EXTENDED REPORT

Influence of disease activity and medications on offspring birth weight, pre-eclampsia and preterm birth in systemic lupus erythematosus: a population-based study

Carina Götestam Skorpen,[1,2] Stian Lydersen,[3] Inge-Margrethe Gilboe,[4] Johan Fredrik Skomsvoll,[5] Kjell Å Salvesen,[6,7] Øyvind Palm,[4] Hege Suorza Svean Koksvik,[5] Bente Jakobsen,[5] Marianne Wallenius[1,5]

ABSTRACT

Objectives Exploring the associations between disease activity and medications with offspring birth weight, pre-eclampsia and preterm birth in systemic lupus erythematosus (SLE).

Methods Data from the Medical Birth Registry of Norway (MBRN) were linked with data from RevNatus, a nationwide observational register recruiting women with inflammatory rheumatic diseases. Singleton births in women with SLE included in RevNatus 2006–2015 were cases (n=180). All other singleton births registered in MBRN during this time (n=498 849) served as population controls. Z-score for birth weight adjusted for gestational age and gender was calculated. Disease activity was assessed using Lupus Activity Index in Pregnancy. We compared z-scores for birth weight, pre-eclampsia and preterm birth in cases with inactive disease, cases with active disease and population controls.

Results Z-scores for birth weight in offspring were lower in inactive (−0.64) and active (−0.53) diseases than population controls (−0.11). Inactive disease did not predict pre-eclampsia while active disease yielded OR 5.33 and OR 3.38 compared with population controls and inactive disease, respectively. Preterm birth occurred more often in inactive (OR 2.57) and active (OR 8.66) diseases compared with population controls, and in active compared with inactive disease (OR 3.36).

Conclusions SLE has an increased odds for low birth weight and preterm birth, amplified by active disease. The odds for pre-eclampsia is elevated in active, but not inactive disease. This calls for tight follow-up targeting inactive disease before and throughout pregnancy.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic rheumatic disease often affecting women in fertile age. In SLE, there is an increased risk of unfavourable pregnancy outcomes including low birth weight and preterm birth and complications like pre-eclampsia, even though there is evidence for less elevated risk over the last decades.[1] Pre-eclampsia is one of the risk factors for preterm birth. The increased risk of pre-eclampsia including early-onset pre-eclampsia (before 34 weeks) in SLE may be independent of traditional risk factors such as pregestational hypertension and body mass index (BMI).[2] High disease activity and flare shortly before or during pregnancy are factors predictive for complications,[3–5] whereas no or low disease activity is favourable.[6] A recent population-based study reported lower mean birth weight and gestational age in both first and subsequent births in women with SLE compared with references.[7] Low birth weight caused by intrauterine growth restriction is associated with an increased risk of cardiovascular disease and diabetes in the offspring.[8] Pre-eclampsia, preterm birth and low offspring birth weight are events associated with a future higher risk of maternal cardiovascular disease[9] and death.[10] Prednisolone use in pregnancy has been associated with preterm birth and a lower birth weight.[11] In SLE, prednisolone is commonly used to treat disease flares, and confounding by indication may explain this finding. Most studies investigating the influence of disease activity on pregnancy outcomes have found high disease activity or disease flare to be risk factors for adverse pregnancy outcomes. To our knowledge, prospective studies comparing pregnancy outcomes in SLE women with inactive disease, SLE women with active disease and population controls have not been reported. We regard birth weight adjusted for gestational age and gender (z-score) as the relevant birth weight outcome in this context. The aim of this study was to explore the possible associations of disease activity and medications with offspring birth weight z-score and the occurrence of pre-eclampsia and preterm birth in women with SLE.

PATIENTS AND METHODS

Study population

In this population-based cohort, we linked data from the Medical Birth Registry of Norway (MBRN) with data from RevNatus. MBRN is a national health registry with mandatory registration of variables on all births in Norway. It includes information about maternal health before and during pregnancy as well as maternal and neonatal complications during pregnancy and birth. The variables were decided by consensus among obstetricians, neonatologists and epidemiologists. Since December 1998,[12] pre-pregnant maternal diseases including rheumatic diseases have been coded according to the International

Table 1 Characteristics of patients (SLE) and population controls, reported as n (%) unless specified as mean (SD)

Characteristic	SLE	Population controls	P value
Number of deliveries	180	498 849	
Maternal age (years), mean (SD)	31.5 (5.0)	30.4 (5.1)	0.004
<35	138 (76.7)	402 064 (80.6)	
≥35	42 (23.3)	96 569 (19.4)	
Missing	–	–	
Parity			0.91
No children	77 (42.8)	209 978 (42.1)	
≥1 child	103 (57.2)	288 871 (57.1)	
Missing	–	–	
Smoking in pregnancy	12 (6.9)	47 137 (11.2)	0.09
Missing	6	79 171	
BMI first trimester, mean (SD)	23.8 (4.9)	24.3 (4.8)	0.30
Underweight (<18.5)	7 (8.3)	8298 (4.1)	
Normal weight (18.5–24.9)	50 (59.5)	123 903 (61.5)	
Overweight (≥25)	27 (32.1)	69 294 (34.4)	
Missing	96	297 354	

BMI, body mass index; SLE, systemic lupus erythematosus.

Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).

RevNatus is a nationwide Norwegian multicentre, prospective observational register recruiting women with inflammatory rheumatic diseases who plan pregnancy or are pregnant. Women 18 years or older are included, with follow-up in each trimester and at 6 weeks, 6 and 12 months after birth. All women are diagnosed by a specialist in rheumatology prior to inclusion. Information on obstetric history, disease activity and medications as well as maternal and neonatal outcomes including complications is registered. In the present study, singleton births recorded in MBRN 2006–2015 were eligible for inclusion. Births among women with the diagnosis of SLE recorded in MBRN (ICD-10 codes M32.1, M32.8 and M32.9) *and* included in RevNatus formed the patient group (n=180). Population controls were all other singleton births registered in MBRN during the same period (n=498 849), but excluding births among women with any rheumatic inflammatory disease (n=2492) according to ICD-10 diagnoses (online supplementary figure S1). The 2015 age cohort was excluded from the population controls as the registration of ICD diagnoses of maternal pre-pregnant disease was not completed. One woman could have several births during the study period. This applied to 28 (15.6 %) of 180 women in the patient group and an unknown proportion of the women in the control population.

Ethics
All women signed a written informed consent before inclusion. Access to data from MBRN was granted in September 2016 (MBRN assignment 15-1819).

Variables
For both patients and population controls, data on maternal age, parity, smoking and BMI were derived from MBRN, as were data on newborns and complications including pre-eclampsia,[13 14] preterm birth (<37 gestational weeks) and very preterm birth (<34 gestational weeks). BMI was included as a variable in MBRN in 2012 and reported by 40% of the birth institutions, resulting in high missing numbers. For the patient group, educational status, prior obstetric history and disease-specific information were retrieved from RevNatus. Fulfilment of the 1997 American College of Rheumatology criteria for classification of SLE required ≥4 criteria.[15] A positive test for lupus anticoagulant, anticardiolipin antibody IgG and antibeta2 glycoprotein I IgG was defined according to thresholds for positivity at the time of the test.

Assessment of disease activity
Disease activity was assessed by the Lupus Activity Index in Pregnancy (LAI-P), a modification of the Lupus Activity Index (LAI) validated for use in pregnancy.[16] LAI-P is described in detail elsewhere.[17] Briefly, disease activity is assessed on a scale from 0 (inactive disease) to 2.6 (very high disease activity), with a score above 0.5 considered moderate disease activity. It is a composite score, including items describing general and organ-specific clinical manifestations, current medication and certain laboratory findings. LAI-P was assessed in each trimester and at 6 weeks after birth, and dichotomised to inactive disease (LAI-P=0) and active disease of any severity (LAI-P>0). There were missing data on disease activity at all visits, and most frequently among the preterm (39% missing) and very preterm (50% missing) births in the third trimester. The data were not missing completely at random, as many of these women did not attend the third trimester visit due to birth before scheduled visit. Data on disease activity were more complete in the second trimester (missing in 20% of term and 6% of preterm outcomes).

Calculation of birth weight z-score adjusted for gestational age and gender
Recorded pregnancy outcomes in MBRN included birth weight (grams), gender and gestational age at delivery in days based on a mid-trimester ultrasound examination. Birth weight is influenced by gestational age and gender, differs from country to country and has secular changes. Accordingly, z-score for birth weight was calculated using Norwegian birth weight by gestational age standards covering 20–44 completed weeks, separately for males and females.[18] The z-scores were calculated using gestational age in days, with linear interpolation between weeks.

Statistical analyses
Group comparisons were performed using independent t-test for continuous variables and the Pearson χ^2 test or the unconditional z-pooled test for categorical variables.[19] We used linear regression with z-score as dependent variable, and logistic regression for dichotomous-dependent variables (pre-eclampsia and preterm birth). As covariates, we compared population controls with cases with inactive disease (LAI-P=0) and cases with active disease (LAI-P>0) in the second trimester. We carried out the analyses unadjusted, and adjusted for maternal age (<35 years/≥35 years), parity (no birth/≥1 birth) and smoking in pregnancy (yes/no). We also carried out analyses for first and subsequent births separately. Separate analyses were performed concerning use of prednisolone (yes/no) in the second trimester, and adjusting for hydroxychloroquine (yes/no) and azathioprine (yes/no). Missing values were handled by available case analysis. Two-sided P values less than 0.05 were considered statistically significant, and 95% CIs are reported where relevant. The statistical analyses were performed using SPSS V.22.

Clinical and epidemiological research

Table 2 Clinical characteristics of all patients (SLE), and grouped according to disease activity in second trimester, reported as n (%) unless specified as mean (SD)

Characteristic	SLE (total)	Inactive disease (LAI-P=0)	Active disease (LAI-P>0)	Not registered disease activity	P value*
Number of deliveries	180	85	63	32	
Maternal age, mean (SD)	31.5 (5.0)	31.9 (4.6)	31.3 (5.5)	30.8 (4.9)	0.47
<35	138 (76.7)	65 (76.5)	47 (74.6)	26 (81.3)	
≥35	42 (23.3)	20 (23.5)	16 (25.4)	6 (18.8)	
Missing	–	–	–	–	
Nullipara	77 (42.8)	32 (37.6)	29 (46.0)	16 (50.0)	0.39
Missing	–	–	–	–	
Smoking in pregnancy	12 (6.9)	2 (2.4)	7 (11.1)	3 (10.3)	0.032†
Missing	6	3	–	3	
BMI first trimester, mean (SD)	23.8 (4.9)	22.7 (4.4)	24.7 (5.8)	24.5 (3.9)	0.11
<18.5	7 (8.0)	6 (15.0)	1 (3.4)	0	
18.5–25	52 (59.1)	24 (60.0)	19 (65.5)	9 (47.4)	
≥25	29 (33.0)	10 (25.0)	9 (31.0)	10 (52.6)	
Missing	92	45	34	13	
Educational level					0.44
Low‡	13 (7.4)	6 (7.2)	5 (8.1)	2 (6.5)	
Intermediate§	46 (26.1)	18 (21.7)	19 (30.6)	9 (29.0)	
High¶	117 (66.5)	59 (71.1)	38 (61.3)	20 (64.5)	
Missing	4	2	1	1	
ACR criteria fulfilled**	114 (82.3)	51 (77.3)	47 (90.4)	16 (84.2)	0.10
Missing	43	11	19	13	
Disease duration, mean (SD)	8.7 (6.2)	8.8 (5.6)	8.6 (6.2)	8.3 (7.4)	0.86
Missing	9	5	2	2	
Prior pregnancy loss	30 (18.0)	13 (16.9)	15 (24.2)	2 (7.1)	0.39
Missing	13	8	1	4	
Prior pre-eclampsia	13 (7.2)	6 (7.1)	6 (9.5)	1 (3.1)	0.53
Missing	2	1	1	–	
Positive LAC	29 (23.6)	14 (21.9)	12 (27.9)	3 (18.8)	0.63
Missing	57	21	20	16	
Positive aCL IgG	13 (7.4)	8 (9.8)	5 (8.1)	0	0.73
Missing	5	3	1	1	
Positive Aβ2GPI IgG	9 (5.0)	3 (6.1)	6 (18.8)	0	0.089†
Missing	83	36	31	16	
Prior kidney manifestation	40 (35.0)	21 (31.3)	22 (40.0)	7 (33.3)	0.42
Missing	37	18	8	11	

*P value for active compared with inactive disease.
†The unconditional z-pooled exact test.
‡10 years.
§12–13 years.
¶>15 years.
**≥4 criteria according to 1997 American College of Rheumatology diagnostic criteria for SLE.
Aβ2GPI IgG, anti-beta2 glycoprotein I IgG; aCL IgG, anti-cardiolipin IgG; ACR, American College of Rheumatology; BMI, body mass index; LAC, lupus anticoagulant; LAI-P, Lupus Activity Index in Pregnancy; SLE, systemic lupus erythematosus.

RESULTS

Patient recruitment

During 2006–2015, 237 inclusions among 203 women diagnosed with SLE were registered in RevNatus. Of known outcomes (n=223), 5% did not become pregnant, miscarriage was reported in 12%, and 83% resulted in live birth. There were 180 singleton and 6 twin deliveries. Among the singleton births, 26 women had two deliveries and 2 women had three deliveries. The majority (141/180) were included in the first trimester, and the remaining in the second trimester. A total of 498 849 singleton births registered in MBRN during 2006–2014 served as population controls. Maternal mean age among patients was significantly higher compared with population controls (mean difference 1.09 years), a lower proportion smoked, and parity and BMI were similar (table 1).

The cases were grouped according to inactive disease (LAI-P=0) and active disease (LAI-P>0) of any severity in the second trimester. In 32 patients, disease activity was not registered. Clinical characteristics of the disease activity groups and the above group are presented in table 2. The disease activity groups showed no differences of statistical significance except smoking, which was more common in women with active disease.

Between 56.6% and 59.9% of women with SLE had inactive disease during pregnancy and 6 weeks after birth, and less than 10% experienced moderate disease activity or higher (LAI-P>0.5) (table 3). Women delivering preterm mainly had

Table 3 Number and percentages of patients with inactive and active diseases in each trimester and 6 weeks after birth

	Inactive disease n (%)		Active disease n (%)			Missing data on disease activity
	LAI-P=0	Preterm	LAI-P>0	*LAI-P>0.5*	Preterm	n (%)
First trimester	69 (56.6)	10 (14.5)	53 (43.4)	*5 (4.1)*	15 (28.3)	58 (32.2)
Second trimester	85 (57.4)	11 (12.9)	63 (42.6)	*7 (4.7)*	20 (31.7)	32 (17.8)
Third trimester	88 (59.9)	5 (5.7)	59 (40.1)	*8 (5.4)*	15 (25.4)	33 (18.3)
6 weeks pp	90 (59.2)	9 (10.0)	62 (40.8)	*11 (7.2)*	21 (33.9)	28 (15.6)

LAI-P, Lupus Activity Index in Pregnancy; pp, post partum.

active disease (LAI-P>0) on the four scheduled visits (60.0%, 64.5%, 70.0% and 64.7%, respectively). Active disease in the first or second trimester resulted in very preterm birth in 15.4% and 12.9%, respectively, whereas inactive disease resulted in very preterm birth in 6.0% in both groups. The most common disease manifestations in the first and second trimesters were skin (36.0% and 26.3%), joint (26.0% and 17.5%) and haematologic (17.4% and 14.8%). Only 4.2% and 3.6% had active kidney disease, respectively.

Association between SLE disease activity and birth weight z-score, pre-eclampsia and preterm birth

The birth weight z-score was significantly lower in offspring of women with SLE than of population controls (mean difference 0.47). We found significantly lower birth weight z-scores in both disease activity groups compared with population controls, but no significant difference between disease groups (table 4). There was a significantly higher odds of small for gestational age (SGA, ≤10 percentiles) in inactive as well as active diseases compared with 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.

Women with SLE had a statistically significantly higher odds of pre-eclampsia and preterm birth compared with population controls, OR 2.70 (95% CI 1.56 to 4.65), P<0.001 and OR 4.03 (95% CI 2.78 to 6.59), P<0.001, respectively. Regarding pre-eclampsia, we found no statistically significant difference between population controls and women with inactive disease, but statistically significantly higher odds when women had active disease. There was substantially higher odds for pre-eclampsia in women with active compared with inactive disease (table 5). Concerning preterm birth, there was a statistically significantly higher odds compared with population controls, both in women

with inactive and active diseases. Active disease had a more than twofold increased odds compared with inactive disease. In table 5, OR and P value for pre-eclampsia and preterm birth are shown for inactive disease compared with population controls, for active disease compared with population controls, and for active compared with inactive disease.

We adjusted for factors known to influence outcomes.[7 20 21] The results presented in tables 4 and 5 were substantially unchanged after adjusting for maternal age (<35 years/≥35 years), parity (no birth/≥1 birth) and smoking in pregnancy (yes/no) (data not shown). In separate analyses for first and subsequent births, the observed association was greater for subsequent than for first births for z-score and pre-eclampsia, while this was not the case for preterm birth (online supplementary tables S1 and S2). The P values for the interaction between parity and disease activity were 0.78, 0.24 and 0.51, respectively. Although not considered statistically significant, we find it noteworthy that these effects of parity are observed for both disease activity groups.

Influence of medications on birth weight z-score, preterm birth and pre-eclampsia

Prednisolone was used significantly more often in the second and third trimesters among women with active (58.1% and 57.9%) compared with inactive disease (38.1% and 37.5%). There were no significant differences in the use of hydroxychloroquine or azathioprine between the groups in any of the trimesters, or of prednisolone in the first trimester (51.0% and 38.8%). There was similar use of acetylsalicylic acid (online supplementary table

Table 4 Birth weight z-scores in offspring of population controls, women (SLE) with inactive disease and women (SLE) with active disease*

Group	n	Mean (SD)	Mean difference (95% CI)	P value
Population controls	497 959	−0.11 (0.98)		
Inactive disease (LAI-P=0)	85	−0.64 (0.81)	0.53 (0.32 to 0.74)	<0.001†
Active disease (LAI-P>0)	63	−0.54 (0.90)	0.43 (0.18 to 0.67)	0.001†
			−0.10 (−0.40 to 0.22)	0.53‡

*Unadjusted analysis.
†Compared with population controls.
‡Compared with inactive disease.
LAI-P, Lupus Activity Index in Pregnancy; SLE, systemic lupus erythematosus.

Table 5 Risk of pre-eclampsia and preterm birth in population controls, women (SLE) with inactive disease and women (SLE) with active disease. Logistic regression with adverse event as outcome*

Group	n	n (%)	OR (95% CI)	P value
Population controls	498 849			
Pre-eclampsia		15 132 (3.0)		
Preterm birth		27 063 (5.5)		
Inactive disease (LAI-P=0)	85			
Pre-eclampsia		4 (4.7)	1.58 (0.58 to 4.31)	0.37†
Preterm birth		11 (12.9)	2.57 (1.37 to 4.85)	0.003†
Active disease (LAI-P>0)	63			
Pre-eclampsia		9 (14.3)	5.33 (2.63 to 10.79)	<0.001†
			3.38 (0.99 to 11.51)	0.052‡
Preterm birth		21 (33.3)	8.66 (5.13 to 14.62)	<0.001†
			3.36 (1.48 to 7.65)	0.004‡

*Unadjusted analysis.
†Compared with population controls.
‡Compared with inactive disease.
LAI-P, Lupus Activity Index in Pregnancy; SLE, systemic lupus erythematosus.

Table 6 Effect of prednisolone use on birth weight z-score, pre-eclampsia and preterm birth*

Mean (SD) or n (%)	No prednisolone n=78	Prednisolone n=68	Mean difference (95% CI) or OR (95% CI)	P value
Z-score	−0.44 (0.84)	−0.77 (0.83)	0.33 (0.05 to 0.61)	0.022
Pre-eclampsia	5 (5.2)	9 (12.5)	2.33 (0.67 to 8.16)	0.19
Preterm birth	11 (11.5)	23 (31.9)	3.36 (1.40 to 8.09)	0.007

*Unadjusted analysis.

S3). Birth weight z-score was statistically significantly lower in offspring of women using prednisolone (mean difference 0.33). There was a substantially higher odds of pre-eclampsia when using prednisolone (OR=2.33), and we found a statistically significant threefold increase in preterm birth (table 6). Results were substantially unchanged after adjusting for hydroxychloroquine (yes/no) and azathioprine (yes/no) (data not shown).

DISCUSSION

We found a lower birth weight z-score in offspring of the disease group compared with population controls, both in inactive and active diseases. The occurrence of SGA was also increased in the disease groups. Our observations of lower birth weight and restricted fetal growth are in accordance with previous studies.[3 7 22 23] There was no evidence of lower birth weight z-score in offspring of women with active compared with inactive disease. There may be several explanations. Our patients had mainly mild disease, with only 4.7% experiencing moderate to high disease activity in the second trimester (LAI-P>0.5). Antiphospholipid syndrome (APS) is a factor independent of disease activity that increases the risk of intrauterine growth restriction and lower birth weight.[24] There were positive anticardiolipin antibodies of similar occurrence in the two disease groups, even though we do not know the occurrence of APS, representing an increased risk for lower birth weight. We found prednisolone use to be a risk factor for a lower birth weight z-score, contributing in both disease activity groups.

Our findings concerning the occurrence of pre-eclampsia and preterm birth support our hypotheses that disease activity of any severity increases the risk of adverse events. A higher risk of pre-eclampsia in women with SLE is well known.[2 7 25] To our knowledge, it has not been demonstrated earlier that women with inactive disease do not have increased risk compared with population controls. The two disease groups were similar concerning risk factors for pre-eclampsia like maternal age, parity, BMI, diabetes, hypertension, prior kidney disease, positive anticardiolipin antibodies and multiple pregnancies. We believe that a threefold higher odds in active versus inactive disease is clinically relevant, even though it did not reach statistical significance. The odds of preterm birth was elevated both in active and inactive diseases compared with population controls, and in active compared with inactive disease. The most vulnerable, very preterm children were also most commonly delivered in women with active disease. In our cohort, we found a lower proportion of women with active kidney disease than reported in other studies.[6 26] Active kidney disease is an important predictor of pre-eclampsia and preterm birth.[22 23 27] Our results showed similar occurrence of these events to other studies,[6 28] which implies that even less serious disease is an important contributor. There was a twofold increase in the odds of pre-eclampsia in women using prednisolone, and a statistically significant threefold increased odds for preterm birth. The assessment of disease

activity (LAI-P) includes medication as one of four groups, contributing to the score if medication is increased. However, there was a stable use of medication in our cohort, indicating that it did not influence the score. We therefore do not believe this to be a confounding factor. It is difficult to delineate prednisolone use from active disease as prednisolone is the medication of choice to treat flares in pregnancy. Treatment with prednisolone does in itself indicate more severe disease. However, we cannot exclude the independent effect of prednisolone use. In clinical practice, this finding emphasises the importance of stable disease-modifying treatment with hydroxychloroquine and azathioprine, minimising the need for prednisolone when the disease is not active.

A limitation of this study is a possible selection of patients. Women with more severe disease may choose not to become pregnant, and adverse events can discourage later pregnancies. Another limitation is missing data on disease activity scores. We knew from our recent longitudinal study on disease activity in this patient group that disease activity was not higher in third than in second trimester,[29] and used this registration. The 32 women with missing scores had similar outcomes to the inactive disease group (online supplementary table S4). Since there were lacking data on antiphospholipid antibody status in many patients, we cannot exclude a role for these antibodies concerning our outcomes. Another limitation is that 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.

Strengths include the utilisation of two nationwide registers. MBRN has existed for more than 40 years. The validity of information on gestational age including birth weight, preterm birth and pregnancy-related hypertensive complications is very good.[30] According to Norwegian guidelines,[31] women with SLE are offered a multidisciplinary follow-up in pregnancy. We therefore believe there are few women who are not followed up closely and included in RevNatus. The tight follow-up through RevNatus contributes to better controlled disease and improved outcomes. Due to the linkage of registers, we could also confirm a good compliance concerning diagnoses. Of 180 women in RevNatus with the diagnosis of SLE, only 10 (5.6%) did not have this diagnosis in MBRN. This is a lower misclassification rate than earlier reported for pre-pregnant rheumatic diseases in MBRN.[32] Furthermore, the diagnosis in RevNatus had to be confirmed by a rheumatologist prior to inclusion, securing the correct diagnosis. An additional strength is the utilisation of a disease activity score validated for use in pregnancy, avoiding pregnancy-related symptoms to be interpreted as active disease. Finally, the birth weight z-score was based on Norwegian standards and gives a more precise estimate for difference in birth weight. However, birth weights in Scandinavian populations cannot be generalised to all ethnic populations.[18]

In conclusion, we found that offspring of women with SLE have lower birth weight than offspring of population controls without rheumatic diseases. Preterm birth is more common in SLE than population controls, and the risk is amplified by active disease. The risk of pre-eclampsia is elevated in active, but not inactive disease. This calls for tight follow-up targeting inactive disease before and throughout pregnancy.

Author affiliations
[1]Department of Neuromedicine and Movement Science (INB), Norwegian University of Science and Technology (NTNU), Trondheim, Norway

[2]Department of Rheumatology, Ålesund Hospital, Ålesund, Norway
[3]Regional Centre for Child and Youth Mental Health and Child Welfare (RKBU), Norwegian University of Science and Technology (NTNU), Trondheim, Norway
[4]Department of Rheumatology, Oslo University Hospital Rikshospitalet, Oslo, Norway
[5]Norwegian National Advisory Unit on Pregnancy and Rheumatic Diseases, Department of Rheumatology, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[6]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology (NTNU), Trondheim, Norway
[7]Department of Obstetrics and Gynecology, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

REFERENCES

1 Wallenius M, Salvesen KÅ, Daltveit AK, *et al*. Secular trends of pregnancies in women with inflammatory connective tissue disease. *Acta Obstet Gynecol Scand* 2015;94:1195–202.

2 Simard JF, Arkema EV, Nguyen C, *et al*. Early-onset Preeclampsia in Lupus Pregnancy. *Paediatr Perinat Epidemiol* 2017;31:29–36.

3 Baer AN, Witter FR, Petri M. Lupus and pregnancy. *Obstet Gynecol Surv* 2011;66:639–53.

4 Østensen M, Andreoli L, Brucato A, *et al*. State of the art: Reproduction and pregnancy in rheumatic diseases. *Autoimmun Rev* 2015;14:376–86.

5 Soh MC, Nelson-Piercy C. High-risk pregnancy and the rheumatologist. *Rheumatology* 2015;54:572–87.

6 Buyon JP, Kim MY, Guerra MM, *et al*. Predictors of Pregnancy Outcomes in Patients With Lupus: A Cohort Study. *Ann Intern Med* 2015;163:153–63.

7 Wallenius M, Salvesen KÅ, Daltveit AK, *et al*. Systemic lupus erythematosus and outcomes in first and subsequent births based on data from a national birth registry. *Arthritis Care Res* 2014;66:1718–24.

8 Visentin S, Grumolato F, Nardelli GB, *et al*. Early origins of adult disease: low birth weight and vascular remodeling. *Atherosclerosis* 2014;237:391–9.

9 Lindström L, Skjaerven R, Bergman E, *et al*. Chronic Hypertension in Women after Perinatal Exposure to Preeclampsia, Being Born Small for Gestational Age or Preterm. *Paediatr Perinat Epidemiol* 2017;31:89–98.

10 Soh MC, Nelson-Piercy C, Dib F, *et al*. Brief Report: Association Between Pregnancy Outcomes and Death From Cardiovascular Causes in Parous Women With Systemic Lupus Erythematosus: A Study Using Swedish Population Registries. *Arthritis Rheumatol* 2015;67:2376–82.

11 Gur C, Diav-Citrin O, Shechtman S, *et al*. Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. *Reprod Toxicol* 2004;18:93–101.

12 Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand* 2000;79:435–9.

13 Staff A, Henriksen T, Langesæter E, *et al*. Hypertensive svangerskapskomplikasjoner og eklampsi. http://legeforeningen.no/Fagmed/Norsk-gynekologisk-forening/Veiledere/Veileder-i-fodselshjelp-2014/Hypertensive-svangerskapskomplikasjoner-og-eklampsi/

14 Klungsøyr K, Morken NH, Irgens L, *et al*. Secular trends in the epidemiology of pre-eclampsia throughout 40 years in Norway: prevalence, risk factors and perinatal survival. *Paediatr Perinat Epidemiol* 2012;26:190–8.

15 Yu C, Gershwin ME, Chang C. Diagnostic criteria for systemic lupus erythematosus: a critical review. *J Autoimmun* 2014;48-49:10–13.

16 Ruiz-Irastorza G, Khamashta MA. Evaluation of systemic lupus erythematosus activity during pregnancy. *Lupus* 2004;13:679–82.

17 Buyon JP, Kalunian KC, Ramsey-Goldman R, *et al*. Assessing disease activity in SLE patients during pregnancy. *Lupus* 1999;8:677–84.

18 Skjaerven R, Gjessing HK, Bakketeig LS. Birthweight by gestational age in Norway. *Acta Obstet Gynecol Scand* 2000;79:440–9.

19 Lydersen S, Langaas M, Bakke Øyvind, Bakke O. The exact unconditional z -pooled test for equality of two binomial probabilities: optimal choice of the Berger and Boos confidence coefficient. *J Stat Comput Simul* 2012;82:1311–6.

20 Waldenström U, Cnattingius S, Vixner L, *et al*. Advanced maternal age increases the risk of very preterm birth, irrespective of parity: a population-based register study. *BJOG* 2017;124.

21 Wei J, Liu CX, Gong TT, *et al*. Cigarette smoking during pregnancy and preeclampsia risk: a systematic review and meta-analysis of prospective studies. *Oncotarget* 2015;6:43667–78.

22 Smyth A, Oliveira GH, Lahr BD, *et al*. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol* 2010;5:2060–8.

23 Bramham K, Soh MC, Nelson-Piercy C. Pregnancy and renal outcomes in lupus nephritis: an update and guide to management. *Lupus* 2012;21:1271–83.

24 Abou-Nassar K, Carrier M, Ramsay T, *et al*. The association between antiphospholipid antibodies and placenta mediated complications: a systematic review and meta-analysis. *Thromb Res* 2011;128:77–85.

25 Arkema EV, Palmsten K, Sjöwall C, *et al*. What to Expect When Expecting With Systemic Lupus Erythematosus (SLE): A Population-Based Study of Maternal and Fetal Outcomes in SLE and Pre-SLE. *Arthritis Care Res* 2016;68:988–94.

26 Park EJ, Jung H, Hwang J, *et al*. Pregnancy outcomes in patients with systemic lupus erythematosus: a retrospective review of 62 pregnancies at a single tertiary center in South Korea. *Int J Rheum Dis* 2014;17:887–97.

27 Stojan G, Baer AN. Flares of systemic lupus erythematosus during pregnancy and the puerperium: prevention, diagnosis and management. *Expert Rev Clin Immunol* 2012;8:439–53.

28 Clowse ME, Jamison M, Myers E, *et al*. A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol* 2008;199:127.e1–127.e6.

29 Götestam Skorpen C, Lydersen S, Gilboe IM, *et al*. Disease activity during pregnancy and the First Year postpartum in women with systemic lupus erythematosus. *Arthritis Care Res* 2017;69.

30 Moth FN, Sebastian TR, Horn J, *et al*. Validity of a selection of pregnancy complications in the Medical Birth Registry of Norway. *Acta Obstet Gynecol Scand* 2016;95:519–27.

31 Skomsvoll JF, Wallenius M, Salvesen KA. Inflammatoriske revmatiske sykdommer og kollagenoser. http://legeforeningen.no/Fagmed/Norsk-gynekologisk-forening/Veiledere/Veileder-i-fodselshjelp-2014/Inflammatoriske-revmatiske-sykdommer-og-kollagenoser/

32 Skomsvoll J, Østensen M, Baste V, *et al*. Validity of a rheumatic disease diagnosis in the Medical Birth Registry of Norway. *Acta Obstet Gynecol Scand* 2002;81:831–4.

ARD

Influence of disease activity and medications on offspring birth weight, pre-eclampsia and preterm birth in systemic lupus erythematosus: a population-based study

Carina Götestam Skorpen, Stian Lydersen, Inge-Margrethe Gilboe, Johan Fredrik Skomsvoll, Kjell Å Salvesen, Øyvind Palm, Hege Suorza Svean Koksvik, Bente Jakobsen and Marianne Wallenius

Updated information and services can be found at:

http://ard.bmj.com/content/77/2/264

These include:

References	This article cites 28 articles, 1 of which you can access for free at: **http://ard.bmj.com/content/77/2/264#ref-list-1**
Email alerting service	Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes