Term	*Definitions*
OAPS	Patients with at least one obstetric (and no thrombotic) clinical criteria + one of the laboratory criteria
TAPS	Patients with vascular thrombosis (± obstetric) clinical criteria + one of the laboratory criteria
aPL carriers	Patients with aPL positivity without any clinical manifestations
snAPS	Patients with obstetric clinical criteria for APS with persistent negativity for aPL.
ncAPS	a) Patients with obstetric criteria for APS and low aPL titre b) Patients with obstetric criteria for APS but lacking persistent aPL positivity c) Patients with a combination of non-criteria clinical manifestations and one of the laboratory criteria (table 2)
UCTD	Patients with symptoms and persistent positivity of antinuclear antibodies on two separate occasions for at least one year that does not meet criteria for any specific autoimmune rheumatic disease
ncSLE	Patients with some clinical and immunological features of SLE (3 of 4 ACR/SLICC criteria) but not fulfilling the SLE classification criteria[28-29]
ncSS	Patients with some clinical and immunological features of Sjogren Syndrome (SS) but not fulfilling the SS classification criteria[40]
ncSSc	Patients with some clinical and immunological features of systemic sclerosis (SSc) but not fulfilling the SSc classification criteria[41]
HC	Pregnant patients without fulfilling criteria for an autoimmune disease
APO	Adverse Pregnancy Outcomes included were: pre-eclampsia, new onset hypertension after 20 weeks gestation and proteinuria; haemolysis elevated liver enzymes and low platelet count (HELLP) syndrome; preterm birth, <37 weeks gestation; recurrent first trimester pregnancy loss (>2); spontaneous abortion (<20 weeks gestation); stillbirth (>20 weeks gestation); fetal loss (spontaneous abortion plus stillbirth); intrauterine growth restriction (IUGR), below normal growth; small for gestational age (SGA), birth weight below the 10th percentile for the appropriate gestational age.
Standard OAPS treatment	The use of low dose aspirin (75-100mg daily) plus low molecular weight heparin at prophylactic dosage according to current guidelines [42-44]
Non-standard OAPS treatment	The use of more than 100 mg daily of LDA, intermediate or therapeutic doses of LMWH or other non-evidence-based medication for OAPS such as hydroxychloroquine, steroids or statins

Table 1. Definitions of the used terms in this systematic review

Non-clinical criteria	*Non-laboratory criteria*
1. Two unexplained miscarriages 2. Three non-consecutive miscarriages 3. Late pre-eclampsia 4. Placental abruption, late premature birth, 5. Two or more unexplained in vitro fertilisation failures	1. Low positive aCL or aβ2GPI present between the 95th and 99th centiles 2. Presence of intermittent aPL in women with classical clinical manifestations of obstetric APS

Table 2: Non-criteria clinical and laboratory manifestations of OAPS. Definitions proposed by Arachchillage DR et al[31]

Author	Study design	Nº patients (ncAPS/APS/controls)/ pregnancies	Type of ncAPS patients	Titer of aPL in ncAPS patients	Type of treatment	Pregnancy outcomes (ncAPS/APS/controls)	findings	Summary of	Grade of evidence
Alijotas J (11)	Multicenter retrospective and prospective study	1640 patients (ncAPS:640; APS:1000)/ 5189 pregnancies	Subgroup A (27%): nc clinical criteria* + nc laboratory criteria Subgroup B (27%): Sydney clinical criteria + nc laboratory criteria Subgroup C (45%): Sydney laboratory criteria + nc clinical	Persistent low positivity for aCL IgM and/or IgG and/or b2GPI IgM and/or IgG in titre 20-39 units (95-99th centile), or intermittent aPL positivity in titre >40 units	a) ncAPS--> untreated vs treated: 24vs76% (LDA alone: 13%; LMWH: 4%; LDA+LMWH: 59% (SR:47%) b) APS--> untreated vs treated:23vs77% (LDA alone: 10%; LMWH alone: 4%; LDA+LMWH: 63% (SR: 45%) All patients were treated with LDA (98%) and/or LMWH (76%).	ncAPS vs APS--> PB:5vs28%; REM:15vs39%; SA:7vs25%; ST:6vs23%; Pec(<34ws):3vs18%; IUGR(<34ws):3vs16; HELLP (<34ws):1vs3%	Main obstetric complications were higher in APS than ncAPS. Similar obstetrics outcomes were found in both groups when treated with the standard regime for APS	Moderate
Fredi M (19)	Triple centre retrospective study	200 patients (ncAPS:39;TAPS:42;OAPS:85; aPL carriers:34)/283 pregnancies	Sydney laboratory criteria + nc clinical criteria	aCL IgM and/or IgG and/or b2GPI IgM and/or IgG in titre >99th centile, present on two or more occasions at least 12 weeks apart	a) ncAPS--> LDA alone (43%); LMWH alone: 0%; LDA+LMWH (SR): 57%; LDA+LMWH (therapeutic dose): 0%; HCQ: 5%; steroids: 5%. b) OAPS--> LDA alone: 14%; LMWH alone: 0%; LDA+LMWH (SR): 78%; LDA+LMWH (therapeutic dose): 8%; HCQ: 6%; steroids: 3%. c) TAPS: LDA alone: 1%; LMWH alone: 7%; LDA+LMWH (SR): 31%; LDA+LMWH (therapeutic dose): 59%; HCQ: 29%; steroids: 14%. d) aPL carriers: LDA alone: 67%; LMWH alone: 0%; LDA+LMWH (SR): 31%; LDA+LMWH (therapeutic dose): 3%; HCQ: 5%; steroids: 10%.	ncAPS vs TAPS vs OAPS vs aPL carriers--> APO: 9vs24vs18vs18%; SA: 40vs50vs41vs14%; ST:20vs25vs18vs43%; PB: 40vs25vs32vs43%; SGA: 20vs0vs9vs14%	TAPS group had the highest rate of complicated pregnancies.However, not statistical difference in terms of APO between both APS groups, ncAPS group or aPL carriers.	Low
Mekinian A (20)	Single center retrospective study	57 patients (ncAPS:32; APS:25)/ NF	Sydney clinical criteria + persistent low aPL titre	aCL IgM and/or IgG and/or b2GPI IgM and/or IgG in titre 90-99th centile	a) ncAPS treated patients--> LDA alone: 8%; LDA+LMWH with SR: 84% b) APS treated patients --> LDA alone: 9%; LDA+LMWH SR: 84%	ncAPS vs APS (untreated pregnancies)--> REM: 41vs36%;ST: 50vs44%; Pec: 19vs20%; IUGR: 22vs36%. NcAPS vs APS (after standard treatment)--> REM: 0vs0%; ST:6vs0%; Pec: 3vs0%; IUGR: 3vs12%; PB:13vs12%	ncAPS and APS patients had similar APO in untreated pregnancies. Standard APS treatment substantially improved pregnancy and neonatal outcomes in both groups.	Low
Ofer-Shiber S (21)	Single center retrospective study	243 patients (117 ncAPS; 126 APS)/ NF	Sydney clinical criteria + persistent low aPL titre	aCL IgM and/or IgG and/or b2GPI IgM and/or IgG in titre 20-40 units or <99th centile	No data separated by groups--> untreated vs treated: 56vs44% (LDA:38%; anticoagulant (warfarin or LMWH):24%; HCQ:19%; prednisone >5mg at least 3 months during pregnancy: 29%)	ncAPS vs APS--> pregnancy morbidity: 42vs44%; REM: 16vs16%; ST: 12vs19%; IUGR: 6vs6%; Pec: 5vs2%; HELLP:2vs0%; CASP:0vs4%	The overall risk for both vascular and obstetrical complications related is similar in ncAPS compared with APS patients	Low
Sugiura O (22)	Single center retrospective study	740 patients (ncAPS:68; unexplained miscarriages: 672)/ 740 pregnancies	Intermittent positivity for a laboratory criteria + two or three recurrent pregnancy loss	one determination of aCL IgM and/or IgG and/or b2GPI IgM and/or IgG in titre >99th centile	ncAPS--> untreated vs treated with LDA: 24vs76% Unexplained miscarriages were not treated	LB in ncAPS (LDA treated group: 84%; untreated group: 50%); LB in the unexplained miscarriage group (untreated): 76%	LB rate in ncAPS patients treated with LDA was significantly higher than those ncAPS who were not treated and the group with unexplained miscarriages	Low
Lo H (23)	Single center retrospective study	19 patients (ncAPS:7 ; APS:12)/14 pregnancies	Sydney clinical criteria + intermittent positivity for a laboratory criteria	one determination of aCL IgM and/or IgG and/or b2GPI IgM and/or IgG in titre >99th centile	Anticoagulant therapy (ND)	ncAPS vs APS (after anticoagulant therapy) --> LB: 83vs100%; Pec: 0vs25%; PB: 0vs37%	LB rate among women with ncAPS was significantly lower that among those with APS following anticoagulant therapy. APO were more common in APS than ncAPS.	Very low
Spinillo A (24)	Single center prospective study	948 patients (ncAPS:48; APS:62; aPL carriers:53; HC:785)/ 948 pregnancies	Incomplete clinical but fulfilling laboratory criteria or laboratory Sydney criteria with incomplete clinical criteria	Intermittent or low positive (7-10U/ml) positive aCL and/or b2GPI low titre if 7– 10U/mL	a) ncAPS--> LDA:31%; LMWH: 6%; LDA+LMWH : 4%; HCQ: 8%; steroids: 8%. b) APS--> LDA: 85%; LMWH: 100%; LDA+LMWH: 85,5%; HCQ: 14,5%; steroids: 14,5%. c) aPL carriers: LDA : 21%; LMWH: 4%; LDA+LMWH: 0%; HCQ: 7,5%; steroids: 11%.	ncAPS vs APS vs aPL carriers vs HC--> APO: 25vs42vs28vs5,6%; ST:8vs14vs6vs0,6%; PB: 21vs26vs6vs6%; IUGR: 12,5vs19vs17vs2%; Pec: 6vs14,5vs9vs1,5%	All aPL groups (ncAPS, APS and aPL carriers) had an overall risk of APO compared with HC, the APS group having the greatest risk.	Low
Xi F (25)	Single center prospective study	270 patients (ncAPS: 91;APS:44; HC:135)/ 270 pregnancies	NF	NF	a) ncAPS--> LDA:NF; LMWH: NF; HCQ: 34%; steroids: 60%. b) APS--> LDA: NF; LMWH: NF; HCQ: 7%; steroids: 48%.	ncAPSvsAPSvsHC --> ST:2vs4,5vs0%; PB: 7vs14vs8%; IUGR: 8,5vs16vs4%; Pec: 10vs7vs13%	Adverse pregnancy Outcomes did not show significant difference between aPL carriers and normal pregnancies, and between APS and NCAPS. Better pregnant outcomes of aPL positive women, include APS and NCAPS, were achieved in our study with treatment based on LDA plus LMWH.	Low

Table 3. Pregnancy outcomes in ncAPS patients. Original studies of pregnancy outcomes in ncAPS patients.ncAPS: Non-Criteria Antiphospholipid Syndrome; OAPS: Obstetric APS; TAPS: Thrombotic-APS; CAPS: Catastrophic APS; HC: Healthy Controls; APO: adverse Pregnancy Outcomes; LB: Live Birth; PB: Preterm Birth <37 weeks; SA:Spontaneous Abortion (<20 weeks); ST: Stillbirth (>20 weeks); PL: Pregnancy Loss (SA+ST); SGA: Small for Gestational Age; Pec: Preeclampsia; HELLP: hemolysis, elevated liver enzyme and low platelet count syndrome; IUGR: IntraUterine Growth Restriction; LDA: Low Dose Aspirin; LMWH: Low Molecular Weight Heparin; AP: Abruptio Placentae; REM: Recurrent Early Miscarriage; LPL: Late Pregnancy Loss (third trimester); NF: No found.

Nc clinical criteria* are described in table 2.

Author	Study design	Nº patients (UCTD/CTD/controls)/ pregnancies	Pregnancy outcomes (UCTD/CTD/controls)	Summary of findings	Grade of evidence
Mosca M (15)	Single center prospective study	20 UCTD patients/ 25 pregnancies	LB:88%; rate of APO: 36% ; flare during pregnancy: 24 %	UCTD patients had a greater risk of flare during pregnancy.	Low
Grava C (17)	Single center prospective study	41 patients (25 UCTD/ 16 SS)/46 pregnancies	LB: 96%; SA:4%. Incidence of CHB: 4%	A higher incidence of CHB in UCTD and SS patients with positive anti-Ro/SSA antibodies compared with SLE patients	Low
Spinillo A (29)	Single center prospective study	796 patients (131 UCTD; 68 ARD; 597 HC)/ NF	UCTD vs CTD vs HC --> Pec: 14vs22vs3%; IUGR: 16vs26vs4%; SGA: 17vs26vs8%; PB: 5vs7vs3%	Overall pregnancy complications such as Pec, SGA or IUGR, were higher in CTD and UCTD compared to HC. Although, this risk was even higher in the CTD group, the burden of pregnancy complications was similar between UCTD and CTD groups.	moderate
Zucchi D (30)	Single center retrospective study	81 UCTD patients / 100 pregnancies	LB:89%; SA: 11%; SGA: 10%; PB:9%; flares during pregnancy/puerperium: 13%	Patients with stable UCTD have similar rate of APO than the expected for the general population, except for PB which was higher in their cohort. Those UCTD patients with disease activity at conception and/or positive anti-dsDNA antibodies had an increased risk of APO	Low
Spinillo A (31)	Single center prospective study	123 patients (41 UCTD;82 HC)/123 pregnancies	UCTD vs HC--> rate of APO: 39vs13%;Pec:7vs1%; PB: 10vs1%	UCTD patients had an increased risk of APO compared with HC	Low
Radin M (32)	Multicenter retrospective study	133 UCTD patients/ 244 pregnancies	LB:79%; SA: 20%; ST: 1%; SGA: 12%; PB: 17%; IUGR: 3%; Pec:2%; gestational hypertension: 5%; CHB: 1%	UCTD patients had an increased risk of APO compared to the expected for the general population, specially for PB and SGA. In addition, SA and ST were strongly associated with the presence of aPL and anti-ENA antibodies (mainly anti-Ro/SSA antibodies).	Low
Brucato A (33)	Multicenter prospective study	100 patients (19 UCTD;25 SS; 53 SLE; 1 MCTD; 1 APS; 1 SSc)/ 118 pregnancies	Incidence of CHB (UCTD vs SS vs SLE vs MCTD vs SSc vs APS): 5vs4vs0vs0vs0%	UCTD and SS groups with positive anti-Ro/SSA antibodies had a higher incidence of CHB than the SLE group	Low

Table 4. Pregnancy outcomes in UCTD patients. Original studies of pregnancy outcomes in UCTD patients.

UCTD: Undifferentiated Connective Tissue Disease; ARD: Autoimmune Rheumatic Disease; CHB: Complete Heart block; SS: Sjogren Syndrome; HC: Healthy Controls; APO: adverse Pregnancy Outcomes; LB: Live Birth; PB: Preterm Birth <37 weeks; SA: Spontaneous Abortion (<20 weeks); ST: Stillbirth (>20 weeks); PL: Pregnancy Loss (SA+ST); SGA: Small for Gestational Age; Pec: Preeclampsia; IUGR: IntraUterine Growth Restriction; NF: Not found.