Supplementary Table S2. Summary of the results of systematic literature review

Question 1. What is the evidence that the following pre-conception (planned versus unintended pregnancy, disease activity and damage, antibody profile, lupus medications, management of flares, access to specialist services, immunization status and update) and post-conception/delivery (parenting issues, lupus medications, management of flares, access to specialist care) factors influence maternal and foetal outcomes, and thus, should be considered in pregnancy risk stratification and counselling in women with SLE or APS?

1. Women with SLE

1.1. Pre-conception factors associated maternal outcomes

Factor/predictor	Outcome(s) and example(s) of effect size	Best study design[1]	References
Active/flaring SLE (before or at conception)	• **Active/flaring SLE during pregnancy**. SLE flares during the pre-gestation period had OR 5.1 for flare during pregnancy; previous (within 6 months before conception) organ involvement predicted same organ involvement during pregnancy (especially haematological, renal, skin, serological activity); SLE flares during the pre-gestation period had OR 5.1 for development of flare during pregnancy; SLEDAI ≥4 at conception had sensitivity 64% and specificity 75% for SLE exacerbation during pregnancy; remission during the 6-month period prior to conception is associated with lower odds for flare during pregnancy	4	1-21
	• **Organ damage**. Pre-gestational SLE activity (SLAM-R index) correlates with post-partum damage accrual	5	22
	• **Pregnancy-induced hypertension, (pre-)eclampsia/HELLP**. Positive correlation with pre-conception SLEDAI; active SLE within 4 months before conception was associated with pregnancy-induced hypertension (25% versus 11%)	4	12 14 21 23
	• **Adverse maternal outcome (composite outcome or death)**. Active SLE at conception had OR 16.4; all maternal deaths in patients with SLE and lupus nephritis occurred in	5	24 25

	those with active disease, with disease activity/complications and infections (mainly opportunistic) being the two major causes		
Active/flaring lupus nephritis (before or at conception)	•**Active/flaring SLE during pregnancy**. Association with severe flare(s) during pregnancy (RR 8.5; RR 10.0 for renal flare); active lupus nephritis (UPCR ≥0.5, urinary RBCs >5/hpf, SCr >1.2 mg/dL) correlates with increased risk for renal flares during pregnancy •**Pregnancy-induced hypertension, (pre-)eclampsia/HELLP**. Positive correlation (rate approximately 7.6%)	4 3	6 9 13 14 18 19 21 26-31 10 28 32
Serological activity (low C3/C4, high anti-dsDNA) (before or at conception)	•**Active/flaring SLE during pregnancy**. Low C3 at conception or within 4 months before conception correlated with increased risk for renal flare during pregnancy; RR 6.1 for mild-to-moderate flares; •**Pregnancy-induced hypertension, (pre-)eclampsia/HELLP**. Anti-dsDNA +ve patients were at increased risk (OR 2.18) for PE	4 5	6 9 13 14 18 19 21 33
History of (pre-existing) lupus nephritis	•**Active/flaring SLE during pregnancy**. Association (OR 2.6) with SLE flares and with renal flares (OR 8.8) during pregnancy; adjusted OR 5.8 for renal flare •**Pregnancy-induced hypertension, (pre-)eclampsia/HELLP**. 26% versus 10% in SLE women with no renal involvement; association with earlier development of PE	4 3	11 13 14 19 21 24 34 35 2 13 14 21 23 32 36
Antiphospholipid antibodies (aPL) / APS	•**Active/flaring SLE during pregnancy**. Presence of any aPL had OR 6.6 for SLE flare during pregnancy •**Pregnancy-induced hypertension, (pre-)eclampsia/HELLP**. LA positivity had RR 4.9 for development of PE; anti-β2-GP1 IgM were associated (RR 12.3) with subsequent risk for PE	4 3	14 26 6 32 33 37-40
Hydroxychloroquine (HCQ) use (before or at conception)	•**Active/flaring SLE during pregnancy**. Non-use (or discontinuation) is associated with higher rates of flares during pregnancy; *note*: not confirmed by all studies	4	7 13 14 18
Glucocorticoids use (before	•**Active/flaring SLE during pregnancy**. Association with increased risk (RR 1.6) of flares	4	10 18 35

or at conception)	during pregnancy		
Planned pregnancy	• **Active/flaring SLE during pregnancy**. Associated with lower risk (compared to unplanned pregnancies) for flare-ups during pregnancy	5	41 42
	Limited evidence for the prognostic role of the following factors: patient age, SLE duration, primigravida, hypertension, serum uric acid levels, previous miscarriages, discontinuation of immunosuppressive treatment		6 13 14 19 21 35 43 44

1.2. Post-conception factors associated with maternal outcomes

Factor/predictor	Outcome(s) and example(s) of effect size	Best study design[1]	References
Active/flaring SLE (during pregnancy)	• **Active/flaring SLE during pregnancy**. SLE flares during pregnancy are associated (OR 2.9) with new subsequent flare; thrombocytopenia is associated with increased risk for SLE flares and higher disease activity (SLEPDAI) during pregnancy	5	13 18 45
	• **Organ damage**. Active SLE at conception and/or during pregnancy is a risk factor for organ damage accrual	5	9
	• **Pregnancy-induced hypertension, (pre-)eclampsia/HELLP**. 3rd trimester SLE activity is associated with risk for PE (SLEDAI-2K ≥4.5 has 75% sensitivity and 77% specificity); SLE flare during pregnancy correlates with increased risk for HELLP	5	9 12 13 16 23 30 39 45-47
Active/flaring lupus nephritis (during pregnancy)	• **Pregnancy-induced hypertension, (pre-)eclampsia/HELLP**. 10–13 weeks' gestation proteinuria is associated with PE in SLE women with prior history of lupus nephritis	5	36 46 47
	• **Adverse maternal outcome (composite outcome or death)**. Active nephritis during pregnancy is associated (57% vs 11%; hypertension during pregnancy, PE, eclampsia,	5	13 16 48

	stroke, HELLP syndrome, and maternal death)		
Hydroxychloroquine (HCQ) use (during pregnancy)	•**Active/flaring SLE during pregnancy**. Discontinuation of HCQ during pregnancy was associated with higher SLE activity and more flares (84% vs 52% in those who continued HCQ); associated also with increased use of GC and higher average dose of GC during pregnancy •**Pregnancy-induced hypertension**. Use of HCQ during pregnancy was associated with lower rates of hypertension (0% vs. 12%)	4 5	[4] [8] [49-54] [54]
Hypertension (during pregnancy)	•**Pre-eclampsia**. 10–13 weeks' gestation diastolic blood pressure >80 mmHg is associated with PE in SLE women with prior history of lupus nephritis	5	[36]
	Limited evidence for the prognostic role of the following factors: use of glucocorticoids / DMARDs, (PE)	5	[4] [18] [43] [55]

1.3. Pre-conception factors associated foetal outcomes

Factor/predictor	Outcome(s) and example(s) of effect size	Best study design[1]	References
Race/ethnicity	•**Adverse foetal outcome(s) (composite outcome)**. African-American race has been associated with increased rates (foetal or neonatal death; birth before 36 weeks due to placental insufficiency, hypertension, or PE; and SGA neonate <5th percentile); *note*: not confirmed by another study	4	[56-58]
Age	•**Adverse foetal outcome(s) (composite outcome)**. Younger age is associated with increased risk for adverse pregnancy outcome(s) (OR 0.84 per 1-year age increase) •**Pre-term delivery/prematurity**. Younger is associated with higher risk	4 5	[57 59 60] [23 41]

Severe SLE with major organ involvement (*see below for renal disease*)	•**Adverse foetal outcome(s) (composite outcome)**. Major organ disease (nephritis, central nervous system) was associated with severe adverse pregnancy outcomes (as above) (OR 4.3)	4	33 56 60
	•**Pre-term delivery/prematurity**. History of major organ (vascular, haematology, kidney) was associated (RR 7.0) with increased rates of pre-term birth (16% vs. 44%)	5	54
History of (pre-existing) lupus nephritis	•**Adverse foetal outcome(s) (composite outcome)**. Renal damage (SDI) is associated with increased risk (OR 8.4) (foetal loss, prematurity and SGA)	4	34 56 58 61 62
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. Pre-existing lupus nephritis correlated with miscarriages (≤24 weeks; 11% vs. 3.6%)	5	7 21 24 34 49 63
	•**Pre-term delivery/prematurity**. 36.4% vs 21.1% in SLE with no history of nephritis; multi-variable adjusted OR 18.9	4	13 14 21 49 54 64
	•**IUGR/SGA/low birth weight**. Pre-existing lupus nephritis correlated with IUGR (38% vs. 18%); association with increased rates of SGA	4	2 13 14 21 34 36
Active/flaring SLE (before or at conception)	•**Adverse foetal outcome(s) (composite outcome)**. Increased SLEPDAI / PGA (PGA >1 has OR 4.0) at conception or during the first trimester was associated with increased rates of adverse pregnancy outcomes (foetal or neonatal death; birth before 36 weeks due to placental insufficiency, hypertension, or PE; and SGA neonate <5th percentile); increased SLE activity (LAI-P) before/during pregnancy is associated (OR 4.2) with increased risk for adverse foetal outcomes (including foetal loss, prematurity and SGA)	4	12 16 30 34 37 58 65 66
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. Active disease (SLEDAI defined) during 6 months prior to conception is associated (OR 5.7) with foetal losses; SLE remission for ≥6 months before conception (including no use of cytotoxics for the past 12 months) was associated with increased rates of live births	4	6 20 30 67-69
	•**Pre-term delivery/prematurity**. Active SLE during 4 months before conception correlated with pre-term deliveries (46% vs. 26%)	4	15 20 21 70

	•**IUGR/SGA/low birth weight**. SLE activity during 6 months pre-conception and at the time of conception (RR 22.1); *note*: not confirmed by all studies	5	2 63 71
Active/flaring lupus nephritis (before or at conception)	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. Multi-variable adjusted OR 7.3 for pregnancy loss; positive association with UPCR ≥1 at conception	4	14 15 18 26 27 30 49 63 67 68 71-74
	•**Pre-term delivery/prematurity**.	3	18 32 34 49 71 73
	•**IUGR/SGA/low birth weight**. Pre-gestational hypo-albuminemia is associated with lower birth weight	4	14 18
Serological activity (low C3/C4, high anti-dsDNA) (before or at conception)	•**Adverse foetal outcome(s) (composite outcome)**. Low C3/C4 at conception or during the first trimester was associated with increased rates of adverse pregnancy outcomes; anti-dsDNA +ve at conception was associated with risk (OR 2.1) for adverse foetal outcomes	4	34 58 75
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. Evidence for prognostic role of serum C3/C4 only. In women with lupus nephritis, low C3/C4 at conception correlated (adjusted OR 19) with risk for spontaneous abortion or perinatal death; in anti-Ro +ve pregnancies, low C3/C4 is associated with increased rates (OR 5.9)	4	4 7 27 70 76 77
	•**Pre-term delivery/prematurity**. Anti-dsDNA +ve have been associated (RR 2.8)	4	6 70
	•**IUGR/SGA/low birth weight**. Anti-dsDNA +ve have been associated (RR 1.7)	4	15 33
Antiphospholipid antibodies (aPL) / APS	•**Adverse foetal outcome(s) (composite outcome)**. aPL +ve was associated with averse pregnancy outcomes (OR 3.6); stronger association with LA +ve (OR 8.3)	3	57 58 60 65 78-83
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. Medium-high titres of aCL IgM/IgG were associated (OR 4.5); presence of LA is associated with recurrent foetal loss (OR 41.7); LA +ve correlated (OR 3.4) with risk for foetal loss (combined LA and aCL +ve had OR 4.6); aCL IgG +ve with increased risk (OR 2.9) for late miscarriage; in anti-Ro/SSA -ve women, APS co-existence is associated with increased rates (OR 6.4) for pregnancy loss; *note*: less evidence for independent prognostic role of anti-	4	4 7 12 14 18 31 39-41 47 49 62 67 70-72 77 82 84-100

	phosphatidylserine/prothrombin antibodies (OR 8.6-10.8) •**Pre-term delivery/prematurity**. RR 8.0	3	6 7 12 14 18 32 41 49 62 64
Anti-Ro/SSA and/or anti-La/SSB antibodies	•**Adverse foetal outcome(s) (composite outcome)**. Positive association in a single – but not other – studies (ORs ranging 1.47–1.96)	5	33 101 102
	•**Pregnancy loss (miscarriage/foetal loss/neonatal death)**. Weak evidence for association (not confirmed by all studies). No reported association specifically with stillbirth. In anti-Ro/La+ pregnancies with high-degree CHB, there was no effect of anti-Ro titres on foeto-neonatal mortality.	4	15 18 71 102-104
	•**Pre-term delivery/prematurity**. Positive association in a few – but not all – studies (OR 2.3)	5	33 49 103 105
	•**IUGR/SGA/low birth weight**. No strong evidence for association	4	15 49 103 105
	•**Neonatal lupus.** Association with anti-Ro/SSA and to lesser extent with anti-La/SSB (studies in anti-Ro+ pregnancies many of which with SLE diagnosis); primarily cutaneous lupus manifestations; prevalence of higher degree foetal heart block ranges 0.7–2%; high-titre anti-Ro (≥1:32) was predictive of CHB (OR 3.6); 10.5% (2/19) incidence of heart block in children born to mothers who had previously delivered a child with NL vs 0% incidence in children of mothers with a known autoimmune disease but without a previously affected child; Medium-high anti-Ro/SSA (≥50 IU/mL) titres in mothers are associated (OR 7.8) with neonatal cardiac LE, irrespective of anti-La/SSB status.	4	5 39 105-116
Hypertension (pre-existing / at conception)	•**Adverse foetal outcome(s) (composite outcome)**. Use of anti-hypertensives at conception was associated (OR 7.1) with increased rates of adverse pregnancy outcomes (foetal or neonatal death; birth before 36 weeks due to placental insufficiency, hypertension, or PE; and SGA neonate <5th percentile); hypertension before/during pregnancy is associated (OR 6.0) with increased risk for adverse foetal outcomes (including foetal loss, prematurity and SGA)	4	34 56 58 65 74 83

	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. Increased risk for pregnancy loss (OR 2.4) and stillbirths (OR 4.2); multi-variable adjusted OR 17.8 in patients with lupus nephritis	4	6 7 14 31 68 84
	•**Pre-term delivery/prematurity**. Positive association, 48.9% vs 21.2% in SLE women without hypertension at conception	4	14 15 18 49
	•**IUGR/SGA/low birth weight**. RR 8.3 for IUGR	4	6 14 15 18 49 54 117
Obesity	•**Adverse foetal outcome(s) (composite outcome)**. BMI >30 kg/m^2 was associated with increased rates of adverse pregnancy outcomes (foetal or neonatal death; birth before 36 weeks due to placental insufficiency, hypertension, or PE; and SGA neonate <5th percentile)	4	58 83
Vascular thrombosis (prior)	•**Adverse foetal outcome(s) (composite outcome)**. RR 1.9 in SLE or aPL +ve pregnant women	4	57 58 83
	•**Pre-term delivery/prematurity**. Positive association in a single study	5	18
Prior adverse pregnancy outcome	•**Adverse foetal outcome(s)**. Prior foetal death >10 weeks of gestation was associated with increased rates of adverse pregnancy outcome(s) (composite outcome); in aCL +ve SLE women, if a case had one previous adverse outcome, the OR for another adverse outcome was 3.0 and if a case had two previous adverse outcomes, the OR for a third adverse pregnancy outcome was 4.1; cases with a late miscarriage (foetal loss at 14 to 20 weeks' gestation) in their first pregnancy had the highest risk (80%) of an adverse outcome in their second pregnancy; history of >2 prior miscarriages was associated with increased risk (RR 1.38–1.50) for pre-term birth or IUGR in future pregnancy	4	15 26 44 58 78 82 118
Glucocorticoids use (before or at conception)	•**Adverse foetal outcome(s)**. Correlation with the amount of glucocorticoids used during the last year before conception (RR 13.3); *note*: possible confounded by higher disease activity	4	6 56

	Less evidence for the prognostic role of the following factors: tobacco use, diabetes, planned versus unplanned pregnancy		18 41 42 54 119

1.4. Post-conception factors associated with foetal outcomes

Factor/predictor	Outcome(s) and example(s) of effect size	Best study design[1]	References
Active/flaring SLE (during pregnancy)	•**Adverse foetal outcome(s) (composite outcome).** Higher SLEPDAI or PGA during pregnancy (weeks 20-23, 32-35) correlates with increased risk for adverse pregnancy outcomes (composite endpoint: foetal or neonatal death; birth before 36 weeks due to placental insufficiency, hypertension, or PE; and SGA neonate <5th percentile); increased SLE activity (LAI-P) before/during pregnancy is associated (OR 4.2) with increased risk for adverse foetal outcomes (foetal loss, prematurity and SGA)	4	20 34 58
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. SLE flare during pregnancy is associated with multi-variable adjusted OR 1.9; SLE flare was associated (OR 3.5) with foetal loss; 1st-trimester platelet count <150,000/uL was associated with increased risk (OR 3.3) for pregnancy loss (miscarriages, stillbirths)	4	2 9 11 16 45 49 63 72 75 84 101 120-123
	•**Pre-term delivery/prematurity**. Activity during pregnancy correlates with 3-fold increased risk for premature delivery; 2nd trimester flare is associated with OR 5.5	4	9-14 16 19 30 45 47 49 52 64 69 71 101
	•**IUGR/SGA/low birth weight**. Increased rates of IUGR (38.1% vs 20.3%; multi-variable adjusted OR 4.2) in SLE women who flared during pregnancy	4	12-14 19 46 47 49 54 69 72 75
Active/flaring lupus nephritis (during pregnancy)	•**Adverse foetal outcome(s) (composite outcome).** UPCR >0.5 during pregnancy had OR 12.5 for any adverse pregnancy outcome (multivariable analysis); hypo-albimunemia before/during pregnancy is associated (OR 5.6) with increased risk for adverse foetal outcomes (including foetal loss, prematurity and SGA)	5	16 26 34 69 118

	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. 1st-trimester UPCR >0.5 was associated with increased risk for pregnancy loss (OR 2.6) and miscarriage (OR 4.1)	5	31 48 84
	•**Pre-term delivery/prematurity**.	5	48
	•**IUGR/SGA/low birth weight**.	5	28 46
Serological activity (low C3/C4, high anti-dsDNA) (during pregnancy)	•***See the results of the systematic literature review regarding Q7***		
Hydroxychloroquine (HCQ) use (during pregnancy)	•**Adverse foetal outcome(s) (composite outcome)**. Safe to use during pregnancy	3	124 125
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. No significant effect of HCQ use during pregnancy	5	49 50 53 104
	•**Pre-term delivery/prematurity**. Use of HCQ during pregnancy was associated with lower rates of pre-term birth (16% vs. 44%; RR 6 for non-use); *note*: not confirmed by another two observational studies	5	49 53 54
	•**IUGR/SGA/low birth weight**. A single study reporting lower rates of IUGR in SLE patients who used HCQ during pregnancy; *note*: not confirmed by another two observational studies	5	49 53 54
	•**Neonatal lupus**. In SLE mothers with anti-Ro/La antibodies, exposure to HCQ during pregnancy was associated with reduced risk of foetal development of cardiac NL (OR 0.46). Effect independent of the use of non-fluorinated steroids.	5	116 126
Glucocorticoids use (during pregnancy)	•**Adverse foetal outcome(s) (composite outcome)**. In lupus nephritis patients on treatment with azathioprine during pregnancy, use of glucocorticoids was associated (OR 2.0 per 1-mg prednisolone) for any adverse pregnancy outcome (including PE).	4	127
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. No consistent	5	49 104 128

	effect.		
	•**Pre-term delivery/prematurity**. Use of glucocorticoids at dosage ≥10 mg/day (prednisone equivalent) was associated with higher odds for pre-term (50% vs 27%, p=0.04); same effect with higher maintenance doses (≥15, ≥20 mg/day).	4	7 10 15 49 63 64 70 108
	•**IUGR/SGA/low birth weight**. Single study reporting positive association.	5	54
	•**Neonatal lupus**. In anti-Ro +ve mothers (most had SLE), 0/26 infants whose mothers were treated with glucocorticoids before 16 weeks' gestation had CHB, whereas 15/61 infants whose mothers received no medication or were treated after 16 weeks' gestation had CHB. Also amelioration of cutaneous lupus manifestations in neonates.	5	129
Low-dose aspirin use (during pregnancy)	•**Adverse foetal outcome(s) (composite outcome)**. In SLE and/or aPL+ cases, use of LDA had OR 0.41 for severe adverse pregnancy outcomes (PE with delivery at <34 weeks, foetal/neonatal death, indicated preterm delivery <30 weeks)	4	66 83
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. In SLE with history/active lupus nephritis, use of LDA was associated with reduced risk (adjusted OR 0.11) for spontaneous abortion or perinatal death	4	27
	•**Pre-term delivery/prematurity**. LDA non-use was associated with increased rates of pre-term birth	5	54
Hypertension (during pregnancy)	•**Adverse foetal outcome(s) (composite outcome)**. Hypertension before/during pregnancy is associated (OR 6.0) with increased risk for adverse foetal outcomes (including foetal loss, prematurity and SGA)	5	34
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. Associated with increased risk (OR 2.5) for perinatal death	5	16
	•**Pre-term delivery/prematurity**. Use of anti-hypertensives during pregnancy correlates with prematurity (RR 1.8)	4	7 10 70
	•**IUGR/SGA/low birth weight**. Single study showing positive association with IUGR	5	7

Pre-eclampsia (during index pregnancy)	•**Adverse foetal outcome(s) (composite outcome)**. Associated with increased risk (OR 7.0) for adverse foetal outcome	5	[75]
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. Positive association (OR 14.8)	5	[30]
	•**Pre-term delivery/prematurity**. Positive association (OR 8.0)	5	[30 75]
	•**IUGR/SGA/low birth weight**. Associated with increased risk (OR 5.4) for low birth weight	5	[75]

2. Women with APS (SLE-APS or PAPS)

2.1. Pre-conception factors associated with maternal outcomes

Factor/predictor	Outcome(s) and example(s) of effect size	Best study design[1]	References
Antiphospholipid antibodies (aPL)	•**Vascular thrombosis during pregnancy/post-partum**. Positive association especially with high-risk aPL profile (LA, triple aPL, medium-to-high aPL titres); OR 12.1 for LA +ve cases	5	[130-134]
	•**Pre(-eclampsia)/HELLP**. Positive association. LA +ve (confirmed by activated partial thromboplastin time (APTT)-based assays or dilute Russell's viper venom time (dRVVT)] is associated with OR 2.34; also confirmed in general population of pregnant women [135-137]	3	[130 138-145]
SLE co-existence	•**Vascular thrombosis during pregnancy/post-partum**. Positive association	5	[132 146]
Prior thrombosis / thrombotic APS	•**Vascular thrombosis during pregnancy/post-partum**. Positive association (OR 4.8)	5	[134]
	•**Pre(-eclampsia)/HELLP**. History of thrombotic APS was associated with higher risk for PE	5	[145 147]
Prior adverse (APS-related) pregnancy	•**Vascular thrombosis during pregnancy/post-partum**. Positive association in single study of	5	[148]

outcome	catastrophic APS cases • **Pre(-eclampsia)/HELLP**. Prior foetal loss is associated (RR 2.7) with eclampsia or HELLP	4	[149]
Hypertension (pre-existing / at conception)	• **Vascular thrombosis during pregnancy/post-partum**. Positive association with any CVD risk factors (including smoking, hypertension, hypercholesterolemia, diabetes, family history of thrombosis) (OR 3.0)	5	[150]
	• **Pre (-eclampsia)/HELLP**. APS cases with chronic HTN had increased rates of PE as compared to APS cases with normal blood pressure	5	[151]

2.2. Post-conception factors associated with maternal outcomes

Limited evidence for the following risk factors: use of glucocorticoids [152], serum C3/C4 [153], non-traditional aPL [154]; the evidence for the effects of anti-platelet/anti-coagulation treatment is discussed elsewhere

2.3. Pre-conception factors associated foetal outcomes

Factor/predictor	Outcome(s) and example(s) of effect size	Best study design[1]	References
Antiphospholipid antibodies (aPL)	• **Adverse foetal outcome(s) (composite outcome)**. Positive association especially with high-risk aPL profile (LA, triple aPL, medium-to-high aPL titres); triple aPL positivity had OR 9.2 for APS-related pregnancy morbidity	4	[146] [155-162] [159] [161] [163-165]
	• **Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. LA +ve is associated with OR 4.7; in primary or SLE-APS cases, aCL +ve was associated with pregnancy loss (OR 4.6); note: the prognostic role of aPL is also confirmed in the general population of pregnant women [135] [142] [166-177]	3	[130] [139] [141] [143] [146] [149] [171] [178-189]

	•**Pre-term delivery/prematurity**. LA +ve has OR 2.6	4	130 133 143 149 180 190-193
	•**IUGR/SGA/low birth weight**. High-titre aPL were associated with increased risk for SGA (OR 5.7)	3	133 135-137 141-143 149 173 191 194 195
	•**Low neonatal Apgar score**	5	191
SLE co-existence	•**Adverse foetal outcome(s) (composite outcome)**. Positive association, SLE-APS versus PAPS had OR 6.9 for APS-related pregnancy morbidity (stillbirth, prematurity, recurrent spontaneous abortions); note: not confirmed by all studies	4	156 159 180 196 197
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. SLE-APS had increased rates of foetal loss (29% vs. 10%) compared to PAPS; note: not confirmed in another study	5	198 199
	•**Pre-term delivery/prematurity**. SLE-APS had more cases of pre-term births compared to PAPS (single study); opposite effect in another study (i.e., PAPS cases had increased rates of premature births compared to SLE-APS women: 72.3% vs 40%)	4	152 200
	•**IUGR/SGA/low birth weight**. Single study reported increased IUGR rates in PAPS versus SLE-APS pregnancies	4	200
Serological activity (low C3/C4, high anti-dsDNA) (before or at conception)	•**Adverse foetal outcome(s) (composite outcome)**. Low C3/C4 at baseline had OR 5.9 for APS-related pregnancy morbidity	5	159
Prior thrombosis / thrombotic APS	•**Adverse foetal outcome(s) (composite outcome)**. History of thrombosis or mixed thrombotic/obstetric APS had OR 3.6 and OR 12.7 respectively, for APS-related pregnancy morbidity	4	159 196 201
	•**Pregnancy loss (miscarriage/foetal loss)**. History of previous vascular thrombosis is associated with lower rates of live birth (66% vs 85%)	5	152 178
	•**Pre-term delivery/prematurity**. History of APS thrombosis is associated with earlier	5	145 147 191

	gestational age • **IUGR/SGA/low birth weight**. History of vessel thrombosis is associated with lower birth weight	5	147 180 191
Prior adverse pregnancy outcome	• **Adverse foetal outcome(s) (composite outcome)**. History of prior miscarriage or thrombosis was associated with adverse pregnancy outcomes (56% vs 17%); previous placental thrombosis had OR 31.7 for APS-related pregnancy morbidity	5	140 159 163 165 201
	• **Pregnancy loss (miscarriage/foetal loss)**. Prior foetal loss was predictor of subsequent foetal loss	5	149 198 202
	• **Pre-term delivery/prematurity**. Prior foetal loss are associated (RR 3.0) with premature birth in subsequent pregnancy	5	149
	• **IUGR/SGA/low birth weight**. Prior IUGR or foetal death was predictor for IUGR (OR 2.2)	5	134 147
Hypertension (pre-existing / at conception)	• **Pregnancy loss (miscarriage/foetal loss)**. No consistent association	5	151
	• **IUGR/SGA/low birth weight**. APS cases with chronic hypertension had lower average birth weight vs APS cases with normal blood pressure	5	151
Low-dose aspirin use (before or at conception)	• **Pregnancy loss (miscarriage/foetal loss)**. OR 3.3 for subsequent live birth (APS women with 80% obstetric history of pregnancy loss)	4	203
Non-traditional aPL	• **Possible prognostic role that requires further confirmation and/or standardisation**	5	130 172 181 187 188 204-215

2.4. Post-conception factors associated with foetal outcomes

Factor/predictor	Outcome(s) and example(s) of effect size	Best study design[1]	References
Serological activity (low C3/C4, high anti-dsDNA) (during pregnancy)	•**Adverse foetal outcome(s) (composite outcome)**. OR 7.9 for APS-related pregnancy morbidity	5	[159]
	•**Pregnancy loss (miscarriage/foetal loss)**. Low C3/C4 or high anti-dsDNA titres during the first 20 weeks of gestation are associated	5	[153]
	•**Pre-term delivery/prematurity**. Low C3 or C4 during the first 20 weeks of gestation are associated	5	[153]
	•**IUGR/SGA/low birth weight**. Association with low C3/C4 during the first 20 weeks of gestation	5	[153]
Hydroxychloroquine (HCQ) use (during pregnancy)	•**Adverse foetal outcome(s) (composite outcome)**. HCQ non-use during pregnancy was associated with increased rate of pregnancy morbidity (OR 2.2); including placenta-related complications (PE, abruption, IUGR)	5	[165]
	•**Pregnancy loss (miscarriage/foetal loss)**. HCQ use during pregnancy was associated with increased rate of live births (67% vs. 57%)	5	[165 202]
aPL titres (during pregnancy)	•**Pregnancy loss (miscarriage/foetal loss)**. Disappearance of aCL-IgG during pregnancy correlates with lower risk of foetal loss; persistence is associated with RR 7.8 with foetal loss	4	[122 174 216]
Glucocorticoids use (during pregnancy)	•**Pre-term delivery/prematurity**. Association with increased rates of severe pre-term birth	5	[152]
	•**IUGR/SGA/low birth weight**. Association with increased rates of IUGR	5	[152]

Question 2. What is the evidence for the safety of contraceptive measures used pre- and post-pregnancy in women with SLE or APS?

1. WOMEN WITH SLE

1A. Combined pill (oestrogen + progestin)

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
SLE Flares	54 Mex (27 ± 5 yrs)	12 months randomized, single blind trial (30 µg ethinyl E2 plus 150 µg levonorgestrel). No changes in SLEDAI score from baseline to follow-up visits. Rate of flare/patient year was 0.86. Rate of severe flares was 0.049. The median time to first flare was 3 months.	2	[217]
	91 (29.8 yrs); 92 in Pl (30.1)	12 months randomized, Pl-controlled, double-blind, noninferiority trial (triphasic ethinyl E2 plus norethindrone). Rate of mild to moderate flare/patient year was 1.40 and 1.44 in the treatment and Pl group respectively. Rate of severe flares was 0.088 and 0.120 respectively.	2	[218]
	20 It (age not specified)	20 SLE women with cutaneous manifestations received ethinyl E2 0.02 mg/day and gestodene 0.075 mg/day for 12 months. 5 (25%) discontinued the treatment after 4-5 months for disease flare. In a control group (features not described) a similar rate of flares was observed.	5	[219]
	31 Fin (18-44 yrs)	SLE flares in 4 (13%) women during the first six months of treatment (3 renal flares).	6	[220]
Thrombosis	54 Mex (27 ± 5 yrs)	12 months randomized, single-blind trial (30 µg ethinyl E2 plus 150 µg levonorgestrel). aCL and aB2GPI positivity was found in 26% and 19% of patients. 2 cases of thrombosis occurred (incidence rate 4.75 per 100 patient-years); both patients were aPL positive.	2	[217]
	91 (29.8 yrs); 92 in Pl (30.1)	12 months randomized, Pl-controlled, double-blind, noninferiority trial (triphasic ethinyl E2 plus norethindrone). Patients with positive aPL and/or a history of thrombosis were excluded. Three cases of thrombosis were observed: 2 on oral contraceptive, 1 on Pl.	2	[218]
	31 Fin (18-44 yrs)	2 (6%) aPL positive women with a history of DVT developed a recurrence of DVT while on treatment.	6	[220]
Side effects/	54 Mex (27 ± 5 yrs)	12 months randomized, single-blind trial (30 µg ethinyl E2 plus 150 µg levonorgestrel). 35%	2	[221]

Discontinuation		discontinuation for any reason, 11% for non-medical reasons. Nausea was the most frequent side effect.		

1B. Progestin only pill

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
SLE flares	187 (31 ± 7 yrs)	187 received at least one year of PP (CPA or CMA) or both sequentially (overall 6854 women-months). The flare frequency was 0.32/women-year, significantly lower than before PP (2.58).	4	[222]
	54 Mex (27 ± 5 yrs)	12 months randomized, single-blind trial (30 µg levonorgestrel). No changes in SLEDAI score from baseline to follow-up visits. Rate of flare/patient year was 1.14. Rate of severe flares was 0.114. The median time to first flare was 3 months.	2	[217]
	32 Fin (18-44 yrs)	No influence on disease activity was recorded	6	[220]
Thrombosis	187 (31 ± 7 yrs)	187 received at least one year of PP (CPA or CMA) or both sequentially (overall 6854 women-months). aPL were detectable in 29% of the patients. 4 vascular events were recorded. Incidence of DVT: 1.39/1000 women-years. Incidence of arterial disease: 2.79/1000 women-years.	4	[222]
	54 Mex (27 ± 5 yrs)	12 months randomized, single-blind trial (30 µg levonorgestrel). aCL and aB2GPI positivity was found in 22% and 19% of patients. 2 cases of thrombosis occurred (incidence rate 5.44/100 patient-years); both patients were aPL positive.	2	[217]
	32 Fin (18-44 yrs)	One case (3%) of DVT in a high positive aPL woman.	6	[220]
Side effects/ Discontinuation	187 (31 ± 7 yrs)	187 received at least one year of PP (CPA or CMA) or both sequentially (overall 6854 women-months). 41 (22%) breakthrough bleeding (8 discontinuation); 28 (15%) hypoestrogenic symptoms (2 discontinuation).	4	[222]

	54 Mex (27 ± 5 yrs)	12 months randomized, single-blind trial (30 µg levonorgestrel). 55% discontinuation for any reason, 31% for non-medical reasons. Acne and hirsutism were the most frequent side effects.	2	[221]
	32 Fin (18-44 yrs)	25/32 (78%) discontinued the treatment because of poor gynaecological tolerance.	6	[220]

1C. Intrauterine device (IUD)

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
SLE flares	54 Mex (27 ± 5 yrs)	12 months randomized, single-blind trial (copper IUD). No changes in SLEDAI score from baseline to follow-up visits. Rate of flare/patient year was 0.91. Rate of severe flares was 0.046. The median time to first flare was 3 months.	2	[217]
Thrombosis	54 Mex (27 ± 5 yrs)	12 months randomized, single-blind trial (copper IUD). aCL and aB2GPI positivity was found in 32% and 11% of patients. No cases of thrombosis occurred.	2	[217]
Side effects/ Discontinuation	54 Mex (27 ± 5 yrs)	12 months randomized, single-blind trial (copper IUD). 29% discontinuation for any reason, 4% for non-medical reasons. Dysmenorrhea was the most frequent side effect.	2	[221]
	28 Fin	None of the patients experienced a major bleeding complication or severe pelvic infection during the use of IUD, with a 43% continuation rate at 3 years.	5	[223]

2. WOMEN WITH APS or SLE/APS

Petri 2005: aPL positive women and patients with previous cardiovascular events were excluded

Outcome	Sample (age,	Result	Design	Ref.

	ethnicity)			
Variation in menstrual bleeding	16 (42 ± 5 yrs)	16 APS patients with menorrhagia secondary to oral anticoagulation using levonorgestrel releasing IUD. 9/16 (56%) had shorter duration of bleeding/amenorrhea. 12/16 (75%) felt satisfied with the treatment.	6	[224]
Risk of CV events	175 ischemic stroke (39 yrs), 203 myocardial infarction (42 yrs), 628 controls (39 yrs)	LA was positive in 6 (3%) myocardial infarction, 30 (17%) ischemic stroke, 4 (0.6%) controls. Sub-analysis of oral contraceptive users: in women without LA, the risk for myocardial infarction and ischemic stroke was 2.3 (1.6-3.4) and 2.9 (1.9-4.6) respectively; in women with LA, the risk for myocardial infarction and ischemic stroke was 21.6 (1.9-242) and 201 (22-1828) respectively.	5	[225]

Question 3. Are women with SLE or APS at risk for reduced fertility (assessed by validated methods), menstrual irregularities, and premature ovarian failure/early menopause?

Points to consider:

a. Are there any validated methods (including AMH, count of follicles, etc.) for assessing fertility in women with SLE or APS?

b. Identify subgroups of patients at-risk, possible effects of corticosteroids on ovulation and menstrual cycle, consider endometriosis

1. WOMEN WITH SLE

1A. Ovarian damage during chemotherapy with alkylating agents

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Amenorrhea (TA, SA)	Meta-analysis of RCTs (all Ch)	Meta-analysis of 5 studies (225 patients) comparing tacrolimus and ivCYC in the induction treatment for lupus nephritis. Irregular menstruation (or amenorrhea) were significantly lower in the tacrolimus group than in ivCYC group (RR 0.14, 95% CI 0.04-0.50, p=0.003). Included studies: Chen 2011, Li 2011, Xu 2007, Zhang 2006 a, Zhang 2006 b	1	[226]
	Meta-analysis of RCTs	Meta-analysis of 4 studies (618 patients) comparing MMF and ivCYC in the induction treatment for lupus nephritis. Amenorrhea was significantly lower in the MMF group than in ivCYC group (RR 0.14, 95% CI 0.04-0.47, p=0.001). Included studies: Appel 2009, Ginzler 2005, Ong 2005, Chan 2005.	1	[227]
	535 Arabian	188 received ivCYC. 61/535 (11.4%) experienced amenorrhea: 28.2% (SA 13.1%) in CYC users, 3.7% in non-users (p<0.05). Risk factors: older age at initiation of CYC, higher cumulative dose.	5	[228]
	62 Japanese (30 yrs)	29 treated with ivCYC+ high dose steroids; 33 high dose steroids only (multiple indications). SA in 13.8% and 3% respectively (all women were >40). Amenorrhea was associated with age at the initiation of treatment >40 yrs (OR=10.2, 95% CI 1.8-58.7).	5	[229]

	117 Arabian (33 yrs)	117 biopsy-proven lupus nephritis randomized to group I (n=73, ivCYC 10 mg/kg) and group II (n=44, ivCYC 5 mg/kg) (monthly treatment for 6 months). Amenorrhea without pregnancy was more frequent in high dose CYC group (34.6% vs 13.6%, p=0.006).	2	[230]
	61 (29 yrs)	61 premenopausal women receiving ivCYC for various indications: CYC alone (n=39), CYC followed by MMF (n=22). TA: 5.1% vs 9.1%. SA: 51.3% vs 4.5%. Amenorrhea was associated with older age, cumulative CYC dose and anti-Ro/SSA antibodies. SA was associated with older age. Patient on CYC alone have 5-fold higher risk of SA.	5	[231]
	157 (21 yrs)	Group A: 57 treated with conventional dose ivCYC (0.75 mg/body surface); Group B: 50 treated with conventional dose CYC (0.5 mg/body surface); Group C: 50 never received CYC. TA: 12.3%, 20%, 0%. SA: 17.5%, 0%, 0%. Risk factors for menstrual abnormalities were duration of treatment and cumulative dose of CYC.	4	[232]
	35 Indian (25±8)	31.4% TA, 17.1% SA. Cytochrome P450 polymorphism: HZ and EZ for CYP2C19*2 had a significantly lower risk of developing ovarian toxicity when compared to patients with the wild-type allele CYP2C19*1 (3/13 vs 14/22, OR 0.136, 95%CI 0.028-0.653, p<0.01).	5	[233]
	67 Korean (31±8)	67 lupus nephritis treated with ivCYC. 19.4% TA, 17.9% SA. Independent risk factors for SA: older age, high damage index at the initiation of CYC, higher cumulative dosage of CYC.	5	[234]
	67 (27 yrs)	67 (mostly lupus nephritis) treated with ivCYC. 31% SA. Patients>32 yrs: cumulative dose resulting in SA in 50% and 90% of patients was 8 and 12 g/m2 respectively. Patients≤31 yrs: 11.4% SA. Risk factors: SLE duration, anti-Ro/SSA and anti-U1RPN antibodies.	5	[235]
	35 (36 yrs)	35 patients treated with ivCYC: 54% amenorrhea in all ages group and 44% in those treated before the age of 40. Risk factors: older age at start of CYC, longer duration of CYC, lower neutrophil count prior to CYC	5	[236]
	92 Ch (26±7)	Treatment with ORAL CYC for various indications. Menstrual disturbances after treatment in 39%: ST 27%, oligomenorrhea 12%. Linear relationship between age of initiation of treatment and frequency of amenorrhea.	5	[237]
	55 (<40 yrs)	39 treated with CYC (16 short-CYC, 7 doses; 23 long-CYC, 15 or more doses). 16 controls treated	5	[238]

		with steroid pulses. SA in 12% short-CYC and 39% long-CYC (p=0.07); no cases in the control group. SA is related to the number of doses of CYC and to the age of the patients (older than 25).		
POF	Meta-analysis of RCTs	Meta-analysis of 2 randomized controlled trials MMF vs CYC. MMF treated patients had an 85-90% reduced risk of ovarian failure compared with ivCYC (2 studies, 498 participants, RR: 0.15; 95% CI 0.03-0.80). Included studies: Ginzler 2005, Appel 2009	1	[239]
	535 Arabian	188 received ivCYC. 6 cases of POF (3.2% of patients receiving CYC, 6.1% of patients on SA).	5	[228]
	210 Indian (34±12)	60 (29%) treated with CYC. In multivariate analysis, older age at CYC initiation and cumulative dose of CYC were independently associated with POF.	5	[59]
	63 premenopausal	63 patients receiving CYC without any ovarian protection. 60% POF (no difference in oral vs iv). 39% in women <30 yrs. 59% in women 30-40.	5	[240]
	35 (36 yrs)	35 patients treated with CYC. Of the 27 patients treated before 40 years of age, 12 (44%) developed POF.	5	[236]
	92 Ch (26±7)	Treatment with ORAL CYC for various indications. 2 (2%) cases of POF in women who had previously regained menstruation.	5	[237]
Pregnancy (post-CYC)	535 Arabian	188 received ivCYC. 48 women had 90 pregnancies (29 fetal losses and 61 live births). Preterm birth was more frequent in CYC users.	5	[228]
	112 (32±6)	56 exposed to CYC, 56 unexposed. 38 patients sought to became pregnant and 32 (84.2%) succeeded with a median time to pregnancy of 3 months (range 1-48). The risk of failure to conceive was associated with cumulative CYC dose (p=0.007) and older age (p=0.02).	5	[241]
	67 Korean (31±8)	67 lupus nephritis treated with ivCYC. 15 (22%) women became pregnant after CYC (46±17 months) with a total of 19 pregnancies and 17 live births. Failure to conceive was associated with a history of amenorrhea.	5	[234]
	92 Ch (26±7)	Treatment with ORAL CYC for various indications. 14/23 (61%) women who desired to become pregnant conceived, resulting in 20 live births and 2 abortions.	5	[237]

1B. Other risk factors for menstrual irregularities

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Menstrual irregularities	210 Indian (34±12)	78 (37%) had menstrual irregularities. In multivariate analysis, younger age at disease-onset and treatment with CYC were independently associated with menstrual irregularities after disease-onset.	5	[59]
	87 (55% C) (28±6)	Menstrual irregularities in 37.9% and amenorrhea in 11.5%. Corticosteroids as single therapy in 63.2%. Menstrual alterations were not associated with steroid treatment but rather with the use of immunosuppressants (p=0.034) (30% exposed to CYC).	5	[242]
	94 (29±7)	Menstrual irregularities observed in 54%. These women showed higher disease activity (SLEDAI score) than those with normal cycles.	5	[243]
	61 Malays (33±11)	Comparison with 120 age-matched healthy controls. Higher frequency of menstrual irregularities in SLE (49 vs 17%). Independent risk factors for menstrual irregularities were older age group (>30 yrs), treatment with CYC, especially at a cumulative dose >10 g.	5	[244]
	50 (30±6)	50 SLE compared with 31 Hashimoto's thyroiditis and 36 healthy controls. Menstrual irregularities in 30.4%, 38.7%, 16.7%. Anti-CoL were positive in 15.2%, 9.7%, 0%. No association of anti-CoL and menstrual irregularities/hormonal status. Anti-CoL are not a marker of ovarian dysfunction in SLE.	5	[245]
	36 (18-39 yrs)	17 patients (47.2%) with normal cycles and 19 (52.8%) with menstrual irregularities. Normal ovarian function (FSH, LH) was found in both groups. Menstrual irregularities were associated with higher disease activity.	5	[246]
POF	96 Egyptian (30 yrs)	23.1% POF, all cases observed in patients treated with CYC. At multivariate analysis predictors of POF were cumulative CYC dose and age at SLE diagnosis.	5	[247]

	316 multiethnic (LUMINA)	11.7% POF; 32.9% POF among CYC users. Factors associated with POF were: older age at diagnosis, higher disease activity, Texan-Hispanic origin, use of CYC. A number of 1 to 6 CYC pulses was an important predictor of POF (HR: 4.65, 1.55-13.94), while a number >6 pulses was not.	4	[248]
	71 (50% white) (30 yrs)	11 patients (15.5%) with POF compared to 70 patients with normal cycles. Risk factors for POF were: older age at diagnosis, use of CYC, cumulative dose of CYC (especially >10 g), elevation of TSH in women treated with CYC.	5	[249]

1C. Fertility assessment

Parameter	Sample (age, ethnicity)	Result	Design	Ref.
AMH	27 Brazilian (age 18-40)	Case-control study of 27 eumenorrheic SLE women vs. 27 controls. AMH levels were more heterogeneous in SLE patients compared to the control group [1.23 (0.24-4.63) ng/ml versus 1.52 (1.33-1.88) ng/ml]. AMH levels were negatively correlated with the maximal dose of corticosteroid ever used (p = 0.003).	5	[250]
	96 Egyptian (30 yrs)	AMH levels were significantly lower in patients with POF (patients treated with CYC) as compared to patients with normal cycles. AMH could be useful in assessing fertility before starting CYC treatment.	5	[247]
	216 Ch (35±10)	22% exposed to CYC (no ovarian protection measures received). AMH levels were significantly lower in patients exposed to CYC than in non-exposed ones after adjustment for age. No difference upon the use of other immunosuppressants. Lower AMH levels were associated in linear regression with increasing age and each 5 g of CYC exposure. ROC curve for undetectable AMH levels: a cut-off of 5.9 g yielded a sensitivity of 0.75 and a specificity of 0.80. AMH level is a more sensitive indicator of ovarian damage due to previous CYC than is cessation of menstruation.	5	[251]
	42 (29 yrs)	19 SLE exposed to CYC, 23 non-exposed SLE, 21 age-matched healthy controls. All patients had NORMAL menstruation. AMH levels were significantly lower in SLE patients as compared to	5	[252]

		controls, but no difference between CYC exposed and non-exposed patients.		
	48 (33±8)	48 premenopausal SLE patients (11 exposed to CYC, 10 exposed to CYC+GnRH analogues, 27 no exposure). Patients with symptoms of POF were excluded. Post-treatment AMH levels were significantly higher among patients receiving CYC+GnRH analogues compared to CYC alone (and were similar to control group). GnRH-analogues can mitigate CYC-induced ovarian injury.	5	[253]
	112 (32±6)	56 exposed to CYC, 56 unexposed. AMH levels were lower in patients exposed to CYC and in patients older than 30 yrs. AMH level≤1 ng/mL were associated with age (OR:1.1, 1.04-1.19) and CYC exposure (OR:2.6, 1.16-5.71). AMH levels did not predict failure to conceive.	5	[241]
	33 (29.8 yrs)	33 premenopausal SLE patients without previous CYC exposure compared with 33 age-matched healthy controls. AMH levels were significantly lower in SLE patients than controls. There was no correlation between the AMH values and disease duration and disease activity (SLEDAI).	5	[254]
AFC	27 Brazilian (age 18-40)	Case-control study of 27 eumenorrheic SLE women vs. 27 controls. AFC was significantly reduced in SLE women [median (interquartile interval) 7 (5-11) versus 11 (7-12), p = 0.029]. AFC was inversely correlated with organ damage index (p = 0.046) and cumulative dose of CYC (p = 0.028).	5	[250]
	20 (20-29 yrs)	20 SLE patients (never exposed to CYC) and 20 age-matched healthy controls were studied by TV US. AFC and OV were reduced in SLE. AFC was the only significant predictor for menstrual regularity on multivariate analysis (1.32, 1.01-1-37)	5	[255]
	42 (29 yrs)	19 SLE exposed to CYC, 23 non-exposed SLE, 21 age-matched healthy controls. All patients had NORMAL menstruation. AFC was significantly lower in SLE patients as compared to controls, but no difference between CYC exposed and non-exposed patients.	5	[252]
	96 Egyptian (30 yrs)	AFC was significantly lower in patients with POF (patients treated with CYC) as compared to patients with normal cycles. AFC could be useful in assessing fertility before starting CYC treatment.	5	[247]
FSH, LH, E2, progesterone	27 Brazilian (age 18-40)	Case-control study of 27 eumenorrheic SLE women vs. 27 controls. The SLE and control groups had similar serum FSH levels [6.44 (4.19-7.69) versus 7.5 (6.03-8.09) IU/L, p = 0.135].	5	[250]
	20 (20-29 yrs)	20 SLE patients (never exposed to CYC) and 20 age-matched healthy controls. FSH and LH levels	5	[255]

		were lower in SLE. No difference in E2 levels.		
	42 (29 yrs)	19 SLE exposed to CYC, 23 non-exposed SLE, 21 age-matched healthy controls. No difference in FSH and LH levels. E2 levels were higher in SLE patients (no difference upon CYC exposure).	5	[252]
	94 (29±7)	94 SLE compared with 40 age-matched healthy controls. No difference in LH, FSH, E2. Lower levels of progesterone in SLE. By comparing SLE patients upon disease activity, those with higher disease activity had lower progesterone levels.	5	[243]
	26	26 SLE patients with inactive disease compared with 21 healthy controls. Normal ovulatory cycle proved by US. Lower progesterone concentrations were found in SLE patients.	5	[256]
ASAs, aZP	52 (30±4)	52 SLE patients and 25 age-matched healthy fertile women. No difference in ASAs in either serum or cervical ovulatory mucus. aZP IgG were found in 23% SLE 0% controls, IgM in 2% SLE 0% controls. As expected, several autoantibodies against different phospholipid were found more frequently in SLE patients.	5	[257]
hCG	48 females and 4 males	48 SLE women and 243 controls (126 females, 117 males). hCG levels were elevated in 23.8% of patients compared with 12.7% of controls. Autoantibodies against ovarian and endometrial antigens were found in 26.7% and 40% of SLE, compared with 8% and 7.6% in controls.	5	[258]

1D. Childhood-onset SLE

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Ovarian reserve	57 (37% C) (27.2 yrs)	57 c-SLE vs 21 age-matched healthy controls. Patients with SLE had normal FSH, LH, E2 levels and reduced AMH and AFC. Anti-CoL were detected only in c-SLE patients (16% vs 0%, p=0.10) and were not associated with any disease characteristic. CYC-treated patients had higher FSH, lower AMH and AFC in comparison with non-treated patients. A negative correlation was found in 19 patients treated with MTX only between the cumulative dose and AMH levels (r=-0.507, p=0.02).	5	[259]

	30 (50% C) (21.7 yrs)	30 c-SLE patients studied for FSH and LH levels. 13 c-SLE patients were exposed to CYC (31%). CYC use was associated with reduced ovarian reserve (RR=2.8; 95%CI 1.7-4.8, p=0.02). No cases of POF were observed.	4	[260]
	23 (18 yrs)	23 c-SLE were assessed for gonadal function defined as: normal menstrual cycle with or without dysmenorrhea; elevated cervical mucus length; normal levels of FSH, LH, E2, progesterone, prolactin and testosterone; normal urinary hormonal citology; serial pelvic US compatible with ovulatory pattern. 7 (30%) patients showed abnormal gonadal function with no association with any of SLE-related parameters.	5	[261]
Amenorrhea/ menstrual irregularities	298 post-menarche c-SLE	35 (11.7%) patients with amenorrhea. Low FSH and/or LH (still within the normal range) were observed in 7 out of 32 tested patients (22%). Association of low levels of hormones with higher disease activity (SLEDAI), damage (SLICC-DI), and high dose of corticosteroids (hypothalamic-pituitary-ovary axis suppression). No cases of POF were reported.	5	[262]
	30 (17±3)	30 c-SLE patients compared with 30 age-matched healthy controls. Menstrual abnormalities more frequent in c-SLE patients (63% vs 10%, p=0.0001), with higher FSH and lower progesterone vs controls. Among c-SLE patients, those with menstrual abnormalities had lower LH in comparison with those with normal cycles. No differences were observed upon previous use of CYC. No cases of POF were observed.	5	[263]
	298 post-menarche c-SLE	35 (11.7%) patients with amenorrhea. Hormonal levels (FSH, LH, E2) within the normal range (normal ovarian reserve). No cases of POF. Amenorrhea was associated in multivariate analysis with higher disease activity (SLEDAI) and damage (SLICC-DI). No differences were observed upon previous use of CYC.	5	[264]
	30 (below 16 yrs)	30 c-SLE (20 exposed to CYC). Girls who had menstrual disturbances had received higher dose of CYC than those who did not (63 vs 15 g; p<0.05). Menstrual disturbances were observed in 50% of girls receiving oral CYC, while none in girls receiving ivCYC (p=0.01).	6	[265]
Age at menarche	57 (37% C) (27.2 yrs)	57 c-SLE vs 21 age-matched healthy controls. Age at menarche after disease onset was higher in patients than controls (14 yrs, 11-17 vs. 13 yrs 11-15, p=0.03).	5	[259]

	331 (≤18 years old)	331 c-SLE with active disease from the PRINTO study. Delayed pubertal onset was seen in 15.3% and delayed/absent menarche was seen in 21.9%, while 36.1% of the females had some degree of delayed pubertal development.	4	[266]
	30 (17±3)	30 c-SLE patients compared with 30 age-matched healthy controls. Age at menarche after disease onset was higher in patients than controls (13.1 vs. 11.6 yrs, p=0.0008).	5	[263]
	23 (18 yrs)	23 c-SLE compared with 2578 healthy adolescents. Age at menarche after disease onset was higher in patients than controls (13.5 vs. 12.5 yrs, p=0.0002). The delay in menarche correlated with an increase in the duration of the disease (p=0.0085) and the cumulative dose of prednisone (p=0.0013) used until the appearance of menarche.	5	[261]

2. WOMEN WITH APS or SLE/APS

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Menstrual irregularities	80 aPL positive women (ALIWAPAS)	80 women were randomized to LDA+ warfarin (INR=1.5). 10 women (12.5%) switched to LDA alone because of menorrhagia.	2	[267]
Ovarian reserve	18 PAPS (33±5)	18 PAPS women and 24 healthy age-matched controls. No difference in FSH, LH, E2 levels. Frequency of low AFC (≤10) (56% vs 22%, p=0.04) and very low AFC (≤5) (37% vs 9%) were significantly higher in PAPS. Tendency toward reduced levels of AMH (p=0.07) in Primary APS. Anti-CoL was present only in PAPS (11% vs 0%, p=0.177) and was not related to ovarian reserve tests.	5	[268]
Uterine blood flow	109 RPL (29 yrs)	109 with RPL and positive aPL compared with 49 normal fertile age-matched women. Endometrial microvessel density was significantly impaired in aPL women during natural midluteal phase (assessed by 2D and 3D TV US).	5	[269]

	62 RPL (33±6)	35 aPL pos and 27 aPL neg women. Doppler indices of uterine and intraovarian arterial flows were not significantly different during natural midluteal phase (assessed by 2D TV US).	5	[270]
Anti-thyroid antibodies	203 PAPS (33 yrs)	203 PAPS (149 aPL alone, 54 aPL+anti-Thyr) vs 162 RPL + anti-Thyr. Anti-Thyr were found in 27% of PAPS. Patients with aPL alone had higher frequency of spontaneous pregnancies ($p<0.0001$) and live births ($p=0.0003$), when compared with patients positive for anti-Thyr alone or in combination with aPL. Anti-Thyr antibodies in PAPS may be associated with reduced fecundity and poorer pregnancy outcome.	5	[271]

Question 4. What fertility preservation methods are available for women with SLE or APS and what is the evidence for their safety and efficacy?

Points to consider: dosage and age at exposure to CYC, GnRH analogs but also oocytes punction and tissue preservation, and sperm conservation

1. WOMEN WITH SLE

1A. GnRH analogues

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Premature ovarian failure	85 SLE women (pooled data from 4 studies)	Meta-analysis of 4 studies (43 SLE patients treated with GnRH analogs and 40 controls): treatment with GnRH analogs is protective against premature ovarian failure in SLE women exposed to CTX chemotherapy (RR=0.12, 95%CI 0.03-0.41). Included studies: Blumenfeld 2000, Petri 2004, Somers 2005, Cigni 2008	3	[272]
	62 (25±6)	No data were reported on the occurrence of premature ovarian failure in 62 SLE women treated with GnRH analogs (FertiProtekt Network).	4	[273]
	44 (16-38 yrs)	44 patients exposed to CYC (80% SLE). 33 received GnRH-analogues before CYC initiation. 11 patients did not receive any fertility preservation method. In GnRH-a group 1 patient developed POF (3%), while 5 in the control group (45%). The difference remained significant after adjustment for age and cumulative dose of CYC.	5	[274]
Ovarian Suppression	29 (<21 years)	Patients were randomized 4:1 to receive triptorelin (n=23) or Pl (n=6). Treatment with triptorelin at a weight-adjusted dose of 120 mg/kg body weight provided sustained complete ovarian suppression in 90% of the patients. After administration of the initial dose of triptorelin, 22 days were required to achieve complete ovarian suppression.	2	[275]
AMH	48 (33±8)	48 premenopausal SLE patients (11 exposed to CYC, 10 exposed to CYC+GnRH analogues, 27 no exposure). Patients with symptoms of POF were excluded. Post-treatment AMH levels were significantly higher among patients receiving CYC+GnRH analogues compared to CYC alone (and were similar to control group). GnRH-analogues can mitigate CYC-induced ovarian injury.	5	[253]

Subsequent pregnancy	20 (24±1) cases and 20 controls (25±1)	40 SLE women exposed to CTX chemotherapy: 7/20 (35%) GnRH-analogues treated patients and 3/20 (15%) control patients had successful pregnancies following treatment.	5	[276]
	68 (25±6)	No information about subsequent pregnancies are available yet for 68 SLE patients counseled in the FertiProtekt Network prior to CTX treatment.	4	[273]
Safety	20 (24±1) cases and 20 controls (25±1)	20 SLE women treated with GnRH-analogues: 5 (25%) dysfunctional uterine bleeding, 3 (15%) depression. No cases of DVT or stroke. No assessment of bone mineral density was performed.	5	[276]
	62 (25±6)	No thromboembolic events were reported in 62 SLE women treated with GnRH analogs (FertiProtekt Network). No assessment of SLE activity was performed.	4	[273]

1B. Cryopreservation of ovarian tissue

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Safety	17 (26±7)	Less than one ovary was cryoconserved in 16 women (94%) and a unilateral oophorectomy was performed in one patient. No surgical or interventional complications occurred.	4	[273]

1C. Cryopreservation of oocytes (or embryos if partner available)

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Safety	5 (25 yrs, 19-35)	Immature oocyte collection during a natural cycle followed by in vitro maturation of oocytes and vitrification of the matured oocytes (or embryos if partner available). No complications occurred following the oocyte aspiration procedure.	6	[277]

	3 (21, 32, 36 yrs)	3 SLE patients underwent stimulation therapy for cryoconservation of fertilized eggs (after IVF). No thromboembolic events or over-stimulations were reported. No assessment of SLE activity was performed.	4	[273]
Subsequent pregnancy	5 (25 yrs, 19-35)	No information on subsequent pregnancy in 5 women undergoing in vitro maturation of oocytes and vitrification of the matured oocytes.	6	[277]
	3 (21, 32, 36 yrs)	No information on subsequent pregnancy in 3 patients undergoing stimulation therapy for cryoconservation of fertilized eggs (after IVF).	4	[273]

2. WOMEN WITH APS or SLE/APS

No studies included any APS and/or SLE+APS patients.

Question 5. What is the evidence for the safety and efficacy of assisted reproduction technologies (ARTs) in women with SLE or APS?

Points to consider: specific contra-indications to IVF, best method, and optimal management

1. WOMEN WITH SLE

1A. Safety of ARTs

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
SLE Flares	65 Egyptian (23±4)	65 SLE women (38.4% with positive aPL) underwent ARTs (various techniques: OI&TI, IUI, IVF/ICSI). Lupus flare was observed in 4 women (8.9%) (details not reported).	4	[278]
	21 (23±4)	114 OIT cycles in 21 women with SLE and/or APS. Among 13 SLE patients, 7 had flares (54%): 2 were known to be SLE patients, 3 concealed the disease from the gynaecologist, 2 were diagnosed during the OIT cycles.	5	[119]
	19 (no age)	68 OIT/IVF cycles in 19 women with SLE and/or APS. 16 cycles in 7 SLE patients. 4 cycles (25%) resulted in increased SLE activity.	5	[279]
	4 (20-26 yrs)	Four SLE women underwent OIT. 3 developed SLE flare.	6	[280]
	34 (34.7 yrs, 22-45)	82 IVF processes in 34 women with SLE and/or APS. Among 23 SLE patients, 3 flares (13%) were observed (1 patient was diagnosed as having SLE during the IVF cycle; the other 2 flares were associated with poor adherence to immunosuppressive treatment).	5	[281]
Thrombosis	65 Egyptian (23±4)	65 SLE women (38.4% with positive aPL) underwent ARTs (various techniques: OI&TI, IUI, IVF/ICSI). No thrombosis were reported (no data on prophylactic treatment)	4	[278]
	21 (23±4)	114 OIT cycles in 21 women with SLE and/or APS. 2 cases of thrombosis in aPL positive women receiving no prophylaxis (see below in the APS section).	5	[119]
	19 (no age)	68 OIT/IVF cycles in 19 women with SLE and/or APS. No cases of thrombosis were observed (most of the women were receiving prophylaxis with LDA and/or heparin).	5	[279]

	4 (20-26 yrs)	Four SLE women underwent OIT. All patients had positive aPL. One patient developed inferior vena cava and left renal vein thrombosis. No prophylaxis was done.	6	[280]
	34 (34.7 yrs, 22-45)	82 IVF processes in 34 women with SLE and/or APS (7 SLE+aPL, 5 SLE+APS, 11 Primary APS). No cases of thrombosis were observed in SLE patients without aPL.	5	[281]
OHSS	65 Egyptian (23±4)	65 SLE women (38.4% with positive aPL) underwent ARTs (various techniques: OI&TI, IUI, IVF/ICSI). OHSS occurred in 4 women (8.9%) (details not reported).	4	[278]
	21 (23±4)	114 OIT cycles in 21 women with SLE and/or APS. No cases of OHSS were observed.	5	[119]
	19 (no age)	68 OIT/IVF cycles in 19 women with SLE and/or APS. 2 SLE patients with previous nephritis developed OHSS.	5	[279]
	34 (34.7 yrs, 22-45)	82 IVF processes in 34 women with SLE and/or APS. No cases of OHSS were observed.	5	[281]

1B.Efficacy of ARTs

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Implantation/ pregnancy rate	65 Egyptian (23±4)	65 SLE women (38.4% with positive aPL) underwent ARTs (various techniques: OI&TI, IUI, IVF/ICSI). 20 pregnancies occurred (30.7%), 4/20 after IUI (20%) and 2/20 after ICSI (10%). No information on pregnancy outcome nor prophylactic treatment during pregnancy were reported.	4	[278]
	21 (23±4)	114 OIT cycles in 21 women with SLE and/or APS. 18 pregnancies were observed (15.8%). In 13 SLE patients: 3 embryonic losses, 2 fetal death (SLE+APS).	5	[119]
	19 (no age)	68 OIT/IVF cycles in 19 women with SLE and/or APS. 5 pregnancies were induced in 7 SLE patients.	5	[279]
	34 (34.7 yrs, 22-	82 IVF processes in 34 women with SLE and/or APS. 24 pregnancies occurred (29%), including 2	5	A

	45)	miscarriages and one medical termination for trisomy 13.		
Live births	21 (23±4)	114 OIT cycles in 21 women with SLE and/or APS. 18 pregnancies were observed (15.8%). In 13 SLE patients: 6 live births.	5	[119]
	19 (no age)	68 OIT/IVF cycles in 19 women with SLE and/or APS. 5 pregnancies in 7 SLE patients yielded to 9 liveborn children (2 single, 2 twin, 1 triplet).	5	[279]
	34 (34.7 yrs, 22-45)	82 IVF processes in 34 women with SLE and/or APS. 21 live births (87% of pregnancies) yielding to 25 children (4 twin pregnancies).	5	A

2. WOMEN WITH APS or SLE/APS

2A. Safety of ARTs

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Thrombosis	21 (23±4)	114 OIT cycles in 21 women with SLE and/or APS (2 SLE+aPL, 3 SLE+APS, 8 Primary APS). Two cases of thrombosis occurred after gonadotropin administration: 1) one undiagnosed APS patient who did not receive any prophylactic treatment; 2) one SLE+aPL who concealed her disease and did not receive any prophylactic treatment.	5	[119]
	19 (no age)	68 OIT/IVF cycles in 19 women with SLE and/or APS (10 Primary APS, 2 aPL carriers). No cases of thrombosis were observed (most of the women were receiving prophylaxis with LDA and/or heparin).	5	[279]
	4 (20-26 yrs)	Four SLE women underwent OIT. All patients had positive aPL. One patient with high titre IgG aCL developed inferior vena cava and left renal vein thrombosis. No prophylaxis was done.	6	[280]
	34 (34.7 yrs, 22-	82 IVF processes in 34 women with SLE and/or APS (7 SLE+aPL, 5 SLE+APS, 11 Primary APS). Four	5	[281]

	45)	thrombosis were recorded (2 in SLE+APS, 2 in Primary APS), in 2 cases because of interruption of anticoagulation.		
OHSS	21 (23±4)	114 OIT cycles in 21 women with SLE and/or APS (2 SLE+aPL, 3 SLE+APS, 8 Primary APS). No cases of OHSS were observed.	5	[119]
	19 (no age)	68 OIT/IVF cycles in 19 women with SLE and/or APS. No cases of OHSS reported in aPL positive women.	5	[279]
	34 (34.7 yrs, 22-45)	82 IVF processes in 34 women with SLE and/or APS (7 SLE+aPL, 5 SLE+APS, 11 Primary APS). No cases of OHSS were observed.	5	[281]

2B.Efficacy of ARTs

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Implantation rate	21 (23±4)	114 OIT cycles in 21 women with SLE and/or APS. 18 pregnancies were observed (15.8%). In 3 SLE+APS patients: 1 embryonic loss, 2 foetal deaths. In 8 Primary APS: 2 embryonic losses, 2 foetal deaths.	5	[119]
	19 (no age)	68 OIT/IVF cycles in 19 women with SLE and/or APS (10 Primary APS, 2 aPL carriers). 17 pregnancies were induced in 12 women with positive aPL (3 biochemical pregnancies, 3 spontaneous abortions, 1 elective termination, 1 miscarriage in a surrogate carrier).	5	[279]
	34 (34.7 yrs, 22-45)	82 IVF processes in 34 women with SLE and/or APS (7 SLE+aPL, 5 SLE+APS, 11 Primary APS). 24 pregnancies occurred (29%), including 2 miscarriages and one medical termination for trisomy 13.	5	[281]
Live births	21 (23±4)	114 OIT cycles in 21 women with SLE and/or APS. 18 pregnancies were observed (15.8%). In 3 SLE+APS patients: 1 live birth. In 8 Primary APS: 3 live births.	5	[119]
	19 (no age)	68 OIT/IVF cycles in 19 women with SLE and/or APS (10 Primary APS, 2 aPL carriers). 17 pregnancies were induced in 12 women with positive aPL yielding to 5 liveborn children.	5	[279]

	34 (34.7 yrs, 22-45)	82 IVF processes in 34 women with SLE and/or APS (7 SLE+aPL, 5 SLE+APS, 11 Primary APS). 21 live births (87% of pregnancies) yielding to 25 children (4 twin pregnancies).	5	[281]

1C. Factors influencing IVF success in aPL positive women

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Live birth	2 (31, 34)	Case report of 2 APS women with history of pregnancy loss and IVF failures. Live births were observed after Pre-implantation Genetic Diagnosis. The patients received multiple treatments during pregnancy (heparin, LDA, steroid, IvIg).	6	[282]
	Meta-analysis of 1172 cases and 1770 controls	Meta-analysis of case-control studies investigating the relationship between aPL and IVF success rate. The presence of one or more aPL was associated with a 3-fold higher risk of ART failure (20 studies; OR=3.33; 95%CI 1.77-6.26). There was a high grade of heterogeneity across the studies.	2	[283]
	687 (36.2 yrs)	687 women with positive aPL undergoing 1050 IVF cycles. Administration of H/A alone or combined with IvIg in the IVF period. Increased live birth rate in the group H/A vs non-H/A (46% vs 17%). In patients with anti-PE and anti-PS antibodies the birth rate was increase with the combination of H/A and IvIg in comparison with H/A alone (41% vs 17%).	4	[284]
	89 women below 36 yrs	89 infertile women with recurrent IVF failures (52 aPL+, 37 aPL -). All women received H/A in the IVF period and IgIV single infusion 20 g before egg retrieval. Live births were achieved in 42% aPL+ and 19% aPL-. aPL + women seem to benefit from the combination treatment.	5	[285]
	143 (35±5)	143 women positive for anti-nuclear antibodies (22% as single positive autoantibody) and/or aPL and recurrent IVF failure (n≥10), randomized to receive UFH (5000 UI bid) and LDA (100 mg daily) or Pl. No difference between groups in terms of implantation rate and birth rate.	2	[286]

Question 6. In monitoring SLE or APS during pregnancy and post-partum period, how well do clinical, serological and other disease biomarkers correlate with disease and obstetrical outcomes?

1. Women with SLE

Factor/predictor	Outcome(s) and example(s) of effect size	Best study design[1]	References
Active/flaring SLE (during pregnancy)	•**Active/flaring maternal SLE during pregnancy**. See also Q1	4	13 18 45
	•**Organ damage accrual during pregnancy and post-partum**. See also Q1	5	9
	•**Pregnancy-induced hypertension, (pre-)eclampsia/HELLP**. See also Q1	5	9 12 13 16 23 30 39 45-47
	•**Adverse maternal and/or foetal outcome(s) (composite outcome)**.	5	66
	•**Adverse foetal outcome(s) (composite outcome).** See also Q1	4	20 30 34 58
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. See also Q1	4	2 9 11 16 26 45 49 63 72 75 84 101 120-123
	•**Pre-term delivery/prematurity**. See also Q1	4	9-14 16 19 30 45 47 49 52 64 69 71 101
	•**IUGR/SGA/low birth weight**. See also Q1	4	12-14 19 46 47 49 54 69 72 75
	•**Prognostic value of cytopenias (thrombocytopenia, leukopenia)**	4	18 36 45 54 58 66
	•**Use of disease activity indices and modified indices** (SLEPDAI, LAI-P, BILAG2004-P, modified SELENA-SLEDAI flare index) **for monitoring SLE activity/flares during pregnancy.** Validated for their sensitivity in detecting changes in disease activity and for the prognostic impact on maternal/foetal outcomes	4	4 11 30 34 45 58 64 66 287-290
Active/flaring lupus nephritis (during pregnancy)	•**Pregnancy-induced hypertension, (pre-)eclampsia/HELLP**. See also Q1	5	36 46 47

	•**Adverse maternal outcome (composite outcome or death)**. See also Q1	4	13 16 48 118
	•**Adverse foetal outcome(s) (composite outcome).** See also Q1	4	16 26 34 69 118
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. See also Q1	4	31 48 84
	•**Pre-term delivery/prematurity**.	4	18 48
	•**IUGR/SGA/low birth weight**.	5	18 28 46
	•**Prognostic value of serum albumin levels**	5	34
Serological activity (serum C3/C4, anti-dsDNA titres) (during pregnancy)	•**Helpful in monitoring SLE activity and for the differential diagnosis of SLE activity versus eclampsia.** Measurement of serum C3/C4 can help differentiate between SLE activity and PE, since C3/C4 are significantly lower in women with SLE than women with PE, and serum C3/C4 concentrations rise during uncomplicated or pre-eclamptic pregnancy in women with SLE. Of the eight women with SLE in whom serial complement values were determined, three had falling C3 or C4 levels, and in each, there was a flare of SLE activity either during or immediately after pregnancy.	4	39 291-293
	•**Risk for SLE flare-ups**. More evidence for the prognostic role of high-titre anti-dsDNA,	4	81 293 294
	•**Adverse foetal outcome(s) (composite outcome)**. Smaller increases in serum C3 during pregnancy are associated with increased risk for adverse pregnancy outcome(s) (foetal or neonatal death; birth before 36 weeks due to placental insufficiency, hypertension, or PE; and SGA neonate <5th percentile)	4	18 34 37 58 295 296
	•**Pregnancy loss (miscarriage/foetal loss, stillbirth, neonatal death)**. Persistence of high anti-dsDNA is associated with foetal loss (RR 12.0)	4	122 297 298
	•**Pre-term delivery/prematurity**. 2nd-trimester high anti-dsDNA (especially if co-existing clinical activity) is associated with increased risk	4	18 294 297 299
	•**IUGR/SGA/low birth weight**. In SLE women with no clinical activity, low serum C3/C4 during pregnancy is associated with increased rates of IUGR and SGA	4	7 108

2. Women with APS (SLE-APS or PAPS)

Factor/predictor	Outcome(s) and example(s) of effect size	Best study design[1]	References
Thrombocytopenia	• **Adverse pregnancy outcome(s) (composite outcome; APS-defined morbidity).** Persistence of thrombocytopenia during pregnancy was associated with OR 11.5	5	[159]
Serological activity (serum C3/C4, anti-dsDNA titres) (during pregnancy)	• **Adverse pregnancy outcome(s) (composite outcome; APS-defined morbidity)**. Low C3/C4 at the end of pregnancy had OR 7.9 for APS-related pregnancy morbidity	5	[159]
	• **Pregnancy loss (miscarriage/foetal loss).** Low C3/C4 and/or high anti-dsDNA titres during the first 20 weeks of gestation are associated with increased risk for foetal loss	4	[153]
	• **Pre-term delivery/prematurity**.	4	[153]
	• **IUGR/SGA/low birth weight**.	4	[153]
Anti-phospholipid antibodies (aPL) titres (during pregnancy)	• **Pregnancy loss (miscarriage/foetal loss).** Disappearance of aCL-IgG during pregnancy correlates with lower risk of foetal loss; persistence is associated with RR 7.8 with foetal loss	4	[122 174 216]

Question 7. What is the evidence that pregnant women with SLE or APS should undergo more intensive monitoring (including screening for placenta-related complications at week 11-14, foetal echocardiography, serial foetal growth and Doppler scans each 2-3 weeks starting at week 28) for obstetrical problems compared with the general population?

Points to consider:

a. Should all patients with SLE or only subgroups have in addition to routine (1st trimester assessment) have a specific screening for placenta-related complications at week 11-14?
b. When should one start and how often should one perform fetal echocardiography in anti-Ro/SSA positive patients?
c. Should every SLE/APS patient have serial fetal growth and Doppler scans each 2-3 weeks starting at week 28?

1. WOMEN WITH SLE

1A. Doppler-US monitoring

Doppler parameter	Sample (age, ethnicity)	Result	Design	Ref.
Pulsatility Index	64 (32 yrs)	70 pregnancies in 64 SLE women (20% aPL +ve), treated with LDA (100 mg/day) and LMWH in 21% of cases. mUtA-PI was measured between 23+0 and 26+6 weeks. It was a sensitive and specific test for PE, SGA and composite adverse pregnancy outcome.	5	[300]
	135 (34 yrs) mixed cohort	135 women with at least one high-risk condition for PE (15% of the patients had rheumatic disease: SLE, APS, RA) (nearly 40% taking LDA). mUtA-PI was measured at 11-13 weeks and 19-22 weeks. Women with mUtA-PI ≥90°percentile at both time points had a greater risk for early PE (<34 weeks) (OR 21.4, 2.5-184.7).	4	[301]
	20 (no age)	20 SLE pregnant women. Uterine artery Doppler starting from week 12, combined with PI from 26 weeks. Increased RI and presence of notch of uterine arteries was associated with hypertension and low birth weight. Alterations of umbilical artery PI were related to IUGR, low birth weight and PE.	6	[302]
Bilateral	65 (28.8 yrs)	65 pregnant SLE (no LDA treatment). Doppler study was performed at 22-24 weeks. Bilateral	5	[46]

Notch of uterine arteries		notches were found in 13 pregnancies (20%) and were associated with fetal loss, IUGR and/or PE, preterm birth.		
	98 pregnancies	98 pregnancies in SLE (58 without and 40 with previous nephritis). Doppler was performed at 20-24 weeks. Bilateral notches were note in 9 patients without previous nephritis (16%) and none of the patients with previous nephritis. negative predictive value for PE/SGA was 47% for women with previous nephritis and 85% for women without previous nephritis.	5	[36]
	84 (no age)	116 pregnancies in 84 women (44 SLE, 23 SLE+APS, 32 PAPS), treated with LDA in all cases and LMWH in nearly 40% of the cases. Doppler-US was performed in the 2nd trimester. 31 adverse pregnancy outcomes occurred. In multivariate analysis, notched uterine artery was the only predictor (p=0.001).	4	[303]
	40 (no age)	40 pregnancies in 40 women with rheumatic disease (9 SLE, 6 APS, and other rheumatic disease). Abnormal Doppler in 14 pregnancies: only 2 delivered uneventfully, while the other 12 had complications (preterm delivery, PE, IUGR). All the 26 pregnancies with normal Doppler were uneventfully.	5	[304]
End-diastolic velocity	56 (30 yrs)	56 pregnant SLE (5 aPL +ve), 45% treated with LDA. Doppler was performed as early as 24 and as late as 35 weeks. Absent or reversed end-diastolic velocity was detected in 6 (11%) women. This finding was associated with PE, IUGR, preterm delivery, cesarean section.	5	[305]
	26 (28 yrs)	27 pregnancies in 26 SLE. In 9 cases absent end-diastolic velocity was detected, yielding to SGA and perinatal losses. The 18 pregnancies with normal Doppler findings had normal outcomes.	5	[306]
	54 (no age)	56 pregnancies in 54 women (52 SLE, 2 PAPS). Serial Doppler examinations were performed starting week 14 and then every 4 weeks until week 32, then weekly until delivery. Absence of end-diastolic velocity at 20 weeks was likely to result in premature delivery and cesarean section.	4	[307]
	25 (no age)	28 pregnancies in 25 women (19 SLE, 7 PAPS), treated with LDA. Doppler was performed between 20 and 30 weeks. Abnormal finding were detected in 10 pregnancies, with significant association with prematurity ≤32 weeks, foetal distress before labour.	5	[308]

2. WOMEN WITH APS or SLE/APS

2A. Doppler-US monitoring

Doppler Parameter	Sample (age, ethnicity)	Result	Design	Ref.
Bilateral Notch of uterine arteries	25 (30±6)	25 APS pregnant women taking LDA (100 mg/day) and heparin (5,000 UI every 12 hours). Doppler-US was performed at 24 and 32 weeks. 21 women with no notch at uterine artery evaluation delivered at term without any complication. 4 women with bilateral/unilateral notches: 1 PE at 28 weeks; 1 with hypertension, preterm birth with SGA baby; 2 women delivered at term without any complication.	4	[309]
	51 (31±5)	51 pregnant women with PAPS, treated with LDA (100 mg/day) and LMWH. Doppler-US was performed in 30 women at 22-24 weeks. 46.7% of women had Doppler uterine artery notches. This finding was associated with prematurity and IUGR.	5	[178]
	31 (31±5)	33 pregnancies in 33 women treated with LDA (100 mg/day) and LMWH (once a day). Doppler-US was performed during the 1st trimester (12-15 weeks), 2nd trimester (22 weeks), 3rd trimester (32 weeks). Bilateral notch of the uterine arteries was found in 38% of the cases during the 1st trimester. It was associated with significantly lower birth weight compared to cases with absent or unilateral notch. The NPP of uterine Doppler was 92% at 12-15 weeks of gestation and remained high throughout pregnancy.	4	[310]
	170 (33 yrs, 21-43)	170 pregnant women with PAPS treated with LDA (75 mg/day) and LMWH (enoxaparin 20 mg/day). Doppler-US was performed at 16-18 weeks and 22-24 weeks. At 16-18 weeks bilateral notching was not predictive of PE and/or SGA infants. At 24 weeks, bilateral notching had 89% negative predictive value and 40% positive predictive value for PE and SGA. In LA positive women, 94% negative predictive value and 75% positive predictive value.	4	[311]
RI of uterine	24 (31 yrs, 19-	28 pregnancies in 24 women (17 PAPS, 7 SLE+APS) on treatment with prednisone (40 mg/day) and	5	[160]

arteries	42)	LDA (100 mg/day). Doppler-US was performed at 18-24 weeks. An abnormal RI of the uterine arteries predicted poor pregnancy outcome in terms of: delivery<32 weeks, birth weight<1750 g, PE, IUGR<10°percentile.		
	41 (no age)	43 pregnancies in 41 women (36 PAPS, 7 SLE+APS). Doppler-US was performed at a median of 23 weeks, range 19-34. 26% of cases had abnormal uterine artery waveforms, associated with birthweight<10°percentile and preterm delivery (<34 weeks). 3 cases of PE were observed.	5	[312]
	67 (no age)	67 pregnant women with various diseases (17 rheumatic disease+thrombophilia, 8 APS, 41 rheumatic disease). Doppler-US was performed at 10-16-18-21-28 weeks. At week 21, abnormal RI of the uterine arteries was associated with PE, preterm delivery, low birth weight. RI values of more than 0.58 (taken as cut-off) were able to identify patients at risk at 16/18 weeks, if confirmed at week 21.	4	[313]
RI of umbilical artery	56 (29.7 yrs, 16-40)	77 pregnancies in 56 APS women (38 PAPS, 18 SLE+APS), treated with LDA (100 mg/day) and LMWH in 17%. Adverse pregnancy outcome was predicted by abnormal umbilical artery Doppler at 23-26 weeks (OR 18.5, 1.6-55.1).	5	[203]
S/D ratio	28 (no age)	28 pregnant patients with positive LA (24 PAPS, 4 SLE+APS), treated with prednisone (40-60 mg/day) and LDA (100 mg/day). Five of the six patients who delivered SGA babies had abnormal umbilical arterial S/D ratios, whereas only 2 of them demonstrated abnormally elevated uterine S/D ratios. In 10 patients with PE, abnormal umbilical arterial S/D ratios was found in 5 patients (all SGA babies) and abnormal uterine arterial S/D ratios in 2 patients.	6	[314]

3. WOMEN WITH POSITIVE ANTI-Ro/SSA and ANTI-La/SSB ANTIBODIES

3A. Foetal echocardiography

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
PR interval	89 foetuses (84	Echocardiography performed WEEKLY between 18 and 24 weeks of gestation. 27 foetuses with	4	[315]

measurement	pregnancies) in 65 anti-Ro/SSA +ve women (Sweden)	prolonged PR interval (1st degree AVB) detected in utero. 12 babies had 1st degree AVB confirmed by electrocardiogram at birth and it spontaneously recovered within 1 month of age, while 15 babies had normal electrocardiogram at birth. The technique has excellent negative predictive value but a positive predictive value less than 50%. Complete CHB occurred in two foetuses (one from 1st degree AVB at 19 weeks to 3rd degree AVB at 20 weeks; one from normal PR at 20 weeks to 2nd degree AVB at 23 weeks).		
	70 foetuses (67 pregnancies) in 56 anti-Ro/SSA +ve women (Israel)	Echocardiography performed WEEKLY between 13-18 weeks (median 16) and 24 weeks of gestation. Monthly examination from week 25 until delivery if no evidence of AVB, weekly examination if diagnosis of 1st degree AVB. 6 cases of 1st degree AVB (3: 21-26 w; 2: 32-33 w; 1: 34 w) were identified. All cases were treated with dexamethasone 4 mg/day with normalization of PR interval in 3-14 days. No cases of complete CHB.	4	[316]
	98 foetuses (98 pregnancies) in 95 anti-Ro/SSA +ve women (USA, multiethnic)	Echocardiography performed WEEKLY between 16 weeks and 26 weeks of gestation and the biweekly until 34 weeks. 6 foetuses had cardiac conduction abnormalities. 3 foetuses with 1st degree AVB (1 at 20 w, 1 at 22 w, 1 at birth –missed prenatally), the 2 diagnosed antenatally were treated with dexamethasone 4 mg/day for less than 7 days and reverted to normal sinus rhythm. 3 foetuses developed 3rd degree AVB at 23 w, 21 w, 20 w, starting from a normal PR at 22 w, 19 w, 18 w respectively. COMPLETE CHB CAN DEVELOP FROM A NORMAL RHYTHM IN A WEEK.	4	[317]
	24 foetuses (24 pregnancies) in 24 anti-Ro/SSA +ve women (Sweden)	Echocardiography performed WEEKLY between 18 and 24 weeks of gestation. 8 foetuses with 1st degree AVB: 6 cases of spontaneous recovery; 1 case of progression to 3rd degree AVB in 6 cases; 1 case of progression from normal to 2nd degree AVB in 3 weeks and recovery to 1st degree after few days of treatment with dexamethasone.	4	[318]
Time of onset of CHB	45 foetuses born to anti-Ro/SSA positive women (France, 2002-2012)	45 foetuses diagnosed with 2nd-3rd degree block. The median gestational week at diagnosis of AVB was 23 (interquartile range 22-24)	4	[319]

	113 infants diagnosed with CHB (born between 1970 and 1997)	No cases were detected before week 17. Detection was most frequently clustered between 20 and 24 weeks. The median time of in utero detection was 23 weeks. 14 cases (16%) were detected in the 3rd trimester. 82% of the cases were detected before 30 weeks. The recurrence rate of CHB in a mother who already had a baby with CHB was 16%.	4	320

Question 8. What are the benefits and harms of therapeutic agents (including different classes of drugs and dosages) used to manage SLE flares during pregnancy?

Drug	Efficacy/safety in SLE during pregnancy	Best study design[1]	References
Glucocorticoids (GC)	•**Safety of maintenance treatment during pregnancy.** See Q1 •**Used to control disease activity / manage flares.** High-dose GC (including pulses of intravenous methylprednisolone) used in treatment of severe SLE flares.	6	[See Q1] 10 21 31 37 53 61 287
Hydroxychloroquine (HCQ)	•**Safe to use during pregnancy / post-partum**. See also Q1. •**Used to control disease activity / manage flares**. See also Q1	3 2	50 124 125 321-323 13 49 324 50
Azathioprine	•**Used to disease activity / manage flares. Acceptable benefit/risk ratio.**	6	10 21 31 75 127 325
IVIG	•**Used to disease activity / manage flares. Acceptable benefit/risk ratio.**	6	10 11
Calcineurin inhibitors (ciclosporin, tacrolimus)	•**Used to disease activity / manage flares. Acceptable benefit/risk ratio.**	6	326-328
Plasma exchange therapy	•**Used to disease activity / manage flares. Acceptable benefit/risk ratio.**	6	329 330
Cyclophosphamide	•**Use during the 1st trimester of pregnancy has been associated with increased risk for foetal loss**. Reserved only for the management of severe, life-threatening or refractory SLE manifestations during the second or third trimester.	6	63 68 331-333

Question 9. Besides measures indicated for general obstetric population (such as folic acid supplementation), what is the evidence for the benefit of preventative treatments (including LDA, heparin, HCQ, calcium/vitamin D supplementation) in pregnant women with SLE or APS (including specific subgroups of patients with hypertension, lupus nephritis, non-criteria aPL, previous pre-eclampsia)?

1. WOMEN WITH SLE

1A. LDA

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Prevention of PE		No specific trials have been performed to address the use of LDA to prevent PE in SLE. LDA could lower the risk for lupus patients to an extent comparable to the risk reduction demonstrated in trials assessing LDA treatment for other risk groups (up to 20% risk reduction). The benefit on the prevention of preterm PE (not term PE) and severe PE was demonstrated for initiation of LDA prior to 16 weeks of gestation (2 meta-analysis by Roberge S 2012 and Villa PM 2013).		
Live birth	56 (29.7 yrs, 16-40)	77 pregnancies in 56 APS women (38 PAPS, 18 SLE+APS), treated with LDA (100 mg/day) and LMWH in 17%. In multivariate analysis, live birth was predicted by the pre-conceptional use of LDA (OR 3.32, 1.04-10.6).	5	[203]
	81 C (30±5)	113 pregnancies in 81 biopsy-proven lupus nephritis patients. Live birth rate was 91%. Use of LDA during pregnancy (starting from 10-15 weeks) in 60% cases. At multivariate analysis, the use of LDA was protective against foetal and maternal adverse outcomes (RR=0.11, 0.03-0.38).	4	[27]

1B. Low molecular weight heparin

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Live birth	58 (36±4)	62 pregnancies in 58 SLE women (20 aPL carrier, 7 APS, 31 aPL negative). APS patients received	5	[80]

		LDA+prophylactic LMWH. aPL carriers received prophylactic LMWH. aPL negative women were not treated. aPL carriers had pregnancy outcomes similar to aPL negative women.		

1C. HCQ

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
SLE flares	20 (29±3)	Double-blind, Pl-controlled study on 20 SLE patients randomized to receive HCQ (n=10) or Pl (n=10) starting between 8 and 18 weeks of gestation (average of 11 weeks). The HCQ group had no flare-ups, while 3 in the Pl group. Prednisone dosage was significantly reduced at delivery in the HCQ group.	2	[324]
	197, multiethnic	257 pregnancies in 197 SLE women (163 no HCQ during pregnancy, 56 continuous use of HCQ during pregnancy, 38 cessation of HCQ either in the 3 months prior to or during the first trimester of gestation). The rate of pregnancy losses and complications was not different among the 3 groups. Patients who stopped HCQ had higher disease activity and higher rate of flares during pregnancy. Women who continued taking HCQ were maintained on a lower average dose of prednisone during pregnancy.	5	[50]
	128 Korean (31 yrs, 28-33)	179 pregnancies in 128 SLE patients with 90.5% live births. 80 pregnancies (44.7%) experienced lupus flares. Lupus flares were predicted by HCQ discontinuation, history of lupus nephritis, high pre-pregnancy serum uric acid and low C4 levels.	5	[334]
CHB	257 pregnancies	257 pregnancies in anti-Ro/SSA positive women with a previous child with cardiac NL. 44 pregnancies occurred in SLE women. Out of 257 pregnancies, 40 were exposed to HCQ and 217 unexposed. The recurrence of cardiac-NL in foetuses exposed to HCQ was 7.5% compared with 21.2% in the unexposed group (p=0.05). In adjusted multivariate analysis, HCQ was significantly associated with a decreased risk of cardiac NL (OR 0.23, 95%CI 0.06-0.92, p=0.037).	5	[116]
	33 women (29.2	20 (61%) women had SLE. When the mother was treated with HCQ±low dose prednisone, 93% of	5	[335]

	yrs) with anti-Ro/SSA antibodies	the fetuses maintained normal conduction, compared with 63% in the untreated group (OR 0.14, 0.002-0.98, p=0.04).		
	84 pregnancies	84 pregnancies in anti-Ro/SSA positive women with a previous child with cardiac NL. Recurrent cardiac NL occurred in 20.2% of the cases. The recurrence rate was 26.9% in fetuses who were not exposed to HCQ (14/52), compared with 9.4% in those exposed to HCQ (3/32) (p=0.052).	5	(A)

(A) Levesque, K., et al. French Cohort study of 141 cases of autoimmune congenital heart block. ACR abstract supplement October 2012, presentation 1649: S704.

2. WOMEN WITH APS or SLE/APS

2A. LDA

Patient subgroup	**Sample (age, ethnicity)**	**Result**	**Design**	**Ref.**
Non-criteria APS patients / aPL carriers				
Incomplete clinical criteria	114 (34±4)	139 pregnancies in 114 aPL positive women not fulfilling the criteria for definite APS (no previous obstetric history –aPL carriers-; incomplete obstetric criteria). 104 treated with LDA, 35 untreated. No difference in the rate of pregnancy loss (7.7% treated vs 2.9% untreated). LDA does not appear to improve outcome in women not fulfilling APS criteria.	5	[193]
	146 (36 yrs)	73 obstetric PAPS and 73 aPL carriers (no obstetric criteria) and 292 controls. All women were given LDA. LMWH was added to definite APS in nearly 50% of the cases. aPL carriers had outcomes that were similar to controls. aPL carriers may not need as intense treatment (LMWH) and monitoring as definite APS women.	5	[336]
Incomplete laboratory	57 (36 yrs, 27-45)	57 women fulfilling clinical obstetric criteria for APS. Divided into 2 groups upon aPL parameters: aPL criteria – "definite APS" (n=25) and low titre aPL (n=32). The 2 groups had similar frequency in	5	[155]

criteria		adverse pregnancy outcome before treatment. After treatment with LDA and LMWH, outcomes significantly improved in both groups.		
	68 Japanese (30 yrs)	68 patients with RPL and occasionally positive aPL (single occasion positivity, not confirmed). 52 patients were treated with LDA, 16 were not. The rate of live birth was 84.6% and 50% respectively (p=0.01). LDA could be useful also in non-persistently positive aPL women with RPL.	5	[337]
	40 (31 yrs)	Double-blind, Pl-controlled study on 40 women with RPL (early miscarriages) and positive aPL (women with SLE and prior thrombosis excluded). 20 received LDA (75 mg/day starting 6-7 weeks of gestation) and 20 Pl. Nearly 50% of the patients in both groups had low titre aPL. No difference in the rate of live births (17/20 vs 16/20).	2	[338]

2B. Low molecular weight heparin

Outcome	**Sample (age, ethnicity)**	**Result**	**Design**	**Ref.**
Live birth				
Women with aPL and RPL	Meta-analysis of RCTs	The combination of LDA and UFH increased live birth rates compared with LDA alone (RR 1.54, 95% CI 1.25-1.89) (Kutteh 1996, Rai 1997, Goel 2006). The combination of LDA and LMWH resulted in a similar rate of live births as LDA alone (RR 1.07, 0.88-1.29) (Farquharson 2002, Laskin 2009). The combination of LDA and LMWH did increase live births compared to IvIg (RR 1.64, 1.21-2.22) (Triolo 2003, Dendrinos 2009).	1	[339]
	Meta-analysis of RCTs	334 patients from 5 RCTs. The combination LDA+heparin (UFH+LMWH) is superior to LDA alone in achieving more live births in patients with positive aPL and RPL (RR 1.301, 95% CI 1.040-1.629). The number needed to treat of LDA+heparin to achieve one live birth is 5.6. Included studies: Kutteh 1996, Franklin and Kutteh 1996, Rai 1997, Farquharson 2002, Laskin 2009).	1	[340]
	Meta-	The combination of LDA and heparin (UFH+LMWH) was superior to LDA alone against first-trimester	1	[341]

	analysis of RCTs	losses (OR 0.39, 95%CI 0.24-0.65; number needed to treat=6 patients). UFH displayed a significant effect (OR 0.26, 0.14-0.48; number needed to treat=4) (Kutteh 1996, Rai 1997, Goel 2006), while the pooled effect of LMWH was insignificant (OR 0.70, 0.34-1.45). Combination therapy of either UFH or LMWH with LDA failed to display any significant effect in the prevention of late pregnancy losses (OR 1.07, 0.36-3.16) (Rai 1997, Goel 2006, Farquharson 2002, Laskin 2009).		
Dose of LMWH	33 (35±4)	33 obstetric PAPS treated during pregnancy with LDA + adjusted prophylactic doses of nadroparin (adjustment according to maternal body weight). Live birth rate was 97%. One case of premature birth. Once case of spontaneous abortion at week 8. No bleeding complications recorded.	5	[342]
	60 (27±4)	60 women with obstetric PAPS 8 (≥3 consecutive abortions before 10 weeks of gestation + positive LA and/or aCL), randomized to enoxaparin 40 mg+LDA (n=30) or enoxaparin 20 mg+LDA (n=30). The live birth rate was 76.7% and 70% respectively (p=0.55). No difference between groups with respect to neonatal outcome, obstetric and maternal complications during pregnancy and puerperium. Non cases of severe bleeding, thrombocytopenia or spontaneous fractures in both groups.	2	[343]
Bone mass	123 (34 yrs, 23-46)	123 wowen with PAPS treated with LDA and heparin (46 UFH, 77 LMWH) throughout pregnancy and puerperium. BMD was measured by dual energy X-ray absorptiometry at 12 weeks of gestation, immediately postpartum, and 12 weeks postpartum. A small but significant reduction of BMD was found at lumbar spine (3.7%) and neck of femur (0.9%). This decrease is similar to that previously reported to occur in untreated pregnancies. No difference was observed between the two heparin preparations. Lactation was associated with a significant decrease in BMD.	4	[344]
	55 (32.5 yrs)	55 PAPS and 20 age-matched controls with idiopathic RPL not requiring LMWH. PAPS were treated with LDA+LMWH 5000 U/day throughout pregnancy and 6 weeks postpartum. BMD was measured at the lumbar spine by dual energy X-ray absorptiometry within 6 months prior to conception and within 6 weeks after delivery. Both groups showed a similar loss of bone (4.17% vs 3.65%). No patient suffered vertebral fractures.	4	[345]

2C. Additional treatments

Patient subgroup	Sample (age, ethnicity)	Result	Design	Ref.
Refractory obstetric APS	18 (36 yrs)	18 PAPS who had previous pregnancy loss on conventional treatment with LDA and heparin. In 23 pregnancies supplemented with low dose prednisolone (10 mg/day) from positive pregnancy index to 14 weeks of gestation, 14 live births were obtained (61%), in comparison to 4/97 (4%) of previous treated pregnancies. No maternal side effects of steroids were noted.	5	[346]
High-risk APS	156 (33±4)	196 pregnancies in 156 high-risk APS patients (diagnosis of SLE, previous thrombosis, triple aPL positivity). All patients received conventional treatment (LDA+LMWH). 21 women (10.7%) were prescribed additional treatments (IvIg, plasmapheresis, low-dose prednisolone). In multivariate analysis, additional treatments were the only independent factor associated with a favourable pregnancy outcome (OR=9.7, 1.1-88.9).	5	[347]
APS patients with prior cerebrovascular event	20 (31 yrs, 19-40)	23 pregnancies in 20 APS women who experienced cerebrovascular (8 transient ischemic attack, 12 stroke) with a median period of 81 months (12-240) prior to pregnancy. 13 patients had also SLE (56.5%). All patients received LDA and LMWH during pregnancy (full anticoagulant dose if on warfarin, prophylactic dose in the other cases). Live birth was obtained in 91%. 8 pregnancies (35%) were complicated by PE. The risk of PE was increased in patients with multiple aPL positive tests (OR 3.06, 1.01-9.32). 3/20 women experienced further cerebrovascular in the context of pregnancy (2 with PE). Additional treatments may be needed to prevent PE and subsequent cerebrovascular in this subgroup of APS women.	5	[145]

Question 10. What is the evidence for the efficacy (in terms of relief of peri-menopausal symptoms/signs) and safety (in terms of disease activity/flares, thrombo-embolic risk, cardiovascular risk) of hormone replacement treatment (HRT) in women with SLE (including patients with positive aPL antibodies) or APS?

Points to consider: options of HRT, optimal duration and monitoring while on HRT (including repeating serology, aPL)

1. WOMEN WITH SLE

1A. Efficacy of HRT

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Relief of symptoms				
Estrogen + progestin	106 Mex; 52 in HRT (47±7 yrs); 54 in Pl(50±8 yrs)	24 months randomized, double blind, Pl-controlled trial. Improvement of vasomotor symptoms but not of other menopausal symptoms (psychological and somatic). Maximum effects were observed among the most symptomatic women.	2	[348]
Tibolone	30; 15 in tibolone (52±2 yrs), 15 in Pl(52±2 yrs)	12 months randomized, double blind, Pl-controlled trial (2.5 mg tibolone/day). Hypoestrogenism symptoms by Kupperman index: greater reduction in tibolone group than in Pl group.	2	[349]
Unspecified HRT	60: 30 in HRT (50.9 yrs), 30 non-HRT (48.2 yrs)	HRT users were significantly improved in terms of depression, general well being and libido.	5	[350]
Variation of bone mass				
Estrogen + progestin	28 Ch (37±6 yrs)	24 months randomized open trial of HRT vs. calcitriol in SLE patients on chronic steroids and osteopenia and proven ovarian failure for at least 2 yrs. HRT but not calcitriol was able to prevent bone loss.	4	[351]

Transdermal estrogen + oral progestin	32 (55 yrs, range 42-70)	12 months randomized, double-blind, Pl-controlled trial of E2 (50 µg transdermal; n=15) or Pl (n=17). Both groups received 5 mg continuous oral medroxyprogesterone acetate, 500 mg calcium and 400 IU vitamin D3. Reduced loss of bone mass in the E2 group.	2	[352]
Variation of CV risk markers				
Tibolone	30; 15 in tibolone (52±2 yrs), 15 in Pl(52±2 yrs)	In the tibolone group reduction of triglycerides and HDL cholesterol at 6 and 12 months as compared to baseline.	2	[349]

1B. Safety of HRT

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
SLE flare				
Estrogen + progestin	106 Mex; 52 in HRT (47±7 yrs); 54 in Pl (50±8 yrs)	No difference in the frequency of flares (85% in HRT, 72% in P). Only one severe flare in the Pl group. The probability of flare at 1 and 2 years in the group receiving HRT and the group receiving Pl was 0.91 and 0.75 (p=0.29) and 0.94 and 0.79 (p=0.25), respectively.	2	[353]
Estrogen + progestin	28 Ch (37±6 yrs)	13 SLE patients on HRT for 24 months: no significant change in SLE disease activity.	4	[351]
Estrogen + progestin	174 in HRT (50.6 yrs); 177 in Pl (49.5); multiethnic	12 months randomized, double-blind, Pl-controlled non-inferiority trial (0.625 mg of conjugated estrogen daily, plus 5 mg medroxyprogesterone for 12 days a month) (SELENA-SLEDAI). HRT group showed increased risk for any type of flare (flare/person-year 0.64 vs. 0.51, p=0.01) and for mild to moderate flares (1.14 vs. 0.86, p=0.01), but not for severe flares (0.081 vs. 0.049, p=0.23). Women with positive aPL and/or history of cardiovascular events were excluded.	2	[354]
Estrogen +	34 Ch: 11 in HRT (39	11 patients received low dose conjugated estrogen (Premarin) and progesterone (Provera).	5	[355]

progestin	yrs); 23 non-HRT (41 yrs)	No difference between groups in the rate of flares. Total flares: 0.123 vs 0.156/patient-year. Major flares: 0.021 vs 0.026. Minor flares: 0.102 vs 0.130.		
Transdermal estrogen + oral progestin	32 (55 yrs, range 42-70)	12 months randomized, double-blind, Pl-controlled trial of E2 (50 µg transdermal; n=15) or Pl (n=17). Both groups received 5 mg continuous oral medroxyprogesterone acetate, 500 mg calcium and 400 IU vitamin D3. No changes in SLE disease activity were observed.	2	[352]
Unspecified HRT	72 (post-menopausal)	32 (44%) HRT users and 40 (56%) non-users. The mean (SD) total HRT exposure time for the 32 women was 38.1 (35.6) months, representing 60% of the total disease duration. There was a negative association between HRT use and disease activity over time which was not explained by confounding by indication.	5	[356]
Unspecified HRT	48 multiethnic: 16 in HRT (46.8 yrs); 32 non-HRT (46.7 yrs)	Use of HRT for at least 12 months. No difference in the rate of flares (62% in HRT users, 56% in non-users).	5	[357]
Unspecified HRT	60: 30 in HRT (50.9 yrs), 30 non-HRT (48.2 yrs)	No lupus flares related to HRT use were reported.	5	[350]
Tibolone	30; 15 in tibolone (52±2 yrs), 15 in Pl (52±2 yrs)	No differences in SLEDAI score between the groups during the study. No differences in the frequency of SLE flare (tibolone: 2/15 [13.3%] vs. Pl: 1/15 [6.7%]; p = 0.54). All cases of flares were considered mild to moderate.	2	[349]
Thrombosis				
Estrogen + progestin	106 Mex; 52 in HRT (47±7 yrs); 54 in Pl (50±8 yrs)	Four cases of thrombosis: 3/52 (5.8%) in HRT group, 1/54 (1.9%) in Pl group. Overall aPL frequency 38% in HRT group, 43% in Pl group. Only the patient receiving Pl had low titre aPL.	2	[348, 353]
Estrogen + progestin	174 in HRT (50.6 yrs); 177 in Pl (49.5); multiethnic	12 months randomized, double-blind, Pl-controlled noninferiority trial (0.625 mg of conjugated estrogen daily, plus 5 mg medroxyprogesterone for 12 days a month) (SELENA-SLEDAI). Women with positive aPL and/or history of cardiovascular events were excluded. 4 thrombotic events in the HRT group (1 arterial, 3 venous), 1 venous event in the Pl group.	2	[354]

Transdermal estrogen + oral progestin	32 (55 yrs, range 42-70)	1/15 (6.7%) on transdermal E2 developed a DVT after 3 months of treatment. She was aPL negative and had no history of cancer.	2	[352]
Estrogen + progestin	34 Ch: 11 in HRT (39 yrs); 23 non-HRT (41 yrs)	11 patients received low dose conjugated estrogen (Premarin) and progesterone (Provera). None of the 34 women had thrombotic events. aPL positivity was similar between groups (data not shown).	5	[355]
Cardiovascular events				
Unspecified HRT	114 HRT group (43 ± 7 yrs), 227 non-HRT group (46 ± 5 yrs)	A similar percentage of HRT users and non-users developed coronary artery disease at 13 (11.4%) and 31 (13.7%). The average time to coronary artery disease was slightly longer for HRT users compared with non-users 14.1 (±7.2) years in the HRT group and 9.2 (±7.1) in the non-HRT group (t-test P = 0.05). Age and SLEDAI-2K were the significant risk factors for coronary artery disease (HR = 1.12, P < 0.0001 and HR = 1.11, P = 0.0009, respectively). HRT use was not an independent risk factor for coronary artery disease.	5	[358]
Unspecified HRT	32 HRT group (54 ± 8 yrs), 40 non-HRT group (53 ± 11 yrs); multiethnic (LUMINA)	HRT was not associated with the occurrence of vascular (both arterial and venous) events (OR: 0.56, 95% CI 0.03-11.32), after adjusting for the propensity score ("counfounding by indication"). Arterial events occurred in 6.3% and 27.5% of HRT users and non-users, respectively. Venous thrombotic events occurred in 9.4% and 12.5% of HRT users and non-users, respectively.	5	[359]
Side effects				
Estrogen + progestin	106 Mex; 52 in HRT (47±7 yrs); 54 in Pl (50±8 yrs)	Headaches, nausea, melasma, galactorrhea, and dysmenorrhea were presented in the 2 treatment groups, intermittently and at low frequency (<6.0%). Mastalgia had a higher frequency among hormone users versus the Pl group at 1 and 6 months of treatment (10.2% and 13.33%, respectively; P<0.03).	2	[348]
Discontinuation				
Estrogen + progestin	106 Mex; 52 in HRT (47±7 yrs); 54 in Pl	Rates of discontinuation for all reason not different between HRT (29%) and Pl (30%). No differences in discontinuation for medical and non-medical reasons.	2	[348]

	(50±8 yrs)			
Transdermal estrogen + oral progestin	32 (55 yrs, range 42-70)	8/15 (53%) HRT users dropped out of the study. 4 for breast tenderness and vaginal spotting, 1 DVT (aPL negative), 2 allergic skin reaction to patch, 1 lost to follow-up.	2	[352]
Overall safety				
Tibolone	30; 15 in tibolone (52±2 yrs), 15 in Pl (52±2 yrs)	No severe adverse events (breast cancer, venous thromboembolism, arterial thrombosis, death and other cancers) were observed in either group within the 12-month study period.	2	[349]

2. WOMEN WITH APS or SLE/APS

Fernandez 2007 (LUMINA); Buyon 2005 (SELENA-SLEDAI): aPL positive women and patients with previous cardiovascular events were excluded

Question 11. Is there any evidence that patients with SLE or APS should undergo more intensive screening for certain malignancies (breast, cervical, endometrial, ovarian) compared to the general population?

1. WOMEN WITH SLE

1A. Breast Cancer

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Incidence	42,171 females (multiethnic)	Meta-analysis of 5 large cohort studies. 42,171 females observed for 282,533 patient years. 376 breast cancers were recorded, less than expected in the general population with a SIR of 0.76 (95% CI: 0.69, 0.85). Included studies: Bernatsky S Arthritis Rheum 2005 (a), Bertnatsky S Arthritis Rheum 2005 (b), Kang KY Clin Rheumatol 2010, Mellemkjaer L Arthritis Rheum 1997, Parikh-Patel A Cancer Causes Control 2008.	3	[360]
	14,768 females (multiethnic)	Multi-centre cohort study of 14,768 females with a mean follow-up time of 7.4 years. 114 breast cancers were recorded, less than expected in the general population with a SIR of 0.73 (95% CI: 0.61, 0.88).	4	[361]
	595 SLE patients (M+F)	5 cases of breast cancer were observed, less than the expected 10.5, with a SIR of 0.48 (95% CI: 0.35, 0.64).	5	[362]
Type of cancer	144 multiethic (54 yrs)	144 breast cancers in SLE patients with histological information. 66% ductal carcinoma (up to 80% in the general population), 8% lobular adenocarcinoma, 10% mixed histology, 16% special types. Independent risk factors for lobular vs ductal subtype was age at cancer diagnosis (OR 1.07, 95% CI 1.01-1.14) and for the special subtypes it was age (OR 1.06, 95% CI 1.01-1.10) and SLE duration (OR 1.05, 95% CI 1.00-1.11).	5	[363]
Timing of detection	1193 females (81% C)	16 breast cancers were recorded (all C women with a mean age of 55 yrs), 9 at a localized stage (56%), similarly at the general population (62%). Breast cancer in SLE patients do not seem to be	5	[364]

		diagnosed at earlier stages than in the general population.		
Race/ethnicity	6657 females, multiethnic	59 breast cancers were recorded, less than the 82 expected (SIR 0.72, 0.55-0.93). White patients had a frequency similar to the general population (SIR 0.87, 0.65-1.15), while black patients had less frequency (SIR 0.39, 0.16-0.81). No cases were observed in Asian, Hispanic and Native North America.	4	[365]
Risk factors	3,659 general population women and 4,897 controls from UK	Women with breast cancer from the general population were investigated for 10 SLE-associated single nucleotide polymorphisms found in European populations, with no associations (genome wide association study). SLE genetic polymorphisms do not seem to account for decreased breast cancer risk observed in SLE women.	5	[366]
	871 C (41±13)	15 cases of breast cancer occurred compared with 7.2 predicted by the Gail Model (SIR 2.1, 95% CI 1.1, 3.5). Adjusted estimates were similar for women exposed to HRT and OC and those never exposed.	5	[367]
	583 (70% C), 78% below 50 yrs	12 cases of breast cancer occurred compared with 5.6 predicted by the Gail Model (SIR 2.1, 95% CI 1.1, 3.7). The risk of breast cancer is not completely explained by traditional risk factors found in the Gail Model.	4	[368]

1B. Uterine cervix dysplasia and cancer

Outcome	**Sample (age, ethnicity)**	**Result**	**Design**	**Ref.**
Incidence	445 cases and 3379 controls	Meta-analysis of 7 case-control studies. Positive association between SLE and pre-malignant cervical lesions, OR 4.17 (95%CI 3.03, 5.74). Included studies: Tam LS Arthritis Rheum 2004; Dhar JP Gynecol Oncol 2001; Blumenfeld Z Lupus 1994; Nyberg G Arthritis Rheum 1981; Febronio MV Lupus 2007; Klumb EM Lupus 2010 (HPV DNA genotyping).	3	[369]

	Systematic literature review	15/18 studies showed a higher frequency of abnormal pre-malignant lesions in SLE as compared to controls. 14/15 studies did not found an increased frequency of cervical cancer in SLE.	3	[370]
	416 cases and 11,408 controls	Meta-analysis of 7 case-control studies. Positive association between SLE and HSIL, OR 8.66 (95%CI 3.75, 20.00). Included studies: CostaPinto L Rheumatol Int 2012; Abdulgaffar B Diagn Cytopathol 2012; Barros BRC Rev Bras Rheumatol 2007; Dhar JP Gynecol Oncol 2001; Juarez RV Arthritis Rheum 2011; Rojo-Contreras W Lupus 2012; Tam LS Arthritis Rheum 2004.	3	[371]
	595 SLE patients (M+F)	2 cases of cervical cancer were observed, more than the expected 0.5, with a SIR of 4.00 (95% CI: 3.5, 4.5).	5	[362]
	508 females (C), 33 yrs	Danish cohort with a median follow-up period of 13.2 yrs. 24 cases of cervical dysplasia/carcinoma in situ were observed, more than the expected 13.4, with a SIR of 1.8 (95% CI: 1.2, 2.7). 1 case of cervical cancer was observed, similarly to the 1.6 expected, with a SIR of 0.6 (95% CI: 0.1, 4.5).	4	[372]
	34 SLE females (38±8)	No significant difference in the frequency of HPV infection (HPV DNA genotyping) between SLE and RA controls (n=43) and healthy controls (n= 146).	5	[373]
Risk factors	61 CYC-treated (36±12); 49 non-treated (41±13); multiethnic	Cervical dysplasia was more frequent in SLE women who received intravenous CYC than in SLE women who never received it (16.4% vs 4.1%, $p<0.05$).	5	[374]
	1015 multiethnic (42 yrs)	Questionnaire for self-reported abnormal Pap tests and on factors traditionally associated with cervical dysplasia. In adjusted analysis, history of sexually-transmitted disease (OR 2.5, 1.6-4.1), oral contraceptives (OR 2.9, 1.9-4.4), and use of immunosuppressive drugs (OR 1.6, 1.0-2.7) were positively associated with reports of cervical dysplasia.	5	[375]
	61	61 SLE women followed up with cervical smears for 7 years (baseline, 3 yrs, 7 yrs). The 3-year-incidence of CIN was 0% in patients treated with steroids only and azathioprine only, while it was	4	[376]

		25% in ivCYC treated patients and 15% in CYC + azathioprine +prednisone treated patients. A dose relationship was observed between cumulative IVCYC exposure and CIN; each increase of 1 g of IVCYC exposure corresponded to a 13% increased risk of CIN (p = 0.04).		
	171 SLE (40±11) and 222 controls (38±10)	The presence of pre-malignant cervical lesions was more frequent in SLE patients on long-term use (more than 12 months) of immunosuppressive drugs (68.7% vs 31.1%, p=0.03).	5	[377]

1C. Other reproductive cancers (ovary, endometrium, vulva)

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Incidence	42,171 females (multiethnic)	Meta-analysis of 5 large cohort studies. 42,171 females observed for 282,533 patient years. 66 endometrial cancers and 44 ovarian cancers were recorded, less than expected in the general population with SIRs of 0.71 (95% CI: 0.55, 0.91) and 0.66 (95% CI: 0.49, 0.90) respectively. Included studies: Bernatsky S Arthritis Rheum 2005 (a), Bertnatsky S Arthritis Rheum 2005 (b), Kang KY Clin Rheumatol 2010, Mellemkjaer L Arthritis Rheum 1997, Parikh-Patel A Cancer Causes Control 2008.	3	[360]
	14,768 females (multiethnic)	Multi-centre cohort study of 14,768 females with a mean follow-up time of 7.4 years. 12 endometrial cancers and 13 ovarian cancers were recorded, less than expected in the general population with SIRs of 0.44 (95% CI: 0.23, 0.77) and 0.64 (95% CI: 0.34, 1.10) respectively. 7 cancers of the vulva occurred, more than expected in the general population with SIRs of 3.78 (95% CI: 1.52, 7.78).	4	[361]
	508 females (C), 33 yrs	Danish cohort with a median follow-up period of 13.2 yrs. 2 cases of vagina/vulva cancer were observed, more than the expected 0.2, with a SIR of 9.1 (95% CI: 2.3, 36.5).	4	[372]

1D. Adherence to cancer screening

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Participation to screening	48 females, 50-69 yrs	Participation of SLE patients to cancer screening in comparison with the general population. Mammography: 50% vs 74%. Cervical Pap smear: 44% vs 52%. Logistic regression: non-white, lower education, high SLE damage score were associated with less probability of undergoing cervical Pap testing.	5	[378]
	685 SLE females, multiethnic	In comparison to the general population (n=18,013) and to patients with non-rheumatic chronic conditions (n=4,515), SLE patients with younger age and lower educational attainment were less likely of receiving preventive services. Nearly one third of SLE patients did not receive recommended cancer screening tests.	5	[379]

2. WOMEN WITH APS or SLE/APS

No specific studies exist on the relationship between APS and occurrence of malignancy. Few data can be derived from long-term observational cohorts.

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Incidence of cancer	360 consecutive Italian patients (39 yrs)	Five-year follow-up study of patients with aPL (118 males and 242 females). Five patients (age range 42 to 70 yrs) developed malignancy after a median follow-up time of 32 months (range 12 to 88). One 42-years-old woman had breast carcinoma. Four patients presented NHL.	4	[201]
	135 consecutive patients (33.3 years)	89 patients with Primary APS and 46 with Secondary APS with a mean duration of follow-up of 7.55 yrs (±4.89). No malignancies were reported in this study.	5	[380]
	35 C patients	33 females and 2 males with Primary APS and a median follow-up time of 20.5 years (range 15-30).	5	[381]

	(32 yrs)	Cancer occurred in 3 patients (8%). Two breast cancers and one colon carcinoma.		
Cancer as a cause of death	1000 European patients (42±14 yrs)	Ten-year follow-up study of patients with APS (820 females and 180 males; 53.1% Primary APS, 36.2% SLE+APS, 5.7% APS+ other autoimmune diseases). 93 deaths were recorded, 13 (13.9%) due to malignancy (single malignancies not reported).	4	[200]

Q12. What is the evidence for the efficacy and safety of HPV immunization in women with SLE or APS?

Points to consider: should the indications differ from the general population, contra-indications?

1. WOMEN WITH SLE

1A. Efficacy and Safety of HPV immunization

Outcome	Sample (age, ethnicity)	Result	Design	Ref.
Efficacy	27 (12-26 yrs; mean 20.5 yrs; 51.8% AA, 40.7% C, 7.4% H)	Seropositivity rates after 3 doses of the vaccine (at month 7) were 94.4%, 100%, 100%, and 94.4% for HPV 6, 11, 16, and 18. One patient who received rituximab between the 2nd and 3rd doses did not show any antibody response against HPV.	4	[382]
	50 (18-35 yrs; mean 25.8; all Ch)	Seropositivity rates after 3 doses of the vaccine (at month 12) were 82%, 89%, 95%, and 76% for HPV 6, 11, 16, and 18. Seroconversion rate was not different from healthy controls, except for HPV 6 (82% vs 98%). The use of prednisolone and MMF was associated with significantly lower anti-HPV titres. No differences for HCQ, azathioprine, ciclosporin, and Tacrolimus.	4	[383]
Safety	27 (12-26 yrs; mean 20.5 yrs; 51.8% AA, 40.7% C, 7.4% H)	9/27 (33.3%) patients had a mild-moderate flare during the study period, with symptom similar to those they experienced in flare before vaccination. 5 arthralgias, 4 rash, 2 pleuritis, 1 peripheral neuropathy, 2 class IV nephritis progressed to renal failure (kidney biopsy showed marked glomerular sclerosis, so no attribution was done to the vaccination). No induction of new autoantibodies.	4	[382]
	50 (18-35 yrs; mean 25.8; all Ch)	SLE disease flare rate not different between cases and 50 SLE controls (0.22/patient/year vs 0.20/patient/year, p=0.81). No significant changes in the titres of anti-DNA, anti-C1q, C3, C4, SLEDAI and PGA scores from baseline to 2, 6 and 12 months. Injection site reaction was the commonest adverse event (5%) and the incidence of adverse events was comparable between patients with SLE and controls.	4	[383]

	45 and 58 yrs; Philippines	A 45-year-old housewife with a 11-years Rheumatoid Arthritis diagnosis developed a multi-organ SLE flare with multiple autoantibodies 4 months after having received 2 doses of HPV vaccine. A 58-year-old housewife with a longstanding SLE remission died for acute cytopenia and renal failure 3 months after having received 2 doses of HPV vaccine.	6	[384]
	19 yrs, C	A 19-year-old female with a stable remission SLE (diagnosis 4 years before) developed skin rash, lymphoadenopathy and arthralgias after a single dose of HPV vaccine. Despite being discouraged, she decided to receive the second dose and her symptoms rapidly worsened.	6	[385]

1B. Indications and contra-indications to HPV immunization

None of the studies had sufficient power to identify contra-indications to HPV immunization in SLE women. Study #1 excluded patients with a flare in the month prior to study entry and patients who had received rituximab and CYC six months before. Study #2 included patients with stable medications in the previous 3 months.

2. WOMEN WITH APS or SLE/APS

None of the studies declared the inclusion of APS/SLE+APS patients.

Study Design: 1: meta-analysis of RCTs; 2: RCT (including long-term follow-up or post-hoc analysis or RCT); 3: meta-analysis of epidemiological studies; 4: prospective (longitudinal) cohort study (or non-randomized controlled trial); 5: retrospective cohort study, cross-sectional or case-control study; 6: case series

Abbreviations: AA: African-American; aβ2GPI: anti-beta2glycoprotein I antibody; aCL: anti-cardiolipin; AFC: antral follicle count; AMH: anti-Müllerian Hormone; anti-CoL: anti-corpus luteum antibody; anti-Thyr: anti-thyroid antibodies; aPL: anti-phospholipid antibodies; AVB: atrio-ventricular block;

BILAG2004-P: British Isles Lupus Assessment Group 2004 – Pregnancy; BMI: body mass index; c-SLE: childhood-onset Systemic Lupus Erythematosus; C: Caucasian; Ch: Chinese; CHB: congenital heart block; 95% CI: 95% confidence interval; CIN: Cervical Intraepithelial Neoplasia; CMA: chlormadinone acetate; CPA: cyproterone acetate; CYC: Cyclophosphamide; DVT: deep venous thrombosis; E2: estradiol; Fin: Finnish; FSH: Follicle-Stimulating Hormone; GnRH: gonadotropin-releasing hormone; H: Hispanic; H/A: mini-dose heparin + aspirin; HCQ: hydroxychloroquine; Hpf: high-power field; HRT: Hormonal Replacement Therapy; HSIL: high-grade squamous intraepithelial lesions; ICSI: intracytoplasmic sperm injection; IUD: intra-uterine device; IUGR: intra-uterine growth restriction; IUI: Intrauterine Insemination; ivCYC: intravenous cyclophosphamide; IVF: in vitro fertilization; IVIG: intravenous immunoglobulin; LA: lupus anticoagulant; LAI-P: Lupus Activity Index in Pregnancy; LDA: low dose aspirin; LH: Luteinizing Hormone; LMWH: low molecular weight heparin; Mex: Mexican; MMF: mycophenolate mofetil; mUtA-PI: mean uterine artery pulsatility index; NHL: Non-Hodgkin's lymphoma; NL: Neonatal Lupus; OHSS: Ovarian Hyperstimulation Syndrome; OI&TI: Ovulation Induction and Timed Intercourse; OIT: Ovulation Induction Therapy; OR: odds ratio; OV: ovarian volume; Pl: Placebo; PAPS: Primary Antiphospholipid Syndrome; PE: pre-eclampsia; PGA: physician global assessment; PI: pulsatility index; POF: premature ovarian failure (below 40 years of age); PP: Pregnane Progestins; RA: Rheumatoid Arthritis; RBC: red blood cell; RI: Resistance Index; RPL: Recurrent Pregnancy Loss; RR: relative risk; SA: sustained amenorrhea (>12 months); SCr: serum creatinine; SDI: SLICC/ACR damage index; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SGA: small for gestational age; SIR: Standardized Incidence Ratio; SLAM-R: Systemic Lupus Activity Measure – Revised; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLEPDAI: SLE Pregnancy Disease Activity Index; TA: transient amenorrhea (3-12 months); TSH: Thyroid Stimulation Hormone; TV: transvaginal; UFH: unfractionated heparin; UK: United Kingdom; UPCR: urine protein-to-creatinine ratio; US: ultrasound;

References

1. Aggarwal N, Raveendran A, Suri V, et al. Pregnancy outcome in systemic lupus erythematosus: Asia's largest single centre study. Archives of gynecology and obstetrics 2011;**284**(2):281-5.
2. Carmona F, Font J, Cervera R, et al. Obstetrical outcome of pregnancy in patients with systemic Lupus erythematosus. A study of 60 cases. European journal of obstetrics, gynecology, and reproductive biology 1999;**83**(2):137-42.
3. Tandon A, Ibanez D, Gladman DD, et al. The effect of pregnancy on lupus nephritis. Arthritis and rheumatism 2004;**50**(12):3941-6.
4. Luo Y, Zhang L, Fei Y, et al. Pregnancy outcome of 126 anti-SSA/Ro-positive patients during the past 24 years--a retrospective cohort study. Clinical rheumatology 2015;**34**(10):1721-8.
5. Tedeschi SK, Massarotti E, Guan H, et al. Specific systemic lupus erythematosus disease manifestations in the six months prior to conception are associated with similar disease manifestations during pregnancy. Lupus 2015;**24**(12):1283-92.
6. Borella E, Lojacono A, Gatto M, et al. Predictors of maternal and fetal complications in SLE patients: a prospective study. Immunologic research 2014;**60**(2-3):170-6.
7. Cortes-Hernandez J, Ordi-Ros J, Paredes F, et al. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: a prospective study of 103 pregnancies. Rheumatology 2002;**41**(6):643-50.
8. Ruiz-Irastorza G, Lima F, Alves J, et al. Increased rate of lupus flare during pregnancy and the puerperium: a prospective study of 78 pregnancies. British journal of rheumatology 1996;**35**(2):133-8.
9. Yang H, Liu H, Xu D, et al. Pregnancy-related systemic lupus erythematosus: clinical features, outcome and risk factors of disease flares--a case control study. PloS one 2014;**9**(8):e104375.
10. Chakravarty EF, Colon I, Langen ES, et al. Factors that predict prematurity and preeclampsia in pregnancies that are complicated by systemic lupus erythematosus. American journal of obstetrics and gynecology 2005;**192**(6):1897-904.
11. Clowse ME, Magder LS, Witter F, et al. The impact of increased lupus activity on obstetric outcomes. Arthritis and rheumatism 2005;**52**(2):514-21.
12. Ko HS, Ahn HY, Jang DG, et al. Pregnancy outcomes and appropriate timing of pregnancy in 183 pregnancies in Korean patients with SLE. International journal of medical sciences 2011;**8**(7):577-83.
13. Koh JH, Ko HS, Kwok SK, et al. Hydroxychloroquine and pregnancy on lupus flares in Korean patients with systemic lupus erythematosus. Lupus 2015;**24**(2):210-7.
14. Kwok LW, Tam LS, Zhu T, et al. Predictors of maternal and fetal outcomes in pregnancies of patients with systemic lupus erythematosus. Lupus 2011;**20**(8):829-36.
15. Le Thi Huong D, Wechsler B, Piette JC, et al. Pregnancy and its outcome in systemic lupus erythematosus. QJM : monthly journal of the Association of Physicians 1994;**87**(12):721-9.
16. Phadungkiatwattana P, Sirivatanapa P, Tongsong T. Outcomes of pregnancies complicated by systemic lupus erythematosus (SLE). Journal of the Medical Association of Thailand = Chotmaihet thangphaet 2007;**90**(10):1981-5.
17. Foocharoen C, Nanagara R, Salang L, et al. Pregnancy and disease outcome in patients with systemic lupus erythematosus (SLE): a study at Srinagarind Hospital. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 2009;**92**(2):167-74.

18. Molad Y, Borkowski T, Monselise A, et al. Maternal and fetal outcome of lupus pregnancy: a prospective study of 29 pregnancies. Lupus 2005;**14**(2):145-51.
19. Saavedra M, Sanchez A, Morales S, et al. Primigravida is associated with flare in women with systemic lupus erythematosus. Lupus 2014.
20. Chen S, Sun X, Wu B, et al. Pregnancy in Women with Systemic Lupus Erythematosus: A Retrospective Study of 83 Pregnancies at a Single Centre. Int J Environ Res Public Health 2015;**12**(8):9876-88.
21. Koh JH, Ko HS, Lee J, et al. Pregnancy and patients with preexisting lupus nephritis: 15 years of experience at a single center in Korea. Lupus 2015;**24**(7):764-72.
22. Andrade RM, McGwin G, Jr., Alarcon GS, et al. Predictors of post-partum damage accrual in systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (XXXVIII). Rheumatology 2006;**45**(11):1380-4.
23. Fatemi A, Fard RM, Sayedbonakdar Z, et al. The role of lupus nephritis in development of adverse maternal and fetal outcomes during pregnancy. International journal of preventive medicine 2013;**4**(9):1004-10.
24. Saavedra MA, Cruz-Reyes C, Vera-Lastra O, et al. Impact of previous lupus nephritis on maternal and fetal outcomes during pregnancy. Clinical rheumatology 2012;**31**(5):813-9.
25. Ritchie J, Smyth A, Tower C, et al. Maternal deaths in women with lupus nephritis: a review of published evidence. Lupus 2012;**21**(5):534-41.
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. International journal of rheumatic diseases 2014.
27. Imbasciati E, Tincani A, Gregorini G, et al. Pregnancy in women with pre-existing lupus nephritis: predictors of fetal and maternal outcome. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2009;**24**(2):519-25.
28. Gladman DD, Tandon A, Ibanez D, et al. The effect of lupus nephritis on pregnancy outcome and fetal and maternal complications. The Journal of rheumatology 2010;**37**(4):754-8.
29. Jungers P, Dougados M, Pelissier C, et al. Lupus nephropathy and pregnancy. Report of 104 cases in 36 patients. Archives of internal medicine 1982;**142**(4):771-6.
30. Liu J, Zhao Y, Song Y, et al. Pregnancy in women with systemic lupus erythematosus: a retrospective study of 111 pregnancies in Chinese women. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2012;**25**(3):261-6.
31. Moroni G, Quaglini S, Banfi G, et al. Pregnancy in lupus nephritis. American journal of kidney diseases : the official journal of the National Kidney Foundation 2002;**40**(4):713-20.
32. 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. Clinical journal of the American Society of Nephrology : CJASN 2010;**5**(11):2060-8.
33. Barnado A, Wheless L, Meyer AK, et al. Pregnancy outcomes among African-American patients with systemic lupus erythematosus compared with controls. Lupus science & medicine 2014;**1**(1):e000020.
34. Lv J, Wang W, Li Y. Clinical outcomes and predictors of fetal and maternal consequences of pregnancy in lupus nephritis patients. Int Urol Nephrol 2015;**47**(8):1379-85.

35. Carvalheiras G, Vita P, Marta S, et al. Pregnancy and systemic lupus erythematosus: review of clinical features and outcome of 51 pregnancies at a single institution. Clinical reviews in allergy & immunology 2010;**38**(2-3):302-6.
36. Bramham K, Hunt BJ, Bewley S, et al. Pregnancy outcomes in systemic lupus erythematosus with and without previous nephritis. The Journal of rheumatology 2011;**38**(9):1906-13.
37. Derksen RH, Bruinse HW, de Groot PG, et al. Pregnancy in systemic lupus erythematosus: a prospective study. Lupus 1994;**3**(3):149-55.
38. Dreyfus M, Hedelin G, Kutnahorsky R, et al. Antiphospholipid antibodies and preeclampsia: a case-control study. Obstetrics and gynecology 2001;**97**(1):29-34.
39. Hendawy SF, Abdel-Mohsen D, Ebrahim SE, et al. Pregnancy related complications in patients with systemic lupus erythematosus, an egyptian experience. Clinical medicine insights Reproductive health 2011;**5**:17-24.
40. Mok MY, Chan EY, Fong DY, et al. Antiphospholipid antibody profiles and their clinical associations in Chinese patients with systemic lupus erythematosus. The Journal of rheumatology 2005;**32**(4):622-8.
41. Le Huong D, Wechsler B, Vauthier-Brouzes D, et al. Outcome of planned pregnancies in systemic lupus erythematosus: a prospective study on 62 pregnancies. British journal of rheumatology 1997;**36**(7):772-7.
42. Wei Q, Ouyang Y, Zeng W, et al. Pregnancy complicating systemic lupus erythematosus: a series of 86 cases. Archives of gynecology and obstetrics 2011;**284**(5):1067-71.
43. Egerman RS, Ramsey RD, Kao LW, et al. Hypertensive disease in pregnancies complicated by systemic lupus erythematosus. American journal of obstetrics and gynecology 2005;**193**(5):1676-9.
44. Gunnarsdottir J, Stephansson O, Cnattingius S, et al. Risk of placental dysfunction disorders after prior miscarriages: a population-based study. American journal of obstetrics and gynecology 2014;**211**(1):34 e1-8.
45. Xu X, Liang MY, Wang JL, et al. Clinical features and outcome of pregnancy with SLE-associated thrombocytopenia. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2016;**29**(5):789-94.
46. Madazli R, Yuksel MA, Oncul M, et al. Obstetric outcomes and prognostic factors of lupus pregnancies. Archives of gynecology and obstetrics 2014;**289**(1):49-53.
47. Jakobsen IM, Helmig RB, Stengaard-Pedersen K. Maternal and foetal outcomes in pregnant systemic lupus erythematosus patients: an incident cohort from a stable referral population followed during 1990-2010. Scandinavian journal of rheumatology 2015;**44**(5):377-84.
48. Wagner SJ, Craici I, Reed D, et al. Maternal and foetal outcomes in pregnant patients with active lupus nephritis. Lupus 2009;**18**(4):342-7.
49. Al Arfaj AS, Khalil N. Pregnancy outcome in 396 pregnancies in patients with SLE in Saudi Arabia. Lupus 2010;**19**(14):1665-73.
50. Clowse ME, Magder L, Witter F, et al. Hydroxychloroquine in lupus pregnancy. Arthritis and rheumatism 2006;**54**(11):3640-7.
51. Lockshin MD, Reinitz E, Druzin ML, et al. Lupus pregnancy. Case-control prospective study demonstrating absence of lupus exacerbation during or after pregnancy. The American journal of medicine 1984;**77**(5):893-8.
52. Petri M, Howard D, Repke J. Frequency of lupus flare in pregnancy. The Hopkins Lupus Pregnancy Center experience. Arthritis and rheumatism 1991;**34**(12):1538-45.

53. Buchanan NM, Toubi E, Khamashta MA, et al. Hydroxychloroquine and lupus pregnancy: review of a series of 36 cases. Annals of the rheumatic diseases 1996;**55**(7):486-8.
54. Leroux M, Desveaux C, Parcevaux M, et al. Impact of hydroxychloroquine on preterm delivery and intrauterine growth restriction in pregnant women with systemic lupus erythematosus: a descriptive cohort study. Lupus 2015;**24**(13):1384-91.
55. Palmsten K, Hernandez-Diaz S, Kuriya B, et al. Use of disease-modifying antirheumatic drugs during pregnancy and risk of preeclampsia. Arthritis care & research 2012;**64**(11):1730-8.
56. Andrade R, Sanchez ML, Alarcon GS, et al. Adverse pregnancy outcomes in women with systemic lupus erythematosus from a multiethnic US cohort: LUMINA (LVI) [corrected]. Clinical and experimental rheumatology 2008;**26**(2):268-74.
57. Lockshin MD, Kim M, Laskin CA, et al. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. Arthritis and rheumatism 2012;**64**(7):2311-8.
58. Buyon JP, Kim MY, Guerra MM, et al. Predictors of Pregnancy Outcomes in Patients With Lupus: A Cohort Study. Annals of internal medicine 2015;**163**(3):153-63.
59. Gupta R, Deepanjali S, Kumar A, et al. A comparative study of pregnancy outcomes and menstrual irregularities in northern Indian patients with systemic lupus erythematosus and rheumatoid arthritis. Rheumatology international 2010;**30**(12):1581-5.
60. Feld J, Kibari A, Rozenbaum M, et al. The fetal outcomes of pregnancies of systemic lupus erythematosus patients in northern Israel. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2015;**28**(5):564-7.
61. Huong DL, Wechsler B, Vauthier-Brouzes D, et al. Pregnancy in past or present lupus nephritis: a study of 32 pregnancies from a single centre. Annals of the rheumatic diseases 2001;**60**(6):599-604.
62. Julkunen H, Jouhikainen T, Kaaja R, et al. Fetal outcome in lupus pregnancy: a retrospective case-control study of 242 pregnancies in 112 patients. Lupus 1993;**2**(2):125-31.
63. Cavallasca JA, Laborde HA, Ruda-Vega H, et al. Maternal and fetal outcomes of 72 pregnancies in Argentine patients with systemic lupus erythematosus (SLE). Clinical rheumatology 2008;**27**(1):41-6.
64. Clark CA, Spitzer KA, Nadler JN, et al. Preterm deliveries in women with systemic lupus erythematosus. The Journal of rheumatology 2003;**30**(10):2127-32.
65. Soubassi L, Haidopoulos D, Sindos M, et al. Pregnancy outcome in women with pre-existing lupus nephritis. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 2004;**24**(6):630-4.
66. Haddad A, Gladman DD, Ibanez D, et al. Vascular- and pregnancy-related outcomes in patients with systemic lupus erythematosus with positive antiphospholipid profile and thrombocytopenia. Lupus 2015;**24**(8):822-6.
67. Martinez-Rueda JO, Arce-Salinas CA, Kraus A, et al. Factors associated with fetal losses in severe systemic lupus erythematosus. Lupus 1996;**5**(2):113-9.
68. Silva CA, Hilario MO, Febronio MV, et al. Pregnancy outcome in juvenile systemic lupus erythematosus: a Brazilian multicenter cohort study. The Journal of rheumatology 2008;**35**(7):1414-8.

69. Sittiwangkul S, Louthrenoo W, Vithayasai P, et al. Pregnancy outcome in Thai patients with systemic lupus erythematosus. Asian Pacific journal of allergy and immunology / launched by the Allergy and Immunology Society of Thailand 1999;**17**(2):77-83.
70. Petri M, Howard D, Repke J, et al. The Hopkins Lupus Pregnancy Center: 1987-1991 update. American journal of reproductive immunology 1992;**28**(3-4):188-91.
71. Mok MY, Leung PY, Lao TH, et al. Clinical predictors of fetal and maternal outcome in Chinese patients with systemic lupus erythematosus. Annals of the rheumatic diseases 2004;**63**(12):1705-6.
72. Hamed HO, Ahmed SR, Alzolibani A, et al. Does cutaneous lupus erythematosus have more favorable pregnancy outcomes than systemic disease? A two-center study. Acta obstetricia et gynecologica Scandinavica 2013;**92**(8):934-42.
73. Rahman FZ, Rahman J, Al-Suleiman SA, et al. Pregnancy outcome in lupus nephropathy. Archives of gynecology and obstetrics 2005;**271**(3):222-6.
74. Rahman P, Gladman DD, Urowitz MB. Clinical predictors of fetal outcome in systemic lupus erythematosus. The Journal of rheumatology 1998;**25**(8):1526-30.
75. Saavedra MA, Sanchez A, Morales S, et al. Azathioprine during pregnancy in systemic lupus erythematosus patients is not associated with poor fetal outcome. Clinical rheumatology 2015;**34**(7):1211-6.
76. Shibata S, Sasaki T, Hirabayashi Y, et al. Risk factors in the pregnancy of patients with systemic lupus erythematosus: association of hypocomplementaemia with poor prognosis. Annals of the rheumatic diseases 1992;**51**(5):619-23.
77. Ideguchi H, Ohno S, Uehara T, et al. Pregnancy outcomes in Japanese patients with SLE: retrospective review of 55 pregnancies at a university hospital. Clinical reviews in allergy & immunology 2013;**44**(1):57-64.
78. Ramsey-Goldman R, Kutzer JE, Kuller LH, et al. Previous pregnancy outcome is an important determinant of subsequent pregnancy outcome in women with systemic lupus erythematosus. American journal of reproductive immunology 1992;**28**(3-4):195-8.
79. Gillis JZ, Panopalis P, Schmajuk G, et al. Systematic review of the literature informing the systemic lupus erythematosus indicators project: reproductive health care quality indicators. Arthritis care & research 2011;**63**(1):17-30.
80. Mecacci F, Bianchi B, Pieralli A, et al. Pregnancy outcome in systemic lupus erythematosus complicated by anti-phospholipid antibodies. Rheumatology 2009;**48**(3):246-9.
81. Mosca M, Strigini F, Doria A, et al. Anti-C1q antibodies in pregnant patients with systemic lupus erythematosus. Clinical and experimental rheumatology 2007;**25**(3):449-52.
82. Ramsey-Goldman R, Kutzer JE, Kuller LH, et al. Pregnancy outcome and anti-cardiolipin antibody in women with systemic lupus erythematosus. American journal of epidemiology 1993;**138**(12):1057-69.
83. Kim MY, Buyon JP, Guerra MM, et al. Angiogenic factor imbalance early in pregnancy predicts adverse outcomes in patients with lupus and antiphospholipid antibodies: results of the PROMISSE study. American journal of obstetrics and gynecology 2015.
84. Clowse ME, Magder LS, Witter F, et al. Early risk factors for pregnancy loss in lupus. Obstetrics and gynecology 2006;**107**(2 Pt 1):293-9.
85. Aguirre V, Cuchacovich R, Barria L, et al. Prevalence and isotype distribution of antiphospholipid antibodies in Chilean patients with systemic lupus erythematosus (SLE). Lupus 2001;**10**(2):75-80.
86. Balada E, Ordi-Ros J, Paredes F, et al. Antiphosphatidylethanolamine antibodies contribute to the diagnosis of antiphospholipid syndrome in patients with systemic lupus erythematosus. Scandinavian journal of rheumatology 2001;**30**(4):235-41.

87. Ginsberg JS, Brill-Edwards P, Johnston M, et al. Relationship of antiphospholipid antibodies to pregnancy loss in patients with systemic lupus erythematosus: a cross-sectional study. Blood 1992;**80**(4):975-80.
88. Sahin M, Duzgun N, Tunc SE, et al. Clinical manifestations and antiphosphatidylserine antibodies in patients with systemic lupus erythematosus: is there an association? Clinical rheumatology 2007;**26**(2):154-60.
89. Kutteh WH, Lyda EC, Abraham SM, et al. Association of anticardiolipin antibodies and pregnancy loss in women with systemic lupus erythematosus. Fertility and sterility 1993;**60**(3):449-55.
90. Shoenfeld Y, Carp HJ, Molina V, et al. Autoantibodies and prediction of reproductive failure. American journal of reproductive immunology 2006;**56**(5-6):337-44.
91. Danowski A, Kickler TS, Petri M. Anti-beta2-glycoprotein I: prevalence, clinical correlations, and importance of persistent positivity in patients with antiphospholipid syndrome and systemic lupus erythematosus. The Journal of rheumatology 2006;**33**(9):1775-9.
92. Kaburaki J, Kuwana M, Yamamoto M, et al. Clinical significance of phospholipid-dependent anti-beta 2-glycoprotein I (beta 2-GPI) antibodies in systemic lupus erythematosus. Lupus 1995;**4**(6):472-6.
93. Kiss E, Bhattoa HP, Bettembuk P, et al. Pregnancy in women with systemic lupus erythematosus. European journal of obstetrics, gynecology, and reproductive biology 2002;**101**(2):129-34.
94. Bertolaccini ML, Atsumi T, Escudero Contreras A, et al. The value of IgA antiphospholipid testing for diagnosis of antiphospholipid (Hughes) syndrome in systemic lupus erythematosus. The Journal of rheumatology 2001;**28**(12):2637-43.
95. Meijide H, Sciascia S, Sanna G, et al. The clinical relevance of IgA anticardiolipin and IgA anti-beta2 glycoprotein I antiphospholipid antibodies: a systematic review. Autoimmunity reviews 2013;**12**(3):421-5.
96. Bertolaccini ML, Murru V, Sciascia S, et al. The clinical value of testing for antibodies to phosphatidylethanolamine (aPE) in patients with systemic lupus erythematosus (SLE). Thrombosis research 2012;**130**(6):914-8.
97. Bertolaccini ML, Sciascia S, Murru V, et al. Prevalence of antibodies to prothrombin in solid phase (aPT) and to phosphatidylserine-prothrombin complex (aPS/PT) in patients with and without lupus anticoagulant. Thrombosis and haemostasis 2013;**109**(2):207-13.
98. Kaburaki J, Kuwana M, Yamamoto M, et al. Clinical significance of anti-annexin V antibodies in patients with systemic lupus erythematosus. American journal of hematology 1997;**54**(3):209-13.
99. Munoz-Rodriguez FJ, Reverter JC, Font J, et al. Clinical significance of acquired activated protein C resistance in patients with systemic lupus erythematosus. Lupus 2002;**11**(11):730-5.
100. Madazli R, Bulut B, Erenel H, et al. Systemic lupus erythematosus and pregnancy. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 2010;**30**(1):17-20.
101. Georgiou PE, Politi EN, Katsimbri P, et al. Outcome of lupus pregnancy: a controlled study. Rheumatology 2000;**39**(9):1014-9.
102. Mavragani CP, Dafni UG, Tzioufas AG, et al. Pregnancy outcome and anti-Ro/SSA in autoimmune diseases: a retrospective cohort study. British journal of rheumatology 1998;**37**(7):740-5.
103. Brucato A, Doria A, Frassi M, et al. Pregnancy outcome in 100 women with autoimmune diseases and anti-Ro/SSA antibodies: a prospective controlled study. Lupus 2002;**11**(11):716-21.

104. Levesque K, Morel N, Maltret A, et al. Description of 214 cases of autoimmune congenital heart block: Results of the French neonatal lupus syndrome. Autoimmunity reviews 2015;**14**(12):1154-60.
105. Costedoat-Chalumeau N, Amoura Z, Lupoglazoff JM, et al. Outcome of pregnancies in patients with anti-SSA/Ro antibodies: a study of 165 pregnancies, with special focus on electrocardiographic variations in the children and comparison with a control group. Arthritis and rheumatism 2004;**50**(10):3187-94.
106. Brucato A, Frassi M, Franceschini F, et al. Risk of congenital complete heart block in newborns of mothers with anti-Ro/SSA antibodies detected by counterimmunoelectrophoresis: a prospective study of 100 women. Arthritis and rheumatism 2001;**44**(8):1832-5.
107. Cimaz R, Spence DL, Hornberger L, et al. Incidence and spectrum of neonatal lupus erythematosus: a prospective study of infants born to mothers with anti-Ro autoantibodies. The Journal of pediatrics 2003;**142**(6):678-83.
108. Kobayashi N, Yamada H, Kishida T, et al. Hypocomplementemia correlates with intrauterine growth retardation in systemic lupus erythematosus. American journal of reproductive immunology 1999;**42**(3):153-9.
109. Lawrence S, Luy L, Laxer R, et al. The health of mothers of children with cutaneous neonatal lupus erythematosus differs from that of mothers of children with congenital heart block. The American journal of medicine 2000;**108**(9):705-9.
110. Llanos C, Izmirly PM, Katholi M, et al. Recurrence rates of cardiac manifestations associated with neonatal lupus and maternal/fetal risk factors. Arthritis and rheumatism 2009;**60**(10):3091-7.
111. Spence D, Hornberger L, Hamilton R, et al. Increased risk of complete congenital heart block in infants born to women with hypothyroidism and anti-Ro and/or anti-La antibodies. The Journal of rheumatology 2006;**33**(1):167-70.
112. Singalavanija S, Limpongsanurak W, Aoongern S. Neonatal lupus erythematosus: a 20-year retrospective study. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 2014;**97 Suppl 6**:S74-82.
113. Dorner T, Chaoui R, Feist E, et al. Significantly increased maternal and fetal IgG autoantibody levels to 52 kD Ro (SS-A) and La(SS-B) in complete congenital heart block. Journal of autoimmunity 1995;**8**(5):675-84.
114. Jaeggi E, Laskin C, Hamilton R, et al. The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythematosus a prospective study of 186 antibody-exposed fetuses and infants. Journal of the American College of Cardiology 2010;**55**(24):2778-84.
115. Strandberg L, Salomonsson S, Bremme K, et al. Ro52, Ro60 and La IgG autoantibody levels and Ro52 IgG subclass profiles longitudinally throughout pregnancy in congenital heart block risk pregnancies. Lupus 2006;**15**(6):346-53.
116. Izmirly PM, Costedoat-Chalumeau N, Pisoni CN, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. Circulation 2012;**126**(1):76-82.
117. Julkunen H, Kaaja R, Palosuo T, et al. Pregnancy in lupus nephropathy. Acta obstetricia et gynecologica Scandinavica 1993;**72**(4):258-63.
118. Shand AW, Algert CS, March L, et al. Second pregnancy outcomes for women with systemic lupus erythematosus. Annals of the rheumatic diseases 2013;**72**(4):547-51.
119. Huong DL, Wechsler B, Vauthier-Brouzes D, et al. Importance of planning ovulation induction therapy in systemic lupus erythematosus and antiphospholipid syndrome: a single center retrospective study of 21 cases and 114 cycles. Seminars in arthritis and rheumatism 2002;**32**(3):174-88.

120. Chandran V, Aggarwal A, Misra R. Active disease during pregnancy is associated with poor foetal outcome in Indian patients with systemic lupus erythematosus. Rheumatology international 2005;**26**(2):152-6.
121. Johns KR, Morand EF, Littlejohn GO. Pregnancy outcome in systemic lupus erythematosus (SLE): a review of 54 cases. Australian and New Zealand journal of medicine 1998;**28**(1):18-22.
122. Salazar-Paramo M, Jara LJ, Ramos A, et al. Longitudinal study of antinuclear and anticardiolipin antibodies in pregnant women with systemic lupus erythematosus and antiphospholipid syndrome. Rheumatology international 2002;**22**(4):142-7.
123. Teh CL, Wong JS, Ngeh NK, et al. Systemic lupus erythematosus pregnancies: the Sarawak experience and review of lupus pregnancies in Asia. Rheumatology international 2011;**31**(9):1153-7.
124. Costedoat-Chalumeau N, Amoura Z, Duhaut P, et al. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: a study of one hundred thirty-three cases compared with a control group. Arthritis and rheumatism 2003;**48**(11):3207-11.
125. Sperber K, Hom C, Chao CP, et al. Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases. Pediatric rheumatology online journal 2009;**7**:9.
126. Izmirly PM, Kim MY, Llanos C, et al. Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. Annals of the rheumatic diseases 2010;**69**(10):1827-30.
127. Fischer-Betz R, Specker C, Brinks R, et al. Low risk of renal flares and negative outcomes in women with lupus nephritis conceiving after switching from mycophenolate mofetil to azathioprine. Rheumatology 2013;**52**(6):1070-6.
128. al-Momen AK, Moghraby SA, el-Rab MO, et al. Pregnancy outcome in women with antiphospholipid antibodies. Clinical rheumatology 1993;**12**(3):381-6.
129. Shinohara K, Miyagawa S, Fujita T, et al. Neonatal lupus erythematosus: results of maternal corticosteroid therapy. Obstetrics and gynecology 1999;**93**(6):952-7.
130. Alijotas-Reig J, Casellas-Caro M, Ferrer-Oliveras R, et al. Are anti-beta-glycoprotein-I antibodies markers for recurrent pregnancy loss in lupus anticoagulant/anticardiolipin seronegative women? American journal of reproductive immunology 2008;**60**(3):229-37.
131. Bergrem A, Jacobsen EM, Skjeldestad FE, et al. The association of antiphospholipid antibodies with pregnancy-related first time venous thrombosis--a population-based case-control study. Thrombosis research 2010;**125**(5):e222-7.
132. Lefevre G, Lambert M, Bacri JL, et al. Thrombotic events during long-term follow-up of obstetric antiphospholipid syndrome patients. Lupus 2011;**20**(8):861-5.
133. Simchen MJ, Dulitzki M, Rofe G, et al. High positive antibody titers and adverse pregnancy outcome in women with antiphospholipid syndrome. Acta obstetricia et gynecologica Scandinavica 2011;**90**(12):1428-33.
134. Stone S, Hunt BJ, Khamashta MA, et al. Primary antiphospholipid syndrome in pregnancy: an analysis of outcome in a cohort of 33 women treated with a rigorous protocol. Journal of thrombosis and haemostasis : JTH 2005;**3**(2):243-5.
135. Chauleur C, Galanaud JP, Alonso S, et al. Observational study of pregnant women with a previous spontaneous abortion before the 10th gestation week with and without antiphospholipid antibodies. Journal of thrombosis and haemostasis : JTH 2010;**8**(4):699-706.
136. Ganzevoort W, Rep A, De Vries JI, et al. Relationship between thrombophilic disorders and type of severe early-onset hypertensive disorder of pregnancy. Hypertension in pregnancy 2007;**26**(4):433-45.

137. Faden D, Tincani A, Tanzi P, et al. Anti-beta 2 glycoprotein I antibodies in a general obstetric population: preliminary results on the prevalence and correlation with pregnancy outcome. Anti-beta2 glycoprotein I antibodies are associated with some obstetrical complications, mainly preeclampsia-eclampsia. European journal of obstetrics, gynecology, and reproductive biology 1997;**73**(1):37-42.
138. Nodler J, Moolamalla SR, Ledger EM, et al. Elevated antiphospholipid antibody titers and adverse pregnancy outcomes: analysis of a population-based hospital dataset. BMC pregnancy and childbirth 2009;**9**:11.
139. Oron G, Ben-Haroush A, Goldfarb R, et al. Contribution of the addition of anti-beta2-glycoprotein to the classification of antiphospholipid syndrome in predicting adverse pregnancy outcome. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2011;**24**(4):606-9.
140. Rodriguez-Garcia JL, Bertolaccini ML, Cuadrado MJ, et al. Clinical manifestations of antiphospholipid syndrome (APS) with and without antiphospholipid antibodies (the so-called 'seronegative APS'). Annals of the rheumatic diseases 2012;**71**(2):242-4.
141. Abou-Nassar K, Carrier M, Ramsay T, et al. The association between antiphospholipid antibodies and placenta mediated complications: a systematic review and meta-analysis. Thrombosis research 2011;**128**(1):77-85.
142. Clark CA, Davidovits J, Spitzer KA, et al. The lupus anticoagulant: results from 2257 patients attending a high-risk pregnancy clinic. Blood 2013;**122**(3):341-7; quiz 466.
143. Alijotas-Reig J, Ferrer-Oliveras R, Ruffatti A, et al. The European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS): A survey of 247 consecutive cases. Autoimmunity reviews 2015;**14**(5):387-95.
144. Ferrer-Oliveras R, Llurba E, Cabero-Roura L, et al. Prevalence and clinical usefulness of antiphospholipid and anticofactor antibodies in different Spanish preeclampsia subsets. Lupus 2012;**21**(3):257-63.
145. Fischer-Betz R, Specker C, Brinks R, et al. Pregnancy outcome in patients with antiphospholipid syndrome after cerebral ischaemic events: an observational study. Lupus 2012;**21**(11):1183-9.
146. Singh NK, Behera DR, Agrawal A, et al. Hospital based prospective longitudinal clinical and immunologic study of 179 patients of primary anti-phospholipid syndrome. International journal of rheumatic diseases 2013;**16**(5):547-55.
147. Bramham K, Hunt BJ, Germain S, et al. Pregnancy outcome in different clinical phenotypes of antiphospholipid syndrome. Lupus 2010;**19**(1):58-64.
148. Gomez-Puerta JA, Cervera R, Espinosa G, et al. Catastrophic antiphospholipid syndrome during pregnancy and puerperium: maternal and fetal characteristics of 15 cases. Annals of the rheumatic diseases 2007;**66**(6):740-6.
149. Bouvier S, Cochery-Nouvellon E, Lavigne-Lissalde G, et al. Comparative incidence of pregnancy outcomes in treated obstetric antiphospholipid syndrome: the NOH-APS observational study. Blood 2014;**123**(3):404-13.
150. Bertero MT, Bazzan M, Carignola R, et al. Antiphospholipid syndrome in northwest Italy (APS Piedmont Cohort): demographic features, risk factors, clinical and laboratory profile. Lupus 2012;**21**(7):806-9.
151. Canti V, Maggio L, Ramirez GA, et al. Hypertension negatively affects the pregnancy outcome in patients with antiphospholipid syndrome. Lupus 2012;**21**(7):810-2.
152. Huong DL, Wechsler B, Bletry O, et al. A study of 75 pregnancies in patients with antiphospholipid syndrome. The Journal of rheumatology 2001;**28**(9):2025-30.

153. De Carolis S, Botta A, Santucci S, et al. Complementemia and obstetric outcome in pregnancy with antiphospholipid syndrome. Lupus 2012;**21**(7):776-8.
154. Branch DW, Porter TF, Rittenhouse L, et al. Antiphospholipid antibodies in women at risk for preeclampsia. American journal of obstetrics and gynecology 2001;**184**(5):825-32; discussion 32-4.
155. Mekinian A, Loire-Berson P, Nicaise-Roland P, et al. Outcomes and treatment of obstetrical antiphospholipid syndrome in women with low antiphospholipid antibody levels. Journal of reproductive immunology 2012;**94**(2):222-6.
156. Ofer-Shiber S, Molad Y. Frequency of vascular and pregnancy morbidity in patients with low vs. moderate-to-high titers of antiphospholipid antibodies. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis 2014.
157. Ruffatti A, Olivieri S, Tonello M, et al. Influence of different IgG anticardiolipin antibody cut-off values on antiphospholipid syndrome classification. Journal of thrombosis and haemostasis : JTH 2008;**6**(10):1693-6.
158. Ruffatti A, Tonello M, Cavazzana A, et al. Laboratory classification categories and pregnancy outcome in patients with primary antiphospholipid syndrome prescribed antithrombotic therapy. Thrombosis research 2009;**123**(3):482-7.
159. Ruffatti A, Tonello M, Visentin MS, et al. Risk factors for pregnancy failure in patients with anti-phospholipid syndrome treated with conventional therapies: a multicentre, case-control study. Rheumatology 2011;**50**(9):1684-9.
160. Caruso A, De Carolis S, Ferrazzani S, et al. Pregnancy outcome in relation to uterine artery flow velocity waveforms and clinical characteristics in women with antiphospholipid syndrome. Obstetrics and gynecology 1993;**82**(6):970-7.
161. Matsuki Y, Atsumi T, Yamaguchi K, et al. Clinical features and pregnancy outcome in antiphospholipid syndrome patients with history of severe pregnancy complications. Mod Rheumatol 2015;**25**(2):215-8.
162. Erkan D, Barbhaiya M, George D, et al. Moderate versus high-titer persistently anticardiolipin antibody positive patients: are they clinically different and does high-titer anti-beta 2-glycoprotein-I antibody positivity offer additional predictive information? Lupus 2010;**19**(5):613-9.
163. Jeremic K, Stefanovic A, Dotlic J, et al. Neonatal outcome in pregnant patients with antiphospholipid syndrome. Journal of perinatal medicine 2015;**43**(6):761-8.
164. Carmo-Pereira S, Bertolaccini ML, Escudero-Contreras A, et al. Value of IgA anticardiolipin and anti-beta2-glycoprotein I antibody testing in patients with pregnancy morbidity. Annals of the rheumatic diseases 2003;**62**(6):540-3.
165. Sciascia S, Branch DW, Levy RA, et al. The efficacy of hydroxychloroquine in altering pregnancy outcome in women with antiphospholipid antibodies. Evidence and clinical judgment. Thrombosis and haemostasis 2015;**115**(2).
166. Gris JC, Quere I, Monpeyroux F, et al. Case-control study of the frequency of thrombophilic disorders in couples with late foetal loss and no thrombotic antecedent--the Nimes Obstetricians and Haematologists Study5 (NOHA5). Thrombosis and haemostasis 1999;**81**(6):891-9.
167. Silver RM, Parker CB, Reddy UM, et al. Antiphospholipid antibodies in stillbirth. Obstetrics and gynecology 2013;**122**(3):641-57.
168. Helgadottir LB, Skjeldestad FE, Jacobsen AF, et al. The association of antiphospholipid antibodies with intrauterine fetal death: a case-control study. Thrombosis research 2012;**130**(1):32-7.
169. Ogasawara M, Aoki K, Matsuura E, et al. Anti beta 2glycoprotein I antibodies and lupus anticoagulant in patients with recurrent pregnancy loss: prevalence and clinical significance. Lupus 1996;**5**(6):587-92.
170. Balasch J, Font J. Antiphospholipid antibodies, low-dose aspirin and pregnancy losses. Human reproduction 1996;**11**(5):1140-1.

171. Balasch J, Creus M, Fabregues F, et al. Antiphospholipid antibodies and the outcome of pregnancy after the first in-vitro fertilization and embryo transfer cycle. Human reproduction 1998;**13**(5):1180-3.
172. Kitaori T, Sugiura-Ogasawara M, Oku K, et al. Determination of clinically significant tests for antiphospholipid antibodies and cutoff levels for obstetric antiphospholipid syndrome. Lupus 2015;**24**(14):1505-19.
173. Birdsall MA, Lockwood GM, Ledger WL, et al. Antiphospholipid antibodies in women having in-vitro fertilization. Human reproduction 1996;**11**(6):1185-9.
174. Kwak JY, Barini R, Gilman-Sachs A, et al. Down-regulation of maternal antiphospholipid antibodies during early pregnancy and pregnancy outcome. American journal of obstetrics and gynecology 1994;**171**(1):239-46.
175. Chilcott IT, Margara R, Cohen H, et al. Pregnancy outcome is not affected by antiphospholipid antibody status in women referred for in vitro fertilization. Fertility and sterility 2000;**73**(3):526-30.
176. Hornstein MD, Davis OK, Massey JB, et al. Antiphospholipid antibodies and in vitro fertilization success: a meta-analysis. Fertility and sterility 2000;**73**(2):330-3.
177. Lee SR, Park EJ, Kim SH, et al. Influence of antiphospholipid antibodies on pregnancy outcome in women undergoing in vitro fertilization and embryo transfer. American journal of reproductive immunology 2007;**57**(1):34-9.
178. Serrano F, Nogueira I, Borges A, et al. Primary antiphospholipid syndrome: pregnancy outcome in a portuguese population. Acta reumatologica portuguesa 2009;**34**(3):492-7.
179. Liu XL, Xiao J, Zhu F. Anti-beta2 glycoprotein I antibodies and pregnancy outcome in antiphospholipid syndrome. Acta obstetricia et gynecologica Scandinavica 2013;**92**(2):234-7.
180. Canti V, Castiglioni MT, Rosa S, et al. Pregnancy outcomes in patients with systemic autoimmunity. Autoimmunity 2012;**45**(2):169-75.
181. Alijotas-Reig J, Ferrer-Oliveras R, Rodrigo-Anoro MJ, et al. Anti-beta(2)-glycoprotein-I and anti-phosphatidylserine antibodies in women with spontaneous pregnancy loss. Fertility and sterility 2010;**93**(7):2330-6.
182. Branch DW, Silver RM. Criteria for antiphospholipid syndrome: early pregnancy loss, fetal loss, or recurrent pregnancy loss? Lupus 1996;**5**(5):409-13.
183. Cuadrado MJ, Tinahones F, Camps MT, et al. Antiphospholipid, anti-beta 2-glycoprotein-I and anti-oxidized-low-density-lipoprotein antibodies in antiphospholipid syndrome. QJM : monthly journal of the Association of Physicians 1998;**91**(9):619-26.
184. Samarkos M, Davies KA, Gordon C, et al. IgG subclass distribution of antibodies against beta(2)-GP1 and cardiolipin in patients with systemic lupus erythematosus and primary antiphospholipid syndrome, and their clinical associations. Rheumatology 2001;**40**(9):1026-32.
185. Samarkos M, Davies KA, Gordon C, et al. Clinical significance of IgA anticardiolipin and anti-beta2-GP1 antibodies in patients with systemic lupus erythematosus and primary antiphospholipid syndrome. Clinical rheumatology 2006;**25**(2):199-204.
186. Selva-O'Callaghan A, Ordi-Ros J, Monegal-Ferran F, et al. IgA anticardiolipin antibodies--relation with other antiphospholipid antibodies and clinical significance. Thrombosis and haemostasis 1998;**79**(2):282-5.
187. von Landenberg P, Matthias T, Zaech J, et al. Antiprothrombin antibodies are associated with pregnancy loss in patients with the antiphospholipid syndrome. American journal of reproductive immunology 2003;**49**(1):51-6.

188. Falcon CR, Martinuzzo ME, Forastiero RR, et al. Pregnancy loss and autoantibodies against phospholipid-binding proteins. Obstetrics and gynecology 1997;**89**(6):975-80.
189. Lee RM, Emlen W, Scott JR, et al. Anti-beta2-glycoprotein I antibodies in women with recurrent spontaneous abortion, unexplained fetal death, and antiphospholipid syndrome. American journal of obstetrics and gynecology 1999;**181**(3):642-8.
190. Clark CA, Spitzer KA, Crowther MA, et al. Incidence of postpartum thrombosis and preterm delivery in women with antiphospholipid antibodies and recurrent pregnancy loss. The Journal of rheumatology 2007;**34**(5):992-6.
191. Ruffatti A, Calligaro A, Hoxha A, et al. Laboratory and clinical features of pregnant women with antiphospholipid syndrome and neonatal outcome. Arthritis care & research 2010;**62**(3):302-7.
192. Brewster JA, Shaw NJ, Farquharson RG. Neonatal and pediatric outcome of infants born to mothers with antiphospholipid syndrome. Journal of perinatal medicine 1999;**27**(3):183-7.
193. Del Ross T, Ruffatti A, Visentin MS, et al. Treatment of 139 pregnancies in antiphospholipid-positive women not fulfilling criteria for antiphospholipid syndrome: a retrospective study. The Journal of rheumatology 2013;**40**(4):425-9.
194. Gonzalez-Echavarri C, Villar I, Ugarte A, et al. Prevalence and Significance of Persistently Positive Antiphospholipid Antibodies in Women with Preeclampsia. The Journal of rheumatology 2014.
195. Mekinian A, Lachassinne E, Nicaise-Roland P, et al. European registry of babies born to mothers with antiphospholipid syndrome. Annals of the rheumatic diseases 2013;**72**(2):217-22.
196. Bowman ZS, Wunsche V, Porter TF, et al. Prevalence of antiphospholipid antibodies and risk of subsequent adverse obstetric outcomes in women with prior pregnancy loss. Journal of reproductive immunology 2014.
197. Owaidah TM, Qurashi FH, Al Nounou RM, et al. Single center review of clinicopathological characterization in 77 patients with positive lupus anticoagulant antibodies. Hematology 2003;**8**(4):249-57.
198. Giron-Gonzalez JA, Garcia del Rio E, Rodriguez C, et al. Antiphospholipid syndrome and asymptomatic carriers of antiphospholipid antibody: prospective analysis of 404 individuals. The Journal of rheumatology 2004;**31**(8):1560-7.
199. Danowski A, de Azevedo MN, de Souza Papi JA, et al. Determinants of risk for venous and arterial thrombosis in primary antiphospholipid syndrome and in antiphospholipid syndrome with systemic lupus erythematosus. The Journal of rheumatology 2009;**36**(6):1195-9.
200. Cervera R, Serrano R, Pons-Estel GJ, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Annals of the rheumatic diseases 2014.
201. Finazzi G, Brancaccio V, Moia M, et al. Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies: a four-year prospective study from the Italian Registry. The American journal of medicine 1996;**100**(5):530-6.
202. Mekinian A, Costedoat-Chalumeau N, Masseau A, et al. Obstetrical APS: is there a place for hydroxychloroquine to improve the pregnancy outcome? Autoimmunity reviews 2015;**14**(1):23-9.
203. Carmona F, Font J, Azulay M, et al. Risk factors associated with fetal losses in treated antiphospholipid syndrome pregnancies: a multivariate analysis. American journal of reproductive immunology 2001;**46**(4):274-9.
204. Cesarman-Maus G, Rios-Luna NP, Deora AB, et al. Autoantibodies against the fibrinolytic receptor, annexin 2, in antiphospholipid syndrome. Blood 2006;**107**(11):4375-82.

205. Hoxha A, Ruffatti A, Tonello M, et al. Antiphosphatidylserine/prothrombin antibodies in primary antiphospholipid syndrome. Lupus 2012;**21**(7):787-9.
206. Hoxha A, Ruffatti A, Pittoni M, et al. The clinical significance of autoantibodies directed against prothrombin in primary antiphospholipid syndrome. Clinica chimica acta; international journal of clinical chemistry 2012;**413**(9-10):911-3.
207. Obayashi S, Ozaki Y, Sugi T, et al. Antiphosphatidylethanolamine antibodies might not be an independent risk factor for further miscarriage in patients suffering recurrent pregnancy loss. Journal of reproductive immunology 2010;**85**(2):186-92.
208. Ao W, Zheng H, Chen XW, et al. Anti-annexin II antibody is associated with thrombosis and/or pregnancy morbidity in antiphospholipid syndrome and systemic lupus erythematosus with thrombosis. Rheumatology international 2011;**31**(7):865-9.
209. Bu C, Zhang C, Li Z, et al. Autoantibodies to plasminogen and tissue plasminogen activator in women with recurrent pregnancy loss. Clinical and experimental immunology 2007;**149**(1):31-9.
210. Denis AL, Guido M, Adler RD, et al. Antiphospholipid antibodies and pregnancy rates and outcome in in vitro fertilization patients. Fertility and sterility 1997;**67**(6):1084-90.
211. Eldar-Geva T, Wood C, Lolatgis N, et al. Cumulative pregnancy and live birth rates in women with antiphospholipid antibodies undergoing assisted reproduction. Human reproduction 1999;**14**(6):1461-6.
212. Tebo AE, Jaskowski TD, Hill HR, et al. Clinical relevance of multiple antibody specificity testing in anti-phospholipid syndrome and recurrent pregnancy loss. Clinical and experimental immunology 2008;**154**(3):332-8.
213. Figueredo MA, Rodriguez A, Ruiz-Yague M, et al. Autoantibodies against C-reactive protein: clinical associations in systemic lupus erythematosus and primary antiphospholipid syndrome. The Journal of rheumatology 2006;**33**(10):1980-6.
214. Abu-Shakra M, Gladman DD, Urowitz MB, et al. Anticardiolipin antibodies in systemic lupus erythematosus: clinical and laboratory correlations. The American journal of medicine 1995;**99**(6):624-8.
215. Bertolaccini ML, Sanna G, Ralhan S, et al. Antibodies directed to protein S in patients with systemic lupus erythematosus: prevalence and clinical significance. Thrombosis and haemostasis 2003;**90**(4):636-41.
216. Topping J, Quenby S, Farquharson R, et al. Marked variation in antiphospholipid antibodies during pregnancy: relationships to pregnancy outcome. Human reproduction 1999;**14**(1):224-8.
217. Sanchez-Guerrero J, Uribe AG, Jimenez-Santana L, et al. A trial of contraceptive methods in women with systemic lupus erythematosus. The New England journal of medicine 2005;**353**(24):2539-49.
218. Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. The New England journal of medicine 2005;**353**(24):2550-8.
219. Rampone A, Rampone B, Tirabasso S, et al. Contraception with the latest estroprogestagens in women suffering from systemic lupus erythematosus. Minerva ginecologica 2001;**53**(1 Suppl 1):75-7.
220. Julkunen HA. Oral contraceptives in systemic lupus erythematosus: side-effects and influence on the activity of SLE. Scandinavian journal of rheumatology 1991;**20**(6):427-33.
221. Cravioto MD, Jimenez-Santana L, Mayorga J, et al. Side effects unrelated to disease activity and acceptability of highly effective contraceptive methods in women with systemic lupus erythematosus: a randomized, clinical trial. Contraception 2014;**90**(2):147-53.

222. Chabbert-Buffet N, Amoura Z, Scarabin PY, et al. Pregnane progestin contraception in systemic lupus erythematosus: a longitudinal study of 187 patients. Contraception 2011;**83**(3):229-37.
223. Julkunen HA, Kaaja R, Friman C. Contraceptive practice in women with systemic lupus erythematosus. British journal of rheumatology 1993;**32**(3):227-30.
224. Pisoni CN, Cuadrado MJ, Khamashta MA, et al. Treatment of menorrhagia associated with oral anticoagulation: efficacy and safety of the levonorgestrel releasing intrauterine device (Mirena coil). Lupus 2006;**15**(12):877-80.
225. Urbanus RT, Siegerink B, Roest M, et al. Antiphospholipid antibodies and risk of myocardial infarction and ischaemic stroke in young women in the RATIO study: a case-control study. The Lancet Neurology 2009;**8**(11):998-1005.
226. Deng J, Huo D, Wu Q, et al. A meta-analysis of randomized controlled trials comparing tacrolimus with intravenous cyclophosphamide in the induction treatment for lupus nephritis. The Tohoku journal of experimental medicine 2012;**227**(4):281-8.
227. Liu LL, Jiang Y, Wang LN, et al. Efficacy and safety of mycophenolate mofetil versus cyclophosphamide for induction therapy of lupus nephritis: a meta-analysis of randomized controlled trials. Drugs 2012;**72**(11):1521-33.
228. Alarfaj AS, Khalil N. Fertility, ovarian failure, and pregnancy outcome in SLE patients treated with intravenous cyclophosphamide in Saudi Arabia. Clinical rheumatology 2014;**33**(12):1731-6.
229. Baba S, Katsumata Y, Kawaguchi Y, et al. Association between low-dose pulsed intravenous cyclophosphamide therapy and amenorrhea in patients with systemic lupus erythematosus: a case-control study. BMC women's health 2011;**11**:28.
230. Mitwalli AH, Al Wakeel JS, Hurraib S, et al. Comparison of high and low dose of cyclophosphamide in lupus nephritis patients: a long-term randomized controlled trial. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia 2011;**22**(5):935-40.
231. Laskari K, Zintzaras E, Tzioufas AG. Ovarian function is preserved in women with severe systemic lupus erythematosus after a 6-month course of cyclophosphamide followed by mycophenolate mofetil. Clinical and experimental rheumatology 2010;**28**(1):83-6.
232. Appenzeller S, Blatyta PF, Costallat LT. Ovarian failure in SLE patients using pulse cyclophosphamide: comparison of different regimes. Rheumatology international 2008;**28**(6):567-71.
233. Singh G, Saxena N, Aggarwal A, et al. Cytochrome P450 polymorphism as a predictor of ovarian toxicity to pulse cyclophosphamide in systemic lupus erythematosus. The Journal of rheumatology 2007;**34**(4):731-3.
234. Park MC, Park YB, Jung SY, et al. Risk of ovarian failure and pregnancy outcome in patients with lupus nephritis treated with intravenous cyclophosphamide pulse therapy. Lupus 2004;**13**(8):569-74.
235. Ioannidis JP, Katsifis GE, Tzioufas AG, et al. Predictors of sustained amenorrhea from pulsed intravenous cyclophosphamide in premenopausal women with systemic lupus erythematosus. The Journal of rheumatology 2002;**29**(10):2129-35.
236. McDermott EM, Powell RJ. Incidence of ovarian failure in systemic lupus erythematosus after treatment with pulse cyclophosphamide. Annals of the rheumatic diseases 1996;**55**(4):224-9.
237. Wang CL, Wang F, Bosco JJ. Ovarian failure in oral cyclophosphamide treatment for systemic lupus erythematosus. Lupus 1995;**4**(1):11-4.
238. Boumpas DT, Austin HA, 3rd, Vaughan EM, et al. Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. Annals of internal medicine 1993;**119**(5):366-9.

239. Henderson LK, Masson P, Craig JC, et al. Induction and maintenance treatment of proliferative lupus nephritis: a meta-analysis of randomized controlled trials. American journal of kidney diseases : the official journal of the National Kidney Foundation 2013;**61**(1):74-87.
240. Manger K, Wildt L, Kalden JR, et al. Prevention of gonadal toxicity and preservation of gonadal function and fertility in young women with systemic lupus erythematosus treated by cyclophosphamide: the PREGO-Study. Autoimmunity reviews 2006;**5**(4):269-72.
241. Morel N, Bachelot A, Chakhtoura Z, et al. Study of anti-Mullerian hormone and its relation to the subsequent probability of pregnancy in 112 patients with systemic lupus erythematosus, exposed or not to cyclophosphamide. The Journal of clinical endocrinology and metabolism 2013;**98**(9):3785-92.
242. Nonato DR, Barbosa VS, Rodrigues DL, et al. Menstrual disturbances in systemic lupus erythematosus patients using immunossuppressants. Revista brasileira de reumatologia 2010;**50**(5):501-15.
243. Shabanova SS, Ananieva LP, Alekberova ZS, et al. Ovarian function and disease activity in patients with systemic lupus erythematosus. Clinical and experimental rheumatology 2008;**26**(3):436-41.
244. Fatnoon NN, Azarisman SM, Zainal D. Prevalence and risk factors for menstrual disorders among systemic lupus erythematosus patients. Singapore medical journal 2008;**49**(5):413-8.
245. Cabral de Sousa D, das Chagas Medeiros MM, Trindade Viana VS, et al. Anti-corpus luteum antibody and menstrual irregularity in patients with systemic lupus erythematosus and Hashimoto's thyroiditis. Lupus 2005;**14**(8):618-24.
246. Pasoto SG, Mendonca BB, Bonfa E. Menstrual disturbances in patients with systemic lupus erythematosus without alkylating therapy: clinical, hormonal and therapeutic associations. Lupus 2002;**11**(3):175-80.
247. Ghaleb RM, Fahmy KA. Anti-Mullerian hormone: a marker for ovarian function in systemic lupus erythematosus patients treated with cyclophosphamide. Joint, bone, spine : revue du rhumatisme 2013;**80**(4):434-5.
248. Gonzalez LA, McGwin G, Jr., Duran S, et al. Predictors of premature gonadal failure in patients with systemic lupus erythematosus. Results from LUMINA, a multiethnic US cohort (LUMINA LVIII). Annals of the rheumatic diseases 2008;**67**(8):1170-3.
249. Medeiros MM, Silveira VA, Menezes AP, et al. Risk factors for ovarian failure in patients with systemic lupus erythematosus. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica [et al] 2001;**34**(12):1561-8.
250. Malheiro OB, Rezende CP, Rocha AL, et al. Regular menstrual cycles do not rule out ovarian damage in adult women with systemic lupus erythematosus. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 2014;**30**(10):701-4.
251. Mok CC, Chan PT, To CH. Anti-mullerian hormone and ovarian reserve in systemic lupus erythematosus. Arthritis and rheumatism 2013;**65**(1):206-10.
252. Ma W, Zhan Z, Liang X, et al. Subclinical impairment of ovarian reserve in systemic lupus erythematosus patients with normal menstruation not using alkylating therapy. Journal of women's health (2002) 2013;**22**(12):1023-7.
253. Marder W, McCune WJ, Wang L, et al. Adjunctive GnRH-a treatment attenuates depletion of ovarian reserve associated with cyclophosphamide therapy in premenopausal SLE patients. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 2012;**28**(8):624-7.

254. Lawrenz B, Henes J, Henes M, et al. Impact of systemic lupus erythematosus on ovarian reserve in premenopausal women: evaluation by using anti-Muellerian hormone. Lupus 2011;**20**(11):1193-7.
255. Ulug P, Oner G, Kasap B, et al. Evaluation of ovarian reserve tests in women with systemic lupus erythematosus. American journal of reproductive immunology (New York, NY : 1989) 2014;**72**(1):85-8.
256. Arnalich F, Benito-Urbina S, Gonzalez-Gancedo P, et al. Inadequate production of progesterone in women with systemic lupus erythematosus. British journal of rheumatology 1992;**31**(4):247-51.
257. Ulcova-Gallova Z, Mockova A, Cedikova M. Screening tests of reproductive immunology in systemic lupus erythematosus. Autoimmune diseases 2012;**2012**:812138.
258. Moncayo R, Moncayo HE. A new endocrinological and immunological syndrome in SLE: elevation of human chorionic gonadotropin and of antibodies directed against ovary and endometrium antigens. Lupus 1995;**4**(1):39-45.
259. de Araujo D, Yamakami L, Aikawa N, et al. Ovarian reserve in adult patients with childhood-onset lupus: a possible deleterious effect of methotrexate? Scandinavian journal of rheumatology 2014:1-9.
260. Brunner HI, Bishnoi A, Barron AC, et al. Disease outcomes and ovarian function of childhood-onset systemic lupus erythematosus. Lupus 2006;**15**(4):198-206.
261. Silva CA, Leal MM, Leone C, et al. Gonadal function in adolescents and young women with juvenile systemic lupus erythematosus. Lupus 2002;**11**(7):419-25.
262. Silva CA, Deen ME, Febronio MV, et al. Hormone profile in juvenile systemic lupus erythematosus with previous or current amenorrhea. Rheumatology international 2011;**31**(8):1037-43.
263. Medeiros PB, Febronio MV, Bonfa E, et al. Menstrual and hormonal alterations in juvenile systemic lupus erythematosus. Lupus 2009;**18**(1):38-43.
264. Silva CA, Hilario MO, Febronio MV, et al. Risk factors for amenorrhea in juvenile systemic lupus erythematosus (JSLE): a Brazilian multicentre cohort study. Lupus 2007;**16**(7):531-6.
265. Gonzalez-Crespo MR, Gomez-Reino JJ, Merino R, et al. Menstrual disorders in girls with systemic lupus erythematosus treated with cyclophosphamide. British journal of rheumatology 1995;**34**(8):737-41.
266. Rygg M, Pistorio A, Ravelli A, et al. A longitudinal PRINTO study on growth and puberty in juvenile systemic lupus erythematosus. Annals of the rheumatic diseases 2012;**71**(4):511-7.
267. Cuadrado MJ, Bertolaccini ML, Seed PT, et al. Low-dose aspirin vs low-dose aspirin plus low-intensity warfarin in thromboprophylaxis: a prospective, multicentre, randomized, open, controlled trial in patients positive for antiphospholipid antibodies (ALIWAPAS). Rheumatology (Oxford, England) 2014;**53**(2):275-84.
268. Yamakami L, Serafini P, de Araujo D, et al. Ovarian reserve in women with primary antiphospholipid syndrome. Lupus 2014;**23**(9):862-67.
269. Chen L, Quan S, Ou XH, et al. Decreased endometrial vascularity in patients with antiphospholipid antibodies-associated recurrent miscarriage during midluteal phase. Fertility and sterility 2012;**98**(6):1495-502.e1.
270. Jirous J, Diejomaoh ME, Al-Abdulhadi F, et al. A comparison of the uterine and intraovarian arterial flows in nonpregnant women having a history of recurrent spontaneous miscarriage associated with antiphospholipid syndrome. Archives of gynecology and obstetrics 2004;**270**(2):74-8.

271. De Carolis C, Greco E, Guarino MD, et al. Anti-thyroid antibodies and antiphospholipid syndrome: evidence of reduced fecundity and of poor pregnancy outcome in recurrent spontaneous aborters. American journal of reproductive immunology 2004;**52**(4):263-6.
272. Ben-Aharon I, Gafter-Gvili A, Leibovici L, et al. Pharmacological interventions for fertility preservation during chemotherapy: a systematic review and meta-analysis. Breast cancer research and treatment 2010;**122**(3):803-11.
273. Henes M, Henes JC, Neunhoeffer E, et al. Fertility preservation methods in young women with systemic lupus erythematosus prior to cytotoxic therapy: experiences from the FertiPROTEKT network. Lupus 2012;**21**(9):953-8.
274. Blumenfeld Z, Mischari O, Schultz N, et al. Gonadotropin releasing hormone agonists may minimize cyclophosphamide associated gonadotoxicity in SLE and autoimmune diseases. Seminars in arthritis and rheumatism 2011;**41**(3):346-52.
275. Brunner HI, Silva CA, Reiff A, et al. Randomized, double-blind, dose-escalation trial of triptorelin for ovary protection in childhood-onset systemic lupus erythematosus. Arthritis & rheumatology 2015;**67**(5):1377-85.
276. Somers EC, Marder W, Christman GM, et al. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. Arthritis and rheumatism 2005;**52**(9):2761-7.
277. Elizur SE, Chian RC, Pineau CA, et al. Fertility preservation treatment for young women with autoimmune diseases facing treatment with gonadotoxic agents. Rheumatology 2008;**47**(10):1506-9.
278. Ragab A, Barakat R, Ragheb M, et al. Subfertility treatment in women with systemic lupus erythematosus. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 2012;**32**(6):569-71.
279. Guballa N, Sammaritano L, Schwartzman S, et al. Ovulation induction and in vitro fertilization in systemic lupus erythematosus and antiphospholipid syndrome. Arthritis and rheumatism 2000;**43**(3):550-6.
280. Huong DL, Wechsler B, Piette JC, et al. Risks of ovulation-induction therapy in systemic lupus erythematosus. British journal of rheumatology 1996;**35**(11):1184-6.
281. Orquevaux P, Masseau A, Le Guern V, et al. [In vitro fertilization and systemic lupus erythematosus or antiphospholipid syndrome: An update]. La Revue de medecine interne / fondee par la Societe nationale francaise de medecine interne 2015;**36**(3):154-8.
282. Ulcova-Gallova Z. Repeated miscarriages in patients with antiphospholipid syndrome and subjected to in vitro fertilization: the importance of preimplantation genetic diagnosis. Lupus 2012;**21**(7):744-6.
283. Di Nisio M, Rutjes AW, Ferrante N, et al. Thrombophilia and outcomes of assisted reproduction technologies: a systematic review and meta-analysis. Blood 2011;**118**(10):2670-8.
284. Sher G, Matzner W, Feinman M, et al. The selective use of heparin/aspirin therapy, alone or in combination with intravenous immunoglobulin G, in the management of antiphospholipid antibody-positive women undergoing in vitro fertilization. American journal of reproductive immunology (New York, NY : 1989) 1998;**40**(2):74-82.
285. Sher G, Zouves C, Feinman M, et al. A rational basis for the use of combined heparin/aspirin and IVIG immunotherapy in the treatment of recurrent IVF failure associated with antiphospholipid antibodies. American journal of reproductive immunology (New York, NY : 1989) 1998;**39**(6):391-4.
286. Stern C, Chamley L, Norris H, et al. A randomized, double-blind, placebo-controlled trial of heparin and aspirin for women with in vitro fertilization implantation failure and antiphospholipid or antinuclear antibodies. Fertility and sterility 2003;**80**(2):376-83.

287. Bonaminio PN, de Regnier R, Chang E, et al. Minor physical anomalies are not increased in the offspring of mothers with systemic lupus erythematosus. Annals of the rheumatic diseases 2006;**65**(2):246-8.
288. Buyon JP, Kalunian KC, Ramsey-Goldman R, et al. Assessing disease activity in SLE patients during pregnancy. Lupus 1999;**8**(8):677-84.
289. Ruiz-Irastorza G, Khamashta MA, Gordon C, et al. Measuring systemic lupus erythematosus activity during pregnancy: validation of the lupus activity index in pregnancy scale. Arthritis and rheumatism 2004;**51**(1):78-82.
290. Yee CS, Akil M, Khamashta M, et al. The BILAG2004-Pregnancy index is reliable for assessment of disease activity in pregnant SLE patients. Rheumatology 2012;**51**(10):1877-80.
291. Buyon JP, Cronstein BN, Morris M, et al. Serum complement values (C3 and C4) to differentiate between systemic lupus activity and pre-eclampsia. The American journal of medicine 1986;**81**(2):194-200.
292. Wong KL, Chan FY, Lee CP. Outcome of pregnancy in patients with systemic lupus erythematosus. A prospective study. Archives of internal medicine 1991;**151**(2):269-73.
293. Abramson SB, Buyon JP. Activation of the complement pathway: comparison of normal pregnancy, preeclampsia, and systemic lupus erythematosus during pregnancy. American journal of reproductive immunology 1992;**28**(3-4):183-7.
294. Tomer Y, Viegas OA, Swissa M, et al. Levels of lupus autoantibodies in pregnant SLE patients: correlations with disease activity and pregnancy outcome. Clinical and experimental rheumatology 1996;**14**(3):275-80.
295. Rubbert A, Pirner K, Wildt L, et al. Pregnancy course and complications in patients with systemic lupus erythematosus. American journal of reproductive immunology 1992;**28**(3-4):205-7.
296. Devoe LD, Loy GL. Serum complement levels and perinatal outcome in pregnancies complicated by systemic lupus erythematosus. Obstetrics and gynecology 1984;**63**(6):796-800.
297. Clowse ME, Magder LS, Petri M. The clinical utility of measuring complement and anti-dsDNA antibodies during pregnancy in patients with systemic lupus erythematosus. The Journal of rheumatology 2011;**38**(6):1012-6.
298. Lockshin MD, Harpel PC, Druzin ML, et al. Lupus pregnancy. II. Unusual pattern of hypocomplementemia and thrombocytopenia in the pregnant patient. Arthritis and rheumatism 1985;**28**(1):58-66.
299. Clowse ME, Wallace DJ, Weisman M, et al. Predictors of preterm birth in patients with mild systemic lupus erythematosus. Annals of the rheumatic diseases 2013;**72**(9):1536-9.
300. Pagani G, Reggia R, Andreoli L, et al. The role of second trimester uterine artery Doppler in pregnancies with systemic lupus erythematosus. Prenatal diagnosis 2014.
301. Herraiz I, Escribano D, Gomez-Arriaga PI, et al. Predictive value of sequential models of uterine artery Doppler in pregnancies at high risk for pre-eclampsia. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2012;**40**(1):68-74.
302. Giancotti A, Spagnuolo A, Bisogni F, et al. Pregnancy and systemic lupus erythematosus: role of ultrasound monitoring. European journal of obstetrics, gynecology, and reproductive biology 2011;**154**(2):233-4.
303. Le Thi Huong D, Wechsler B, Vauthier-Brouzes D, et al. The second trimester Doppler ultrasound examination is the best predictor of late pregnancy outcome in systemic lupus erythematosus and/or the antiphospholipid syndrome. Rheumatology (Oxford, England) 2006;**45**(3):332-8.

304. Castellino G, Capucci R, Govoni M, et al. Uterine artery Doppler in predicting pregnancy outcome in women with connective tissue disorders. Rheumatology (Oxford, England) 2006;**45**(9):1174-5.
305. Farine D, Granovsky-Grisaru S, Ryan G, et al. Umbilical artery blood flow velocity in pregnancies complicated by systemic lupus erythematosus. Journal of clinical ultrasound : JCU 1998;**26**(8):379-82.
306. Guzman E, Schulman H, Bracero L, et al. Uterine-umbilical artery Doppler velocimetry in pregnant women with systemic lupus erythematosus. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 1992;**11**(6):275-81.
307. Kerslake S, Morton KE, Versi E, et al. Early Doppler studies in lupus pregnancy. American journal of reproductive immunology (New York, NY : 1989) 1992;**28**(3-4):172-5.
308. Benifla JL, Tchobroutsky C, Uzan M, et al. Predictive value of uterine artery velocity waveforms in pregnancies complicated by systemic lupus erythematosus and the antiphospholipid syndrome. Fetal diagnosis and therapy 1992;**7**(3-4):195-202.
309. Calderon AC, Berezowski AT, Marcolin AC, et al. Ultrasonography in pregnant women with antiphospholipid syndrome using salicylic acid and heparin. Archives of gynecology and obstetrics 2011;**284**(1):79-84.
310. Bats AS, Lejeune V, Cynober E, et al. Antiphospholipid syndrome and second- or third-trimester fetal death: follow-up in the next pregnancy. European journal of obstetrics, gynecology, and reproductive biology 2004;**114**(2):125-9.
311. Venkat-Raman N, Backos M, Teoh TG, et al. Uterine artery Doppler in predicting pregnancy outcome in women with antiphospholipid syndrome. Obstetrics and gynecology 2001;**98**(2):235-42.
312. Farrell T, Dawson T. Can uterine artery Doppler velocimetry predict adverse pregnancy outcome in women with antiphospholipid syndrome? Acta obstetricia et gynecologica Scandinavica 2001;**80**(7):609-10.
313. Capucci R, Pivato E, Carboni S, et al. The use of uterine artery doppler as a predictive tool for adverse gestational outcomes in pregnant patients with autoimmune and thrombophilic disease. Journal of prenatal medicine 2011;**5**(2):54-8.
314. Carroll BA. Obstetric duplex sonography in patients with lupus anticoagulant syndrome. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 1990;**9**(1):17-21.
315. Bergman G, Wahren-Herlenius M, Sonesson SE. Diagnostic precision of Doppler flow echocardiography in fetuses at risk for atrioventricular block. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2010;**36**(5):561-6.
316. Rein AJ, Mevorach D, Perles Z, et al. Early diagnosis and treatment of atrioventricular block in the fetus exposed to maternal anti-SSA/Ro-SSB/La antibodies: a prospective, observational, fetal kinetocardiogram-based study. Circulation 2009;**119**(14):1867-72.
317. Friedman DM, Kim MY, Copel JA, et al. Utility of cardiac monitoring in fetuses at risk for congenital heart block: the PR Interval and Dexamethasone Evaluation (PRIDE) prospective study. Circulation 2008;**117**(4):485-93.
318. Sonesson SE, Salomonsson S, Jacobsson LA, et al. Signs of first-degree heart block occur in one-third of fetuses of pregnant women with anti-SSA/Ro 52-kd antibodies. Arthritis and rheumatism 2004;**50**(4):1253-61.
319. Kuleva M, Le Bidois J, Decaudin A, et al. Clinical course and outcome of antenatally detected atrioventricular block: experience of a single tertiary centre and review of the literature. Prenatal diagnosis 2014.

320. Buyon JP, Hiebert R, Copel J, et al. Autoimmune-associated congenital heart block: demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. Journal of the American College of Cardiology 1998;**31**(7):1658-66.
321. Borba EF, Turrini-Filho JR, Kuruma KA, et al. Chloroquine gestational use in systemic lupus erythematosus: assessing the risk of child ototoxicity by pure tone audiometry. Lupus 2004;**13**(4):223-7.
322. Diav-Citrin O, Blyakhman S, Shechtman S, et al. Pregnancy outcome following in utero exposure to hydroxychloroquine: a prospective comparative observational study. Reproductive toxicology 2013;**39**:58-62.
323. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, et al. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. Annals of the rheumatic diseases 2010;**69**(1):20-8.
324. Levy RA, Vilela VS, Cataldo MJ, et al. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. Lupus 2001;**10**(6):401-4.
325. Al Maimouni H, Gladman DD, Ibanez D, et al. Switching treatment between mycophenolate mofetil and azathioprine in lupus patients: indications and outcomes. Arthritis care & research 2014;**66**(12):1905-9.
326. Hussein MM, Mooij JM, Roujouleh H. Cyclosporine in the treatment of lupus nephritis including two patients treated during pregnancy. Clin Nephrol 1993;**40**(3):160-3.
327. Webster P, Wardle A, Bramham K, et al. Tacrolimus is an effective treatment for lupus nephritis in pregnancy. Lupus 2014;**23**(11):1192-6.
328. Paziana K, Del Monaco M, Cardonick E, et al. Ciclosporin use during pregnancy. Drug safety 2013;**36**(5):279-94.
329. Abou-Nassar K, Karsh J, Giulivi A, et al. Successful prevention of thrombotic thrombocytopenic purpura (TTP) relapse using monthly prophylactic plasma exchanges throughout pregnancy in a patient with systemic lupus erythematosus and a prior history of refractory TTP and recurrent fetal loss. Transfus Apher Sci 2010;**43**(1):29-31.
330. Takeshita Y, Turumi Y, Touma S, et al. Successful delivery in a pregnant woman with lupus anticoagulant positive systemic lupus erythematosus treated with double filtration plasmapheresis. Ther Apher 2001;**5**(1):22-4.
331. Clowse ME, Magder L, Petri M. Cyclophosphamide for lupus during pregnancy. Lupus 2005;**14**(8):593-7.
332. Cooper WO, Cheetham TC, Li DK, et al. Brief report: Risk of adverse fetal outcomes associated with immunosuppressive medications for chronic immune-mediated diseases in pregnancy. Arthritis & rheumatology 2014;**66**(2):444-50.
333. Huong DL, Amoura Z, Duhaut P, et al. Risk of ovarian failure and fertility after intravenous cyclophosphamide. A study in 84 patients. The Journal of rheumatology 2002;**29**(12):2571-6.
334. Koh JH, Ko HS, Kwok SK, et al. Hydroxychloroquine and pregnancy on lupus flares in Korean patients with systemic lupus erythematosus. Lupus 2014.
335. Tunks RD, Clowse ME, Miller SG, et al. Maternal autoantibody levels in congenital heart block and potential prophylaxis with antiinflammatory agents. American journal of obstetrics and gynecology 2013;**208**(1):64.e1-7.
336. Soh MC, Pasupathy D, Gray G, et al. Persistent antiphospholipid antibodies do not contribute to adverse pregnancy outcomes. Rheumatology 2013;**52**(9):1642-7.
337. Sugiura-Ogasawara M, Ozaki Y, Nakanishi T, et al. Occasional antiphospholipid antibody positive patients with recurrent pregnancy loss also merit aspirin therapy: a retrospective cohort-control study. American journal of reproductive immunology (New York, NY : 1989) 2008;**59**(3):235-41.

338. Pattison NS, Chamley LW, Birdsall M, et al. Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial. American journal of obstetrics and gynecology 2000;**183**(4):1008-12.
339. Wu CQ, Kustec VE, Brown RN, et al. The medical management of antiphospholipid syndrome in pregnancy: a meta-analysis. Obstetrics and gynecology 2014;**123 Suppl 1**:178s-9s.
340. Mak A, Cheung MW, Cheak AA, et al. Combination of heparin and aspirin is superior to aspirin alone in enhancing live births in patients with recurrent pregnancy loss and positive anti-phospholipid antibodies: a meta-analysis of randomized controlled trials and meta-regression. Rheumatology 2010;**49**(2):281-8.
341. Ziakas PD, Pavlou M, Voulgarelis M. Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: a systematic review and meta-analysis. Obstetrics and gynecology 2010;**115**(6):1256-62.
342. Ruffatti A, Gervasi MT, Favaro M, et al. Adjusted prophylactic doses of nadroparin plus low dose aspirin therapy in obstetric antiphospholipid syndrome. A prospective cohort management study. Clinical and experimental rheumatology 2011;**29**(3):551-4.
343. Fouda UM, Sayed AM, Ramadan DI, et al. Efficacy and safety of two doses of low molecular weight heparin (enoxaparin) in pregnant women with a history of recurrent abortion secondary to antiphospholipid syndrome. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology 2010;**30**(8):842-6.
344. Backos M, Rai R, Thomas E, et al. Bone density changes in pregnant women treated with heparin: a prospective, longitudinal study. Human reproduction (Oxford, England) 1999;**14**(11):2876-80.
345. Carlin AJ, Farquharson RG, Quenby SM, et al. Prospective observational study of bone mineral density during pregnancy: low molecular weight heparin versus control. Human reproduction (Oxford, England) 2004;**19**(5):1211-4.
346. Bramham K, Thomas M, Nelson-Piercy C, et al. First-trimester low-dose prednisolone in refractory antiphospholipid antibody-related pregnancy loss. Blood 2011;**117**(25):6948-51.
347. Ruffatti A, Salvan E, Del Ross T, et al. Treatment strategies and pregnancy outcomes in antiphospholipid syndrome patients with thrombosis and triple antiphospholipid positivity. A European multicentre retrospective study. Thrombosis and haemostasis 2014;**112**(4):727-35.
348. Cravioto MD, Durand-Carbajal M, Jimenez-Santana L, et al. Efficacy of estrogen plus progestin on menopausal symptoms in women with systemic lupus erythematosus: a randomized, double-blind, controlled trial. Arthritis care & research 2011;**63**(12):1654-63.
349. Vieira CS, Pereira FV, de Sa MF, et al. Tibolone in postmenopausal women with systemic lupus erythematosus: a pilot study. Maturitas 2009;**62**(3):311-6.
350. Arden NK, Lloyd ME, Spector TD, et al. Safety of hormone replacement therapy (HRT) in systemic lupus erythematosus (SLE). Lupus 1994;**3**(1):11-3.
351. Kung AW, Chan TM, Lau CS, et al. Osteopenia in young hypogonadal women with systemic lupus erythematosus receiving chronic steroid therapy: a randomized controlled trial comparing calcitriol and hormonal replacement therapy. Rheumatology (Oxford, England) 1999;**38**(12):1239-44.
352. Bhattoa HP, Bettembuk P, Balogh A, et al. The effect of 1-year transdermal estrogen replacement therapy on bone mineral density and biochemical markers of bone turnover in osteopenic postmenopausal systemic lupus erythematosus patients: a randomized, double-blind, placebo-controlled trial. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2004;**15**(5):396-404.

353. Sanchez-Guerrero J, Gonzalez-Perez M, Durand-Carbajal M, et al. Menopause hormonal therapy in women with systemic lupus erythematosus. Arthritis and rheumatism 2007;**56**(9):3070-9.
354. Buyon JP, Petri MA, Kim MY, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Annals of internal medicine 2005;**142**(12 Pt 1):953-62.
355. Mok CC, Lau CS, Ho CT, et al. Safety of hormonal replacement therapy in postmenopausal patients with systemic lupus erythematosus. Scandinavian journal of rheumatology 1998;**27**(5):342-6.
356. Fernandez M, McGwin G, Jr., Bertoli AM, et al. Systemic lupus erythematosus in a multiethnic cohort (LUMINAXXXIX): relationship between hormone replacement therapy and disease activity over time. Lupus 2006;**15**(9):621-2.
357. Kreidstein S, Urowitz MB, Gladman DD, et al. Hormone replacement therapy in systemic lupus erythematosus. The Journal of rheumatology 1997;**24**(11):2149-52.
358. Hochman J, Urowitz MB, Ibanez D, et al. Hormone replacement therapy in women with systemic lupus erythematosus and risk of cardiovascular disease. Lupus 2009;**18**(4):313-7.
359. Fernandez M, Calvo-Alen J, Bertoli AM, et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA L II): relationship between vascular events and the use of hormone replacement therapy in postmenopausal women. Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases 2007;**13**(5):261-5.
360. Bernatsky S, Ramsey-Goldman R, Foulkes WD, et al. Breast, ovarian, and endometrial malignancies in systemic lupus erythematosus: a meta-analysis. British journal of cancer 2011;**104**(9):1478-81.
361. Bernatsky S, Ramsey-Goldman R, Labrecque J, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. Journal of autoimmunity 2013;**42**:130-5.
362. Dey D, Kenu E, Isenberg DA. Cancer complicating systemic lupus erythematosus--a dichotomy emerging from a nested case-control study. Lupus 2013;**22**(9):919-27.
363. Tessier Cloutier B, Clarke AE, Ramsey-Goldman R, et al. Breast cancer in systemic lupus erythematosus. Oncology 2013;**85**(2):117-21.
364. Bernatsky S, Clarke A, Ramsey-Goldman R, et al. Breast cancer stage at time of detection in women with systemic lupus erythematosus. Lupus 2004;**13**(6):469-72.
365. Bernatsky S, Boivin JF, Joseph L, et al. Race/ethnicity and cancer occurrence in systemic lupus erythematosus. Arthritis and rheumatism 2005;**53**(5):781-4.
366. Bernatsky S, Easton DF, Dunning A, et al. Decreased breast cancer risk in systemic lupus erythematosus: the search for a genetic basis continues. Lupus 2012;**21**(8):896-9.
367. Bernatsky S, Clarke A, Ramsey-Goldman R, et al. Hormonal exposures and breast cancer in a sample of women with systemic lupus erythematosus. Rheumatology (Oxford, England) 2004;**43**(9):1178-81.
368. Bernatsky S, Ramsey-Goldman R, Boivin JF, et al. Do traditional Gail model risk factors account for increased breast cancer in women with lupus? The Journal of rheumatology 2003;**30**(7):1505-7.
369. Liu H, Ding Q, Yang K, et al. Meta-analysis of systemic lupus erythematosus and the risk of cervical neoplasia. Rheumatology 2011;**50**(2):343-8.

370. Santana IU, Gomes Ado N, Lyrio LD, et al. Systemic lupus erythematosus, human papillomavirus infection, cervical pre-malignant and malignant lesions: a systematic review. Clinical rheumatology 2011;**30**(5):665-72.
371. Zard E, Arnaud L, Mathian A, et al. Increased risk of high grade cervical squamous intraepithelial lesions in systemic lupus erythematosus: A meta-analysis of the literature. Autoimmunity reviews 2014;**13**(7):730-5.
372. Dreyer L, Faurschou M, Mogensen M, et al. High incidence of potentially virus-induced malignancies in systemic lupus erythematosus: a long-term followup study in a Danish cohort. Arthritis and rheumatism 2011;**63**(10):3032-7.
373. Rojo-Contreras W, Olivas-Flores EM, Gamez-Nava JI, et al. Cervical human papillomavirus infection in Mexican women with systemic lupus erythematosus or rheumatoid arthritis. Lupus 2012;**21**(4):365-72.
374. Bateman H, Yazici Y, Leff L, et al. Increased cervical dysplasia in intravenous cyclophosphamide-treated patients with SLE: a preliminary study. Lupus 2000;**9**(7):542-4.
375. Bernatsky S, Ramsey-Goldman R, Gordon C, et al. Factors associated with abnormal Pap results in systemic lupus erythematosus. Rheumatology 2004;**43**(11):1386-9.
376. Ognenovski VM, Marder W, Somers EC, et al. Increased incidence of cervical intraepithelial neoplasia in women with systemic lupus erythematosus treated with intravenous cyclophosphamide. The Journal of rheumatology 2004;**31**(9):1763-7.
377. Klumb EM, Araujo ML, Jr., Jesus GR, et al. Is higher prevalence of cervical intraepithelial neoplasia in women with lupus due to immunosuppression? Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases 2010;**16**(4):153-7.
378. Bernatsky SR, Cooper GS, Mill C, et al. Cancer screening in patients with systemic lupus erythematosus. The Journal of rheumatology 2006;**33**(1):45-9.
379. Yazdany J, Tonner C, Trupin L, et al. Provision of preventive health care in systemic lupus erythematosus: data from a large observational cohort study. Arthritis research & therapy 2010;**12**(3):R84.
380. Grika EP, Ziakas PD, Zintzaras E, et al. Morbidity, mortality, and organ damage in patients with antiphospholipid syndrome. The Journal of rheumatology 2012;**39**(3):516-23.
381. Dall'Ara F, Reggia R, Taraborelli M, et al. Patients with longstanding primary antiphospholipid syndrome: retrospective analysis of organ damage and mortality. Lupus 2014;**23**(12):1255-8.
382. Soybilgic A, Onel KB, Utset T, et al. Safety and immunogenicity of the quadrivalent HPV vaccine in female Systemic Lupus Erythematosus patients aged 12 to 26 years. Pediatric rheumatology online journal 2013;**11**:29.
383. Mok CC, Ho LY, Fong LS, et al. Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. Annals of the rheumatic diseases 2013;**72**(5):659-64.
384. Soldevilla HF, Briones SF, Navarra SV. Systemic lupus erythematosus following HPV immunization or infection? Lupus 2012;**21**(2):158-61.
385. Gatto M, Agmon-Levin N, Soriano A, et al. Human papillomavirus vaccine and systemic lupus erythematosus. Clinical rheumatology 2013;**32**(9):1301-7.