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Review

Pregnancy outcome predictors in antiphospholipid syndrome: A systematic review and meta-analysis

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ABSTRACT

Objective: To identify and assess the magnitude of effect of pregnancy outcome predictors in women with antiphospholipid syndrome (APS) by means of systematic review and meta-analysis.
Methods: PubMed and Embase were searched (13th June 2020) for studies reporting on pre-pregnancy risk factors of pregnancy outcomes in APS patients. Literature screening and data extraction were conducted by two reviewers independently, in a blinded standardized manner. Pooled univariate odds ratios (OR) were computed using a random effects model. Heterogeneity was assessed by I^2%.
Results: The search yielded 3013 unique results; 27 records were included in this meta-analysis. Previous thrombosis was associated with a decreased live birth risk (OR 0.60, $p < 0.01$, $I^2 = 40\%$), increased neonatal mortality (OR 15.19, $p < 0.01$, $I^2 = 0\%$), an increased risk of antenatal or postpartum thrombosis (OR 6.26, $p < 0.01$, $I^2 = 0\%$) and an increased risk of delivering a small for gestational age neonate (SGA) (OR 2.60, $p = 0.01$, $I^2 = 0\%$). Patients with an APS laboratory category I (double or triple positivity) profile had a decreased live birth risk (OR 0.66, $p < 0.01$, $I^2 = 0\%$), an increased risk of SGA (OR 1.86, $p = 0.01$, $I^2 = 43\%$) and preterm birth (OR 1.35, $p < 0.01$, $I^2 = 49\%$). Triple positivity was associated with a decreased live birth risk (OR 0.33, $p < 0.01$, $I^2 = 68\%$), an increased risk of preeclampsia (OR 2.43, $p = 0.02$, $I^2 = 35\%$) and SGA (OR 2.47, $p = 0.04$, $I^2 = 61\%$). Patients with lupus anticoagulant positivity had an increased risk of preeclampsia (OR 2.10, $p = 0.02$, $I^2 = 48\%$), SGA (OR 1.78, $p < 0.01$, $I^2 = 0\%$) and preterm birth (OR 3.56, $p = 0.01$, $I^2 = 48\%$). Risk of bias assessment suggested considerable bias on study participation and statistical methods.
Conclusions: The results of this meta-analysis identified previous thrombosis, laboratory category I, triple positivity and lupus anticoagulant positivity as the most important predictors of adverse pregnancy outcomes. This up-to-date knowledge, can be used in preconception counseling and tailoring of obstetric care.

1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the occurrence of arterial or venous thrombotic events and/or pregnancy morbidity in the presence of at least one type of circulating antiphospholipid antibody (aPL) [1]. Although APS is regarded a rare disease with an estimated prevalence of 0.05% in the general population, it is 3.5-times more common in women compared to men [2,3]. Women with APS are at increased risk of adverse pregnancy outcomes such as preeclampsia, pregnancy loss, thromboembolism, preterm delivery and perinatal mortality [3,4]. Without treatment, only 25% of APS patients are able to give birth to a healthy neonate [5]. This number has greatly improved to about 70% with the introduction of low-dose aspirin and low-molecular-weight-heparin treatment [3,6–8].

Given the high risks of pregnancy complications, preconception counseling is key. Such counseling should include information on which

Abbreviations: +, positivity; −, negativity; ab2GP1, anti-β_2-glycoprotein-I antibody; aCL, anticardiolipin antibody; ANA, antinuclear antibody; APS, antiphospholipid syndrome; aPL, antiphospholipid antibodies; AID, autoimmune disease; CI, confidence interval; FGR, fetal growth restriction; IV, inverse variance; LA, lupus anticoagulant; LMWH, low-molecular-weight-heparin; IgG/IgM, Immunoglobulin G/M; NC-APS, non-criteria antiphospholipid syndrome; OR, odds ratio; SGA, small for gestational age; SLE, systemic lupus erythematosus.

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drugs to initiate or withhold during pregnancy, as well as risk assessment of major maternal, fetal and neonatal morbidity and mortality. To this end, knowledge on well-recognized predictors of adverse pregnancy outcomes is of great value. Multiple clinical studies have reported on various risk factors for obstetric complications in women with APS [6,7,9–12]. Triple positivity and a history of thrombotic events are regarded as two of the strongest predictors [13]. Although reviews on predictors of adverse pregnancy outcomes in APS have been conducted [13–15], none performed a formal meta-analysis pooling their effect sizes. Such a meta-analysis is of importance, as effect sizes of predictors vary between studies [6–8,16]. Consequently, the magnitude of effect of risk factors of adverse pregnancy outcome remains unclear, which makes an individualized risk assessment during preconception counseling cumbersome. Hence, the purpose of this study was to perform a systematic review and meta-analysis on predictors of adverse pregnancy outcomes in women diagnosed with APS.

2. Methods

2.1. Literature search and selection

Eligible publications were identified by searching PubMed and Embase on June 13th 2020 without restrictions concerning language or publication date. The search string consisted of three main constituents: prediction studies, APS and pregnancy (full search string in Table A.1). The filter reported by Ingui et al. was used to identify prediction studies [17,18]. Besides full-text articles, conference abstracts and letters were included to reduce the risk of publication bias. The search was enhanced by snowballing, using the reference list of the review by De Carolis et al. [14].

To be eligible for inclusion, studies must present original, quantitative data on pregnant women with APS and report on preconceptionally available risk factors on at least one of the outcomes of interest. Treatment effects were beyond the scope of this review. APS should be defined by the Sydney or Sapporo classification criteria [1,19]. Studies that included pregnant women with a history of obstetric or thrombotic morbidity in combination with the presence of lupus anticoagulant positivity (LA+) or medium or high titer anticardiolipin (aCL+) or anti-β_2 glycoprotein-I antibody >99th percentile (ab2GP1+), but not fulfilling the Sydney or Sapporo criteria, were also considered eligible for inclusion (non-criteria APS). Studies reporting on both primary APS and APS with another concomitant autoimmune disease were included.

We excluded studies with a sample size of less than 20 pregnancies [14], or populations restricted to multiple pregnancies or studies reporting solely on a composite outcome without information on the individual outcome components.

2.2. Study selection and data extraction

Study selection for inclusion, data extraction and risk of bias assessment were all conducted by two reviewers (I.J.W, M.J.K.H.) independently, in a blinded standardized manner. Disagreements between reviewers were resolved by consensus or by consulting an independent third reviewer (J.K.). Corresponding authors were contacted in case of missing data.

A data extraction sheet was developed based on the CHARMS-PF checklist; a modified version of the checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies (CHARMS) for predictor studies [20,21]. For categorical predictors event rates or, when available, univariate odds ratios were extracted. Continuous predictors were extracted as means with standard deviations or a median and interquartile range. Risk of bias assessment of included studies was performed using the quality in prognostic studies (QUIPS) tool [22].

A risk factor commonly reported by studies was APS laboratory category I. APS laboratory category I is defined as a double or triple positivity aPL profile, compared to laboratory category II with only one type of criteria aPL present [1]. For definitions of other predictors, see Appendix B.

2.3. Study outcomes

Outcomes of interests were live birth, preeclampsia, small for gestational age (SGA), fetal growth restriction (FGR), preterm birth, fetal death, perinatal mortality, neonatal mortality and antenatal or postpartum thrombotic events. Eligibility criteria for inclusion in the systematic review were not restricted to the use of specific definitions. Definitions of predictors and outcomes in the pooled analyses are presented in Appendix B. The timeframe for all outcomes was defined as the beginning of pregnancy until a maximum of six weeks after birth.

2.4. Statistical analyses

Meta-analysis was performed if at least two studies independently reported the odds ratio or a contingency table of the same predictor and outcome. The modified Haldane-Anscombe correction was applied if a contingency table contained a zero cell [23]. Summary estimates were calculated using meta-analysis (generic inverse variance) by random effects models with restricted maximum likelihood (REML) estimations for calculation of 95% prediction intervals. The amount of between-study heterogeneity was calculated using the I^2 (0–100%). As an $I^2 \geq$ 75% or higher represents considerable heterogeneity according to the Cochrane handbook, pooled results were exclusively reported if I^2 was below 75% [24]. To study possible causes of between-study heterogeneity, subgroup analyses were planned stratified for APS diagnostic criteria (Sydney, Sapporo, non-criteria APS), concomitant systemic lupus erythematosus (SLE) and low-molecular-weight-heparin (LMWH) treatment. If at least ten studies were included in a meta-analysis, publication bias was assessed by visual inspection of a funnel plot, and by use of Egger's test for continuous outcomes and Harbord's test for dichotomous outcomes [24–26].

We chose not to pool risk factors for the outcome of miscarriage, given the large diversity in definition of this study outcome. After data collection was performed, we found that some studies report aCL immunoglobulin M (IgM) and immunoglobulin G (IgG) positivity separately, without knowledge of how many participants were positively tested for both. In this case, we chose to pool IgG values as it has been found to have superior predictive value for thrombotic and obstetric morbidity over IgM [27]. The effect of this choice was assessed in a sensitivity analysis. All analyses were conducted using R-studio version 4.0.1 with packages "dmetar", "meta" and "forestplot" [28–31].

Methods of the analysis and inclusion criteria were specified in advance and are available at the PROSPERO database (record ID: CRD42020200303).

3. Results

3.1. Study selection

The search of Embase and PubMed resulted in 3977 records (Fig. 1). After removal of duplicates 3013 unique publications were identified. Of those, 2910 were excluded during title-abstract screening because they did not meet eligibility criteria. The hierarchy of reasons of exclusion can be found in Appendix C. Of the 103 full-text records assessed for eligibility, 27 met all criteria and were included in our systematic review and meta-analysis. Twenty two out of 27 studies applied either the Sydney or Sapporo APS criteria for participant inclusion. Eleven out of 27 studies reported inclusion of patients with concomitant SLE. Patients were treated with LMWH in seventeen out of 27 studies. Characteristics of included studies are presented in Table 1, with an extension in Table D.1. Predictors that could not be pooled in a meta-analysis are listed in Appendix E.

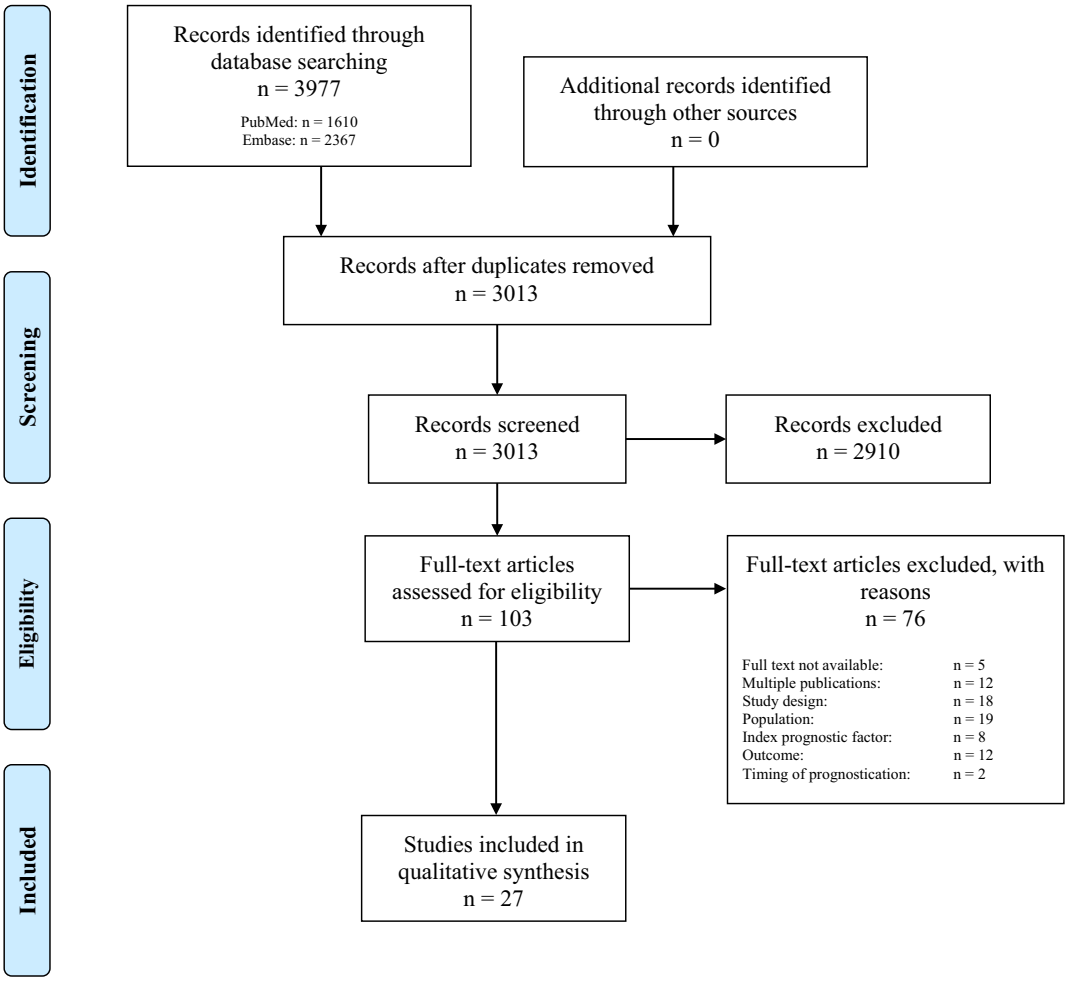


Fig. 1. Flow diagram. Template source: Moher et al. [60].

3.2. Meta-analysis (Fig. 2)

3.2.1. Live birth

For the outcome of live birth, a history of arterial, venous or small vessel thrombosis ($n = 7$), concomitant autoimmune disease ($n = 3$) or the presence of APS laboratory category I (n = 7), triple positivity ($n = 6$), LA+ (n = 3), aCL+ ($n = 4$), ab2GP1+ (n = 3) and antinuclear antibody positivity (ANA+) ($n = 2$) were studied as potential predictors [6,9–11,16,32–36].

Women with a previous thrombotic event had a significantly decreased risk of a live birth outcome of pregnancy (OR 0.60, 95% CI: 0.50–0.71; $p < 0.01$, $I^2 = 40\%$). Women with a triple positive aPL or an APS laboratory category I profile had a decreased risk of a live birth outcome as well, with ORs of 0.33 (95% CI: 0.16–0.71; $p < 0.01$, $I^2 = 68\%$) and 0.66 (95% CI: 0.53–0.82; $p < 0.01$, $I^2 = 0\%$), respectively. Concomitant autoimmune disease was not associated with a statistically significant lower risk of having a live birth (OR 0.66, 95% CI: 0.31–1.41; $p = 0.28$, $I^2 = 0\%$). This was also the case for LA+ (OR 0.82, 95% CI: 0.45–1.47; $p = 0.50$, $I^2 = 0\%$), aCL+ (OR 0.72, 95% CI: 0.40–1.30; $p = 0.28$, $I^2 = 0\%$) and ANA+ (OR 0.35, 95% CI: 0.11–1.09; $p = 0.07$, $I^2 = 32\%$). Each individual meta-analysis can be found in Fig. F.1.

As definitions of fetal death and perinatal mortality outcomes vary greatly between studies in timing of diagnosis, no pooled analyses were performed for these outcomes. However, studies on predictors of fetal loss during whole pregnancy were considered for meta-analysis. These pooled odds ratios and forest plots are nearly the reciprocal of the live birth results, and are therefore reported in Fig. F.2.

Effects of aCL+ on the outcomes live birth and fetal loss were reported for both IgM and IgG by the study of Li et al. [33]. None of the other studies differentiated between IgM and IgG measurements. Sensitivity analyses showed similar effect sizes for both outcomes if either aCL type from Li et al. was pooled (Fig. F.3). Pooled analyses on the association between ab2GP1+ and live birth or fetal loss during whole pregnancy outcome were not reported because of considerable heterogeneity with I^2: 82% and I^2: 81%, respectively.

3.2.2. Preeclampsia

Arterial, venous or small vessel thrombosis ($n = 3$), APS laboratory category I (n = 3), triple positivity (n = 3), LA+ ($n = 2$), IgM aCL+ (n = 2), IgG aCL+ (n = 2), IgG ab2GP1+ (n = 2) and IgM ab2GP1+ (n = 2) were studied as potential predictors of preeclampsia development during pregnancy [6–9,11,34,37–39].

Women with a triple positive aPL profile had a statistically significant increased risk of developing preeclampsia compared to women with a double or single positivity aPL profile, with an OR of 2.43 (95% CI: 1.17–5.04; $p = 0.02$, $I^2 = 35\%$). Although with moderate heterogeneity, a similar association was found for LA+ compared to LA- patients (OR 2.10, 95% CI: 1.14–3.85; p = 0.02, $I^2 = 48\%$). No statistically significant association was identified for previous thrombosis (OR 1.46, 95% CI: 0.67–3.20; $p = 0.35$, $I^2 = 4\%$) or IgM ab2GP1+ (OR 1.25, 95% CI: 0.55–2.87; $p = 0.59$, $I^2 = 27\%$). Pooled analyses of studies reporting on the association between preeclampsia and APS laboratory category I, IgM/IgG aCL+ and IgG ab2GP1+ were not reported because of considerable heterogeneity. Each individual meta-analysis is presented in Fig. F.4.

Table 1
Characteristics of included studies.

Author	Year of publication	Study design	Location	Participants	Enrolment period participants	Index prognostic factor	Outcome
Alijotas-Reig et al. [9]	2015	R	Europe[a]	247 women with OAPS (Sydney)	Unknown – 2013	Antiphospholipid antibody type, laboratory category, triple positivity	Early onset preeclampsia/HELLP, preterm birth, FGR, miscarriage, fetal loss/stillbirth
Alijotas-Reig et al. [52]	2016	R	Europe[a]	147 women with OAPS (Sydney)	Unknown	Inherited thrombophilia	Early onset preeclampsia, late onset preeclampsia, preterm birth, early onset FGR, fetal loss, stillbirth, arterial/venous thrombotic event during pregnancy or puerperium
Alijotas-Reig et al. [8]	2019	R	Europe, Argentina[a]	1000 women with OAPS (Sydney)	Unknown – 2017	Laboratory category	Preeclampsia <34 wks GA, Preeclampsia >34 wks GA, preterm birth, FGR <34 wks GA, FGR >34 wks GA, miscarriage (latest), fetal loss, stillbirth
Bouvier et al. [7]	2014	P	France	517 women with OAPS (Sydney)	1995–2005	Maternal age, BMI, family history, ethnicity, smoking history, varicose veins, pre-existing hypertension, previous embryonic pregnancy loss, previous fetal pregnancy loss, primary/secondary loss, prior inflammatory disease, hypercholesterolemia, hypertriglyceridemia, antiphospholipid antibody type, triple positivity, thrombophilia associated gene polymorphisms	Preeclampsia, early onset preeclampsia, premature birth <37 wks GA, premature birth <34 wks GA, SGA neonate, abortion/ embryonic loss <10 wks GA, fetal loss >10 wks GA
Bramham et al. [37]	2010	R	United Kingdom	83 APS pregnancies (Sapporo)	2000–2007	Thrombotic APS	Preeclampsia, preterm birth, SGA, thromboembolic event
Brewster et al. [53]	1999	R	United Kingdom	61 NC-APS pregnancies	1992–1997	Antiphospholipid antibody type combinations	SGA
Canti et al. [54]	2018	P	Italy[a]	47 women with APS (Sydney)	Unknown	Antiphosphatidylserine/prothrombin antibodies	Preeclampsia and/or HELLP, intrauterine growth restriction, pregnancy loss <10 wks GA, pregnancy loss >10wks GA, intrauterine fetal death
Chauleur et al. [39]	2010	P	France	142 women with NC-OAPS	1999–2004	Antiphospholipid antibody type, BMI	Preeclampsia, FGR, embryonic loss <10 wks GA
De Carolis et al. [55]	2004	P	Italy	85 women with APS (Sapporo)	Unknown	Anti-thyroid antibodies	Live birth
Deguchi et al. [16]	2017	R	Japan[a]	81 APS pregnancies (Sydney)	2008–2013	Maternal age, secondary APS, history of thrombosis, history of 3 or more pregnancy loss <10 wks GA, history of 2 or more pregnancy loss ≥10 wks GA, history of premature birth <32 wks GA, nulliparity, history of hypertensive disorders of pregnancy, antiphospholipid antibody type, antinuclear antibody, activated partial thromboplastin time prolongation, low complements	Live birth, premature birth <34 wks GA, light-for-date neonate, pregnancy loss
Diejomaoh et al. [56]	2002	P	Kuwait	43 women with APS (Sapporo)	1998–1999	Previous primary pregnancy loss	Live birth, preterm birth <37 wks GA, miscarriage first trimester, miscarriage second trimester, perinatal loss
Fredi et al. [40]	2018	R	Italy and France	180 APS pregnancies (Sydney)	2000–2014	Thrombotic APS	Preterm delivery <34 wks GA, spontaneous abortion, fetal death,
Gabbay-Benziv et al. [38]	2017	R	Israel	99 women with APS (Sydney)	2012–2016	Thrombotic APS, antiphospholipid antibody type	Preeclampsia, preterm birth, FGR
Högdén et al. [34]	2019	R	Sweden	30 women with PAPS (Sydney)	2000–2016	Thrombotic APS, triple positivity	Live birth, preeclampsia, intrauterine growth restriction, SGA, miscarriage
Huong et al. [42]	2001	R	France	74 APS pregnancies (Sapporo)	1984–1998	Secondary APS	Preterm birth
Latino et al. [10]	2017	R	Argentina	106 women with APS (Sydney)	2007–2014	SLE, previous thrombosis, ≥4 previous pregnancy losses, antiphospholipid antibody type, triple positivity	Live birth, miscarriage, fetal loss, pregnancy loss, arterial/venous thrombotic event during pregnancy or puerperium
Latino et al. [57]	2018	R	Argentina	97 women with APS (Sydney)	2009–2016	Baseline serological risk	Live birth, pregnancy loss
Lima et al. [32]	1996	R	United Kingdom	47 women with NC-APS	1989–1994	Previous pregnancy loss, previous thrombocytopenia, previous thrombosis, antiphospholipid antibody type	Live birth, arterial/venous thrombotic event during pregnancy or puerperium

(*continued on next page*)

Table 1 (*continued*)

Author	Year of publication	Study design	Location	Participants	Enrolment period participants	Index prognostic factor	Outcome
Liu et al. [58]	2013	R	China	191 women with NC-OAPS	2006–2010	Antiphospholipid antibody type	Live birth
Li et al. [33]	2020	P	China	128 women with NC-APS/ APS (Sydney)	2018–2020	Maternal age, ≥3 previous adverse pregnancy outcome, previous miscarriage, SLE, preconception counseling, antinuclear antibody, triple positivity, antiphospholipid antibody type, complement, serum IgG/M/A	Live birth, fetal loss
Mayer-Pickel et al.	2017	R	Austria	74 APS pregnancies (Sydney)	Unknown	Thrombotic APS	Live birth, preeclampsia/HELLP, preterm birth, intrauterine growth restriction, early fetal loss, late fetal loss
Rezk et al. [11]	2016	P	Egypt	162 women with PAPS (Sydney)	2012–2015	Maternal age > 30, previous thrombosis, previous preterm birth, antiphospholipid antibody type, triple positivity	Live birth, preeclampsia, preterm birth, SGA, miscarriage, intrauterine fetal death, pregnancy loss, neonatal mortality, venous thromboembolism
Ruffatti et al. [12]	2010	R	Italy	93 women with PAPS (Sydney)	1991–2008	Previous thrombosis, previous pregnancy morbidity, antiphospholipid antibody type, triple positivity	Neonatal death
Ruffatti et al. [35]	2009	R	Italy	97 PAPS pregnancies (Sydney)	1995–2007	Laboratory category	Unsuccessful pregnancy
Ruffatti et al. [36]	2006	R	Italy	47 women with PAPS (Sydney)	1989–2004	Maternal age, previous late fetal loss, previous thrombosis, triple positivity	Unsuccessful pregnancy
Saccone et al. [6]	2017	R	Italy[a]	750 women with PAPS (Sydney)	2007–2016	Previous thrombosis, laboratory category, triple positivity	Live birth, preeclampsia, preterm birth <37 wks GA, intrauterine growth restriction, severe very preterm intrauterine growth restriction, pregnancy loss, stillbirth, neonatal death, venous thromboembolism in current pregnancy
Simchen et al. [59]	2011	R	Israel	55 APS pregnancies (Sydney)	Unknown	High positive antibody titers (≥4 times upper limit of normal)	Preterm birth, SGA, pregnancy loss, maternal thrombotic event

[a] Multicenter study; APS: antiphospholipid syndrome; BMI: body mass index; FGR: fetal growth restriction; GA: gestational age; HELLP: hemolysis, elevated liver enzymes, low platelet count; NC-APS: non-criteria antiphospholipid syndrome; NC-OAPS: non-criteria obstetric antiphospholipid syndrome; OAPS: obstetric antiphospholipid syndrome; P: prospective study; PAPS: primary antiphospholipid syndrome; R: retrospective study; SGA: small for gestational age; SLE: systemic lupus erythematosus; wks: weeks.

3.2.3. *Small for gestational age/fetal growth restriction outcome*

A definition of FGR was lacking in the majority of included studies reporting this outcome. Consequently, we pooled all studies on SGA and FGR together, considering them as studying the outcome of SGA. A history of arterial, venous or small vessel thrombosis ($n = 3$), APS laboratory category I ($n = 4$), triple positivity (n = 3), LA+ (n = 3), aCL+ ($n = 2$), IgG aCL+ (n = 2), IgM aCL+ (n = 2), IgG ab2GP1+ (n = 2) and IgM ab2GP1+ (n = 2) were considered potential predictors of SGA [6–9,16,34,37,39].

Previous thrombosis was associated with the development of SGA (OR 2.60, 95% CI: 1.22–5.54; $p = 0.01$, $I^2 = 0\%$). A statistically significant association was identified between SGA and APS laboratory category I compared to laboratory category II, with an OR of 1.86 (95% CI: 1.13–3.06; p = 0.01, $I^2 = 43\%$). Comparable results were observed for a triple positivity profile (OR 2.47, 95% CI: 1.05–5.80; $p = 0.04$, $I^2 = 61\%$). Additionally, LA+ was associated with SGA with an OR of 1.78 (95% CI: 1.16–2.74; $p < 0.01$, $I^2 = 0\%$). No statistically significant association was discerned for aCL+ (OR 0.75, 95% CI: 0.32–1.78; $p = 0.52$, $I^2 = 0\%$), IgM aCL+ (OR 1.49, 95% CI: 0.75–2.97; $p = 0.26$, $I^2 = 43\%$), IgG aCL+ (OR 1.41, 95% CI: 0.53–3.74; $p = 0.49$, $I^2 = 64\%$) and IgM ab2GP1+ (OR 1.28, 95% CI: 0.82–1.98; $p = 0.28$, $I^2 = 0\%$) (Fig. F.5). Pooled analysis of the association between SGA and IgG ab2GP1+ was not reported because of considerable heterogeneity ($I^2 = 85\%$).

3.2.4. *Preterm birth*

For the outcome of preterm birth a history of arterial, venous or small vessel thrombosis ($n = 5$), concomitant autoimmune disease ($n = 2$), APS laboratory category ($n = 3$), LA+ (n = 2), aCL+ (n = 2), IgG aCL+ (n = 2) and IgM aCL+ (n = 2) were studied as potential predictors [6–9,11,16,37,38].

No association was found between previous thrombosis and preterm birth (OR 1.42, 95% CI: 0.87–2.32; $p = 0.16$, $I^2 = 0\%$). However, APS laboratory category I compared to laboratory category II was associated with an increased risk of preterm birth, with an OR of 1.35 (95% CI: 1.13–1.61; $p < 0.01$, $I^2 = 49\%$). An increased risk of preterm birth was found for LA+ patients (OR 3.56, 95% CI: 1.34–9.49; $p = 0.01$, $I^2 = 48\%$). No significant associations were identified for concomitant autoimmune disease (OR 1.91, 95% CI: 0.78–4.65; p = 0.16, $I^2 = 5\%$), aCL+ (OR 0.91, 95% CI: 0.50–1.64; $p = 0.75$, $I^2 = 0\%$), IgG aCL+ (OR 1.25, 95% CI: 0.88–1.79; $p = 0.22$, $I^2 = 0\%$) and IgM aCL+ (OR 1.22, 95% CI: 0.69–2.15; $p = 0.49$, $I^2 = 47\%$) (Fig. F.6).

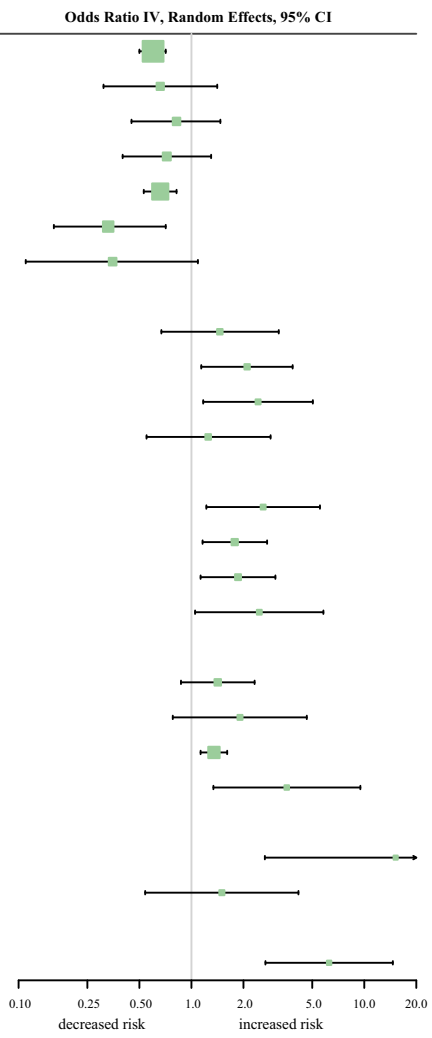
3.2.5. *Neonatal mortality*

Data of neonatal mortality and APS in current literature is sparse. Meta-analyses on two potential predictors could be performed, previous thrombosis ($n = 2$) and APS laboratory category (n = 2) [6,11,12]. Previous thrombosis was associated with neonatal mortality in women with APS (OR 15.19 95% CI: 2.66–86.86; $p < 0.01$, $I^2 = 0\%$). No statistically significant association was identified for APS laboratory category I compared to laboratory category II (OR 1.50, 95% CI: 0.54–4.16; $p = 0.44$, $I^2 = 0\%$) (Fig. F.7).

3.2.6. *Antenatal or postpartum thrombotic event*

Few studies ($n = 7$) described risk factors for antenatal or postpartum

Outcome	Predictor	Pooled OR	[95% CI]	Studies	N	I^2	Overall Effect
	Previous thrombosis	0.60	[0.50; 0.71]	7	1383	40%	p < 0.01
	Concomitant AID	0.66	[0.31; 1.41]	3	315	0%	p = 0.28
	LA+	0.82	[0.45; 1.47]	3	256	0%	p = 0.50
Live birth	aCL+	0.72	[0.40; 1.30]	4	362	0%	p = 0.28
	Laboratory category I	0.66	[0.53; 0.82]	7	1439	0%	p < 0.01
	Triple positivity	0.33	[0.16; 0.71]	6	1223	68%	p < 0.01
	ANA+	0.35	[0.11; 1.09]	2	209	32%	p = 0.07
	Previous thrombosis	1.46	[0.67; 3.20]	3	344	4%	p = 0.35
Preeclampsia	LA+	2.10	[1.14; 3.85]	2	760	48%	p = 0.02
	Triple positivity	2.43	[1.17; 5.04]	3	1023	35%	p = 0.02
	ab2GP1-M+	1.25	[0.55; 2.87]	2	389	27%	p = 0.59
	Previous thrombosis	2.60	[1.22; 5.54]	3	243	0%	p = 0.01
SGA	LA+	1.78	[1.16; 2.74]	3	821	0%	p < 0.01
	Laboratory category I	1.86	[1.13; 3.06]	4	1841	43%	p = 0.01
	Triple positivity	2.47	[1.05; 5.80]	3	1027	61%	p = 0.04
	Previous thrombosis	1.42	[0.87; 2.32]	5	585	0%	p = 0.16
Preterm birth	Concomitant AID	1.91	[0.78; 4.65]	2	105	5%	p = 0.16
	Laboratory category I	1.35	[1.13; 1.61]	3	1801	49%	p < 0.01
	LA+	3.56	[1.34; 9.49]	2	298	48%	p = 0.01
Neonatal mortality	Previous thrombosis	15.19	[2.66; 86.86]	2	255	0%	p < 0.01
	Laboratory category I	1.50	[0.54; 4.16]	2	843	0%	p = 0.44
Antenatal/postpartum thrombosis	Previous thrombosis	6.26	[2.68; 14.63]	3	435	0%	p < 0.01



+: positivity; ab2GP1-M: anti-β_2-glycoprotein-I immunoglobulin M; aCL: anticardiolipin; AID: autoimmune disease; ANA: antinuclear antibody; CI: confidence interval; IV: inverse variance; LA: lupus anticoagulant; N: number of observations; OR: odds ratio; SGA: small for gestational age.

Fig. 2. Summary of meta-analyses. Pooled ORs per predictor for each outcome, 95% confidence interval, number of pooled studies, number of observations, heterogeneity and test of overall effect are presented. Forest plots of each meta-analysis with study-specific effect size and weight can be found in Appendix F.

thrombotic events. A pooled analysis with a history of arterial, venous or small vessel thrombosis as predictor could be conducted, including three studies [11,37,40]. Women with a previous thrombosis were at an increased risk of developing an arterial and/or venous thrombotic event during pregnancy or puerperium with an OR of 6.26 (95% CI: 2.68–14.63; $p < 0.01$, $I^2 = 0\%$) (Fig. F.8).

3.3. Subgroup analysis and reporting bias

The predefined subgroups analyses (concomitant SLE, LMWH use, APS diagnostic criteria) could not be performed, as there were too few studies in each meta-analysis to assemble appropriate subgroups. Furthermore, the presence of reporting bias could not be assessed because none of the pooled analyses contained ten or more studies.

3.4. Risk of bias assessment (Fig. 3)

In general, the risk of bias of included studies was considerable. Risk of bias was especially considered high for Domain 1: *Study participation*, Domain 5: *Study confounding* and Domain 6: *Statistical analysis and reporting*. Domain 1 studies the risk of bias induced by a different relationship between the predictor and the outcome for participants and eligible non-participants. Frequently, included studies were considered high risk of bias on this domain, as recruitment strategies or inclusion and exclusion criteria were not (clearly) described. Domain 5 and 6 represent the adjustment for other predictors and their handling in the statistical analysis. Most included studies reported event rates or performed univariable analysis. The few studies that adjusted for other predictors often identified these predictors by univariable analysis, retaining those that were statistically significant, instead of selecting predictors to adjust for based on previous literature. This resulted in a high risk of bias. Moreover, often too many candidate predictors were considered compared to the number of outcome events, which makes overfitting likely [41].

4. Discussion

To our knowledge, this is the first meta-analysis on predictors of pregnancy outcome in women diagnosed with APS. Previous thrombosis, laboratory category I, triple positivity and presence of LA+ were identified as predictors of adverse pregnancy outcomes. In general, previous thrombosis and triple positivity yielded the highest risk of obstetric complications, with most ORs varying between 2 and 6.

In line with previous reviews [13–15], we corroborate that previous

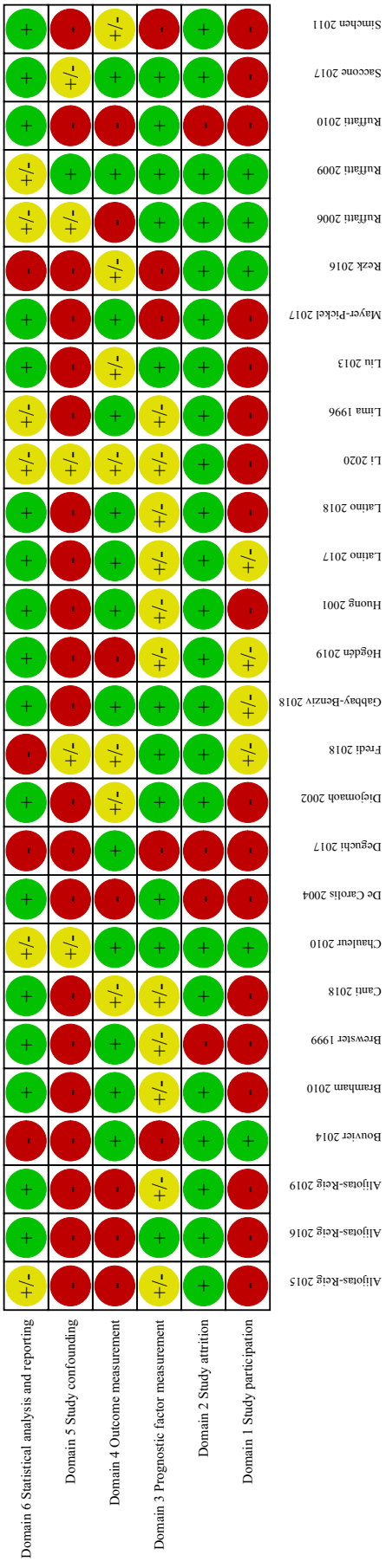


Fig. 3. Risk of bias assessment. Red (−): high risk; yellow (+/−): moderate risk; green (+): low risk.

thrombosis, triple positivity and laboratory category I are associated with various adverse pregnancy outcomes, as depicted in Fig. 2. Considering specific antiphospholipid antibodies, LA+ has been presented as the chief predictor of poor pregnancy outcome by two reviews [13,15], while De Carolis et al. points out that evidence on the predictive value of LA+ remains conflicting [14]. Our meta-analysis identified statistically significant associations between LA+ and several adverse pregnancy outcomes with low levels of heterogeneity. Included studies reported less frequently on the associations between ab2GP1+ or aCL+ and pregnancy outcomes. Consequently, available data was too sparse to pool or resulted in considerable heterogeneity. Another conclusion made by previous reviews is that the presence of concomitant autoimmune disease is associated with poor obstetric outcome [13–15]. However, the results of our meta-analysis do not support such statements. The presence of concomitant autoimmune disease in relation to the studied adverse pregnancy outcomes has only been analyzed by four studies [10,16,33,42]. On top of that, the studies that did analyze this relationship yielded no (clinically or statistically) significant results.

It is unclear, and beyond the scope of the study, whether the predictors identified by this meta-analysis causally interfere with the course of pregnancy. LA+, triple positivity and laboratory category I are considered high risk aPL profiles for both thrombotic and adverse obstetric events by the European League Against Rheumatism (EULAR) [43]. It could be postulated that these antibodies interfere with placentation, predisposing patients to fetal loss, placental insufficiency and preeclampsia [44]. Another subgroup identified by this meta-analysis as high-risk of pregnancy complications consists of patients with thrombotic APS. Notably, while placental infarction is more common in aPL positive women compared to those without aPL, it is not the universal characteristic in cases of fetal loss [45]. Moreover, spiral artery, placental vessel or intervillous thromboses are not commonly found in placentas of aPL positive women [45,46]. Current evidence suggests that obstetric morbidity is primarily explained by placental inflammation, inhibition of trophoblast proliferation and function and complement activation [44,47]. Immune cell and complement activation are also thought to have an important role in thrombotic APS [44]. It could therefore be hypothesized that thrombosis does not directly cause adverse obstetric events, but that both presentations of APS share a common pathway. The same reasoning could also provide an explanation of the fact that previous thrombosis is one of the strongest predictors of pregnancy complications.

An important finding of this meta-analysis is the lack of a standardized outcome set for studies about APS, which resulted in outcome definitions that varied (sometimes even widely) between studies, as such we were unable to pool predictors on the outcomes of miscarriage and perinatal death. This is cumbersome, as these endpoints are especially relevant to the APS population. This finding highlights the need for consistency of predictor and outcome definitions across studies. Initiatives such as CROWN (CoRe Outcomes in WomeN's health) and COMET (Core Outcome Measures in Effectiveness Trials) might resolve this important matter in the future [48]. Until then, we would suggest to use predictor and outcome definitions as defined by international guidelines such as EULAR [49], European Society of Human Reproduction and Embryology (ESHRE) [50] and International Society for the Study of Hypertension in Pregnancy (ISSHP) [51].

The strength of this systematic review and meta-analysis is reflected by the pooled analyses, which provide clinicians with up-to-date knowledge on the effect sizes of pregnancy outcome predictors in women with APS. Such knowledge supports patient-tailored therapy and preconception counseling. We used guideline recommended, state-of-the-art techniques in our search strategy, data extraction and risk of bias assessment [17,18,20–22]. Consequently, the results of our meta-analysis are reliable and can be extrapolated to daily practice. The results of this meta-analysis can also be used in the development of a prediction model of pregnancy outcomes in women with APS. At this time, no such model is available, which is unfortunate as it would

strongly improve preconception counseling and assignment of appropriate treatment strategies to high-risk individuals. This meta-analysis differs from existing reviews by an extensive systematic search of multiple databases, blinded standardized screening, pooling of odds ratios and a risk of bias assessment of current literature.

The results of our meta-analyses are limited by the use of clinically heterogeneous data disregarding differences in APS diagnostic criteria (Sapporo, Sydney or non-criteria APS), scientific unit (number of pregnancies vs. patients) and sometimes (unknown) differences in predictor or outcome definitions. A good example of the latter is preterm birth, for which cut-offs of gestational age at birth differ between studies (generally <34 weeks or < 37 weeks of gestation). Nonetheless, the majority of pooled odds ratios showed low levels of between-study heterogeneity. Unfortunately, some of the pooled results (5/36 pooled odds ratios) of our meta-analysis did show substantial heterogeneity (i.e. I^2 between 50 and 90% [24], meta-analyses with $I^2 > 75\%$ were not reported). Due to the limited number of studies included per meta-analysis, we were unable to study plausible causes of between-study heterogeneity by use of subgroup analyses. The results of pooled ORs with substantial heterogeneity should thus be interpreted with caution. Another limitation of our meta-analysis is that we were unable to study the presence of reporting bias as none of the meta-analyses comprised ten or more studies.

5. Conclusions

This meta-analysis summarizes current evidence on pre-pregnancy available predictors of adverse pregnancy outcomes in women diagnosed with APS. Pooled analyses identified previous thrombosis, laboratory category I, triple positivity and lupus anticoagulant positivity as important predictors of various adverse pregnancy outcomes. The results presented provide clinicians with up-to-date knowledge of predictors of pregnancy outcome in women with APS that allows for a personalized risk assessment during preconception counseling.

Take home message

Current evidence of predictors of pregnancy outcomes in women diagnosed with APS is heterogeneous.

Previous thrombosis, double or triple positivity and lupus anticoagulant positivity were identified as key predictors of adverse pregnancy outcomes, with most odds ratios varying between 2 and 6.

The results of this meta-analysis can be used to guide individualized risk assessment during preconception counseling.

For future research, it is of great importance to develop core outcome sets for studies in APS.

Declaration of Competing Interest

None.

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Acknowledgements

We would like to express our gratitude to Dr. Amelia Ruffatti of the Rheumatology Unit, Department of Medicine, University of Padua, Padua, Italy and Dr. Ariela Hoxha of the Internal Medicine Unit, Department of Medicine, San Bortolo Hospital, Vicenza, Italy for providing us with the essential data to pool results for the neonatal mortality outcome.

Appendix A. Search string

Table A.1
Search string.

Pubmed	Embase
((((Validat* [tiab] OR Predict*[tiab] OR Rule* [tiab]) OR (Predict* [tiab] AND (Outcome* [tiab] OR Risk* [tiab] OR Model* [tiab])) OR ((History [tiab] OR Variable* [tiab] OR Criteria [tiab] OR Scor* [tiab] OR Characteristic* [tiab] OR Finding* [tiab] OR Factor* [tiab]) AND (Predict* [tiab] OR Model* [tiab] OR Decision* [tiab] OR Identif* [tiab] OR Prognos*[tiab])) OR (Decision* [tiab] AND (Model* [tiab] OR Clinical* [tiab] OR "Logistic Models"[tiab])) OR (Prognostic [tiab] AND (History [tiab] OR Variable* [tiab] OR Criteria [tiab] OR Scor* [tiab] OR Characteristic* [tiab] OR Finding* [tiab] OR Factor* [tiab] OR Model* [tiab]))) OR (Stratification [tiab] OR "ROC Curve" [Mesh] OR Discrimination [tiab] OR Discriminate [tiab] OR c-statistic [tiab] OR "Area under the curve" [tiab] OR AUC [tiab] OR Calibration [tiab] OR Indices [tiab] OR Algorithm [tiab] OR Multivariable [tiab]) OR (Pregnancy risk factor*[tiab] OR Obstetric outcome*[tiab] OR Neonatal outcome*[tiab] OR Pregnancy outcome*[tiab] OR Maternal outcome*[tiab] OR Foetal-maternal outcome*[tiab] OR Fetal-maternal outcome*[tiab])) AND ("Antibodies, Antiphospholipid"[MeSH] OR "Antiphospholipid Syndrome"[MeSH] OR "APS"[tiab] OR "OAPS"[tiab] OR "APLS"[tiab] OR Antiphospholipid syndrome*[tiab] OR Antiphospholipid antibody syndrome*[tiab] OR Antiphospholipid antibod*[tiab] OR Antiphospholipid autoantibod*[tiab] OR "aPL"[tiab] OR Anti-phospholipid antibod* [tiab] OR Anti-phospholipid autoantibod*[tiab] OR "Hughes Syndrome"[tiab] OR "Anti-Phospholipid Syndrome"[tiab])) AND ("Pregnancy"[MeSH] OR "Pregnancy Outcome"[MeSH] OR "Pregnancy Complications"[MeSH] OR "Preeclampsia"[MeSH] OR "Infant"[MeSH] OR Pregnan*[tiab] OR "Obstetric"[tiab] OR "Abortion"[tiab] OR "Fetal death"[tiab] OR "Foetal death"[tiab] OR "Fetal demise"[tiab] OR "Foetal demise"[tiab] OR Miscarriage*[tiab] OR "Preeclampsia"[tiab] OR Stillbirth[tiab] OR "Fetal growth restriction"[tiab] OR "Foetal growth restriction"[tiab] OR Intrauterine growth restrict* [tiab] OR Intra uterine growth restrict*[tiab] OR IUGR[tiab] OR "Small for gestational age"[tiab] OR SGA[tiab] OR Birth[tiab] OR Labour[tiab] OR Maternal[tiab] OR Perinatal [tiab] OR Neonat*[tiab] OR "Newborn"[tiab] OR "Newborns"[tiab] OR "Infant"[tiab] OR "Infants"[tiab] OR "Baby"[tiab] OR "Babies"[tiab])	(validat*:ti,ab,kw OR predict*:ti,ab,kw OR rule*:ti,ab,kw OR (predict*:ti,ab,kw AND (outcome*:ti,ab,kw OR risk*:ti,ab,kw OR model*:ti,ab,kw)) OR ((history:ti,ab,kw OR variable*:ti,ab,kw OR criteria:ti,ab,kw OR scor*:ti,ab,kw OR characteristic*:ti,ab,kw OR finding*:ti,ab,kw OR factor*:ti,ab,kw) AND (predict*:ti,ab,kw OR model*:ti,ab,kw OR decision*:ti,ab,kw OR identif*:ti,ab,kw OR prognos*:ti,ab,kw)) OR (decision*:ti, ab,kw AND (model*:ti,ab,kw OR clinical*:ti,ab,kw OR 'logistic models':ti,ab,kw)) OR (prognostic:ti,ab,kw AND (history:ti,ab,kw OR variable*:ti,ab,kw OR criteria:ti,ab,kw OR scor*:ti,ab,kw OR characteristic*:ti,ab,kw OR finding*:ti,ab,kw OR factor*:ti,ab, kw OR model*:ti,ab,kw)) OR stratification:ti,ab,kw OR 'receiver operating characteristic'/exp. OR discrimination:ti,ab,kw OR discriminate:ti,ab,kw OR 'c-statistic':ti,ab,kw OR 'area under the curve':ti,ab,kw OR auc:ti,ab,kw OR calibration: ti,ab,kw OR indices:ti,ab,kw OR algorithm:ti,ab,kw OR multivariable:ti,ab,kw OR 'pregnancy risk factor*':ti,ab,kw OR 'obstetric outcome*':ti,ab,kw OR 'neonatal outcome*':ti,ab,kw OR 'pregnancy outcome*':ti,ab,kw OR 'maternal outcome*':ti,ab, kw OR 'foetal-maternal outcome*':ti,ab,kw OR 'fetal-maternal outcome*':ti,ab,kw) AND ('phospholipid antibody'/exp. OR 'antiphospholipid syndrome'/exp. OR aps:ti, ab,kw OR oaps:ti,ab,kw OR apls:ti,ab,kw OR 'antiphospholipid syndrome*':ti,ab,kw OR 'antiphospholipid antibody syndrome*':ti,ab,kw OR 'antiphospholipid antibod*': ti,ab,kw OR 'antiphospholipid autoantibod*':ti,ab,kw OR apl:ti,ab,kw OR 'anti-phospholipid antibod*':ti,ab,kw OR 'anti-phospholipid autoantibod*':ti,ab,kw OR 'hughes syndrome':ti,ab,kw OR 'anti-phospholipid syndrome':ti,ab,kw) AND ('pregnancy'/exp. OR 'pregnancy outcome'/exp. OR 'pregnancy complication'/exp. OR 'preeclampsia'/exp. OR 'infant'/exp. OR 'pregnan*':ti,ab,kw OR obstetric:ti,ab,kw OR abortion:ti,ab,kw OR 'fetal death':ti,ab,kw OR 'foetal death':ti,ab,kw OR 'fetal demise':ti,ab,kw OR 'foetal demise':ti,ab,kw OR 'miscarriage*':ti,ab,kw OR 'preeclampsia':ti,ab,kw OR stillbirth:ti,ab,kw OR 'fetal growth restriction':ti,ab,kw OR 'foetal growth restriction':ti,ab,kw OR 'intrauterine growth restrict*':ti,ab,kw OR 'intra uterine growth restrict*':ti,ab,kw OR iugr:ti,ab,kw OR 'small for gestational age':ti,ab,kw OR sga:ti,ab,kw OR birth:ti,ab,kw OR labour:ti,ab,kw OR maternal:ti,ab, kw OR perinatal:ti,ab,kw OR 'neonat*':ti,ab,kw OR newborn:ti,ab,kw OR newborns:ti, ab,kw OR infant:ti,ab,kw OR infants:ti,ab,kw OR baby:ti,ab,kw OR babies:ti,ab,kw)

No filters applied.

(*continued on next page*)

Table A.1 (*continued*)

Pubmed	Embase
	Source: EMBASE, EMBASE AND MEDLINE Publication type: Article, article in press, conference abstract, conference paper and letter.
Results 13-06-2020: 1610	Results 13-06-2020: 2367

Appendix B. Predictors and outcomes definition

Appendix_B_Predictors_and_outcomes_definition.xlsx.

Appendix C. Exclusion hierarchy

Title & abstract screening approach

1. Study design
   a. Must be observational, quantitative study in humans.
   b. At least 20 participants.
   c. Must *not* be reviews, opinion pieces, commentaries and clinical case studies that do not use new data.
2. Population
   a. Must be a patient population including pregnant women with APS.
   b. Sydney/Sapporo APS criteria
   c. aPL + clinical feature, but not fulfilling Sydney/Sapporo APS criteria.
   d. Must *not* be a patient population only about multiple pregnancy.
   e. Must *not* be a patient population including women only diagnosed with SLE and no APS.
3. Index prognostic factor
   a. Must be reporting on preconceptionally available risk factors.
   b. Must *not* be publications solely based on characteristics that are not yet known at the preconception stage
4. Outcomes
   a. Must be reporting on at least one of the following outcomes: 1) live birth, 2) Preeclampsia, 3) SGA, 4) Fetal growth restriction, 5) preterm birth, 6) Fetal death, 7) Perinatal mortality, 8) Neonatal death and 9) Antenatal or postpartum thrombotic event.
   b. Must not be a composite outcome.
5. Timing of prognostication
   a. Timeframe for the outcome is defined as the beginning of pregnancy until 28 days after birth. (pregnancy + neonatal period)
   b. Prediction should take place at preconception counseling.
6. Setting of prognostication
   a. Secondary/tertiary care

Full-text screening approach

1. Full text (not) available
   a. Contact author in case not available
2. Multiple publications: Same cohort and PICOTS as other included study
   a. Include most recent or relevant study.
3. Sample size <20
4. Study design

a. Must be observational, quantitative study in humans.
b. Must *not* be reviews, opinion pieces, commentaries and clinical case studies that do not use new data.
c. Poster/conference abstract with insufficient data.
d. Insufficient data reported.

5. Population
   a. Must be a patient population including pregnant women with APS.
   b. Sydney/Sapporo APS criteria or aPL + clinical feature, but not fulfilling Sydney/Sapporo APS criteria.
   c. Must *not* be a patient population only about multiple pregnancy.
   d. Must *not* be a patient population including women only diagnosed with SLE and no APS.
   e. Must *not* be a patient population selected based on clinically significant comorbidities.
7. Index prognostic factor
   a. Must be reporting on preconceptionally available risk factors.
   b. Must *not* be publications solely based on characteristics that are not yet known at the preconception stage.
   c. There must be a prognostic factor.
8. Outcomes

a. Must be reporting on at least one of the following outcomes: 1) live birth, 2) Preeclampsia, 3) SGA, 4) Fetal growth restriction, 5) preterm birth, 6) Fetal death, 7) Perinatal mortality, 8) Neonatal death and 9) Antenatal or postpartum thrombotic event.
b. Must not be a composite outcome.

9. Timing of prognostication
   a. Timeframe for the outcome is defined as the beginning of pregnancy until 28 days after birth. (pregnancy + neonatal period)
   b. Prediction should take place at preconception counseling.
10. Setting of prognostication
   a. Secondary/tertiary care

Appendix D. Extended study characteristics

Table D.1
Extended characteristics of included studies.

Author	Year of publication	Study design	Location	Participants	Enrolment period participants	SLE n (%)	LMWH n (%)	Index prognostic factor	Outcome
Alijotas-Reig et al. [9]	2015	Retrospective multicenter	Europe	247 women with OAPS (Sydney)	Unknown – 2013	Unknown	182 (73.7)	Antiphospholipid antibody type, laboratory category, triple positivity	Early onset preeclampsia/ HELLP, preterm birth, FGR, miscarriage, fetal loss/stillbirth
Alijotas-Reig et al. [52]	2016	Retrospective multicenter	Europe	147 women with OAPS (Sydney)	Unknown	Unknown	Unknown	Inherited thrombophilia	Early onset preeclampsia, late onset preeclampsia, preterm birth, early onset FGR, fetal loss, stillbirth, arterial/ venous thrombotic event during pregnancy or puerperium
Alijotas-Reig et al. [8]	2019	Retrospective multicenter	Europe, Argentina	1000 women with OAPS (Sydney)	Unknown – 2017	76 (7.6)	673 (67.3)	Laboratory category	Preeclampsia <34 wks GA, Preeclampsia >34 wks GA, preterm birth, FGR <34 wks GA, FGR >34 wks GA, miscarriage (latest), fetal loss, stillbirth
Bouvier et al. [7]	2014	Prospective monocenter	France	517 women with OAPS (Sydney)	January 1995–January 2005	Unknown	517 (100)	Maternal age, BMI, family history, ethnicity, smoking history, varicose veins, pre-existing hypertension, previous embryonic pregnancy loss, previous fetal pregnancy loss, primary/ secondary loss, prior inflammatory disease, hypercholesterolemia, hypertriglyceridemia, antiphospholipid antibody type, triple positivity, thrombophilia associated gene polymorphisms	Preeclampsia, early onset preeclampsia, premature birth <37 wks GA, premature birth <34 wks GA, SGA neonate, abortion/embryonic loss <10 wks GA, fetal loss >10 wks GA
Bramham et al. [37]	2010	Retrospective monocenter	United Kingdom	83 APS pregnancies (Sapporo)	January 2000–December 2007	19 (22.8)	Unknown	Thrombotic APS	Preeclampsia, preterm birth, SGA, thromboembolic event
Brewster et al. [53]	1999	Nonnested case-control monocenter	United Kingdom	61 NC-APS pregnancies	1992–1997	Unknown	Unknown	Antiphospholipid antibody type combinations	SGA
Canti et al. [54]	2018	Prospective multicenter	Italy	47 women with APS (Sydney)	Unknown	9 (19.1)	47 (100)	Antiphosphatidylserine/ prothrombin antibodies	Preeclampsia and/or HELLP, intrauterine growth restriction, pregnancy loss <10 wks GA, pregnancy loss >10wks GA, intrauterine fetal death
Chauleur et al. [39]	2010	Prospective monocenter	France	142 women with NC-OAPS	January 1999–February 2004	0 (0)	0 (0)	Antiphospholipid antibody type, BMI	Preeclampsia, FGR, embryonic loss <10 wks GA

(continued on next page)

Table D.1 (*continued*)

Author	Year of publication	Study design	Location	Participants	Enrolment period participants	SLE n (%)	LMWH n (%)	Index prognostic factor	Outcome
De Carolis et al. [55]	2004	Prospective monocenter	Italy	85 women with APS (Sapporo)	Unknown	0 (0)	0 (0)	Anti-thyroid antibodies	Live birth
Deguchi et al. [16]	2017	Retrospective multicenter	Japan	81 APS pregnancies (Sydney)	November 2008–October 2013	35 (43.2)	0 (0)	Maternal age, secondary APS, history of thrombosis, history of 3 or more pregnancy loss <10 wks GA, history of 2 or more pregnancy loss ≥10 wks GA, history of premature birth <32 wks GA, nulliparity, history of hypertensive disorders of pregnancy, antiphospholipid antibody type, antinuclear antibody, activated partial thromboplastin time prolongation, low complements	Live birth, premature birth <34 wks GA, light-for-date neonate, pregnancy loss
Diejomaoh et al. [56]	2002	Prospective monocenter	Kuwait	43 women with APS (Sapporo)	March 1998–December 1999	0 (0)	0 (0)	Previous primary pregnancy loss	Live birth, preterm birth <37 wks GA, miscarriage first trimester, miscarriage second trimester, perinatal loss
Fredi et al. [40]	2018	Retrospective multicenter	Italy and France	190 APS pregnancies (Sydney)	January 2000 – December 2014	0 (0)	167 (87.9%)	Thrombotic APS	Preterm birth <34 wks GA, spontaneous abortion, fetal death, arterial/venous thrombotic event during pregnancy or puerperium
Gabbay-Benziv et al. [38]	2017	Retrospective monocenter	Israel	99 women with APS (Sydney)	January 2012–December 2016	17 (17.2)	99 (100)	Thrombotic APS, antiphospholipid antibody type	Preeclampsia, preterm birth, FGR
Högdén et al. [34]	2019	Retrospective monocenter	Sweden	30 women with PAPS (Sydney)	2000–2016	0 (0)	30 (100)	Thrombotic APS, triple positivity	Live birth, preeclampsia, intrauterine growth restriction, SGA, miscarriage
Huong et al. [42]	2001	Retrospective monocenter	France	74 APS pregnancies (Sapporo)	1984–1998	31 (41.9)	Unknown	Secondary APS	Preterm birth
Latino et al. [10]	2017	Retrospective monocenter	Argentina	106 women with APS (Sydney)	April 2007–December 2014	18 (17)	106 (100)	SLE, previous thrombosis, ≥4 previous pregnancy losses, antiphospholipid antibody type, triple positivity	Live birth, miscarriage, fetal loss, pregnancy loss
Latino et al. [57]	2018	Retrospective monocenter	Argentina	97 women with APS (Sydney)	April 2009–December 2016	0 (0)	97 (100)	Baseline serological risk	Live birth, pregnancy loss
Lima et al. [32]	1996	Retrospective monocenter	United Kingdom	47 women with NC-APS	January 1989–July 1994	31 (66)	Unknown	Previous pregnancy loss, previous thrombocytopenia, previous thrombosis, antiphospholipid antibody type	Live birth, arterial/venous thrombotic event during pregnancy or puerperium
Liu et al. [58]	2013	Retrospective monocenter	China	191 women with NC-OAPS	June 2006–December 2010	0 (0)	191 (100)	Antiphospholipid antibody type	Live birth

(*continued on next page*)

Table D.1 (*continued*)

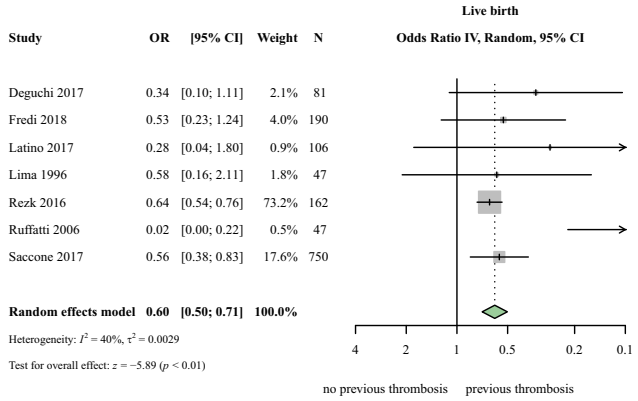
Author	Year of publication	Study design	Location	Participants	Enrolment period participants	SLE n (%)	LMWH n (%)	Index prognostic factor	Outcome
Li et al. [33]	2020	Prospective monocenter	China	128 women with NC-APS/APS (Sydney)	May 2018–January 2020	8 (6.3)	117 (91.4)	Maternal age, ≥3 previous adverse pregnancy outcome, previous miscarriage, SLE, preconception counseling, antinuclear antibody, triple positivity, antiphospholipid antibody type, complement, serum IgG/M/A	Live birth, fetal loss
Mayer-Pickel et al.	2017	Retrospective monocenter	Austria	74 APS pregnancies (Sydney)	Unknown	33 (44.6)	61 (82.4)	Thrombotic APS	Live birth, preeclampsia/HELLP, preterm birth, intrauterine growth restriction, early fetal loss, late fetal loss
Rezk et al. [11]	2016	Prospective monocenter	Egypt	162 women with PAPS (Sydney)	December 2012–December 2015	0 (0)	162 (100)	Maternal age > 30, previous thrombosis, previous preterm birth, antiphospholipid antibody type, triple positivity	Live birth, preeclampsia, preterm birth, SGA, miscarriage, intrauterine fetal death, pregnancy loss, neonatal mortality, venous thromboembolism
Ruffatti et al. [12]	2010	Retrospective monocenter	Italy	93 women with PAPS (Sydney)	August 1991–September 2008	0 (0)	Unknown	Previous thrombosis, previous pregnancy morbidity, antiphospholipid antibody type, triple positivity	Neonatal death
Ruffatti et al. [35]	2009	Retrospective monocenter	Italy	97 PAPS pregnancies (Sydney)	December 1995 – June 2007	0 (0)	60 (61.9)	Laboratory category	Unsuccessful pregnancy
Ruffatti et al. [36]	2006	Retrospective monocenter	Italy	47 women with PAPS (Sydney)	August 1989 – June 2004	0 (0)	20 (42.6)	Maternal age, previous late fetal loss, previous thrombosis, triple positivity	Unsuccessful pregnancy
Saccone et al. [6]	2017	Retrospective multicenter	Italy	750 women with PAPS (Sydney)	January 2007 – April 2016	0 (0)	750 (100)	Previous thrombosis, laboratory category, triple positivity	Live birth, preeclampsia, preterm birth <37 wks GA, intrauterine growth restriction, severe very preterm intrauterine growth restriction, pregnancy loss, stillbirth, neonatal death, venous thromboembolism in the current pregnancy
Simchen et al. [59]	2011	Retrospective monocenter	Israel	55 APS pregnancies (Sydney)	Unknown	19 (34.5)	55 (100)	High positive antibody titers (≥4 times upper limit of normal)	Preterm birth, SGA, pregnancy loss, maternal thrombotic event

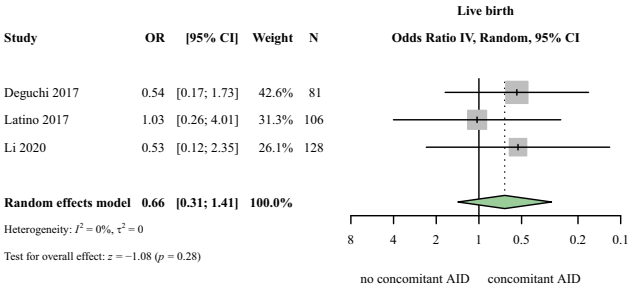
APS: antiphospholipid syndrome; BMI: body mass index; FGR: fetal growth restriction; GA: gestational age; HELLP: haemolysis, elevated liver enzymes, low platelet count; LMWH: low-molecular-weight-heparin; NC-APS: non-criteria antiphospholipid syndrome; NC-OAPS: non-criteria obstetric antiphospholipid syndrome; OAPS: obstetric antiphospholipid syndrome; PAPS: primary antiphospholipid syndrome; SGA: small for gestational age; SLE: systemic lupus erythematosus; wks: weeks.

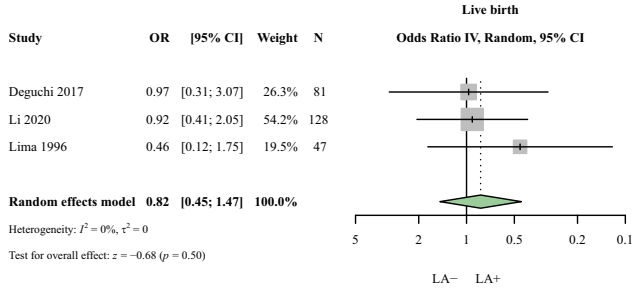
Appendix E. Results systematic review not pooled

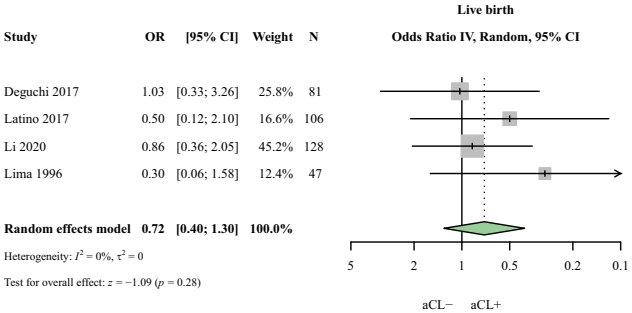
Appendix_E_Results_systematic_review_not_pooled.xlsx.

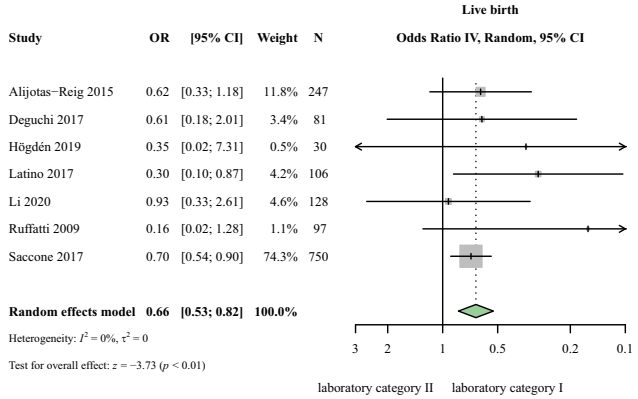
Appendix F. Forest plots

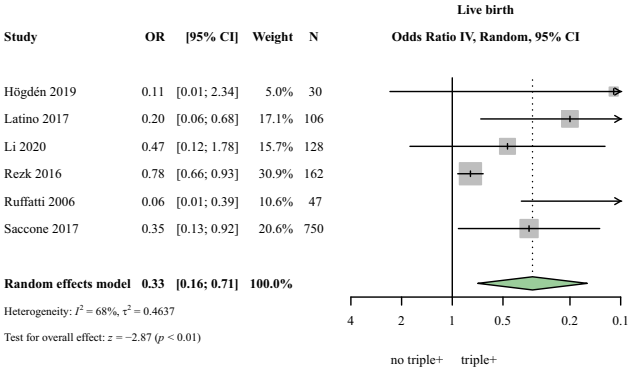


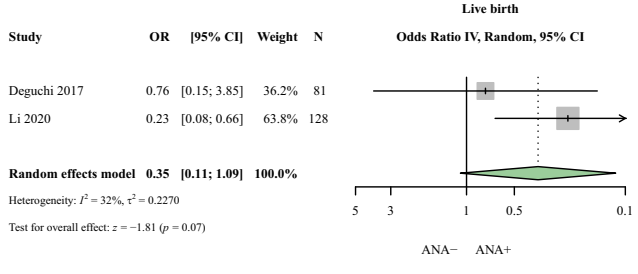






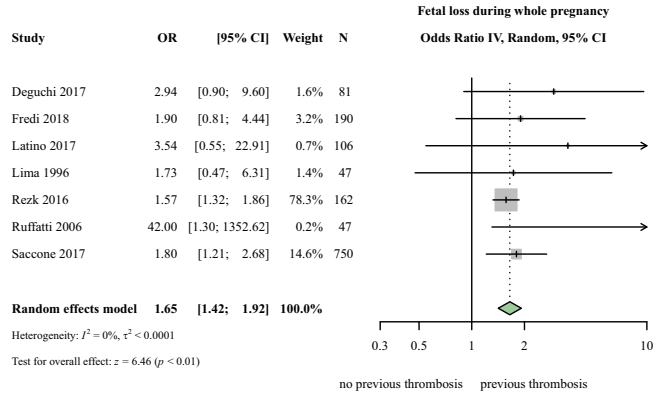


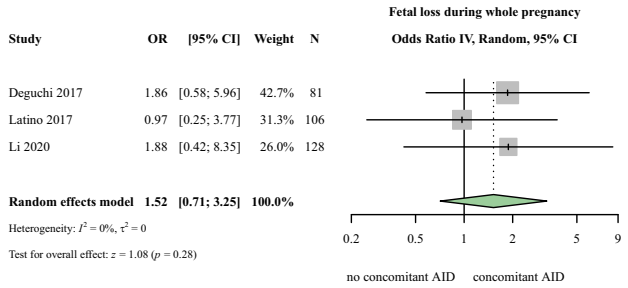


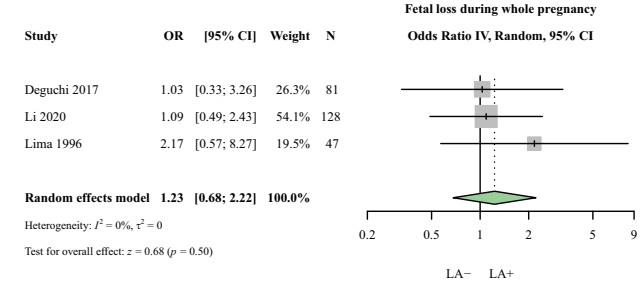


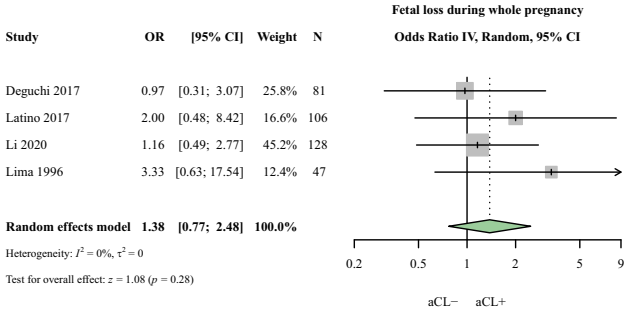
+: positivity; −: negativity; aCL: anticardiolipin; AID: autoimmune disease; ANA: antinuclear antibody; CI: confidence interval; IV: inverse variance; LA: lupus anticoagulant; N: number of women or pregnancies; OR: odds ratio; triple+: triple positivity.

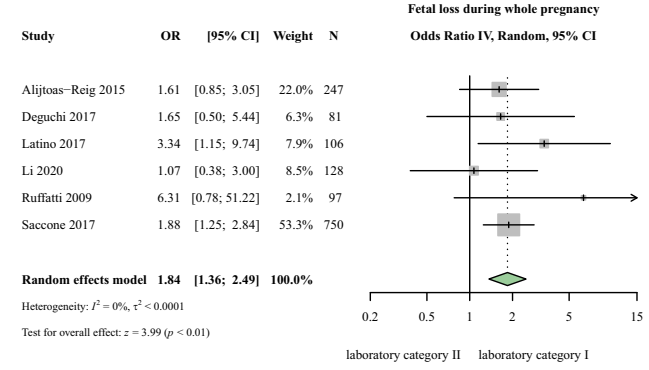
Fig. F.1. Live birth meta-analyses.

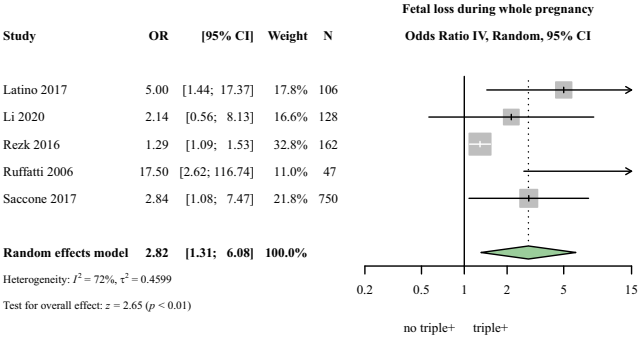


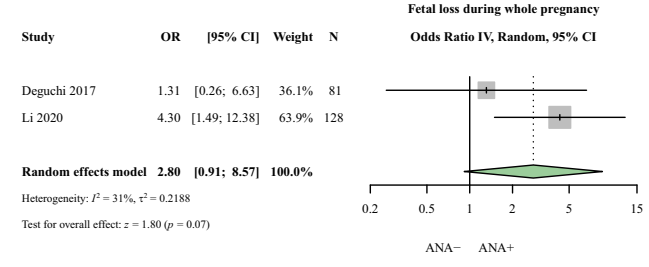






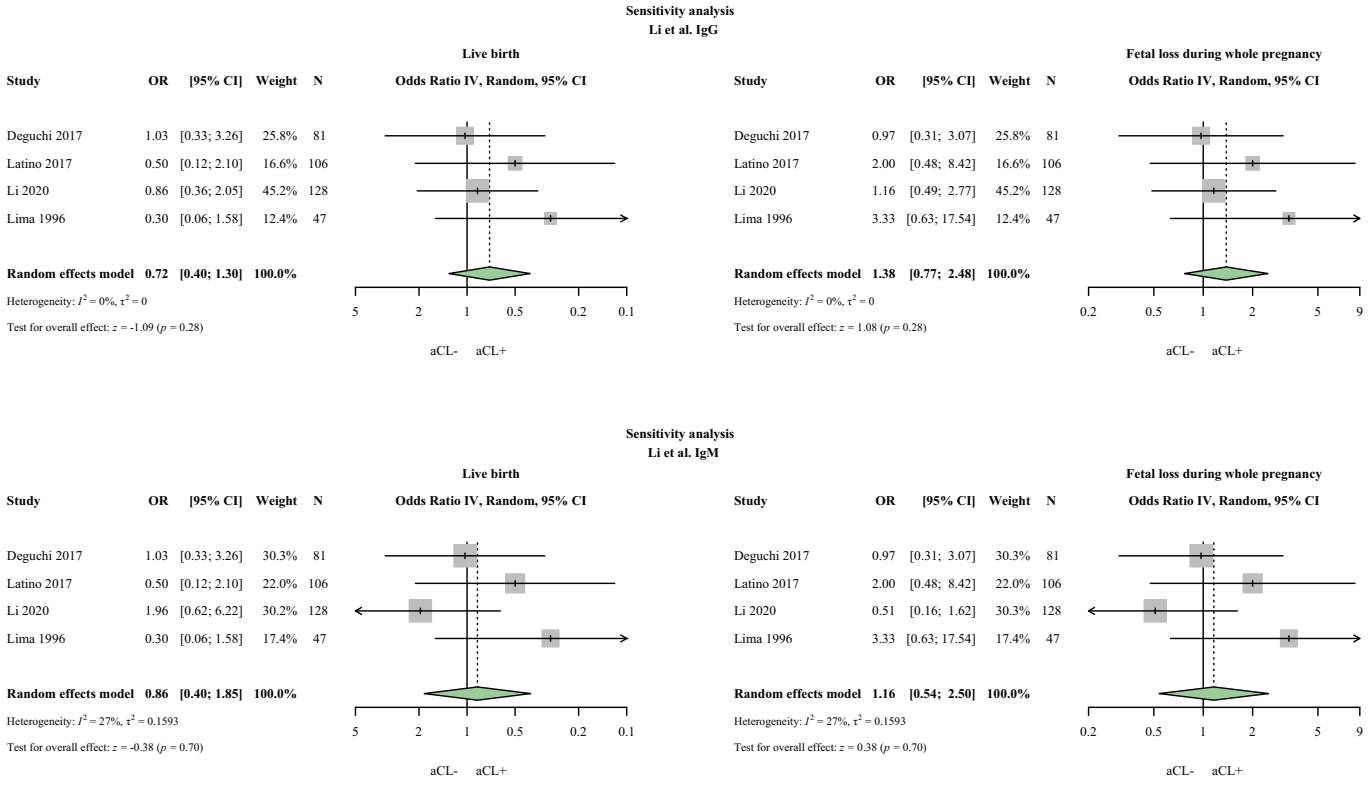






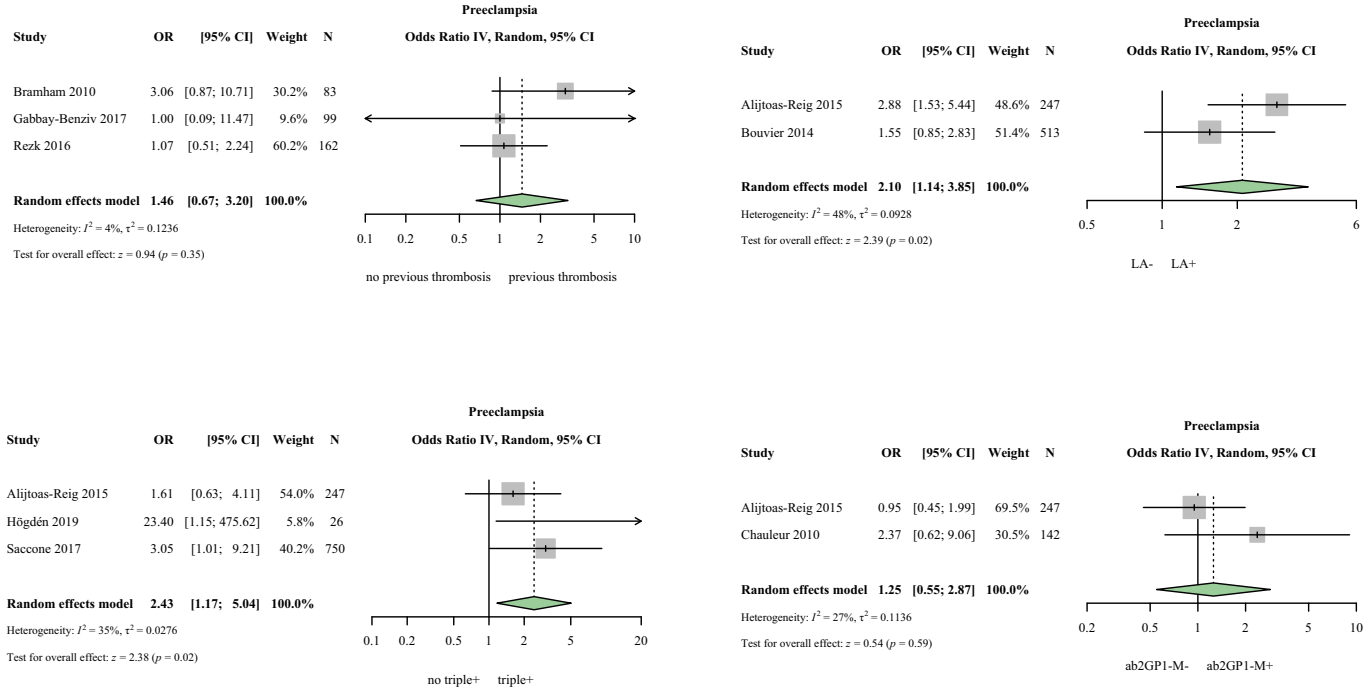
+: positivity; −: negativity; aCL: anticardiolipin; AID: autoimmune disease; ANA: antinuclear antibody; CI: confidence interval; IV: inverse variance; LA: lupus anticoagulant; N: number of women or pregnancies; OR: odds ratio; triple+: triple positivity.

Fig. F.2. Fetal loss during whole pregnancy meta-analyses.



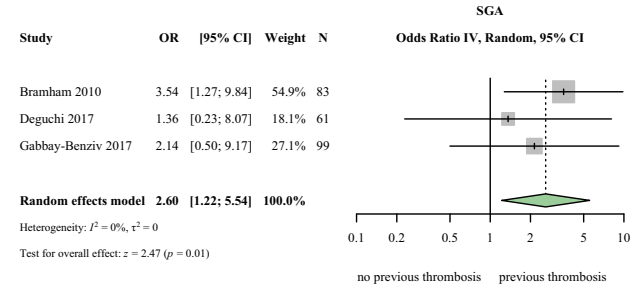
+: positivity; -: negativity; aCL: anticardiolipin; CI: confidence interval; IV: inverse variance; N: number of women or pregnancies; OR: odds ratio.

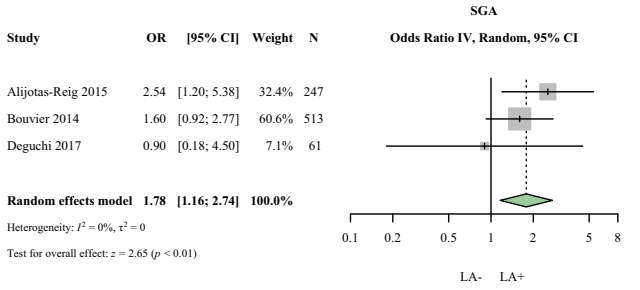
Fig. F.3. Sensitivity analyses live birth and fetal loss during whole pregnancy, where for the study by Li et al. [33] IgG aCL versus IgM aCL were pooled.

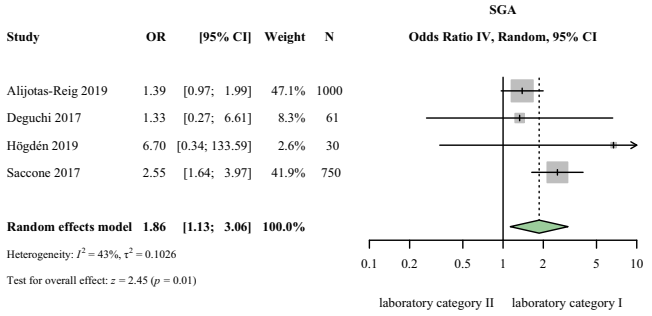


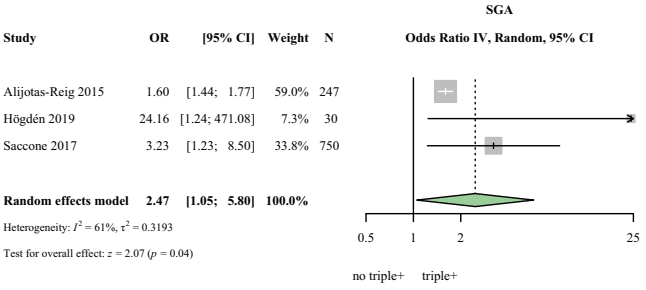
+: positivity; -: negativity; ab2GP1-M: anti-β_2-glycoprotein-I immunoglobulin M; CI: confidence interval; IV: inverse variance; LA: lupus anticoagulant; N: number of women or pregnancies; OR: odds ratio; triple+: triple positivity.

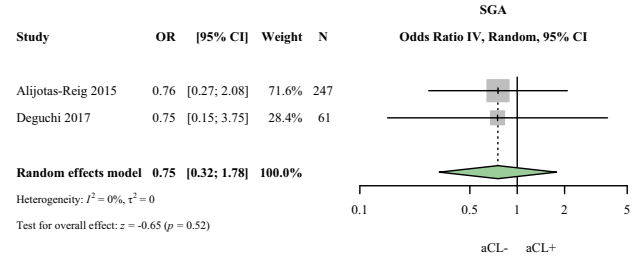
Fig. F.4. Preeclampsia meta-analyses.

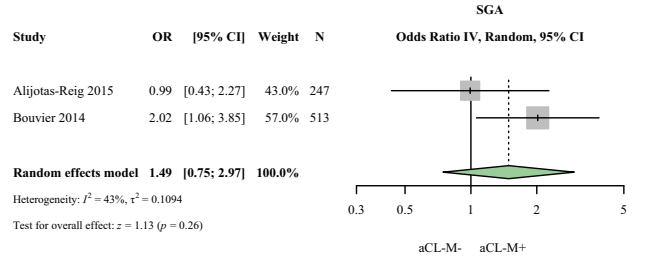


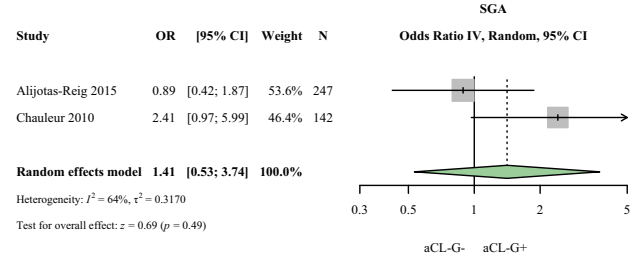


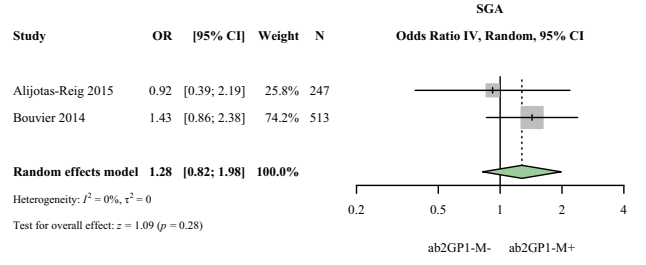






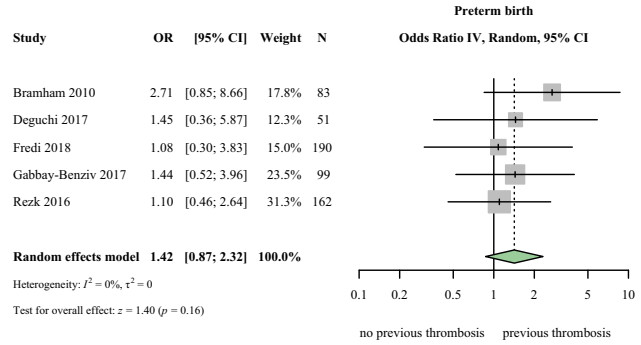


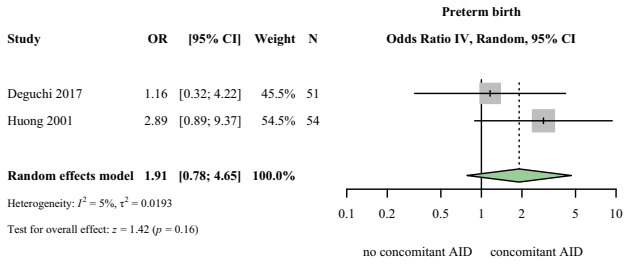


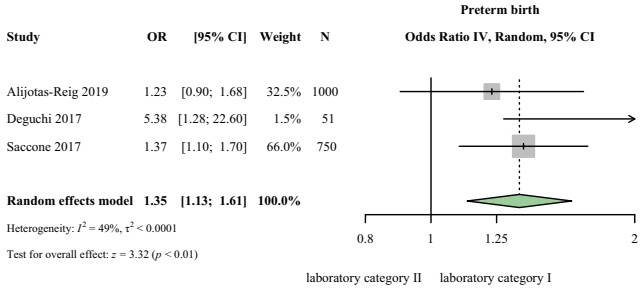


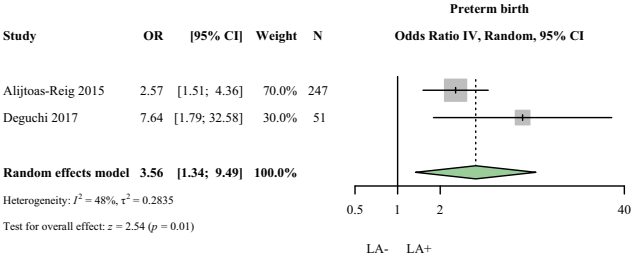
+: positivity; -: negativity; ab2GP1-M: anti-β_2-glycoprotein-I immunoglobulin M; aCL(-G/M): anticardiolipin immunoglobulin G or M; CI: confidence interval; IV: inverse variance; LA: lupus anticoagulant; N: number of women or pregnancies; OR: odds ratio; SGA: small for gestational age; triple+: triple positivity.

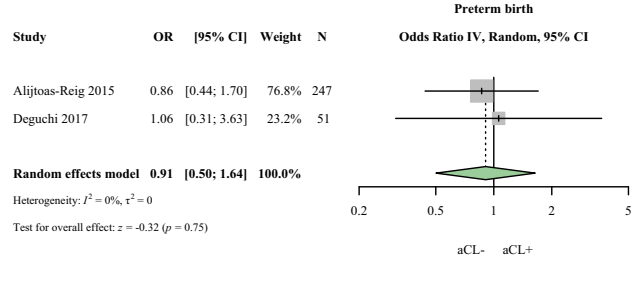
Fig. F.5. Small for gestational age meta-analyses.

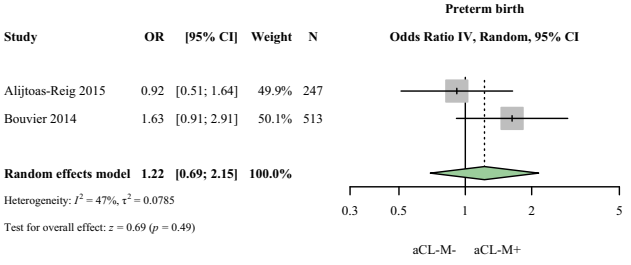


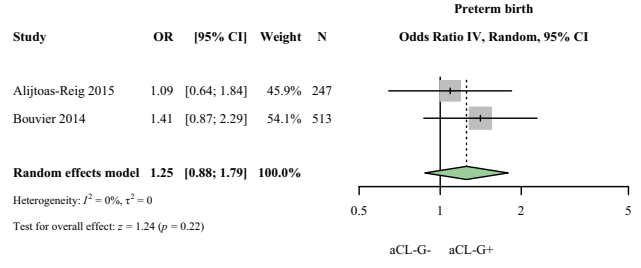






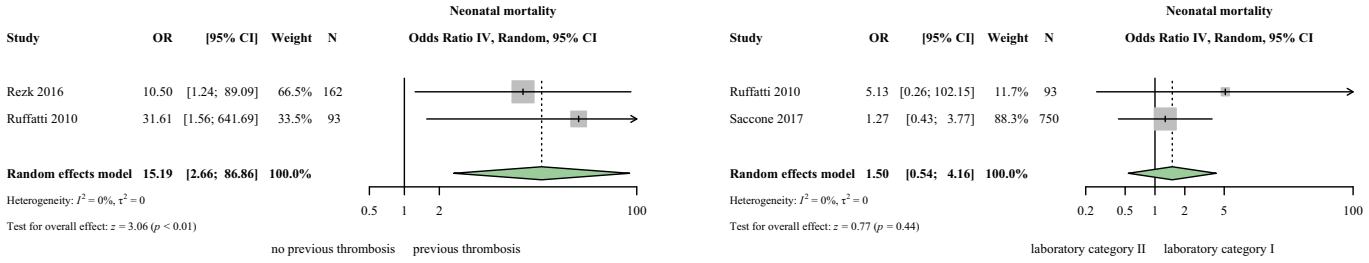






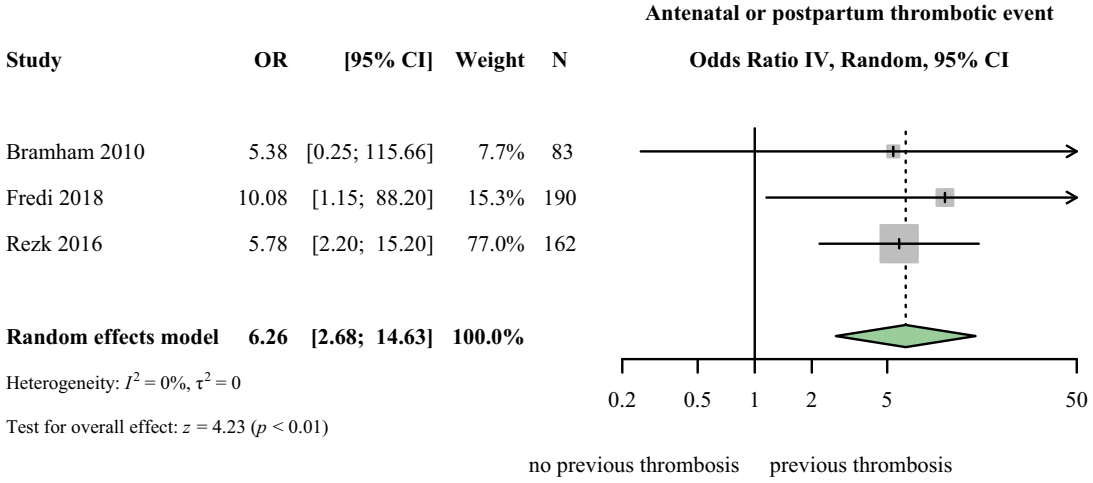
+: positivity; -: negativity; aCL(-G/M): anticardiolipin immunoglobulin G or M; AID: autoimmune disease; CI: confidence interval; IV: inverse variance; LA: lupus anticoagulant; N: number of women or pregnancies; OR: odds ratio; triple+: triple positivity.

Fig. F.6. Preterm birth meta-analyses.



CI: confidence interval; IV: inverse variance; N: number of women or pregnancies; OR: odds ratio.

Fig. F.7. Neonatal mortality meta-analyses.



CI: confidence interval; IV: inverse variance; N: number of women or pregnancies; OR: odds ratio.

Fig. F.8. Antenatal or postpartum thrombotic event meta-analysis.

Appendix G. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2021.102901.

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