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Running head: SLE and disease activity in pregnancy

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

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ABSTRACT

Objectives: 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 Lupus Activity Index (LAI), with a good ability to assess disease activity in pregnant women with SLE. These indexes were used to assess disease activity at six visits (1^{st}, 2^{nd} and 3^{rd} trimester 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 in 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 3rd 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.

SIGNIFICANCE AND 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 follow-up 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 a higher disease activity at 6 and 12 months after delivery.
- The clinical implication is tight follow-up not only before and during pregnancy, but also in the first year postpartum.

Systemic lupus erythematosus (SLE) is a chronic inflammatory connective tissue disease. It mainly affects women, often in their fertile age. 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 one out of 1000 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). Accumulating knowledge about the disease course and treatment options has led to improving outcomes for both mother and child over the last decades (7-9). Established predictors of pregnancy complications are lupus nephritis (LN), hypertension and secondary antiphospholipid antibody 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 displays a typical pattern of higher disease activity (flare) 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 months postpartum (13, 14).

Modification of three established disease activity assessments were proposed in 1999, with the purpose of avoiding physiological changes of pregnancy to be misinterpreted as active SLE (15). The Lupus Activity Index (LAI) was later validated for use in pregnancy and the puerperium (6 weeks after birth), as the only one(15, 16). Four prior studies have utilized disease scores adapted for use in pregnancy, three using the SLE-Pregnancy Disease Activity Index (SLEPDAI)(17-19) and one using the Lupus Activity Index in Pregnancy (LAI-P)(20), only one including assessment after birth. Most commonly SLE Disease Activity Index (SLEDAI)

and Physician Global Assessment (PGA) has been used to evaluate disease activity in pregnant women with SLE (15). Previous studies assessing disease activity after birth, stopped the follow up at 2 months postpartum, with one 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 enrollments of women with SLE 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. Seventeen women participated twice.

Clinical characteristics and variables assessed. The first registration in RevNatus includes demographic data, information on concomitant diseases and history of medical use including traditional and biologic disease modifying drugs, prednisolone and non-steroidal anti-inflammatory drugs. Parity, previous pregnancy outcomes including term and preterm births, pregnancy loss as well as mode of delivery and pregnancy complications (e.g. preeclampsia) are registered. All visits include a general clinical examination, present use

and changes of medication, blood tests, a urine sample and a disease activity assessment. Pregnancy outcomes, mode of delivery and complications during the present pregnancy are registered at the visit 6 weeks postpartum. Breastfeeding status is registered on all postpartum visits.

Assessment of disease activity. SLE disease activity was scored according to LAI-P at the visits 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. 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(22, 23). The index allows comparisons of patients with different disease manifestations, and is appropriate for detecting change in disease activity over time(23). 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 (16, 24). The first section in the original LAI, the PGA, was excluded to decrease the degree of subjectivity to the scale. LAI-P consists of the four sections of items described above for LAI, but 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. (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 three groups contribute with the mean value of the scored items in each group. LAI-P scores disease activity on a continuous scale from 0 – 2.6. Zero indicates no disease activity, while a score ≥ 2 is considered high disease activity (25). To have comparable scales, we modified the original LAI (m-LAI) excluding PGA and using the same items as in LAI-P except fever (fatigue in LAI), graded similarly and giving

the same continuous scale (see Supplementary Table S1). 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 follow-up period. Disease activity was scored according to LAI-P in the 1st, 2nd, 3rd trimester and 6 weeks postpartum, and according to m- LAI 6 and 12 months postpartum.

Ethical considerations. RevNatus was established in 2006 after approval by The Regional committee for medical and health research ethics (REK Mid-Norway). Eligible women signed a written informed consent before inclusion in RevNatus. The present study was approved by REK Mid-Norway in 2012 (2012/1905).

Statistical analyses. Disease activity was highly skewed with 51.6 % of all scores including all visits displaying no disease activity (LAI-P/m-LAI=0), while only 0.9% of the scores were > 1.0, and 0.1% > 2.0. As the assumption of normal distribution was not fulfilled, we categorized the dependent variable (LAI-P or m-LAI) into four groups (0, 1, 2 and 3). A change in disease activity score ≥ 0.25 is perceived a clinically relevant change indicating worsening (flare) or improvement of disease (16, 24). The categories chosen accordingly were no disease activity (LAI-P/m-LAI = 0), very low disease activity (0 < LAI-P/m-LAI ≤ 0.25), low disease activity (0.25 < LAI-P/m-LAI ≤ 0.50), and moderate disease activity (LAI-P/m-LAI > 0.50). The longitudinal course of disease activity was analyzed using a proportional odds ordinal logistic mixed model regression analyses with visit number as categorical covariate and patient as random effect. These 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 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 21, and the mixed model analyses were performed using Stata 13.1.

RESULTS

Patient recruitment. During the study period, 237 women earlier diagnosed with SLE by a specialist in rheumatology, were enrolled in RevNatus. A flow chart demonstrates numbers and reasons for exclusion (Figure 1). In the 208 pregnancies with 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 three twin births. Twenty-six women were included before pregnancy (all of whom attended the visit in 1st trimester), 96 in the 1st, 23 in the 2nd and one in the 3rd trimester. There was 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 (n=26), 1st trimester n = 122, 2nd trimester n = 134, 3rd trimester n = 131, 6 weeks postpartum n = 139, 6 months postpartum n = 121 and 12 months postpartum n = 110. Disease activity assessed at the visit before pregnancy was not included in the analysis.

Clinical characteristics. Table 1 presents clinical characteristics of the women with SLE enrolled in RevNatus, included and excluded cases presented separately. In all, 88 of 105 (84%) included and 46 of 60 (78%) excluded women fulfilled the lupus ACR-criteria (≥ 4 criteria). ACR-classification criteria were not reported in the remaining 23 and 29 women diagnosed with SLE. Eleven and four women were diagnosed less than one year before pregnancy. Positive anticardiolipin antibodies were defined according to the International consensus statement on an update of the classification criteria for definite antiphospholipid

syndrome (APS) (26). Information on whether or not the women were diagnosed with APS, was not available. In the subgroup of excluded women experiencing miscarriage nine of 17 had positive anticardiolipin antibodies, and all of these were lupus anticoagulant positive.

Table 2 shows disease activity at inclusion for the present cohort and the excluded cases (total and split into reasons 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 LAI-P or m-LAI if there were more than one neurological symptom (see online Supplementary Table 2). 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 hematological manifestations. In the present cohort, pulmonary disease was reported in one case 6 weeks postpartum (visit 4), and neurologic disease was reported once 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. Hydroxychloroquine (HCQ), azathioprine (AZA) and prednisolone were the only immunosuppressants used in the cohort.

Active kidney disease was among the six specific organ manifestations scored in 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 four 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 LAI-P. Criteria required doubled proteinuria when 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 (67%) women used hydroxychloroquine, 41 (24%) used azathioprine and 62 (43%) used prednisolone. Sixty-five women used combination therapy, most commonly hydroxychloroquine and prednisolone, followed by a combination of all three drugs. No immunosuppressive medication was used at inclusion in 34 women (23%). Of these, four started hydroxychloroquine in the 2nd trimester either alone or in combination with azathioprine and prednisolone, one started prednisolone in the 3rd trimester and five started immunosuppressive treatment postpartum. Of the total cohort, 15 women stopped and restarted immunosuppressive medication during pregnancy, four stopped during pregnancy, and seven stopped after birth. Eighteen women added immunosuppressive medication in pregnancy and/or after birth, eight in pregnancy and 12 postpartum. No change in immunosuppressive medication was registered in 101 women in the follow-up period.

Disease activity changed over time. Figure 2 demonstrates the distribution of the four disease activity categories at each visit.

Longitudinal course in disease activity. More than half (51.6 %) of the disease activity scores were equal to zero, 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 a LAI-P score = 0. The variation in disease activity between visits was statistically significant (p = 0.035). Figure 3 shows the estimated probability of disease activity above zero, from the ordinal logistic

mixed model analysis, and was highest on visits 5 and 6. The differences of visit 6 compared to visit 3 ($p = 0.009$) and 4 ($p = 0.031$) where statistically significant, and compared to visit 1 ($p = 0.175$) and 2 ($p = 0.084$) 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 of disease activity over time ($p = 0.017$), with a similar pattern of the longitudinal course of disease activity (see online supplementary Figure S1).

When adjusting for use of prednisolone at each visit, 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: OR = 3.10, $p < 0.001$. We found no statistically significant interaction between prednisolone use and visit number (Likelihood ratio test, 5 degrees of freedom: $p = 0.18$). Likewise, when adjusting for use of azathioprine, 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 azathioprine: OR = 2.2, $p = 0.022$. There was no statistically significant interaction between azathioprine use and visit number (Likelihood ratio test, 5 degrees of freedom: $p = 0.97$). When adjusting for use of hydroxychloroquine at each visit, the longitudinal change in disease activity was also preserved ($p = 0.012$), with a non-significant tendency towards lower disease activity when using hydroxychloroquine: OR 0.78, $p = 0.47$. We found no statistically significant interaction between hydroxychloroquine use and visit number (Likelihood ratio test, 5 degrees of freedom: $p = 0.085$).

DISCUSSION

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. In this prospective, observational study, we found that the majority of the disease activity scores in the follow-up period displayed no or low disease activity, with a statistically significant change of disease activity over time, the latter illustrating the relapsing and remitting nature of the disease. Only one registered disease activity score reached a value of 2, indicating high disease activity. This is in accordance with other recent studies (17, 27, 28), and accumulates 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 follow-up of disease and pregnancy together with the counseling of women planning pregnancy when included in a register such as RevNatus, contributes to the observed low disease activity. Only two 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 the disease activity increased six and 12 months postpartum, a novel finding in women with SLE. This was despite a stable use of hydroxychloroquine throughout visits, and a slight increase in the use of prednisolone. Hydroxychloroquine has been shown to protect against increasing disease activity (29, 30), and ideally all women with SLE planning pregnancy should be treated with hydroxychloroquine to avoid potential flares (6, 8). Prednisolone is the most common drug used to control disease flares(31), 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 azathioprine gradually decreased through the follow-up, and azathioprine was stopped either in the 3rd trimester or 6 weeks postpartum in five women, without restarting any other immunosuppressive medication. Four of these women reported breastfeeding on the first postpartum visit, suggesting that they stopped the drug for the purpose of breastfeeding. On this control 6 weeks postpartum, eight women reported that they had stopped breastfeeding due to medication; two women used hydroxychloroquine and six used azathioprine in combination with hydroxychloroquine and/or prednisolone. This underscores the importance of adequate counseling on medication and lactation, to prevent undue cessation of drugs in women that choose to breastfeed (32, 33).

We included both singleton and multiple births in the analysis, as we assume the pregnancy per se may influence the disease activity and vice versa, not whether it is one or two 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 that might have chosen not to. However, the disease activity scores in the first of two included pregnancies compared to the other pregnancies showed a similar pattern, with 48/91 (52.7 %) vs 297/577 (51.5 %) of the scores indicating remission and 5/91 (5.5 %) vs 35/577 (6.4 %) with moderate disease activity. It is well known that women's first pregnancies are more prone to complications than subsequent pregnancies, and this is also shown for mothers with SLE (34). However, we have no reason to believe that parity interacts or have an impact on the disease activity course during pregnancy and the first year postpartum.

Mean age (overall and for the nulliparous group) in these women was slightly higher than for the general Norwegian obstetric population (35), as reported in earlier publications on SLE (10, 34). Maternal age and disease duration were not included as covariates, as these

factors were stable on all visits, and are not expected to be associated with the course of disease activity in the follow-up period. In a previous study (27), neither maternal age nor disease duration had an impact on the incidence of high disease activity. The BMI in the first trimester is normal in 58/92(63%), 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 1st 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 (35).

A strength of this study is that the Norwegian health care system provides equal services, encompassing all citizens independently of socioeconomic or geographic status. Lupus-patients are cared for by specialists in rheumatology, and we believe the cohort represents the majority of pregnant SLE-patients in the study period. The cohort is mainly white European minimizing the issue of ethnicity influencing on the disease severity and organ manifestations (36). 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 648/757 (85.6 %) of the visits had registered disease activity scores. We used mixed models for analysis of longitudinal data. This implies that subjects with missing data at one or more visit 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 implies

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. 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 % (26/145) 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 a few weeks up to one year before conception. To overcome this challenge, we choose visit 6 as the reference visit, providing a non-pregnant 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, implying 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 under-reporting of no or low disease activity. On the other hand, women with high disease activity or very severe prior organ affection might choose not to become pregnant, and therefore not be included in RevNatus. High disease activity increases the risk of miscarriages, and we do not know the number of women with SLE who conceived and had an early miscarriage without being registered. The data shows that in the women who were included in RevNatus and miscarried, more than 1/3 experienced moderate to high disease activity at inclusion (Table 2), in contrast to the women giving birth where only 7% had moderate disease activity at inclusion. This is a concern when the focus is pregnancy outcome, but does not impact the results in the present study.

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 of disease activity over time. Increased disease activity of clinical importance was not demonstrated during pregnancy or 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 have been participants in this study and assisted in patient recruitment, study design and/or data interpretation. All authors have reviewed and made comments on the drafts involved in the development of this manuscript, and have approved the final version.

ETHICS APPROVAL

The Regional committee for medical and health research ethics (REK Mid-Norway).

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

Clinical characteristics	**Included pregnancies N = 145 Mean (SD) or n/N* (%)**	Excluded pregnancies N = 92 Mean (SD) or n/N× (%)	
		All excluded pregnancies	*Not followed 1 year pp or lost to follow up*
Age in 1st trimester, years	**30.4 (4.95)**	31.0 (4.63)α	*31.4 (4.81)α*
Disease duration, years	**8.0 (6.34)**	9.7 (6.89)	*9.6 (5.75)*
Body mass index 18.5- 24.9	**58/92 (63.0)**	45/75 (60.0)	*28/45 (62.2)*
Smoking in 1st trimester	**10/119 (8.4)**	6/86 (7.0)α	*3/55 (5.5)α*
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 1st trimester	**5/102 (4.9)**	7/79 (8.9)α	*3/47 (6.4)α*
Positive anticardiolipin antibodiesβ at inclusion	**28/96 (29.2)**	23/60 (38.3)	*13/35 (37.1)*
Positive lupus anticoagulant at inclusion	**22/96 (22.9)**	18/58 (31.0)	*8/35 (22.9)*

SD = standard deviation. N* # 145 due to missing data. N× # 92 due to missing data. α At inclusion (preconception or in pregnancy). β Presence of one, two or three of lupus anticoagulant present in plasma and/or anticardiolipin antibody IgG and/or IgM > 40 GPL or MPL and/or Anti-b2 glycoprotein-I antibody IgG and/or IgM in serum or plasma

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

Disease activity	**Included pregnancies N = 145** **n/N* (%)**	Excluded pregnancies N = 92 n/N* (%)				
		All excluded pregnancies	*Not yet pregnant*	*Miscarriage*	*Not followed 1 year pp*	*Lost to follow up*
No activity (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 activity (0 < LAI-P/ m-LAI ≤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 activity (LAI-P/ m-LAI> 0.5)	**9/129 (7.0)**	8/79 (10.1)	*1/9 (11.1)*	*7/19 (36.8)*	*0*	*0*

N* # 145 due to missing data. N× # 92 due to missing data

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Table 3. Immunosuppressive treatment and disease activity including active kidney disease in women with SLE, as reported on each visit.

N = 145 pregnancies	n/N* (%)	n/N* (%)	n/N* (%)
Immunosuppressive treatment	**hydroxychloroquine**	**prednisolone**	**azathioprine**
1st trimester (Visit 1)	84/120 (70.0)	52/120 (43.4)	36/120 (30.0)
2nd trimester (Visit 2)	87/132 (65.9)	55/132 (41.7)	37/133 (27.8)
3rd trimester (Visit 3)	89/128 (69.5)	57/128 (44.5)	34/130 (26.2)
6 weeks postpartum (Visit 4)	93/133 (69.9)	64/132 (48.5)	29/134 (21.6)
6 months postpartum (Visit 5)	83/114 (72.8)	56/113 (49.6)	27/113 (23.9)
12 months postpartum (Visit 6)	73/105 (69.5)	53/105 (50.5)	20/102 (19.6)
Disease activity	**No activity$^{\alpha}$**	**Moderate activity$^{\beta}$**	**Active kidney disease**
1st trimester (Visit 1)	56/109 (51.4)	6/109 (5.5)	5/102 (4.9)
2nd trimester (Visit 2)	60/114 (52.6)	7/114 (6.1)	4/118 (3.4)
3rd trimester (Visit 3)	70/114 (61.4)	5/114 (4.4)	5/112 (4.5)
6 weeks postpartum (Visit 4)	68/119 (57.1)	7/119 (5.9)	7/119 (5.9)
6 months postpartum (Visit 5)	41/97 (42.3)	7/97 (7.2)	4/100 (4.0)
12 months postpartum (Visit 6)	44/95 (46.3)	9/95 (9.5)	3/98 (3.1)

N* # 145 due to missing data. $^{\alpha}$ m-LAI or LAI-P = 0 $^{\beta}$ m-LAI or LAI-P > 0.5

Figure 1. Flow chart on selection process of eligible cases

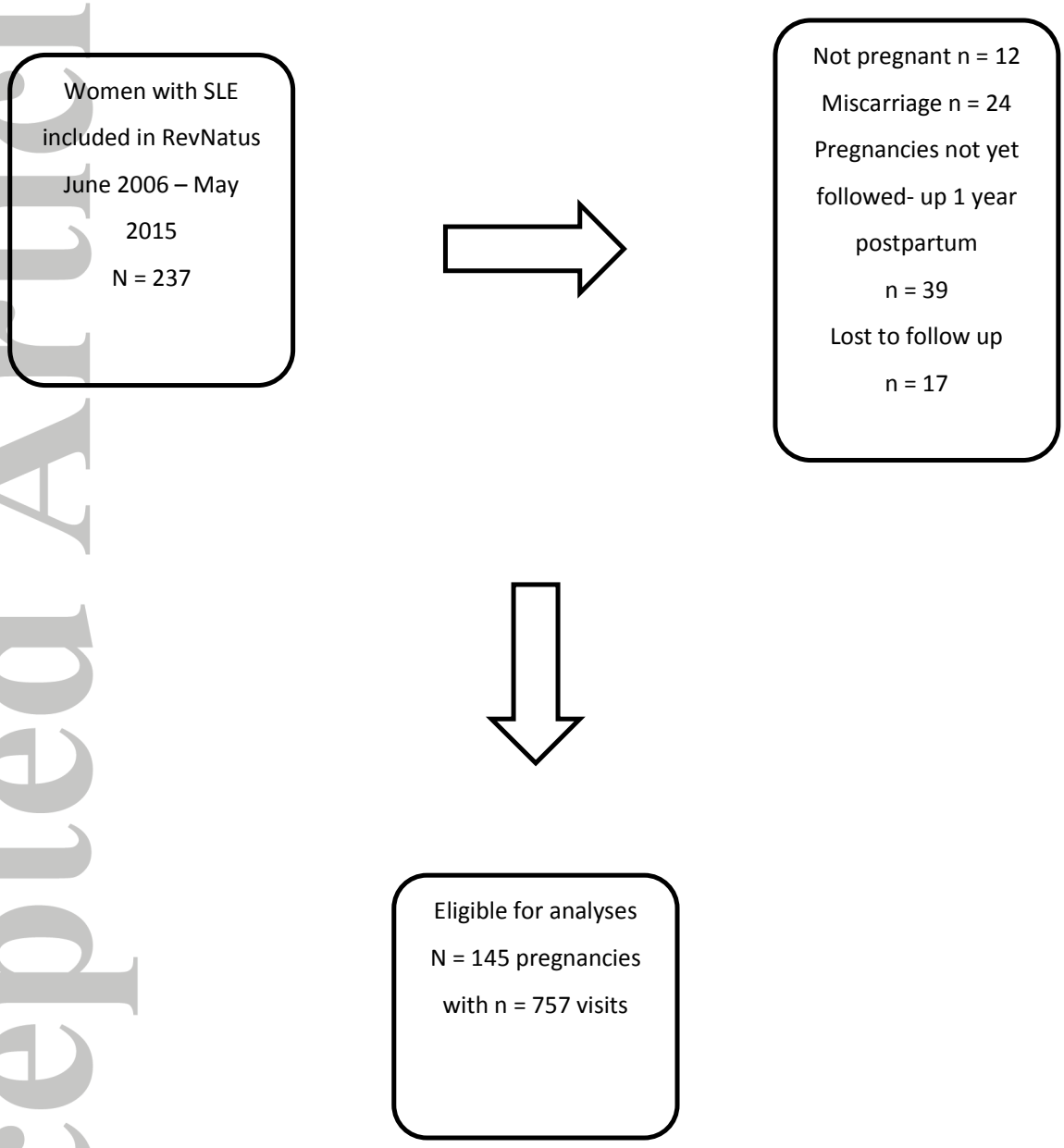


Figure 2. Distribution of disease activity categories by visit

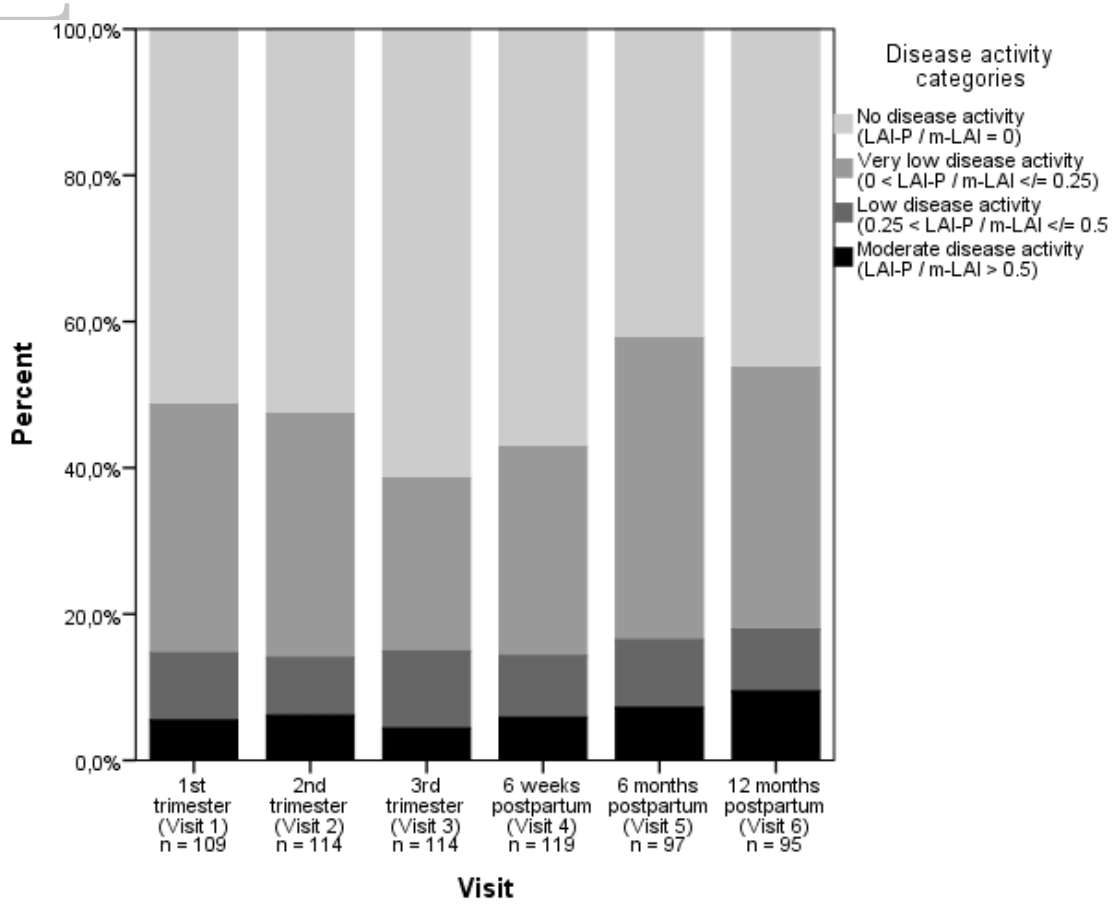
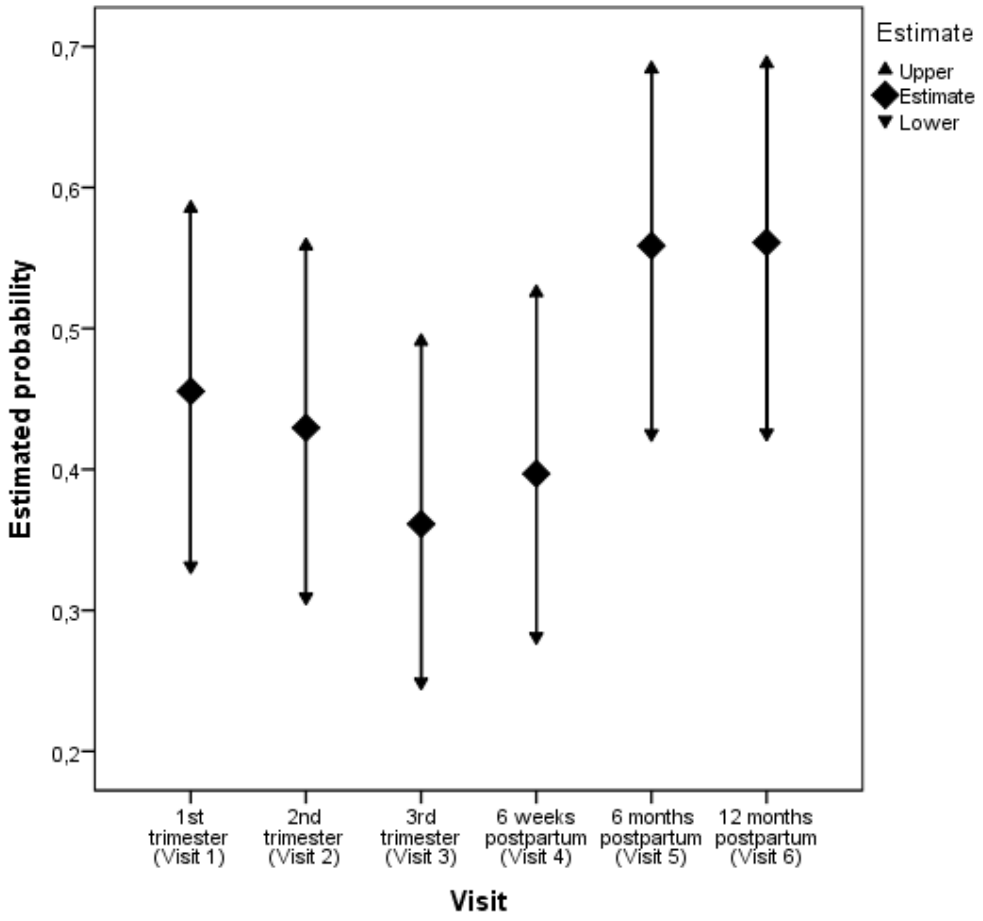


Figure 3. Longitudinal variation in probability of disease activity above zero. Estimate and 95% CI (lower to upper) from the ordinal logistic mixed model analysis.



Supplementary Table S1. Modified Lupus Activity Index (m-LAI) and Lupus Activity Index in Pregnancy (LAI-P) score

Group 1	Fatigue(m-LAI)/Fever(LAI-P)	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= $\frac{a+b+c+d}{4}$

Supplementary Table S2. Disease manifestations at each visit in women with reported disease activity (LAI-P/m-LAI > 0)*

	Joint	Skin	Hematologic	Kidney	Neurologic	Lung	Cardiac
1st trimester, n = 121	21/107	28/106	18/100	4/101	1/106	0/107	3/107
(Visit 1, LAI-P > 0)	19.6 %	26.4 %	18.0 %	4.0 %	0.9 %		2.8 %
Missing	14	15	21	20	15	14	14
2nd trimester, n = 134	14/126	23/126	13/119	5/118	2/124	1/125	0/125
(Visit 2, LAI-P > 0)	11.1 %	18.3%	10.9%	4.2%	1.6%	0.8%	
Missing	8	8	15	16	10	9	9
3rd trimester, n = 132	14/124	16/126	5/109	5/113	4/120	0/124	1/126
(Visit 3, LAI-P > 0)	11.3%	12.7%	4.6%	4.4%	3.3%		0.8%
Missing	8	6	23	19	12	8	6
6 weeks pp, n = 139	20/123	14/126	7/110	7/119	1/124	3/124	0/126
(Visit 4, LAI-P > 0)	16.2%	11.1%	6.4%	5.9%	0.8%	2.4%	
Missing	16	13	29	20	15	15	13
6 Months pp, n = 120	24/107	17/108	5/93	4/100	4/106	1/107	0/109
(Visit 5, m-LAI > 0))	22.4%	15.7%	5.4%	4.0%	3.8%	0.9%	
Missing	13	12	27	20	14	13	11
12 months pp, n = 110	20/100	10/102	5/93	3/98	1/101	0/102	0/105
(Visit 6, m-LAI > 0))	20.0%	9.8%	5.3%	3.1%	1.0%		
Missing	10	8	17	12	9	8	5

* Reported symptoms might not be included in LAI-P or m-LAI, if other parameters were missing (ie laboratpry findings)

Supplementary Figure S1. Longitudinal variation in probability of disease activity above zero. Estimate and 95% CI (lower to upper) from the binary logistic regression mixed model analyses.