (161). A revision defines laboratory criteria with a clear statement of threshold for positivity (162). This definition was used to define the presence of aPL in our population.

Health-related quality of life (HRQoL)

RAND- 36 (163) is a composite measure of different aspects of health-related quality of life (HRQoL). It has eight domains: Physical Function, Role Physical, Bodily Pain, General Health, Vitality, Social Function, Role Emotional and Mental Health, each including 2 - 10 items and translating to a score of 0 – 100. Physical and mental health summary scores may also be calculated. A higher score indicates a better HRQoL. A change in score of ≥ 5 points is considered a minimal clinically important difference (MCID), with ≥ 5 and < 10 perceived a marginal change and ≥ 10 a clear change (164). It is a generic measure, useful for comparing HRQoL between diseases (71). RAND 36 is validated for use in SLE (165) and RA (166).

Variables assessed in MBRN

MBRN provided data for patients and population controls in paper 2. Data included maternal age, parity, smoking and body mass index (BMI), complications including preeclampsia (167, 168) and preterm (< 37 gestational weeks) birth as well as gestational age, weight and gender of the newborn.

Calculation of birthweight z-score

Z-score for birthweight was calculated using Norwegian birthweight by gestational age standards covering 20 to 44 completed weeks, separately for males and females (169), and used gestational age in days, with linear interpolation between weeks.

4 STATISTICAL ANALYSES

Two-sided P-values less than 0.05 were considered statistically significant, and 95% confidence intervals (CI) were reported where relevant.

Group comparisons

Group comparisons were performed using independent t-test for continuous variables and the Pearson Chi squared test, the unconditional z-pooled test (170) or the exact -Wilcoxon-Mann-Whitney for categorical variables. When one or both samples are small, asymptotic methods like the common asymptotic Pearson's chi-squared test should not be used, and a test computing an exact p-value is preferred (171). Unconditional tests preserve the significance level and are more powerful than Fisher's exact test for moderate to small samples. The unconditional z-pooled test was therefore suitable in our studies (171).

Mixed models

In paper 1 mixed models were applied. The dependent variable (LAI-P/m-LAI) was heavily skewed, with 51.6% of the observations indicating no disease activity (LAI-P/m-LAI = 0). A change of 0.25 in LAI-P is regarded clinically relevant (156, 157). The dependent variable was categorized in accordance with this, defined by the values 0, > 0 to 0.25, > 0.25 to 0.5 and > 0.5. The longitudinal course of disease activity was analyzed using a proportional odds ordinal logistic mixed model regression analysis with visit number as categorical covariate and patient as random effect. The analyses were carried out unadjusted, as well as adjusted for use of prednisolone, azathioprine and hydroxychloroquine at each visit (yes/no). To confirm the results, we also carried out corresponding binary logistic regression mixed model analysis with the dependent variable dichotomized at no disease activity.

The mixed model analysis implies that subjects with missing data at one or more visits are included in the analysis with their available data, whereas a complete case analysis would have discarded those subjects from the analysis. Further, a complete case analysis would give unbiased results only under the missing completely at random (MCAR) assumption, while mixed models give unbiased results under the less restrictive missing at random (MAR) assumption. This means that if subjects with measured low disease activity at one visit are more likely not to show up at the next visit, the results will still be unbiased. Even if there is some degree of missing not at random (MNAR), a mixed model gives less bias than a complete case analysis.

Regression analyses

Multiple linear regression analyses

In paper 2 we used linear regression with z-score birthweight as dependent variable. As covariates, we compared population controls, cases with inactive disease (LAI-P = 0) and

cases with active disease (LAI-P > 0) in the 2nd trimester. We carried out the analyses unadjusted, and adjusted for maternal age (<35years/≥ 35 years), parity (no birth/≥ 1 birth) and smoking in pregnancy (yes/no). There were missing data on smoking in 15.9% of the population controls, and we also carried out the unadjusted analyses restricted to the cases with data on all variables (available case analysis), and compared these results with the adjusted analyses. Furthermore, we carried out analyses for first and subsequent births separately. Separate analyses were performed splitting on use of prednisolone (yes/no) in the 2nd trimester, with adjustment for hydroxychloroquine (yes/no) and azathioprine (yes/no).

Logistic regression analyses

Logistic regression for the dichotomous dependent variables preeclampsia and preterm birth with comparison of population controls, cases with inactive disease (LAI-P = 0) and cases with active disease (LAI-P > 0) in the 2nd trimester was performed in paper 2. We carried out the analyses unadjusted, and adjusted for maternal age (<35years/≥ 35 years), parity (no birth/≥ 1 birth) and smoking in pregnancy (yes/no). As for z-score birth weight, there were missing data for smoking in 15.9% of population controls, and we also carried out the unadjusted analyses restricted to the cases with data on all variables, and compared these results with the adjusted analyses. Additionally, we executed separate analyses for first and subsequent births. Separate analyses were performed splitting on use of prednisolone (yes/no) in the 2nd trimester, with adjustment for hydroxychloroquine (yes/no) and azathioprine (yes/no).

Survival analyses

In paper 3, Kaplan Meier plots were used to visualize time to pregnancy in months and the proportion not achieving pregnancy in women with RA and women with SLE. Comparison of time to pregnancy in women with RA and women with SLE was carried out in Cox

regression analyses with adjustment for maternal age, parity (no children/≥ 1 child) and DMARD-use (yes/no).

Software

In the first paper the descriptive statistics were performed using SPSS 21, and the mixed model analyses were performed using Stata 13.1. In the second paper, the statistical analyses were performed using SPSS version 22. In the third paper the statistical analyses were performed using SPSS version 24 and StatXact11.

5 LEGAL AND ETHICAL ASPECTS

RevNatus was approved in 2006 by The Regional committee for medical and health research ethics (REC Central). All women signed a written informed consent before inclusion.

The present project and linking with MBRN was approved by REC Central (2012/1905). Access to data from MBRN was granted September 2016 (MBRN assignment 15 – 1819).

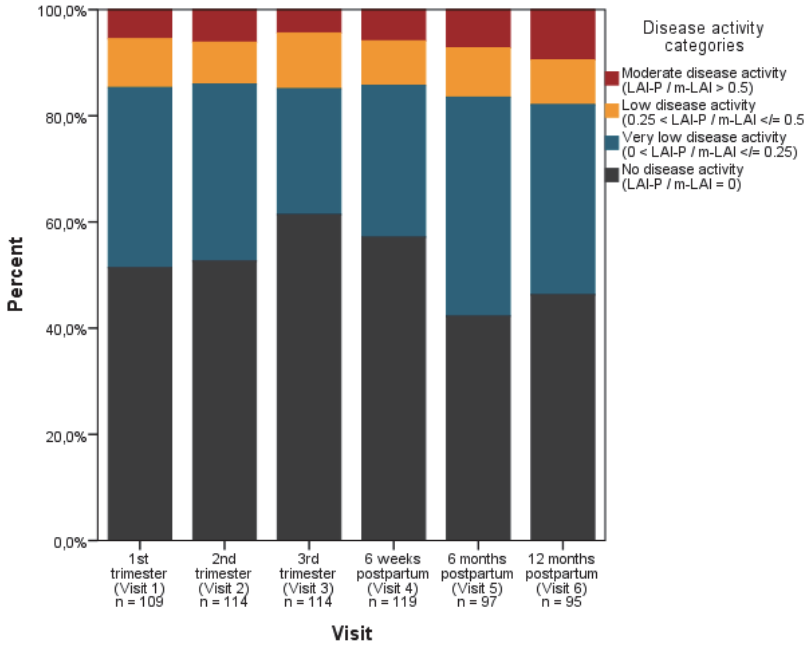
6 SUMMARY OF RESULTS

Paper 1

Disease activity during pregnancy and the first year postpartum in women with systemic lupus erythematosus

To describe the longitudinal course of disease activity throughout pregnancy and the first year postpartum each woman served as her own control, using disease activity scores on visit 1 to 6. A cumulated 757 visits in 145 pregnancies in women with SLE were analyzed. More than half (51.6%) of the disease activity scores indicated remission (LAI-P/m-LAI=0), while the remaining indicated active disease. Only 6.3 % of the scores indicated moderate to high disease activity (LAI-P/m-LAI> 0.5), see Figure 3.

Figure 3. Disease activity visit 1 through 6



The variation in disease activity between visits was clinically relevant and statistically significant (p = 0.035). Disease activity was highest 6 and 12 months postpartum, and disease activity was significantly higher 12 months postpartum compared to 3rd trimester (p = 0.009) and 6 weeks postpartum (p = 0.031), but not compared to 1st trimester (p = 0.175) and 2nd trimester (p = 0.084).

We adjusted for use of medication at each visit, and found maintained variation in disease activity adjusting for prednisolone (p < 0.001), azathioprine (p = 0.009) and HCQ (p = 0.012). We found an increased risk of higher disease activity when using prednisolone (OR = 3.10, p < 0.001) and azathioprine (OR = 2.2, p = 0.022), but not HCQ (OR 0.78, p = 0.47). There were no statistically significant interaction between the use of prednisolone, azathioprine or HCQ and visit number.

Paper 2

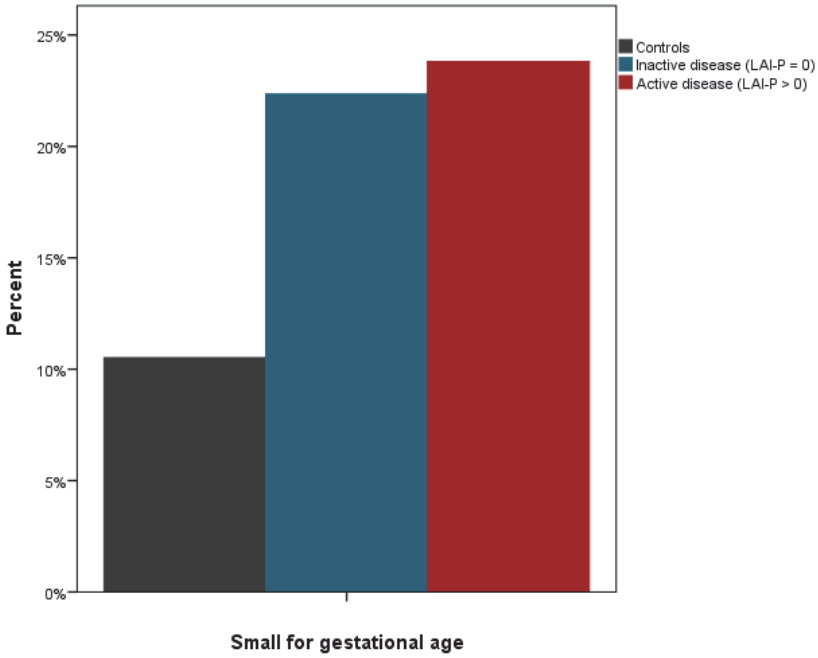
Influence of disease activity and medications on offspring birthweight, preeclampsia and preterm birth in systemic lupus erythematosus. A population-based study.

We linked data from MBRN with data from RevNatus. Singleton births among women with the diagnosis SLE recorded in MBRN and included in RevNatus formed the patient group (n = 180). A total of 498 849 singleton births registered in MBRN during 2006 to 2014 served as population controls.

Z-scores for birthweight in offspring were lower in inactive (mean z-score -0.64, p <0.001) and active (mean z-score -0.53, p = 0.001) disease than population controls (mean z-score -0.11). There was no difference between birthweight z-scores in offspring of women with

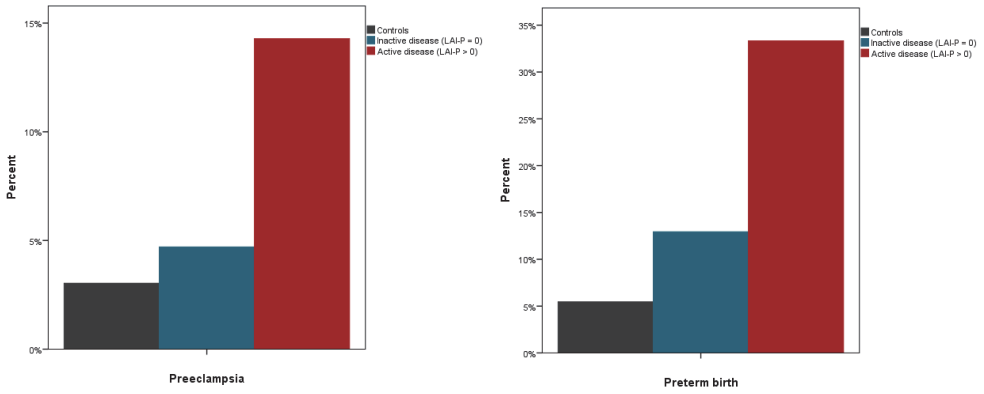
inactive versus active SLE (p = 0.53). There was a significantly higher odds of small for gestational age (SGA, ≤ 10 percentile) in inactive as well as active disease compared to population controls (OR 2.45, 95% CI 1.47 to 4.08, p = 0.001 and OR 2.66, 95% CI 1.49 to 4.75, p = 0.001, respectively) . We found no significant differences between disease groups (Figure 4).

Figure 4. Small for gestational age (%)



Preeclampsia occurred more often in women with inactive and active SLE than population controls (Figure 5).

Figure 5. Preeclampsia and preterm birth (%) in population controls, women with inactive SLE and women with active SLE



Inactive disease did not predict preeclampsia (OR 1.58, p = 0.37) while active disease did, with OR 5.33 (p <0.001) and OR 3.38 (p = 0.052) compared to population controls and inactive disease, respectively. Preterm birth occurred more often in inactive (OR 2.57, p = 0.003) and active (OR 8.66, p <0.001) disease compared to population controls, and in active compared to inactive disease (OR 3.36, p = 0.004).

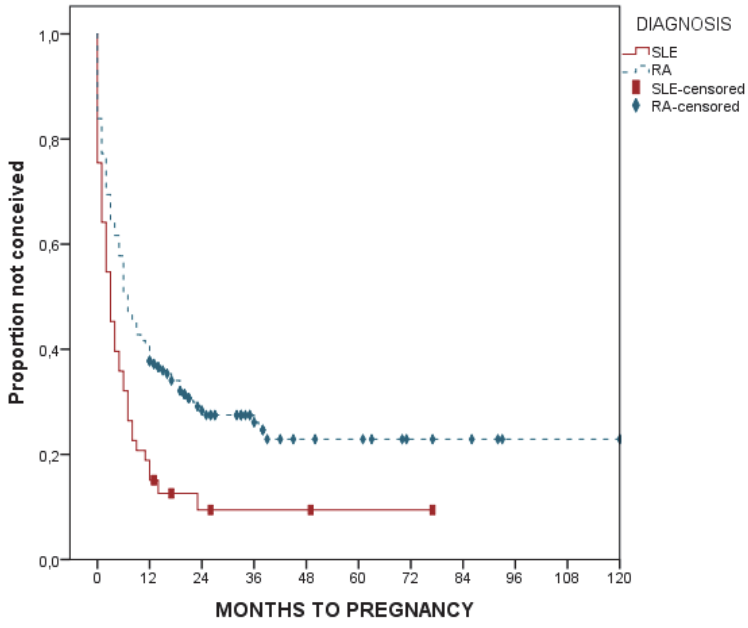
Birthweight z-score was lower in offspring of women using prednisolone (mean difference 0.33, p = 0.02). There was a higher odds of preeclampsia when using prednisolone (OR = 2.33, p = 0.19) and a threefold increase in preterm birth (OR = 3.36, p = 0.007). Results were substantially unchanged after adjusting for hydroxychloroquine and azathioprine.

Paper 3

Women with systemic lupus erythematosus get pregnant more easily than women with rheumatoid arthritis.

We compared 53 women with SLE to 180 women with RA included in RevNatus before pregnancy. During follow-up, a higher proportion of women with SLE achieved pregnancy with an adjusted pregnancy ratio of 1.91 (CI 1.27 to 2.88, p = 0.002) compared to women with RA, as illustrated in Figure 6. Median time to pregnancy (TTP) was substantially shorter in SLE compared to RA (3.0 vs 7.0 months, p = 0.001).

Figure 6. Pregnancy ratio and time to pregnancy in women with SLE and RA



Higher maternal age, medications and lower health-related quality of life (HRQoL) in the physical domains may influence the ability to achieve pregnancy in women with RA.

In women with SLE lower HRQoL may compromise fertility.

7 INTERPRETATION AND COMPARISON WITH OTHER STUDIES

Paper 1

To our knowledge, there are no prior studies following the course of SLE disease activity throughout pregnancy and up to one year after birth, assessing disease activity by an instrument validated for use in pregnancy and the puerperium. Four prior studies have utilized disease scores adapted for use in pregnancy, three using the SLE-Pregnancy Disease Activity Index (SLEPDAI) (108, 172, 173) and one using the Lupus Activity Index in Pregnancy (LAI-P) (174), only one including assessment after birth. The first three were prospective, while the last was retrospective, and the ethnical composition differed from ours. Most commonly SLE Disease Activity Index (SLEDAI) and Physician Global Assessment (PGA) has been used to evaluate disease activity in pregnant women with SLE (175).

We demonstrated a statistically significant and clinically relevant change in disease activity over time, illustrating the relapsing and remitting course of the disease. The disease activity spectrum comprised primarily inactive disease and low disease activity, as defined by LAI-P or m-LAI. Our data revealed that disease activity increased 6 and 12 months postpartum, a novel finding in women with SLE. This was despite a stable use of HCQ throughout visits, and a slight increase in the use of prednisolone.

Earlier studies report measurable disease activity in 40 – 50% (176-183) and moderate to severe flares in 15 – 30% (177, 181, 182). The focus has been specifically on flares before or in pregnancy, as this is a known risk factor of adverse pregnancy outcome (172, 177, 184). In more recent studies pregnant women with SLE have milder disease, with predominantly inactive disease or low disease activity (172, 177, 184), corresponding to our findings. We believe that participating in a register modifies the disease due to the firm follow-up.

It is recommended that women with SLE use HCQ before conception and throughout pregnancy to protect against increasing disease activity (59, 103) and to avoid flares (185, 186). In our study 67% of the women used HCQ at inclusion. Consequently, there is a potential to achieve remission in higher proportion of women in adhering to these recommendations.

Paper 2

Preterm birth is the leading cause of infant morbidity and mortality, and affects the lifelong health of offspring (187). Preeclampsia is one of the risk factors for preterm birth. Low birthweight caused by intrauterine growth restriction is associated with an increased risk of cardiovascular disease and diabetes in the offspring (188). Preeclampsia, preterm birth and low offspring birthweight are events associated with a future higher risk of maternal cardiovascular disease (189) and death (190). These adverse outcomes in SLE-pregnancies are well known, and high disease activity or disease flare is regarded an important risk factor (46). We investigated the role of disease activity in a prospective population-based design not applied in earlier studies on this topic. Many studies investigating adverse pregnancy outcomes in women with SLE did not have access to disease activity assessments (172, 191-194). We found the highest occurrence of SGA, preeclampsia and preterm birth in women with active SLE. The vulnerable very preterm (< 34 weeks) children were most frequently delivered in women with active disease. Active kidney disease is an important predictor of preeclampsia and preterm birth (175, 195, 196). In our cohort we found a lower proportion of women with active kidney disease than earlier reported (172, 174), but in accordance with a very recent study (197). Nevertheless our results showed similar occurrence of preeclampsia and preterm birth (172, 194), suggesting that even less serious disease entails an increased risk. In our population, we did not find higher odds of preeclampsia in inactive disease compared to population controls, a novel finding advocating the beneficial effect of

inactive disease. Our findings supports guidelines underpinning the importance of inactive disease before conception (46, 47, 198).

Paper 3

Studies comparing fertility, fecundity, total fertility rate and influencing factors between SLE and RA patients are rare, although extended data should be of importance to patients and the treating physicians. We studied women with SLE and RA included before pregnancy to obtain women with a pronounced pregnancy wish. Ideally, all patients should be included before pregnancy, to achieve better outcomes for mother and child (77). It has earlier been shown that women with RA have reduced fertility compared to references (81). Time to pregnancy exceeding 1 year implying subfertility occurred in 15.1% of women with SLE and 36.1% of women with RA, and is in accordance with earlier findings (51, 82, 83) in women with RA. Generally, age is one of the main factors to determine subfertility (199). In our study, women with SLE had a mean age similar to the general obstetric population in Norway (200), with no significant difference between women achieving and not achieving pregnancy. Accordingly, age did not seem to influence on fertility, besides the general increase in maternal age at first birth (201). In contrast, women with RA had a substantially higher mean age, found to be statistically significantly higher in women not achieving pregnancy compared to women achieving pregnancy. Women with SLE failing to conceive had poorer HRQoL than women with SLE achieving pregnancy. Reduced HRQoL in the domains social function, role emotional and mental health may impair sexual function, in line with earlier findings (51, 202). Women with RA had low scores whether achieving or not achieving pregnancy concerning physical role and bodily pain, implicating physical hindrance to sexual activity. Low HRQoL scores in SLE and RA concerning vitality and general health may impact TTP and the choice or ability to achieve pregnancy.

8 METHODOLOGICAL CONSIDERATIONS

Our health care system represents an advantage when performing research. Norwegian citizens and inhabitants registered with a personal identity number qualify for a universal health coverage, and the majority have follow-up and receive treatment in the public health care service. In pregnancy, women are entitled to maternity care and the consultations are free of charge. This minimize patient selection, allow us to identify a person through the personal identity number and facilitates linking of information from different registers.

The linkage of RevNatus and MBRN enabled a population-based study, extracting valid information on gestational age, birthweight, preterm birth and pregnancy related hypertensive complications from MBRN (203). Birthweight z-score was based on Norwegian standards (169), providing a precise estimate for our population. The advantage of RevNatus is the longitudinal follow-up and the information on disease activity and other disease related variables. This can give insight to causal relationships of observed differences in population controls and disease groups that are not possible to achieve through national health registers like MBRN.

Applying a disease activity score validated for use in pregnancy increases the reliability, avoiding pregnancy-related symptoms to be confused with active disease.

The present cohort is the largest number of pregnant women with SLE studied prospectively in the Nordic countries to date, and provides important information about disease activity and pregnancy outcomes. The results supplement existing knowledge drawn from prospective studies in more heterogeneous or different ethnic populations that may not fully apply to our population (5, 204-206).

Validity of the results

Internal validity refers to whether the results obtained reflect the truth in the study population (207), and may be compromised by selection bias, information bias and confounding.

External validity refers to the extent to which the study results can be generalized to populations other than the one included in the study (207). Our population consists of mainly Caucasian women with SLE with inactive or low disease activity. We believe that the results are valid not only for women with SLE in Norway, but also for inhabitants of other Nordic and northern European countries with similar health care and social security systems.

Misclassification

According to MBRN, the number of deliveries in women with connective tissue diseases has increased profoundly during the last 40 years. There were 33 births registered in the period 1967 – 1979, increasing to 500 births in the period 2000 – 2009 (49). Women with SLE account for more than half of these pregnancies. Due to the linkage of RevNatus and MBRN, we could confirm a good compliance concerning diagnoses. Of 180 women in RevNatus with SLE, only 10 (5.6%) did not have this diagnosis in MBRN. This is a lower misclassification rate than earlier reported for prepregnant rheumatic diseases in MBRN (208). Additionally, women are diagnosed by a specialist in rheumatology before inclusion in RevNatus, securing a correct diagnosis. For the period 2006 to 2014, there were 283 registered singleton births in women with SLE in MBRN, with a mean of 31 births annually. RevNatus is a nationwide observational register with a gradually increasing participation from the rheumatologic departments across Norway and only one singleton birth in women with SLE was registered in 2006, 11 in 2007 and 15 in 2008. During 2009 to 2014, there were 18 – 30 births annually with a mean of 22 births. This implies a coverage in RevNatus of 71% the last 6 years. According to Norwegian guidelines (209) women with SLE should be offered a

multidisciplinary follow-up in pregnancy. In adhering to these guidelines and with recruitment of patients from all departments of rheumatology, the coverage will increase.

Selection bias

The selection of subjects for participation represents a possible selection bias, and is relevant for all three papers.

In mild disease, women may conceive and have children without inclusion in RevNatus, resulting in an under-reporting of no or low disease activity (paper 1), uncomplicated pregnancies (paper 2) and achieved pregnancies (paper 3). This is more of a concern in RA (paper 3) than SLE (paper 1, 2 and 3). Women with SLE are seen regularly by a specialist in rheumatology regardless of disease severity due to the awareness in the clinicians and patients about SLE as potentially more severe and posing a high risk in pregnancy. Women with RA without specific medication may not have regular follow-up. National and international recommendations state that all pregnant women with rheumatic diseases should have follow-up by a specialist in rheumatology (47, 77, 92, 210), and adherence potentially entail inclusion in RevNatus and reduce this selection bias.

In severe and active disease or after earlier adverse pregnancy outcomes, women may not plan pregnancy, and are not included in RevNatus. High disease activity increases the risk of miscarriage, and we do not know the number of women with SLE or RA who conceived and had an early miscarriage without being registered. This is a concern when the focus is achieving pregnancy (paper 3), but does not impact the results in paper 1 and 2.

Some women were included in RevNatus for more than one pregnancy. It is possible that these women have lower disease activity and less complicated pregnancies, with a bias towards less severe disease. We compared disease activity scores in the first of two included pregnancies to the other pregnancies (paper 1) and found similar patterns, with 48/91 (52.7

%) vs 297/577 (51.5 %) of the scores indicating inactive disease and 5/91 (5.5 %) vs 35/577 (6.4 %) with moderate disease activity. In paper 2 we could not account for dependent observations due to multiple births from the same woman, since this information was unavailable for the population controls. Hence, the precision may be effectively smaller than reported.

In paper 3, not excluding a patient at follow-up if a pregnancy wish is no longer present is a potential bias. However, 22 women were excluded because pregnancy was no longer relevant due to changed social status or other life events, reducing this source of error.

Loss to follow-up in RevNatus is of little concern due to low rates, ranging from 7.2 % in paper 1 and 5.9% in paper 2 to 1.9% (SLE) and 2.9% (RA) in paper 3.

Recall bias

Due to the prospective design, recall bias needs no consideration for most of the collected information. However, questions regarding prior pregnancy complications might be subject to information bias, with a possible better recall in women with SLE (subject bias) and a biased questioning (observer bias) due to the general knowledge of adverse pregnancy outcomes in women with SLE. This is relevant for all three papers.

Potential confounders

In paper 1 we adjusted for medication use, without causing amendments to the results.

In paper 2 we adjusted for maternal age, parity and smoking. The results were substantially the same. As an alternative way of estimating confounding, we stratified on parity in our main analysis and found similar results for the two groups.

In paper 3 we adjusted for maternal age, parity and DMARD-use, with sustained results.

Missing data

The low rate of preconception visits is a limitation.

In paper 1, only 17.9 % of the women were included before conception. Additionally, the preconception visit had a much wider time span than the other visits, as the time of registration was a few weeks up to one year before conception. We therefore chose the 12 months postpartum visit as reference for non-pregnant disease activity status.

In paper 3, only 20% of women with SLE and 48% of women with RA were included before pregnancy. This limits the size of the groups. The difference may reflect that more women with unplanned pregnancies are included for further follow-up if they have SLE than RA, as discussed earlier. It may also reflect that women with RA struggle to achieve pregnancy to a greater extent than women with SLE.

In paper 1 missing data on disease activity scores is a limitation. The choice of mixed models in analyzing data diminish this limitation, as discussed in chapter 4.

Data on antiphospholipid antibody (aPL) status were missing in many patients. Positive aPL is associated with pregnancy loss, and this is well documented in SLE (46). We cannot exclude a role for these antibodies concerning our outcomes (paper 2 and 3).

Diminished ovarian reserve due to SLE and RA itself is discussed as a reason for lower TFR (86, 87, 211, 212), and anti-Müllerian hormone (AMH) levels and antral follicle count are measures to assess this. None of these were available from RevNatus, representing another limitation (paper 3).

9 CONCLUSION AND CLINICAL IMPLICATIONS

Paper 1

We described disease activity during pregnancy and one year after birth with a score validated for pregnancy (LAI-P). A clinically relevant change between visits illustrating the remitting and relapsing pattern of SLE was observed. Women in our cohort had inactive disease or low disease activity during follow-up, with higher disease activity 6 and 12 months after birth than in pregnancy and 6 weeks after birth. This is a novel finding and implicates tight follow-up not only before and during pregnancy, but also in the first year after birth.

Paper 2

We found lower birth weight z-scores in offspring of women with SLE than in offspring of population controls, independently of disease activity status. Preeclampsia and preterm birth was more common in women with inactive and active SLE than in population controls, but women with inactive SLE did not have increased risk for preeclampsia compared to population controls. Active SLE amplified the risk for preeclampsia and preterm birth.

These findings can be used in the counselling of patients and to motivate towards achieving inactive disease before pregnancy. It justifies surveillance during pregnancy to maintain or pursue inactive disease, and facilitates a differentiation in the follow-up of women with SLE based on disease activity.

Paper 3

We found a higher pregnancy ratio and shorter time to pregnancy in women with SLE compared to women with RA. Subfertility occurred in 15.1% of women with SLE and in 36.1% of women with RA. Both groups had a similarly reduced fecundity.

In the studied population women with SLE not achieving pregnancy had low HRQoL. In women with RA higher age, medications and low HRQoLwere factors associated with a compromised fertility.

In western society, many women postpone childbearing until fertility is impaired due to older age. In women with a rheumatic disease, additional compromising factors may represent further delay, resulting in a short reproductive window. Our results put forward the importance to discuss and reveal issues of fertility and fecundity early in the disease.

10 FUTURE PERSPECTIVES

The results of this thesis confirm that inactive disease before and during pregnancy is the optimal state to avoid or reduce complications in pregnancy in women with SLE. To further improve outcomes, continued efforts are required in the clinical work and in research.

Knowledge from our studies strengthens the legitimacy of RevNatus and may promote necessary development. Enhancing the coverage of RevNatus will contribute to the equality of follow-up and improved reliability of research projects to come. There is a potential to increase the proportion of planned pregnancies. Inclusion in RevNatus before pregnancy implies an advantageous clinical evaluation, appraisal of medication and risk assessment. Preconception counselling also allows for addressing fertility and fecundity issues. This improves the quality of follow-up, potentially enhances the outcomes, and generates more complete data for future research projects.

Several observational pregnancy registers in women with rheumatic diseases have been established the last decades. Collaboration through international networking is an important tool to expand our knowledge. The European Network of Pregnancy Registers in Rheumatology (EuNeP) was initiated in 2017, and RevNatus is one of four registers so far. The purpose of the network is to coordinate variables and share data across borders to increase data quantity and thereby improve the quality of our research.

As professionals, we wish to provide the best possible care to women with rheumatic diseases before, during and after pregnancy. Having a family affects all aspects of life and acquiring a chronic disease implicates that an extra piece needs to be fitted in the puzzle of daily living.

Pregnancy registers and international collaboration are important and necessary resources for improving health care, and enable new insights to serve our patients.

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PAPER 1

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ORIGINAL ARTICLE

Disease Activity During Pregnancy and the First Year Postpartum in Women With Systemic Lupus Erythematosus

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Objective. **Disease activity measured by validated methods has been sparsely examined during and after pregnancy in women with systemic lupus erythematosus (SLE). The aim of this study was to describe the longitudinal course of disease activity during pregnancy and the first year postpartum using the Lupus Activity Index in Pregnancy (LAI-P).**

Methods. **RevNatus is a nationwide Norwegian prospective observational register including women diagnosed with inflammatory rheumatic diseases. LAI-P is a modified version of the LAI, with a good ability to assess disease activity in pregnant women with SLE. These indexes were used to assess disease activity at 6 visits (in trimesters 1, 2, and 3, and at 6 weeks, 6 months, and 12 months postpartum). The longitudinal course of disease activity was analyzed using an ordinal logistic mixed model.**

Results. **A total of 757 visits (145 pregnancies) in women with SLE were included in the analysis. More than half (51.6%) of the disease activity scores indicated remission, and only 6.3% indicated moderate disease activity. The model showed a statistically significant and clinically relevant change in disease activity over time, and a higher disease activity 6 and 12 months postpartum compared to the third trimester and 6 weeks postpartum.**

Conclusion. **The majority of women had low or no disease activity at conception and during pregnancy, with higher disease activity at 6 and 12 months after delivery. This points to the importance of tight disease control not only before and during pregnancy but also in the first year postpartum.**

INTRODUCTION

Systemic lupus erythematosus (SLE; lupus) is a chronic inflammatory connective tissue disease that mainly affects women, often in their childbearing years. In Norway, a point prevalence of SLE of 91–102.5 per 100,000 women (1,2) indicates that the disease occurs in at least 1 in 1,000 fertile women. SLE and its treatment may have an impact on pregnancy outcome, and pregnancy may influence the disease course (3,4). Pregnant women with SLE are considered high risk due to increased risk of miscarriage, stillbirth, preeclampsia, growth restriction, and preterm birth (5,6). The accumulation of knowledge about the disease course and treatment options has led to an improvement in outcomes for both mother and child over the last few decades (7–9). Established predictors of pregnancy complications are lupus nephritis, hypertension, and secondary antiphospholipid syndrome (APS) (10,11). Importantly, high disease activity before and during pregnancy also increases the risk of complications, whereas low disease activity is a good basis for a normal or close to normal pregnancy and outcome in most women with SLE (5,7). In general, SLE follows a typical pattern of higher disease activity (flares) alternating with periods of lower disease activity (12). Studies indicate that approximately 50% of women with SLE experience flares during pregnancy or after birth, most commonly during the second half of pregnancy or in the first few months postpartum (13,14).

Modification of 3 established disease activity assessments was proposed in 1999, the purpose of which was to avoid

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Significance & Innovations

- Disease activity measured by validated methods has been sparsely examined during and after pregnancy in women with systemic lupus erythematosus (SLE).
- In a nationwide Norwegian longitudinal followup of pregnancies in women with SLE resulting in live birth, the majority of women had no or low disease activity at conception and during pregnancy, and higher disease activity at 6 and 12 months after delivery.
- The clinical implication of these findings is tight followup not only before and during pregnancy, but also in the first year postpartum.

misinterpreting the physiologic changes of pregnancy as active SLE (15). The Lupus Activity Index (LAI) was later validated for use in pregnancy and the puerperium (6 weeks after birth) and is the only one that has been validated for use in pregnancy (15,16). Four prior studies have utilized disease activity assessments adapted for use in pregnancy; 3 used the SLE Pregnancy Disease Activity Index (SLEPDAI) (17–19) and 1 used the LAI in Pregnancy (LAI-P) (20), and only 1 included assessment after birth. Most commonly, the SLEDAI and physician global assessment (PGA) have been used to evaluate disease activity in pregnant women with SLE (15). Previous studies assessing disease activity after birth stopped the followup at 2 months postpartum, with 1 exception (21). The aim of this study was to describe variation in disease activity during pregnancy and the first year postpartum, using a disease activity score validated for use in pregnancy and the puerperium.

PATIENTS AND METHODS

Study population. The study population was derived from RevNatus, a nationwide Norwegian multicenter, prospective observational register including women with an inflammatory rheumatic disease when planning pregnancy or after conception. The register was established in 2006 and is administered by the national advisory unit on pregnancy and rheumatic diseases. Women 18 years and older are recruited and followed up in each trimester of pregnancy and at 6 weeks, 6 months, and 12 months after birth.

From June 2006 until May 2015, there were 237 women with SLE who were enrolled in RevNatus. They had been diagnosed with SLE by a rheumatologist prior to enrollment. Only pregnancies resulting in live births were included in the present study; both singleton and multiple births were included. There were 17 women who participated twice.

Clinical characteristics and variables assessed. The first registration in RevNatus included demographic data, information on concomitant diseases, and history of medicine use, including traditional and biologic disease-modifying drugs, prednisolone, and nonsteroidal antiinflammatory drugs. Parity, previous pregnancy outcomes including term and preterm births, pregnancy loss, as well as mode of delivery and pregnancy complications (e.g., preeclampsia) were registered. All visits included a general clinical examination, present use and changes in medication, blood tests, a urine sample, and a disease activity assessment. Pregnancy outcomes, mode of delivery, and complications during the present pregnancy were registered at the 6-week postpartum visit. Breastfeeding status was registered at all postpartum visits.

Assessment of disease activity. SLE disease activity was scored according to the LAI-P at the visits during pregnancy and at 6 weeks after birth and according to the modified Lupus Activity Index (M-LAI) at 6 and 12 months after birth. The LAI provides a global score assessing overall disease activity in SLE over the previous 2 weeks. It consists of 5 sections and includes a PGA, and items describing general and organ-specific clinical manifestations, current medication use, and certain laboratory findings, scored on a visual analog scale to indicate presence and severity (22,23). The index allows for comparisons of patients with different disease manifestations, and is appropriate for detecting changes in disease activity over time (23). The LAI-P is a modified version of the LAI, with a good ability to measure disease activity and detect disease flares in pregnancy and the puerperium in women with SLE (16,24). The first section in the original LAI, the PGA, was excluded to decrease the subjectivity of the scale. The LAI-P consists of the same 4 sections of items as the LAI, but the original visual scale is replaced with a graded scale, and asthenia is excluded to avoid the scoring of pregnancy-related symptoms as disease activity (16). The organ-specific manifestations contribute to the final score, with the maximum value on any of the items in the group, while the other 3 groups contribute with the mean value of the scored items in each group. The LAI-P scores disease activity on a continuous scale from 0–2.6, with 0 indicating no disease activity and scores ≥ 2 indicating high disease activity (25). To have comparable scales, we modified the original LAI (M-LAI), excluding the PGA and using the same items as the LAI-P, except for fever (fatigue in the LAI), graded similarly and on the same continuous scale (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23102/abstract). In order to describe the longitudinal course of disease activity throughout pregnancy and the first year postpartum, each woman served as her own control, using disease activity scores on every visit in the followup period. Disease activity was scored using the LAI-P at trimesters 1, 2, and 3, and 6 weeks postpartum, and using the M-LAI at 6 and 12 months postpartum.

Ethical considerations. RevNatus was established in 2006, with approval by the regional committee for medical and health research ethics in Norway (REK Mid-Norway). Eligible women signed a written informed consent form before their inclusion in RevNatus. The present study was approved by REK Mid-Norway in 2012.

Statistical analysis. Disease activity was highly skewed, with 51.6% of the scores including all visits showing no disease activity (LAI-P and M-LAI = 0) while only 0.9% of the

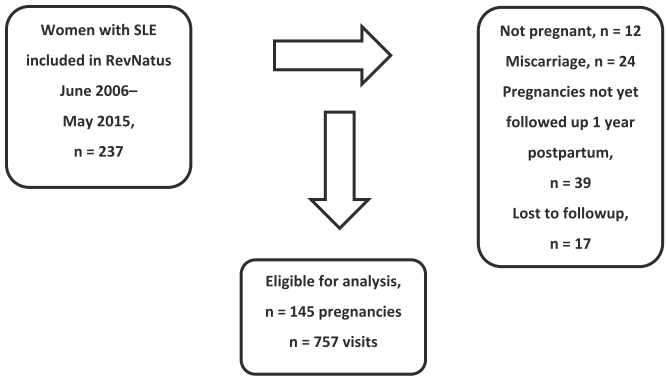

Figure 1. Flow chart on selection process of eligible cases. SLE = systemic lupus erythematosus.

scores were >1.0, and 0.1% were >2.0. As the assumption of normal distribution was not fulfilled, we categorized the dependent variable (LAI-P or M-LAI) into 4 groups (0, 1, 2, and 3). A change in disease activity score of ≥0.25 was deemed a clinically relevant change indicating worsening (flare) or improvement of disease (16,24). The categories chosen accordingly were no disease activity (LAI-P or M-LAI = 0), very low disease activity (LAI-P or M-LAI >0 and ≤0.25), low disease activity (LAI-P or M-LAI >0.25 and ≤0.50), and moderate disease activity (LAI-P or M-LAI >0.50). The longitudinal course of disease activity was analyzed using proportional-odds ordinal logistic mixed-model regression analyses, with the visit number as the categorical covariate and the patient as the random effect. These analyses were carried out unadjusted, and were adjusted for use of prednisolone, azathioprine (AZA), and/or hydroxychloroquine (HCQ) at each visit (yes/no). To confirm the results, we also carried out corresponding binary logistic regression mixed-model analyses, with the dependent variable dichotomized at no disease activity. Two-sided *P* values less than 0.05 were considered statistically significant. The descriptive statistics were performed using SPSS, version 21, and the mixed-model analyses were performed using Stata, version 13.1.

RESULTS

Patient recruitment. During the study period, 237 women previously diagnosed with SLE by a specialist in rheumatology were enrolled in RevNatus. The flow chart in Figure 1 shows the numbers of participants and reasons for exclusion. In the 208 pregnancies with a known outcome, 12% resulted in pregnancy loss and 88% resulted in live birth. The present cohort constitutes 145 pregnancies in 128 women with SLE resulting in live birth followed prospectively throughout pregnancy and the first year after birth. There were 142 singleton and 3 twin births. Twenty-six women were included before pregnancy (all of whom attended the visit in the first trimester); of the others, 96 were included in the first trimester, 23 in the second, and 1 in the third. There were a mean of 4.7 registrations in RevNatus for each pregnancy and a total of 783 registered visits. The visit before pregnancy (visit 0) had the lowest number of attendees, at 26; visit 1 (first trimester) had 122, visit 2 (second trimester) had 134, visit 3 (third trimester) had 131, visit 4 (6 weeks postpartum) had 139, visit 5 (6 months postpartum) had 121, and visit 6 (12 months postpartum) had 110. Disease activity assessed at the visit before pregnancy was not included in the analysis.

Clinical characteristics. Table 1 shows the clinical characteristics of the women with SLE enrolled in RevNatus, with included and excluded cases shown separately. In all, 88 of 105 (84%) included and 46 of 60 (78%) excluded women fulfilled American College of Rheumatology (ACR) classification criteria for SLE (≥4 criteria) (26). ACR classification criteria were not reported in the remaining 23 and 29 women, respectively, diagnosed with SLE. Eleven and 4 women, respectively, were diagnosed less than 1 year before pregnancy. Anticardiolipin antibody positivity was defined in accordance with the international consensus statement on an update of the classification criteria for definite APS (27). Information on whether or not the women had been diagnosed with APS was not available. In the subgroup of excluded women experiencing miscarriage, 9 of 17 had anticardiolipin antibody positivity, and all of them had lupus anticoagulant positivity.

Table 2 shows disease activity at inclusion for the present cohort and the excluded cases (total and separated by reason for exclusion). The disease manifestations most commonly reported were skin, joint, and hematologic features, followed by active kidney disease. Neurologic, pulmonary, or cardiac disease was rarely reported. In women with detected antiphospholipid antibodies, neurologic disease would only be scored in the LAI-P or M-LAI if there were more than 1 neurological symptom (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23102/abstract). Women with moderate disease activity (LAI-P or M-LAI >0.5) were reported to have active kidney disease at similar levels as skin, joint, and

Table 1. Clinical characteristics of women with SLE registered in RevNatus 2006–2015*

Clinical characteristic	Included pregnancies (n = 145)	Excluded pregnancies (n = 92)	
		All excluded pregnancies	Not followed 1 year pp or lost to followup
Age in trimester 1, mean ± SD years	30.4 ± 4.95	31.0 ± 4.63†	31.4 ± 4.81†
Disease duration, mean ± SD years	8.0 ± 6.34	9.7 ± 6.89	9.6 ± 5.75
Body mass index, 18.5–24.9 kg/m^2	58/92 (63.0)	45/75 (60.0)	28/45 (62.2)
Smoking in trimester 1	10/119 (8.4)	6/86 (7.0)†	3/55 (5.5)†
No prior pregnancies	38/143 (26.6)	22/84 (26.2)	10/49 (20.4)
No prior births	46/127 (36.2)	42/84 (50.0)	20/49 (40.8)
No prior miscarriages	94/142 (66.2)	50/82 (61.0)	27/48 (56.3)
Kidney disease prior to pregnancy	41/117 (35.0)	22/71 (31.0)	13/43 (30.2)
Present kidney disease in trimester 1	5/102 (4.9)	7/79 (8.9)†	3/47 (6.4)†
Positive aCL antibodies at inclusion‡	28/96 (29.2)	23/60 (38.3)	13/35 (37.1)
Positive LAC at inclusion	22/96 (22.9)	18/58 (31.0)	8/35 (22.9)

* Values are the no./total no. (%) unless indicated otherwise. Category totals may add up to less than the full sample totals due to missing data. SLE = systemic lupus erythematosus; pp = postpartum; aCL = anticardiolipin; LAC = lupus anticoagulant.
† At inclusion (preconception or in pregnancy).
‡ Presence of 1, 2, or 3 LACs in plasma and/or aCL antibody IgG and/or IgM >40 GPL units/ml or MPL units/ml and/or anti-b2 glycoprotein-I antibody IgG and/or IgM in serum or plasma.

hematological manifestations. In the present cohort, pulmonary disease was reported in 1 case 6 weeks postpartum (visit 4), and neurologic disease was reported in 1 case 6 months postpartum (visit 5). In the excluded cases, women with miscarriages were the most diseased at inclusion, including present kidney disease. Table 3 shows the reported use of immunosuppressive medication and assessed disease activity, including active kidney disease, at every visit. HCQ, AZA, and prednisolone were the only immunosuppressants used in the cohort.

Active kidney disease was among the 6 specific organ manifestations scored in the LAI-P/M-LAI (neurologic, renal, pulmonary, hematologic, vascular, or myogenic), and accounted for the score from this group if there were no other items scoring higher. Active hematologic disease was reported more often than active kidney disease, but mainly with a low or similar score, whereas the other 4 items were infrequently scored as active disease. Accordingly, active kidney disease was the organ-specific disease manifestation most commonly reported with a high score (2 or 3), indicating severe organ disease, even though it was not a frequent event. Active kidney disease was defined according to the LAI-P. Criteria required doubled proteinuria in cases of known earlier nephritis or new-onset proteinuria with a protein/creatinine ratio >30 mg/mmol, an active urine sediment, or decreasing kidney function. Secondary reasons for renal failure were excluded.

At inclusion, 97 women (67%) used HCQ, 41 (24%) used AZA, and 62 (43%) used prednisolone. Sixty-five women used combination therapy, most commonly HCQ and prednisolone, followed by a combination of all 3 drugs. In 34 women (23%), no immunosuppressive medication was used at inclusion. Of these, 4 started HCQ in the second trimester, either alone or in combination with AZA and prednisolone, 1 started prednisolone in the third trimester, and 5 started immunosuppressive treatment postpartum. Of the total cohort, there were 15 women who stopped and restarted immunosuppressive medication during pregnancy, 4 who stopped during pregnancy, and 7 who stopped after giving birth. Eighteen women added immunosuppressive medication in pregnancy and/or

Table 2. Disease activity in women with SLE at time of first registration in RevNatus*

Disease activity	Included pregnancies (n = 145)	Excluded pregnancies (n = 92)				
		All excluded pregnancies	Not yet pregnant	Miscarriage	Not followed 1 year pp	Lost to followup
None (LAI-P/M-LAI = 0)	68/129 (52.7)	44/79 (55.7)	4/9 (44.4)	8/19 (42.1)	26/36 (72.2)	6/15 (40.0)
Very low/low(LAI-P/M-LAI >0 and ≤0.5)	52/129 (40.3)	27/79 (34.2)	4/9 (44.4)	4/19 (21.1)	10/36 (27.8)	9/15 (60.0)
Moderate (LAI-P/M-LAI >0.5)	9/129 (7.0)	8/79 (10.1)	1/9 (11.1)	7/19 (36.8)	0	0

* Values are the no./total no. (%). Category totals may add up to less than the full sample totals due to missing data. SLE = systemic lupus erythematosus; pp = postpartum; LAI-P = Lupus Activity Index in Pregnancy; M-LAI = modified Lupus Activity Index.

Table 3. Immunosuppressive treatment and disease activity including active kidney disease in women with SLE (n = 145 pregnancies), as reported at each visit*

Characteristic	First trimester (visit 1)	Second trimester (visit 2)	Third trimester (visit 3)	6 weeks pp (visit 4)	6 months pp (visit 5)	12 months pp (visit 6)
Immunosuppressive treatment						
Hydroxychloroquine	84/120 (70.0)	87/132 (65.9)	89/128 (69.5)	93/133 (69.9)	83/114 (72.8)	73/105 (69.5)
Prednisolone	52/120 (43.4)	55/132 (41.7)	57/128 (44.5)	64/132 (48.5)	56/113 (49.6)	53/105 (50.5)
Azathioprine	36/120 (30.0)	37/133 (27.8)	34/130 (26.2)	29/134 (21.6)	27/113 (23.9)	20/102 (19.6)
Disease activity						
None†	56/109 (51.4)	60/114 (52.6)	70/114 (61.4)	68/119 (57.1)	41/97 (42.3)	44/95 (46.3)
Moderate‡	6/109 (5.5)	7/114 (6.1)	5/114 (4.4)	7/119 (5.9)	7/97 (7.2)	9/95 (9.5)
Active kidney disease	5/102 (4.9)	4/118 (3.4)	5/112 (4.5)	7/119 (5.9)	4/100 (4.0)	3/98 (3.1)

* Values are the no./total no. (%) unless otherwise indicated. SLE = systemic lupus erythematosus; pp = postpartum.
† Defined as a score of 0 on the Modified Lupus Activity Index or the Lupus Activity Index in Pregnancy.
‡ Defined as a score of >0.5 on the Modified Lupus Activity Index or the Lupus Activity Index in Pregnancy.

after giving birth, 8 in pregnancy, and 12 postpartum. There was no change in immunosuppressive medication in 101 women in the followup period. Disease activity changed over time. Figure 2 shows the distribution of the 4 disease activity categories at each visit.

Longitudinal course of disease activity. More than half (51.6%) of the disease activity scores were equal to 0, and only 6.3% of the scores exceeded 0.5. Fifty-six women (56/109, 51.4%) had no disease activity in the first trimester (visit 1), with an LAI-P score of 0. The variation in disease activity between visits was statistically significant ($P = 0.035$). Figure 3 shows the estimated probability of disease activity above 0, from the ordinal logistic mixed-model analysis, and was highest at visits 5 and 6. The differences between visit 6 and visits 3 ($P = 0.009$) and 4 ($P = 0.031$) were statistically significant, and between visit 6 and visit 1 ($P = 0.175$) and 2 ($P = 0.084$) were not statistically significant.

When dichotomizing the dependent variable into no disease activity (LAI-P/M-LAI = 0) and disease activity (LAI-P/M-LAI >0), we confirmed the statistically significant change in disease activity over time ($P = 0.017$), with a similar pattern in the longitudinal course of disease activity (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23102/abstract). After adjusting for the use of prednisolone at each visit, we found that the change in disease activity over time was maintained ($P < 0.001$), and there was a statistically significant increased risk of higher disease activity when using prednisolone (odds ratio [OR] 3.10;

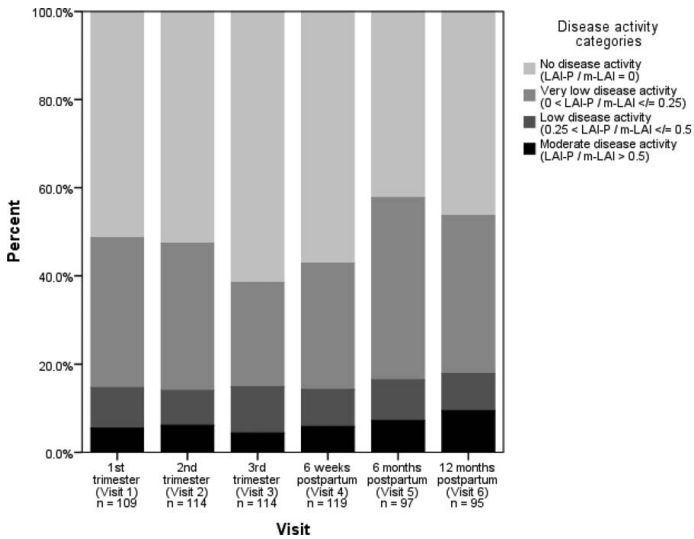

Figure 2. Distribution of disease activity categories by visit. LAI-P = Lupus Activity Index in Pregnancy; m-LAI = modified Lupus Activity Index.

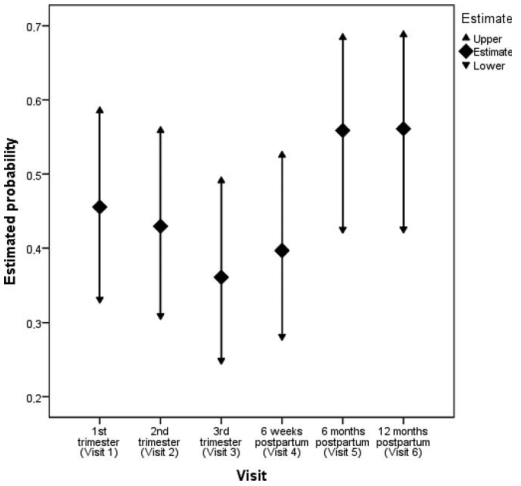

Figure 3. Longitudinal variation in probability of disease activity above 0. Estimates and 95% confidence intervals from the ordinal logistic mixed-model analysis.

$P < 0.001$). We found no statistically significant interaction between prednisolone use and visit number (likelihood ratio test, 5 df, $P = 0.18$). Likewise, when adjusting for the use of AZA, there was a maintained statistically significant change in disease activity over time ($P = 0.009$) and a statistically significant increased risk of higher disease activity when using AZA (OR 2.2; $P = 0.022$). There was no statistically significant interaction between AZA use and visit number (likelihood ratio test, 5 df, $P = 0.97$). After adjusting for the use of HCQ at each visit, we found that the longitudinal change in disease activity was also preserved ($P = 0.012$), with a nonsignificant tendency toward lower disease activity when using HCQ (OR 0.78; $P = 0.47$). We found no statistically significant interaction between HCQ use and visit number (likelihood ratio test, 5 df, $P = 0.085$).

DISCUSSION

To our knowledge, there are no prior studies following the course of SLE disease activity throughout pregnancy and up to 1 year after birth, assessing disease activity by an instrument validated for use in pregnancy and the puerperium. In this prospective, observational study, we found that the majority of the disease activity scores in the followup period showed no or low disease activity, with a statistically significant change in disease activity over time, the latter illustrating the relapsing and remitting nature of the disease. Only 1 registered disease activity score reached a value of 2, indicating high disease activity. This is in accordance with other recent studies (17,28,29), and adds to the evidence that pregnant women with SLE now have better-controlled disease, resulting in better outcomes (9).

It is reasonable to believe that a tight followup of disease and pregnancy together with the counseling of women who are planning pregnancy when included in a register such as RevNatus, contributes to the observed low disease activity. Only 2 women with disease activity assessed before pregnancy experienced a flare in the first trimester, while 19 had stable or remitting disease in the first trimester compared to preconception (data not shown). However, our data revealed that disease activity increased 6 and 12 months postpartum, a novel finding in women with SLE. This was despite stable use of HCQ throughout visits, and a slight increase in the use of prednisolone. HCQ has been shown to protect against increasing disease activity (30,31), and ideally all women with SLE planning pregnancy should be treated with HCQ to avoid potential flares (6,8). Prednisolone is the most common drug used to control disease flares (32), and therefore the finding that prednisolone use was associated with a risk of higher disease activity may be a case of confounding by indication. The use of AZA gradually decreased through the followup, and AZA was stopped either in the third trimester or 6 weeks postpartum in 5 women, without restarting any other immunosuppressive medication. Four of these women reported breastfeeding at the first postpartum visit, suggesting that they stopped taking the drug for the purpose of breastfeeding. In this control, 6 weeks postpartum, 8 women reported that they had stopped breastfeeding due to medication; 2 women used HCQ and 6 used AZA in combination with HCQ and/or prednisolone. This underscores the importance of adequate counseling on medication and lactation, to prevent undue cessation of drugs in women who choose to breastfeed (33,34).

We included both singleton and multiple births in the analysis, as we assume that the pregnancy itself may influence disease activity and vice versa, whether it is 1 or 2 babies. Seventeen women participated twice. It is possible that women with no disease activity and uncomplicated pregnancies chose to get pregnant again in contrast to the more diseased women who might have chosen not to. However, the disease activity scores in the first of 2 included pregnancies compared to the other pregnancies showed a similar pattern, with 48 of 91 (52.7%) versus 297 of 577 (51.5%) of the scores indicating remission and 5 of 91 (5.5%) versus 35 of 577 (6.4%) of the scores indicating moderate disease activity. It is well known that women's first pregnancies are more prone to complications than subsequent pregnancies, and this has also been shown in mothers with SLE (35). However, we have no reason to believe that parity interacts with or has an impact on the course of disease activity during pregnancy and the first year postpartum.

The mean age (overall and for the nulliparous group) in these women was slightly higher than for the general Norwegian obstetric population (36), as reported in earlier publications on SLE (10,35). Maternal age and disease duration were not included as covariates, as these factors were stable at all visits, and are not expected to be associated with the course of disease activity in the followup period. In a previous study (28), neither maternal age nor disease duration had an impact on the incidence of high disease activity. The BMI in the first trimester was normal in 58 of 92 (63%), which is comparable to the general pregnant population in Norway. In the excluded women, there was a higher proportion of overweight, and this was particularly prominent in the subgroup of not yet pregnant women (Table 1). Only 8.4% of the women smoked in the first trimester. This is in

accordance with public data provided by the Medical Birth Registry of Norway, which shows a gradual decline in smokers in the first part of pregnancy, from 15.9% in 2006 to 7.1% in 2014 (36).

A strength of this study is that the Norwegian health care system provides equal services, encompassing all citizens independent of socioeconomic or geographic status. Lupus patients are cared for by specialists in rheumatology, and we believe that the cohort represents the majority of pregnant SLE patients in the study period. The cohort is mainly white European, minimizing the possibility of ethnicity influencing disease severity and organ manifestations (37). Women with SLE included in RevNatus had all been diagnosed by a specialist in rheumatology prior to inclusion, securing the correct diagnosis. Applying a disease activity score validated for use in pregnancy is another strength in interpreting the results. There was a mean of 4.7 visits per participant, and 648 of 757 of the visits (85.6%) had registered disease activity scores. We used mixed models for analysis of longitudinal data. This implies that subjects with missing data at 1 or more visits are included in the analysis with their available data, whereas a complete case analysis would have removed those subjects from the analysis. Further, a complete case analysis would give unbiased results only under the missing completely at random (MCAR) assumption, while mixed models give unbiased results under the less restrictive missing at random (MAR) assumption. This implies that if subjects with measured low disease activity at 1 visit are more likely not to show up at the next visit, the results will still be unbiased. Even if there is some degree of missing not at random (MNAR), a mixed model yields less bias than a complete case analysis. Additionally, the proportion of missing data in our study is low. Accordingly, we do not expect much bias due to missing data.

A limitation of the study is the lack of information on disease activity before pregnancy, with only 17.9% (26 of 145) of the women included before conception. However, the preconception visit had a much wider time span than the other visits, as the time of registration might be from a few weeks to up to 1 year before conception. To overcome this challenge, we chose visit 6 as the reference visit, providing a nonpregnant disease activity status on a well-defined point of time (12 months postpartum). Another limitation is a possible selection bias. Women included in RevNatus are planning pregnancy, and one may expect a better-controlled disease. The majority of study participants were included after conception, suggesting that in at least some of these, pregnancy was not planned. Another concern is that pregnant women with a disease in remission might not have been recruited into the register, resulting in an underreporting of no or low disease activity. On the other hand, women with high disease activity or very severe prior organ damage might choose not to become pregnant, and therefore would not be included in RevNatus. High disease activity increases the risk of miscarriage, and we do not know the number of women with SLE who conceived and had an early miscarriage without being registered. The data show that in the women who were included in RevNatus and miscarried, more than one-third had moderate to high disease activity at inclusion (Table 2), in contrast to the women giving birth, a group in which only 7% had moderate disease activity at inclusion. This is a concern when the focus is pregnancy outcome, but does not affect the results in the present study.

In conclusion, in our study of pregnancies in women with SLE resulting in live births, the majority of women had low or no disease activity at conception, with a statistically significant change in disease activity over time. Increased disease activity of clinical importance was not demonstrated during pregnancy or at 6 weeks postpartum, but at 6 and 12 months postpartum. Our study points to the importance of tight disease control in women with SLE not only before and during pregnancy, but also in the first year after birth.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Götestam Skorpen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Götestam Skorpen, Gilboe, Skomsvoll, Palm, Koksvik, Wallenius.

Acquisition of data. Götestam Skorpen, Gilboe, Skomsvoll, Palm, Koksvik, Jakobsen, Wallenius.

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