

付属資料 1 エビデンスの収集と文献検索

Search Report CQ3-1

I: Review Question

CQ3-1: Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant [Updating Cochrane Review: Empson MB, Lassere M, Craig JC, Scott JR. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD002859. DOI: 10.1002/14651858.CD002859.pub2.]

II: Search Date

July 19, 2015

III: Limitations for Search

Date/Time: No

Language: No

Document Type: No

Publication Status: Published

IV: Resources and Number of Results

Table 1 Search resources details and number of results

Resource	Time Coverage	Search Interface	# of Hits
Cochrane Library (Just CENTRAL)	2009 – Until Search Date	Wiley Online Library	18
EMBASE [Excluding MEDLINE]	2009 – 2015 Week 29	Ovid SP	141
MEDLINE	2009 – Search Date	Ovid SP	144
Subtotal			303
Duplicates			53
Total (for Screening)			250

V: Search Method Section for Paper/Report

Materials and Methods

Search and Selection of Studies

We searched published documents from CENTRAL (in Cochrane Library) and EMBASE and MEDLINE via Ovid SP on July 19, 2015 with no date/time, language, and document type. Keywords were collected through experts' opinion, literature review,

controlled vocabulary (Medical Subject Headings = MeSH and Excerpta Medica Tree = Emtree), and reviewing the primary search results. Search strategies developed by assistance of a medical information specialist were reported in Appendix 1. Search results were de-duplicated in EndNote X5 and then sent to two researchers for screening. 244 were excluded during screening because they were irrelevant to our research question. 6 studies selected for full text assessment using inclusion and exclusion criteria. One study was removed because of non RCT. 5 studies were included in the review for data extraction. Process of selection of studies has been shown in PRISMA flow diagram (Figure 1).

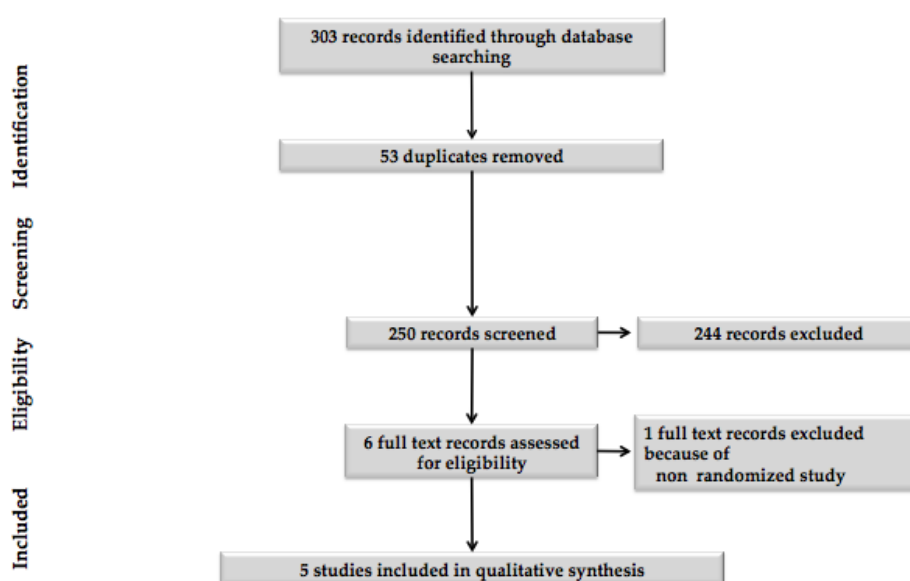


Figure 1 Process of selection of studies for systematic review based on PRISMA flow diagram

Appendix 1: Search Strategies

A. Cochrane Library

- #1 MeSH descriptor: [Abortion, Spontaneous] explode all trees
- #2 MeSH descriptor: [Abortion, Habitual] explode all trees
- #3 MeSH descriptor: [Fetal Death] explode all trees
- #4 fetal loss or miscarriage* or recurrent abortion* or recurrent miscarriage*
- #5 #1 or #2 or #3 or #4
- #6 MeSH descriptor: [Lupus Coagulation Inhibitor] explode all trees
- #7 MeSH descriptor: [Antibodies, Anticardiolipin] explode all trees
- #8 MeSH descriptor: [Antibodies, Antiphospholipid] explode all trees
- #9 MeSH descriptor: [Antiphospholipid Syndrome] explode all trees

#10 lupus inhibitor or lupus anticoagulant or anticardiolipin or antiphospholipid or cardiolipin antibody* or phospholipid antibody*

#11 #6 or #7 or #8 or #9 or #10

#12 #5 and #11 Publication Year from 2009 to 2015, in Trials

C. EMBASE

lupus anticoagulant/ OR phospholipid antibody/ OR antiphospholipid syndrome/ OR cardiolipin antibody/ OR (Anticardiolipin OR antiphospholipid OR lupus inhibitor).tw.

spontaneous abortion/ OR recurrent abortion/ OR fetus wastage/ OR fetus death/ OR (miscarriage\$ OR recurrent miscarriage\$).tw.

(random\$ or factorial\$ or crossover\$ or (cross over\$) or cross-over\$ or placebo\$ or (doubl\$ adj blind\$) or (singl\$ adj blind\$) or assign\$ or allocat\$ or volunteer\$).mp. or crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/

exp animals/ OR exp invertebrate/ OR animal experiment/ OR animal model/ OR animal tissue/ OR animal cell/ OR nonhuman/

human/ OR normal human/ OR human cell/

4 and 5

4 not 6

3 not 7

1 and 2 and 8

Limit 9 to yr="2009 -Current"

D. MEDLINE

lupus coagulation inhibitor/ OR antibodies, anticardiolipin/ OR antibodies, antiphospholipid/ OR antiphospholipid syndrome/ OR (lupus inhibitor OR lupus anticoagulant OR anticardiolipin OR antiphospholipid OR cardiolipin antibody\$ OR phospholipid antibody\$).tw.

fetal death/ OR abortion, spontaneous/ OR abortion, habitual/ OR (fetal loss OR miscarriage\$ OR recurrent abortion\$ OR recurrent miscarriage\$).tw.

(randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or

(randomi?ed or randomly or placebo or trial or groups).ab. or drug therapy.fs. not

(animals not (humans and animals)).sh.

1 and 2 and 3

Limit 4 to yr="2009-current"

Search Report CQ3-2

I: Review Question

CQ3-2: What is the most appropriate treatment for women with severe form of APS to improve pregnancy related outcome?

II: Search Date

July 19, 2015

III: Limitations for Search

Date/Time: No

Language: No

Document Type: No

Publication Status: Published

IV: Resources and Number of Results

Table 1 Search resources details and number of results

Resource	Time Coverage	Search Interface	# of Hits
CINAHL	1937 – Search Date	EBSCOhost	31
Cochrane Library (Including CDSR, CENTRAL, DARE, HTA, CMR, NHS EED)	Until Search Date	Wiley Online Library	135
EMBASE [Excluding MEDLINE]	1974 – 2015 Week 29	Ovid SP	53
MEDLINE	1946 – Search Date	Ovid SP	1487
PubMed [Excluding MEDLINE]	1946 – Search Date	PubMed	40
Subtotal			1746
Duplicates			185
Total (for Screening)			1561

V: Search Method Section for Paper/Report

Materials and Methods

Search and Selection of Studies

We searched published documents from CINAHL via EBSCOhost, Cochrane Library, PubMed, and EMBASE and MEDLINE via Ovid SP on July 19, 2015 with no date/time, language, and document type. Keywords were collected through experts' opinion, literature review, controlled vocabulary (CINAHL Headings, Medical Subject Headings = MeSH and Excerpta Medica Tree = Emtree), and reviewing the primary search

results. Search strategies developed by assistance of a medical information specialist were reported in Appendix 1. Search results were de-duplicated in EndNote X5 and then sent to two researchers for screening. 1494 were excluded during screening because they were irrelevant to our research question. 67 studies selected for full text assessment using inclusion and exclusion criteria. 67 full text records excluded as they did not meet the inclusion criteria because of non RCT and review article. No studies were included in the review for data extraction. Process of selection of studies has been shown in PRISMA flow diagram (Figure 1).

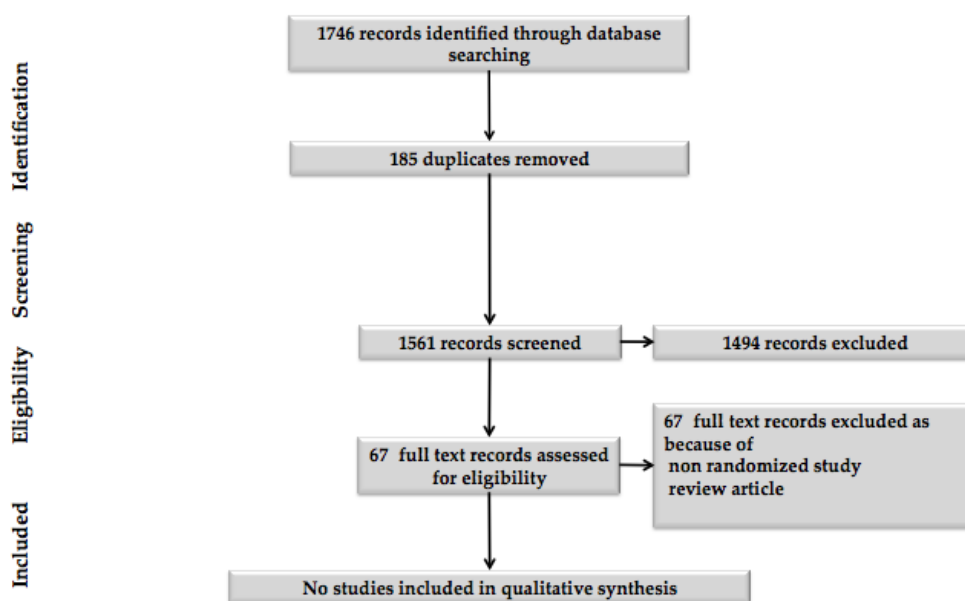


Figure 1 Process of selection of studies for systematic review based on PRISMA flow diagram

Appendix 1: Search Strategies

A. CINHAL

(((MH "Crossover Design") OR (MH "Random Assignment") OR (MH "Clinical Trials+") OR (MH "Factorial Design") OR TI (Randomised OR Randomized OR Randomly OR Randomization OR Randomisation OR Placebo OR Trial OR Factorial* OR "Double Blind" OR "Single Blind" OR Assign* OR Allocat* OR "Controlled Study") OR AB (Randomised OR Randomized OR Randomly OR Randomization OR Randomisation OR Placebo OR Trial OR Factorial* OR "Double Blind" OR "Single Blind" OR Assign* OR Allocat* OR "Controlled Study")) AND (((MH "Pregnancy+") OR (MH "Obstetrics") OR (MH "Obstetric Patients") OR (MH "Pregnancy Outcomes") OR (MH "Delivery,

Obstetric") OR (MH "Pregnancy Complications+") OR (MH "Mothers+")) OR TI (Gestation* OR Pregnant* OR Obstetric* OR Maternal* OR Labor OR Labour* OR Mother* OR Maternal OR Maternity OR Childbirth OR Childbirths OR Birth OR Births OR Parturiency OR Parturiencies OR Parturition OR Parturitions OR Parturient OR Parturients OR Parity OR "Child Bearing" OR Gravidity OR Gravidities) OR AB (Gestation* OR Pregnant* OR Obstetric* OR Maternal* OR Labor OR Labour* OR Mother* OR Maternal OR Maternity OR Childbirth OR Childbirths OR Birth OR Births OR Parturiency OR Parturiencies OR Parturition OR Parturitions OR Parturient OR Parturients OR Parity OR "Child Bearing" OR Gravidity OR Gravidities)) AND ((MH "Antiphospholipid Syndrome") OR TI ("Asherson Syndrome" OR "Ashersons Syndrome" OR "Asherson's Syndrome" OR "Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies") OR AB ("Asherson Syndrome" OR "Ashersons Syndrome" OR "Asherson's Syndrome" OR "Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies"

OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies"))

B. Cochrane Library

#1 MeSH descriptor: [Antiphospholipid Syndrome] explode all trees

#2 MeSH descriptor: [Antibodies, Antiphospholipid] explode all trees

#3 ("Asherson Syndrome" OR "Ashersons Syndrome" OR "Asherson's Syndrome" OR "Hughes Syndrome" or "Hughes Syndromes" or "Antiphospholipid Antibody Syndrome" or "Anti Phospholipid Antibody Syndrome" or "Anti Phospholipid Syndrome" or "Antiphospholipid Syndrome" or "Antiphospholipid Antibody Syndromes" or "Anti Phospholipid Antibody Syndromes" or "Anti Phospholipid Syndromes" or "Antiphospholipid Syndromes" or "Antiphospholipid Antibody" or "Antiphospholipid Antibodies" or "Phospholipid Antiserum" or "Anticardiolipin Antibodies" or "Anticardiolipin Antibody" or "Lupus Coagulation Inhibitor" or "Lupus Coagulation Inhibitors" or "Lupus Anticoagulant" or "Lupus Anticoagulants" or Antiprothrombinase or "Anti Cardiolipin Antibody" or "Anti Cardiolipin Antibodies" or "Anticardiolipin Antibody" or "Anticardiolipin Antibodies" or "Anti Beta2GP1 Antibody" or "Anti Beta2GPI Antibody" or "Beta 2 Glycoprotein 1 Antibody" or "Beta 2 Glycoprotein I Antibody" or "Beta2 Glycoprotein 1 Antibody" or "Beta2 Glycoprotein I Antibody" or "Anti Beta2GP1 Antibodies" or "Anti Beta2GPI Antibodies" or "Beta 2 Glycoprotein 1 Antibodies" or "Beta 2 Glycoprotein I Antibodies" or "Beta2 Glycoprotein 1 Antibodies" or "Beta2 Glycoprotein I Antibodies"):ti,ab

#4 #1 or #2 or #3

#5 MeSH descriptor: [Pregnancy] explode all trees

#6 MeSH descriptor: [Obstetrics] explode all trees

#7 MeSH descriptor: [Obstetric Labor Complications] explode all trees

#8 MeSH descriptor: [Delivery, Obstetric] explode all trees

#9 MeSH descriptor: [Labor, Obstetric] explode all trees

#10 MeSH descriptor: [Pregnancy Complications] explode all trees

#11 MeSH descriptor: [Pregnant Women] explode all trees

#12 MeSH descriptor: [Mothers] explode all trees

#13 (Gestation* or Pregnan* or Obstetric* or Matern* or Labor* or Labour* or Mother*

or Maternal or Maternity OR Childbirth OR Childbirths OR Birth OR Births OR Parturiency OR Parturiencies OR Parturition OR Parturitions OR Parturient OR Parturients OR Parity OR "Child Bearing" OR Gravidity OR Gravidities):ti,ab

#14 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 #4 and #14

C. EMBASE

Antiphospholipid Syndrome/ OR Phospholipid Antibody/ OR Cardiolipin Antibody/ OR Lupus Anticoagulant/ OR Beta2 Glycoprotein 1 Antibody/ OR ("Asherson Syndrome" OR "Ashersons Syndrome" OR "Asherson's Syndrome" OR "Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies").ti,ab.

Exp Pregnancy/ OR Exp Obstetrics/ OR Obstetric Patient/ OR Exp Pregnancy Outcome/ OR Exp Pregnancy Complication/ OR Pregnant Woman/ OR Exp Mother/ OR (Gestation\$ OR Pregnan\$ OR Obstetric\$ OR Matern\$ OR Labor\$ OR Labour\$ OR Mother\$ OR Maternal OR Maternity OR Childbirth OR Childbirths OR Birth OR Births OR Parturiency OR Parturiencies OR Parturition OR Parturitions OR Parturient OR Parturients OR Parity OR "Child Bearing" OR Gravidity OR Gravidities).ti,ab.

(random\$ or factorial\$ or crossover\$ or (cross over\$) or cross-over\$ or placebo\$ or (doubl\$ adj blind\$) or (singl\$ adj blind\$) or assign\$ or allocat\$ or volunteer\$).mp. or crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or

single-blind procedure/

exp animals/ OR exp invertebrate/ OR animal experiment/ OR animal model/ OR animal tissue/ OR animal cell/ OR nonhuman/

human/ OR normal human/ OR human cell/

4 and 5

4 not 6

3 not 7

1 and 2 and 8

limit 9 to exclude medline journals

D. MEDLINE

Anti-Phospholipid Antibody Syndrome/ OR Exp Antibodies, Antiphospholipid/ OR ("Asherson Syndrome" OR "Ashersons Syndrome" OR "Asherson's Syndrome" OR "Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies").ti,ab.

Exp Pregnancy/ OR Obstetrics/ OR Exp Obstetric Labor Complications/ OR Exp Delivery, Obstetric/ OR Exp Labor, Obstetric/ OR Pregnancy Complications/ OR Pregnant Women/ OR Mothers/ OR (Gestation\$ OR Pregnan\$ OR Obstetric\$ OR Matern\$ OR Labor\$ OR Labour\$ OR Mother\$ OR Maternal OR Maternity OR Childbirth OR Childbirths OR Birth OR Births OR Parturiency OR Parturiencies OR Parturition OR Parturitions OR Parturient OR Parturients OR Parity OR "Child Bearing" OR Gravidity OR Gravidities).ti,ab.

(randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or randomly or placebo or trial or groups).ab. or drug therapy.fs. not (animals not (humans and animals)).sh.

1 and 2 and 3

E. PubMed

(Randomised OR Randomized OR Randomly OR Randomization OR Randomisation OR Placebo OR Trial OR Groups OR Factorial* OR "Double Blind" OR "Single Blind" OR Assign* OR Allocat* OR Volunteer* OR "Controlled Study") AND ("Asherson Syndrome" OR "Asherson's Syndrome" OR "Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies") AND (Gestation* OR Pregnan* OR Obstetric* OR Matern* OR Labor OR Labour* OR Mother* OR Maternal OR Maternity OR Childbirth OR Childbirths OR Birth OR Births OR Parturiency OR Parturition OR Parturitions OR Parturient OR Parturients OR Parity OR "Child Bearing" OR Gravidity OR Gravidities) NOT MEDLINE[SB]

Search Report CQ4-1

I: Review Question

CQ4-1 Is therapeutic intervention of therapies needed in APS patients with obstetrical complications for prevention of subsequent possible events of APS?

II: Search Date

July 05, 2015

III: Limitations for Search

Date/Time: No

Language: No

Document Type: No

Publication Status: Published

IV: Resources and Number of Results

Table 1 Search resources details and number of results

Resource	Time Coverage	Search Interface	# of Hits
CINAHL	1937 – Search Date	EBSCOhost	62
Cochrane Library (Including CDSR, CENTRAL, DARE, HTA, CMR, NHS EED)	Until Search Date	Wiley Online Library	96
EMBASE [Excluding MEDLINE]	1974 – 2015 Week 26	Ovid SP	150
MEDLINE	1946 – Search Date	Ovid SP	1633
PubMed [Excluding MEDLINE]	1946 – Search Date	PubMed	48
Integration of Results			
Subtotal			1989
Duplicates			199
Total (for Screening)			1790

V: Search Method Section for Paper/Report

Materials and Methods

Search and Selection of Studies

We searched published documents from CINAHL via EBSCOhost, Cochrane Library, PubMed, and EMBASE and MEDLINE via Ovid SP on July 05, 2015 with no date/time, language, and document type. Keywords were collected through experts' opinion, literature review, controlled vocabulary (CINAHL Headings, Medical Subject Headings = MeSH and Excerpta Medica Tree = Emtree), and reviewing the primary search results. Search strategies developed by assistance of a medical information specialist were reported in Appendix 1. Search results were de-duplicated in EndNote X5 and then sent to two researchers for screening. 1787 were excluded during screening because they were irrelevant to our research question. 3 studies selected for full text

assessment using inclusion and exclusion criteria. 2 studies were removed because of non RCT. One study was included in the review for data extraction. Process of selection of studies has been shown in PRISMA flow diagram (Figure 1).

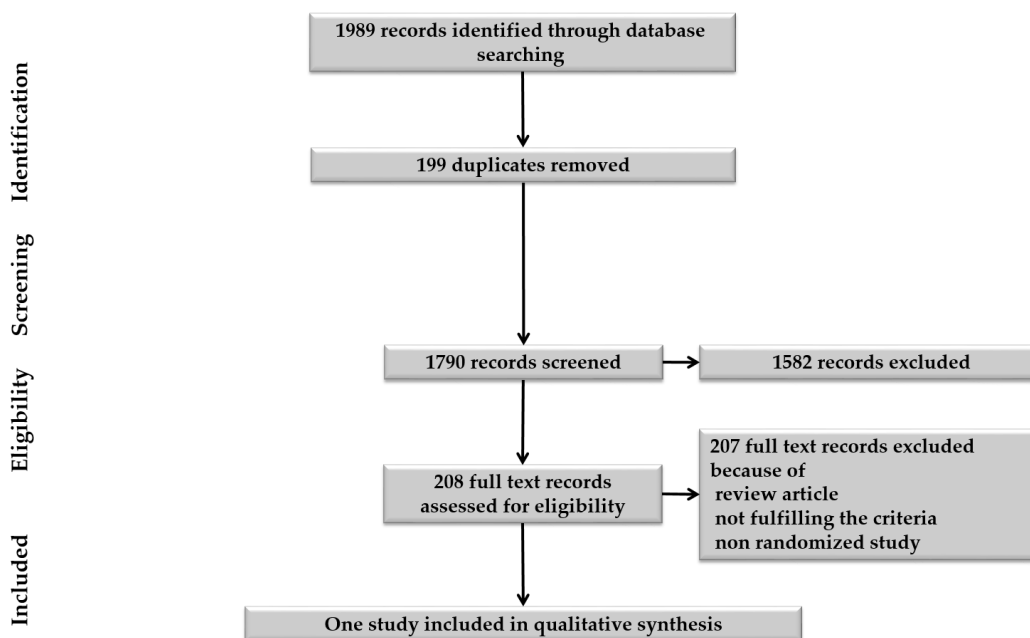


Figure 1 Process of selection of studies for systematic review based on PRISMA flow diagram

Appendix 1: Search Strategies

A. CINHAL

S5 S1 AND S2 AND S3 AND S4

S4 ((MH "Crossover Design") OR (MH "Random Assignment") OR (MH "Clinical Trials+") OR (MH "Controlled Before-After Studies") OR (MH "Factorial Design") OR (MH "Historically Controlled Study") OR (MH "Interrupted Time Series Analysis") OR (MH "Nonrandomized Trials") OR (MH "Pretest-Posttest Design+") OR (MH "Multicenter Studies") OR (MH "Case Control Studies+") OR (MH "Prospective Studies") OR (MH "Concurrent Prospective Studies") OR (MH "Nonconcurrent Prospective Studies") OR (MH "Pseudolongitudinal Studies") OR (MH "Quasi-Experimental Studies+")) OR TI ("Quasi-Experimental" OR "Follow Up" OR Followup OR Cohort OR Longitudinal OR Prospective OR "Case Control" OR "Case Comparison" OR "Case Compeer" OR "Case Referrent" OR "Case Crossover" OR "Case Cross Over" OR "Before After" OR "Before and After" OR "Pretest Posttest" OR "Pre

Test Post Test" OR "Pretest/Posttest" OR "Pre Test/Post Test" OR "Time Series" OR Randomised OR Randomized OR Randomly OR Randomization OR Randomisation OR Placebo OR Trial OR Groups OR Factorial* OR "Double Blind" OR "Single Blind" OR Assign* OR Allocat* OR Volunteer* OR Multicenter OR Multicentre OR "Multi Center" OR "Multi Centre" OR "Controlled Study") OR AB ("Quasi-Experimental" OR "Follow Up" OR Followup OR Cohort OR Longitudinal OR Prospective OR "Case Control" OR "Case Comparison" OR "Case Compeer" OR "Case Referrent" OR "Case Crossover" OR "Case Cross Over" OR "Before After" OR "Before and After" OR "Pretest Posttest" OR "Pre Test Post Test" OR "Pretest/Posttest" OR "Pre Test/Post Test" OR "Time Series" OR Randomised OR Randomized OR Randomly OR Randomization OR Randomisation OR Placebo OR Trial OR Groups OR Factorial* OR "Double Blind" OR "Single Blind" OR Assign* OR Allocat* OR Volunteer* OR Multicenter OR Multicentre OR "Multi Center" OR "Multi Centre" OR "Controlled Study")

S3 ((MH "Anticoagulants+") OR (MH "Platelet Aggregation Inhibitors+") OR (MH "Aspirin") OR (MH "Heparin+") OR (MH "Warfarin")) OR TI ("Anti Coagulant" OR "Anti Coagulants" OR "Anticoagulant" OR "Anticoagulants" OR "Antiplatelet" OR "Antithrombin" OR "Antithrombins" OR "Antithrombotic" OR "Factor Xa Inhibitor" OR "Factor Xa Inhibitors" OR "Platelet Aggregation Inhibitor" OR "Platelet Aggregation Inhibitors" OR "Platelet Antagonist" OR "Platelet Antagonists" OR "Platelet Antiaggregant" OR "Platelet Antiaggregants" OR "Platelet Inhibitor" OR "Platelet Inhibitors" OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR "Thrombocyte Aggregation Inhibitor" OR "Thrombocyte Aggregation Inhibitors" OR Heparin* OR Warfarin* OR Aldocumar OR Ateroid OR Atheroid OR Clexane OR Coumadin* OR "CY 216" OR "CY216" OR Dalteparin OR "EMT 966" OR "EMT 967" OR "EMT966" OR "EMT967" OR Enoxaparin* OR "FR 860" OR "FR860" OR Fragmin* OR Fraxiparin* OR "Kabi 2165" OR "Kabi2165" OR Liquaemin OR "LMF CY 216" OR "LMF CY216" OR LMWH OR Lovenox OR Marevan OR Nadroparin OR "PK 10,169" OR "PK 10169" OR "PK10,169" OR "PK10169" OR Tedelparin OR Tedicumar OR Warfant OR Aspirin* OR "Acetylsalicylic Acid" OR "Acetyl Salicylic Acid" OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin) OR AB ("Anti Coagulant" OR "Anti Coagulants" OR "Anticoagulant" OR "Anticoagulants" OR "Antiplatelet" OR "Antithrombin" OR "Antithrombins" OR "Antithrombotic" OR "Factor Xa Inhibitor" OR "Factor Xa Inhibitors" OR "Platelet Aggregation Inhibitor" OR "Platelet Aggregation Inhibitors" OR "Platelet Antagonist" OR "Platelet Antagonists" OR "Platelet Antiaggregant" OR "Platelet Antiaggregants"

OR "Platelet Inhibitor" OR "Platelet Inhibitors" OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR "Thrombocyte Aggregation Inhibitor" OR "Thrombocyte Aggregation Inhibitors" OR Heparin* OR Warfarin* OR Aldocumar OR Ateroid OR Atheroid OR Clexane OR Coumadin* OR "CY 216" OR "CY216" OR Dalteparin OR "EMT 966" OR "EMT 967" OR "EMT966" OR "EMT967" OR Enoxaparin* OR "FR 860" OR "FR860" OR Fragmin* OR Fraxiparin* OR "Kabi 2165" OR "Kabi2165" OR Liquaemin OR "LMF CY 216" OR "LMF CY216" OR LMWH OR Lovenox OR Marevan OR Nadroparin OR "PK 10,169" OR "PK 10169" OR "PK10,169" OR "PK10169" OR Tedelparin OR Tedicumar OR Warfant OR Aspirin* OR "Acetylsalicylic Acid" OR "Acetyl Salicylic Acid" OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin)

S2 ((MH "Pregnancy+") OR (MH "Obstetrics") OR (MH "Obstetric Patients") OR (MH "Pregnancy Outcomes") OR (MH "Delivery, Obstetric") OR (MH "Pregnancy Complications+") OR (MH "Mothers+")) OR TI (Gestation* OR Pregnan* OR Obstetric* OR Matern* OR Labor OR Labour* OR Mother* OR Maternal OR Maternity) OR AB (Gestation* OR Pregnan* OR Obstetric* OR Matern* OR Labor OR Labour* OR Mother* OR Maternal OR Maternity)

S1 (MH "Antiphospholipid Syndrome") OR TI ("Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies") OR AB ("Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR

"Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GPI Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies")

B. Cochrane Library

#1 MeSH descriptor: [Antiphospholipid Syndrome] explode all trees

#2 MeSH descriptor: [Antibodies, Antiphospholipid] explode all trees

#3 ("Hughes Syndrome" or "Hughes Syndromes" or "Antiphospholipid Antibody Syndrome" or "Anti Phospholipid Antibody Syndrome" or "Anti Phospholipid Syndrome" or "Antiphospholipid Syndrome" or "Antiphospholipid Antibody Syndromes" or "Anti Phospholipid Antibody Syndromes" or "Anti Phospholipid Syndromes" or "Antiphospholipid Syndromes" or "Antiphospholipid Antibody" or "Antiphospholipid Antibodies" or "Phospholipid Antiserum" or "Anticardiolipin Antibodies" or "Anticardiolipin Antibody" or "Lupus Coagulation Inhibitor" or "Lupus Coagulation Inhibitors" or "Lupus Anticoagulant" or "Lupus Anticoagulants" or Antiprothrombinase or "Anti Cardiolipin Antibody" or "Anti Cardiolipin Antibodies" or "Anticardiolipin Antibody" or "Anticardiolipin Antibodies" or "Anti Beta2GP1 Antibody" or "Anti Beta2GPI Antibody" or "Beta 2 Glycoprotein 1 Antibody" or "Beta 2 Glycoprotein I Antibody" or "Beta2 Glycoprotein 1 Antibody" or "Beta2 Glycoprotein I Antibody" or "Anti Beta2GP1 Antibodies" or "Anti Beta2GPI Antibodies" or "Beta 2 Glycoprotein 1 Antibodies" or "Beta 2 Glycoprotein I Antibodies" or "Beta2 Glycoprotein 1 Antibodies" or "Beta2 Glycoprotein I Antibodies"):ti,ab

#4 #1 or #2 or #3

#5 MeSH descriptor: [Pregnancy] explode all trees

#6 MeSH descriptor: [Obstetrics] explode all trees

#7 MeSH descriptor: [Obstetric Labor Complications] explode all trees

#8 MeSH descriptor: [Delivery, Obstetric] explode all trees
 #9 MeSH descriptor: [Labor, Obstetric] explode all trees
 #10 MeSH descriptor: [Pregnancy Complications] explode all trees
 #11 MeSH descriptor: [Pregnant Women] explode all trees
 #12 MeSH descriptor: [Mothers] explode all trees
 #13 (Gestation* or Pregnant* or Obstetric* or Maternal* or Labor* or Labour* or Mother* or Maternal or Maternity):ti,ab
 #14 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
 #15 MeSH descriptor: [Anticoagulants] explode all trees
 #16 MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees
 #17 MeSH descriptor: [Aspirin] explode all trees
 #18 MeSH descriptor: [Heparin] explode all trees
 #19 MeSH descriptor: [Warfarin] explode all trees
 #20 ("Anti Coagulant" or "Anti Coagulants" or "Anticoagulant" or "Anticoagulants" or "Antiplatelet" or "Antithrombin" or "Antithrombins" or "Antithrombotic" or "Factor Xa Inhibitor" or "Factor Xa Inhibitors" or "Platelet Aggregation Inhibitor" or "Platelet Aggregation Inhibitors" or "Platelet Antagonist" or "Platelet Antagonists" or "Platelet Antiaggregant" or "Platelet Antiaggregants" or "Platelet Inhibitor" or "Platelet Inhibitors" or "Thrombin Inhibitor" or "Thrombin Inhibitors" or "Thrombocyte Aggregation Inhibitor" or "Thrombocyte Aggregation Inhibitors" or Heparin* or Warfarin* or Aldocumar or Ateroid or Atheroid or Clexane or Coumadin* or "CY 216" or "CY216" or Dalteparin or "EMT 966" or "EMT 967" or "EMT966" or "EMT967" or Enoxaparin* or "FR 860" or "FR860" or Fragmin* or Fraxiparin* or "Kabi 2165" or "Kabi2165" or Liquaemin or "LMF CY 216" or "LMF CY216" or LMWH or Lovenox or Marevan or Nadroparin or "PK 10,169" or "PK 10169" or "PK10,169" or "PK10169" or Tedelparin or Tedicumar or Warfant or Aspirin* or "Acetylsalicylic Acid" or "Acetyl Salicylic Acid" or Acetysal or Acylpyrin or Aloxiprimum or Colfarit or Dispril or Easprin or Ecotrin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin):ti,ab
 #21 #15 or #16 or #17 or #18 or #19 or #20
 #22 #4 and #14 and #21

C. EMBASE

Antiphospholipid Syndrome/ OR Phospholipid Antibody/ OR Cardiolipin Antibody/ OR Lupus Anticoagulant/ OR Beta2 Glycoprotein 1 Antibody/ OR ("Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti

Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies").ti,ab.

Exp Pregnancy/ OR Exp Obstetrics/ OR Obstetric Patient/ OR Exp Pregnancy Outcome/ OR Exp Pregnancy Complication/ OR Pregnant Woman/ OR Exp Mother/ OR (Gestation\$ OR Pregnan\$ OR Obstetric\$ OR Matern\$ OR Labor\$ OR Labour\$ OR Mother\$ OR Maternal OR Maternity).ti,ab.

Exp Anticoagulant Agent/ OR Exp Antithrombocytic Agent/ OR Acetylsalicylic Acid/ OR Heparinoid/ OR Heparin/ OR Warfarin/ OR Exp Low Molecular Weight Heparin/ OR ("Anti Coagulant" OR "Anti Coagulants" OR "Anticoagulant" OR "Anticoagulants" OR "Antiplatelet" OR "Antithrombin" OR "Antithrombins" OR "Antithrombotic" OR "Factor Xa Inhibitor" OR "Factor Xa Inhibitors" OR "Platelet Aggregation Inhibitor" OR "Platelet Aggregation Inhibitors" OR "Platelet Antagonist" OR "Platelet Antagonists" OR "Platelet Antiaggregant" OR "Platelet Antiaggregants" OR "Platelet Inhibitor" OR "Platelet Inhibitors" OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR "Thrombocyte Aggregation Inhibitor" OR "Thrombocyte Aggregation Inhibitors" OR Heparin\$ OR Warfarin\$ OR Aldocumar OR Ateroid OR Atheroid OR Clexane OR Coumadin\$ OR "CY 216" OR "CY216" OR Dalteparin OR "EMT 966" OR "EMT 967" OR "EMT966" OR "EMT967" OR Enoxaparin\$ OR "FR 860" OR "FR860" OR Fragmin\$ OR Fraxiparin\$ OR "Kabi 2165" OR "Kabi2165" OR Liquaemin OR "LMF CY 216" OR "LMF CY216" OR LMWH OR Lovenox OR Marevan OR Nadroparin OR "PK 10,169" OR "PK 10169" OR "PK10,169" OR "PK10169" OR Tedelparin OR Tedicumar OR Warfant OR Aspirin\$ OR "Acetylsalicylic Acid" OR "Acetyl Salicylic Acid" OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR

Solupsan OR Zorprin).ti,ab.

Crossover-Procedure/ OR Double-Blind Procedure/ OR Randomized Controlled Trial/
OR Single-Blind Procedure/ OR Exp "Clinical Trial (Topic)" OR Exp Controlled Study/
OR Cohort Analysis/ OR Follow Up/ OR Quasi Experimental Study/ OR Time Series
Analysis/ OR Longitudinal Study/ OR Prospective Study/ OR ("Quasi-Experimental" OR
"Follow Up" OR Followup OR Cohort OR Longitudinal OR Prospective OR "Case
Control" OR "Case Comparison" OR "Case Compeer" OR "Case Referrent" OR "Case
Crossover" OR "Case Cross Over" OR "Before After" OR "Before and After" OR "Pretest
Posttest" OR "Pre Test Post Test" OR "Pretest/Posttest" OR "Pre Test/Post Test" OR
"Time Series" OR Randomised OR Randomized OR Randomly OR Randomization OR
Randomisation OR Placebo OR Trial OR Groups OR Factorial\$ OR "Double Blind" OR
"Single Blind" OR Assign\$ OR Allocat\$ OR Volunteer\$ OR Multicenter OR Multicentre
OR "Multi Center" OR "Multi Centre" OR "Controlled Study").ti,ab.

1 and 2 and 3 and 4

exp animals/ OR exp invertebrate/ OR animal experiment/ OR animal model/ OR
animal tissue/ OR animal cell/ OR nonhuman/

human/ OR normal human/ OR human cell/

6 and 7

6 not 8

5 not 9

limit 10 to exclude medline journals

D. MEDLINE

Clinical Trial/ OR Clinical Trial, Phase I/ OR Clinical Trial, Phase II/ OR Clinical Trial,
Phase III/ OR Clinical Trial, Phase IV/ OR Controlled Clinical Trial/ OR Multicenter
Study/ OR Randomized Controlled Trial/ OR Pragmatic Clinical Trial/ OR Cross-Over
Studies/ OR Non-Randomized Controlled Trials/ OR Exp Cohort Studies/ OR
Case-Control Studies/ OR Controlled Before-After Studies/ OR Interrupted Time Series
Analysis/ OR Single-Blind Method/ OR Double-Blind Method/ OR Random Allocation/
OR (Clinical Trial, All OR Clinical Trial, Phase I OR Clinical Trial, Phase II OR Clinical
Trial, Phase III OR Clinical Trial, Phase IV OR Clinical Trial OR Comparative Study
OR Controlled Clinical Trial OR Multicenter Study OR Pragmatic Clinical Trial OR
Randomized Controlled Trial OR Observational Study).pt. OR ("Quasi-Experimental"
OR "Follow Up" OR Followup OR Cohort OR Longitudinal OR Prospective OR "Case
Control" OR "Case Comparison" OR "Case Compeer" OR "Case Referrent" OR "Case
Crossover" OR "Case Cross Over" OR "Before After" OR "Before and After" OR "Pretest

Posttest" OR "Pre Test Post Test" OR "Pretest/Posttest" OR "Pre Test/Post Test" OR "Time Series" OR Randomised OR Randomized OR Randomly OR Randomization OR Randomisation OR Placebo OR Trial OR Groups OR Factorial\$ OR "Double Blind" OR "Single Blind" OR Assign\$ OR Allocat\$ OR Volunteer\$ OR Multicenter OR Multicentre OR "Multi Center" OR "Multi Centre" OR "Controlled Study").ti,ab. OR Drug Therapy.fs.

(Animals NOT (Humans and Animals)).sh.

1 NOT 2

Anti-Phospholipid Antibody Syndrome/ OR Exp Antibodies, Antiphospholipid/ OR ("Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies").ti,ab.

Exp Pregnancy/ OR Obstetrics/ OR Exp Obstetric Labor Complications/ OR Exp Delivery, Obstetric/ OR Exp Labor, Obstetric/ OR Pregnancy Complications/ OR Pregnant Women/ OR Mothers/ OR (Gestation\$ OR Pregnan\$ OR Obstetric\$ OR Matern\$ OR Labor\$ OR Labour\$ OR Mother\$ OR Maternal OR Maternity).ti,ab.

Exp Anticoagulants/ OR Platelet Aggregation Inhibitors/ OR Aspirin/ OR Exp Heparin/ OR Warfarin/ OR ("Anti Coagulant" OR "Anti Coagulants" OR "Anticoagulant" OR "Anticoagulants" OR "Antiplatelet" OR "Antithrombin" OR "Antithrombins" OR "Antithrombotic" OR "Factor Xa Inhibitor" OR "Factor Xa Inhibitors" OR "Platelet Aggregation Inhibitor" OR "Platelet Aggregation Inhibitors" OR "Platelet Antagonist" OR "Platelet Antagonists" OR "Platelet Antiaggregant" OR "Platelet Antiaggregants" OR "Platelet Inhibitor" OR "Platelet Inhibitors" OR "Thrombin Inhibitor" OR

"Thrombin Inhibitors" OR "Thrombocyte Aggregation Inhibitor" OR "Thrombocyte Aggregation Inhibitors" OR Heparin\$ OR Warfarin\$ OR Aldocumar OR Ateroid OR Atheroid OR Clexane OR Coumadin\$ OR "CY 216" OR "CY216" OR Dalteparin OR "EMT 966" OR "EMT 967" OR "EMT966" OR "EMT967" OR Enoxaparin\$ OR "FR 860" OR "FR860" OR Fragmin\$ OR Fraxiparin\$ OR "Kabi 2165" OR "Kabi2165" OR Liquaemin OR "LMF CY 216" OR "LMF CY216" OR LMWH OR Lovenox OR Marevan OR Nadroparin OR "PK 10,169" OR "PK 10169" OR "PK10,169" OR "PK10169" OR Tedelparin OR Tedicumar OR Warfant OR Aspirin\$ OR "Acetylsalicylic Acid" OR "Acetyl Salicylic Acid" OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryina OR Solprin OR Solupsan OR Zorprin).ti,ab.

3 and 4 and 5 and 6

E. PubMed

("Quasi-Experimental" OR "Follow Up" OR Followup OR Cohort OR Longitudinal OR Prospective OR "Case Control" OR "Case Comparison" OR "Case Compeer" OR "Case Referrent" OR "Case Crossover" OR "Case Cross Over" OR "Before After" OR "Before and After" OR "Pretest Posttest" OR "Pre Test Post Test" OR "Pretest/Posttest" OR "Pre Test/Post Test" OR "Time Series" OR Randomised OR Randomized OR Randomly OR Randomization OR Randomisation OR Placebo OR Trial OR Groups OR Factorial* OR "Double Blind" OR "Single Blind" OR Assign* OR Allocat* OR Volunteer* OR Multicenter OR Multicentre OR "Multi Center" OR "Multi Centre" OR "Controlled Study") AND ("Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I

Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies") AND (Gestation* OR Pregnant* OR Obstetric* OR Maternal* OR Labor OR Labour* OR Mother* OR Maternal OR Maternity) AND ("Anti Coagulant" OR "Anti Coagulants" OR "Anticoagulant" OR "Anticoagulants" OR "Antiplatelet" OR "Antithrombin" OR "Antithrombins" OR "Antithrombotic" OR "Factor Xa Inhibitor" OR "Factor Xa Inhibitors" OR "Platelet Aggregation Inhibitor" OR "Platelet Aggregation Inhibitors" OR "Platelet Antagonist" OR "Platelet Antagonists" OR "Platelet Antiaggregant" OR "Platelet Antiaggregants" OR "Platelet Inhibitor" OR "Platelet Inhibitors" OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR "Thrombocyte Aggregation Inhibitor" OR "Thrombocyte Aggregation Inhibitors" OR Heparin* OR Warfarin* OR Aldocumar OR Ateroid OR Atheroid OR Clexane OR Coumadin* OR "CY 216" OR "CY216" OR Dalteparin OR "EMT 966" OR "EMT 967" OR "EMT966" OR "EMT967" OR Enoxaparin* OR "FR 860" OR "FR860" OR Fragmin* OR Fraxiparin* OR "Kabi 2165" OR "Kabi2165" OR Liquaemin OR "LMF CY 216" OR "LMF CY216" OR LMWH OR Lovenox OR Marevan OR Nadroparin OR "PK 10,169" OR "PK 10169" OR "PK10,169" OR "PK10169" OR Tedelparin OR Tedicumar OR Warfant OR Aspirin* OR "Acetylsalicylic Acid" OR "Acetyl Salicylic Acid" OR Acetysal OR Acylpyrin OR Aloxiiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin) NOT MEDLINE[SB]

Search Report CQ4-2

I: Review Question

CQ4-2 Whether the obstetrical events of APS contributes to subsequent exacerbation or flare of SLE when the APS patients were secondary APS complicated with SLE?

II: Search Date

July 05, 2015

III: Limitations for Search

Date/Time: No

Language: No

Document Type: No

Publication Status: Published

IV: Resources and Number of Results

Table 1 Search resources details and number of results

Resource	Time Coverage	Search Interface	# of Hits
CINAHL	1937 – Search Date	EBSCOhost	91
Cochrane Library (Including CDSR, CENTRAL, DARE, HTA, CMR, NHS EED)	Until Search Date	Wiley Online Library	13
EMBASE [Excluding MEDLINE]	1974 – 2015 Week 26	Ovid SP	218
MEDLINE [Excluding MEDLINE]	1946 – Search Date	Ovid SP	1403
PubMed	1946 – Search Date	PubMed	54
Integration of Results			
Subtotal			1779
Duplicates			135
Total (for Screening)			1644

V: Search Method Section for Paper/Report

Materials and Methods

Search and Selection of Studies

We searched published documents from CINAHL via EBSCOhost, Cochrane Library, PubMed, and EMBASE and MEDLINE via Ovid SP on July 05, 2015 with no date/time, language, and document type. Keywords were collected through experts' opinion, literature review, controlled vocabulary (CINAHL Headings, Medical Subject Headings = MeSH and Excerpta Medica Tree = Emtree), and reviewing the primary search results. Search strategies developed by assistance of a medical information specialist were reported in Appendix 1. Search results were de-duplicated in EndNote X5 and then sent to two researchers for screening. 1644 were excluded during screening because they were irrelevant to our research question. No studies selected for full text assessment using inclusion and exclusion criteria. No studies were included in the review for data extraction. Process of selection of studies has been shown in PRISMA flow diagram (Figure 1).

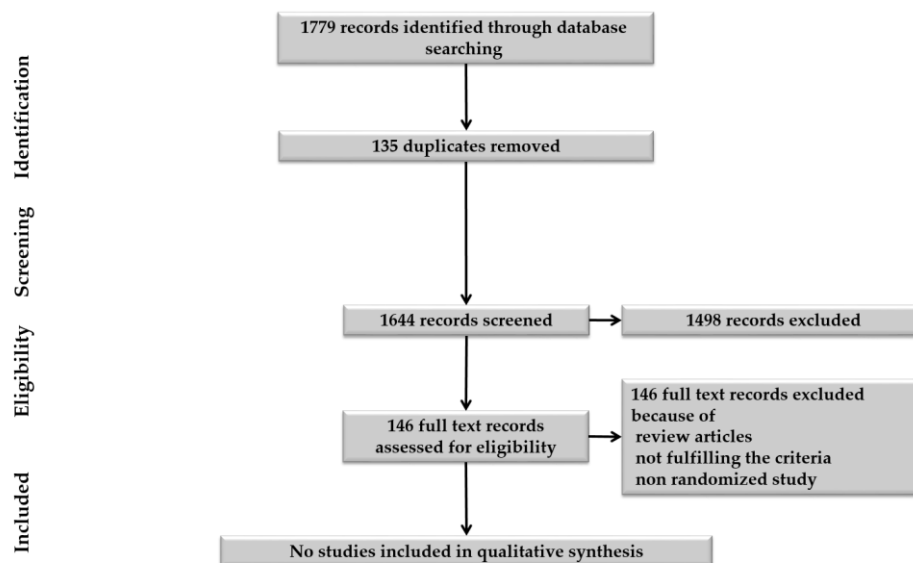


Figure 1 Process of selection of studies for systematic review based on PRISMA flow diagram

Appendix 1: Search Strategies

A. CINHAL

S4 S1 AND S2 AND S3

S3 ((MH "Lupus Erythematosus, Systemic+") OR TI ("Systemic Lupus Erythematosus" OR "Lupus Erythematosus Disseminatus" OR "Libman Sacks Disease" OR "Lupus Nephritis" OR "Lupus Glomerulonephritis" OR "Lupus Nephritides" OR "Lupus Glomerulonephritides" OR "Central Nervous System Lupus Vasculitis" OR "Central Nervous System Lupus" OR "Systemic Lupus Erythematosis" OR "Lupus Meningoencephalitis" OR "Lupus Meningoencephalitides" OR "Disseminated Lupus" OR "Erythematoses Visceralis" OR "Lupovisceritis" OR "Lupus Erythematoses Disseminatus" OR "Lupus Erythematosus Visceralis" OR "Malignant Dermatovisceritism" OR "Systemic Lupus Erythematoses" OR "Systemic Lupus Erythematosus" OR "Systemic Lupus Erythematosus") OR AB ("Systemic Lupus Erythematosus" OR "Lupus Erythematosus Disseminatus" OR "Libman Sacks Disease" OR "Lupus Nephritis" OR "Lupus Glomerulonephritis" OR "Lupus Nephritides" OR "Lupus Glomerulonephritides" OR "Central Nervous System Lupus Vasculitis" OR "Central Nervous System Lupus" OR "Systemic Lupus Erythematosis" OR "Lupus Meningoencephalitis" OR "Lupus Meningoencephalitides" OR "Disseminated Lupus" OR "Erythematoses Visceralis" OR "Lupovisceritis" OR "Lupus Erythematoses Disseminatus" OR "Lupus Erythematosus Visceralis" OR "Malignant Dermatovisceritism" OR "Systemic Lupus Erythematoses" OR "Systemic Lupus

Erythematosus" OR "Systemic Lupus Erythematosus")

S2 ((MH "Pregnancy+") OR (MH "Obstetrics") OR (MH "Obstetric Patients") OR (MH "Pregnancy Outcomes") OR (MH "Delivery, Obstetric") OR (MH "Pregnancy Complications+") OR (MH "Mothers+") OR TI (Gestation* OR Pregnan* OR Obstetric* OR Matern* OR Labor OR Labour* OR Mother* OR Maternal OR Maternity) OR AB (Gestation* OR Pregnan* OR Obstetric* OR Matern* OR Labor OR Labour* OR Mother* OR Maternal OR Maternity)

S1 (MH "Antiphospholipid Syndrome") OR TI ("Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies") OR AB ("Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2

Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies")

B. Cochrane Library

#1 MeSH descriptor: [Antiphospholipid Syndrome] explode all trees

#2 MeSH descriptor: [Antibodies, Antiphospholipid] explode all trees

#3 ("Hughes Syndrome" or "Hughes Syndromes" or "Antiphospholipid Antibody Syndrome" or "Anti Phospholipid Antibody Syndrome" or "Anti Phospholipid Syndrome" or "Antiphospholipid Syndrome" or "Antiphospholipid Antibody Syndromes" or "Anti Phospholipid Antibody Syndromes" or "Anti Phospholipid Syndromes" or "Antiphospholipid Syndromes" or "Antiphospholipid Antibody" or "Antiphospholipid Antibodies" or "Phospholipid Antiserum" or "Anticardiolipin Antibodies" or "Anticardiolipin Antibody" or "Lupus Coagulation Inhibitor" or "Lupus Coagulation Inhibitors" or "Lupus Anticoagulant" or "Lupus Anticoagulants" or Antiprothrombinase or "Anti Cardiolipin Antibody" or "Anti Cardiolipin Antibodies" or "Anticardiolipin Antibody" or "Anticardiolipin Antibodies" or "Anti Beta2GP1 Antibody" or "Anti Beta2GPI Antibody" or "Beta 2 Glycoprotein 1 Antibody" or "Beta 2 Glycoprotein I Antibody" or "Beta2 Glycoprotein 1 Antibody" or "Beta2 Glycoprotein I Antibody" or "Anti Beta2GP1 Antibodies" or "Anti Beta2GPI Antibodies" or "Beta 2 Glycoprotein 1 Antibodies" or "Beta 2 Glycoprotein I Antibodies" or "Beta2 Glycoprotein 1 Antibodies" or "Beta2 Glycoprotein I Antibodies"):ti,ab

#4 #1 or #2 or #3

#5 MeSH descriptor: [Pregnancy] explode all trees

#6 MeSH descriptor: [Obstetrics] explode all trees

#7 MeSH descriptor: [Obstetric Labor Complications] explode all trees

#8 MeSH descriptor: [Delivery, Obstetric] explode all trees

#9 MeSH descriptor: [Labor, Obstetric] explode all trees

#10 MeSH descriptor: [Pregnancy Complications] explode all trees

#11 MeSH descriptor: [Pregnant Women] explode all trees

#12 MeSH descriptor: [Mothers] explode all trees

#13 (Gestation* or Pregnant* or Obstetric* or Matern* or Labor* or Labour* or Mother* or Maternal or Maternity):ti,ab

#14 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#15 MeSH descriptor: [Lupus Erythematosus, Systemic] explode all trees

#16 ("Systemic Lupus Erythematosus" OR "Lupus Erythematosus Disseminatus" OR "Libman Sacks Disease" OR "Lupus Nephritis" OR "Lupus Glomerulonephritis" OR

"Lupus Nephritides" OR "Lupus Glomerulonephritides" OR "Central Nervous System Lupus Vasculitis" OR "Central Nervous System Lupus" OR "Systemic Lupus Erythematosus" OR "Lupus Meningoencephalitis" OR "Lupus Meningoencephalitides" OR "Disseminated Lupus" OR "Erythematodes Visceralis" OR "Lupovisceritis" OR "Lupus Erythematodes Disseminatus" OR "Lupus Erythematosus Visceralis" OR "Malignant Dermatovisceritism" OR "Systemic Lupus Erythematodes" OR "Systemic Lupus Erythematosus" OR "Systemic Lupus Erythematosus"):ti,ab

#17 #15 or #16

#18 #4 and #14 and #17

C. EMBASE

Antiphospholipid Syndrome/ OR Phospholipid Antibody/ OR Cardiolipin Antibody/ OR Lupus Anticoagulant/ OR Beta2 Glycoprotein 1 Antibody/ OR ("Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies").ti,ab.

Exp Pregnancy/ OR Exp Obstetrics/ OR Obstetric Patient/ OR Exp Pregnancy Outcome/ OR Exp Pregnancy Complication/ OR Pregnant Woman/ OR Exp Mother/ OR (Gestation\$ OR Pregnan\$ OR Obstetric\$ OR Matern\$ OR Labor\$ OR Labour\$ OR Mother\$ OR Maternal OR Maternity).ti,ab.

Exp Lupus Erythematosus, Systemic/ OR ("Systemic Lupus Erythematosus" OR "Lupus Erythematosus Disseminatus" OR "Libman Sacks Disease" OR "Lupus Nephritis" OR "Lupus Glomerulonephritis" OR "Lupus Nephritides" OR "Lupus Glomerulonephritides" OR "Central Nervous System Lupus Vasculitis" OR "Central

Nervous System Lupus" OR "Systemic Lupus Erythematosus" OR "Lupus Meningoencephalitis" OR "Lupus Meningoencephalitides" OR "Disseminated Lupus" OR "Erythematoses Visceralis" OR "Lupovisceritis" OR "Lupus Erythematoses Disseminatus" OR "Lupus Erythematosus Visceralis" OR "Malignant Dermatovisceritism" OR "Systemic Lupus Erythematoses" OR "Systemic Lupus Erythematosus" OR "Systemic Lupus Erythematosus").ti,ab.

1 and 2 and 3

exp animals/ OR exp invertebrate/ OR animal experiment/ OR animal model/ OR animal tissue/ OR animal cell/ OR nonhuman/ human/ OR normal human/ OR human cell/

5 and 6

5 not 7

4 not 8

limit 9 to exclude medline journals

D. MEDLINE

Anti-Phospholipid Antibody Syndrome/ OR Exp Antibodies, Antiphospholipid/ OR ("Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies").ti,ab.

Exp Pregnancy/ OR Obstetrics/ OR Exp Obstetric Labor Complications/ OR Exp Delivery, Obstetric/ OR Exp Labor, Obstetric/ OR Pregnancy Complications/ OR Pregnant Women/ OR Mothers/ OR (Gestation\$ OR Pregnan\$ OR Obstetric\$ OR

Matern\$ OR Labor\$ OR Labour\$ OR Mother\$ OR Maternal OR Maternity).ti,ab.

Systemic Lupus Erythematosus/ OR ("Systemic Lupus Erythematosus" OR "Lupus Erythematosus Disseminatus" OR "Libman Sacks Disease" OR "Lupus Nephritis" OR "Lupus Glomerulonephritis" OR "Lupus Nephritides" OR "Lupus Glomerulonephritides" OR "Central Nervous System Lupus Vasculitis" OR "Central Nervous System Lupus" OR "Systemic Lupus Erythematosus" OR "Lupus Meningoencephalitis" OR "Lupus Meningoencephalitides" OR "Disseminated Lupus" OR "Erythematodes Visceralis" OR "Lupovisceritis" OR "Lupus Erythematodes Disseminatus" OR "Lupus Erythematosus Visceralis" OR "Malignant Dermatovisceritism" OR "Systemic Lupus Erythematodes" OR "Systemic Lupus Erythematosus" OR "Systemic Lupus Erythematosus").ti,ab.

1 and 2 and 3

(Animals NOT (Humans and Animals)).sh.

4 NOT 5

E. PubMed

("Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies") AND (Gestation* OR Pregnant* OR Obstetric* OR Matern* OR Labor OR Labour* OR Mother* OR Maternal OR Maternity) AND ("Systemic Lupus Erythematosus" OR "Lupus Erythematosus Disseminatus" OR "Libman Sacks Disease" OR "Lupus Nephritis" OR "Lupus Glomerulonephritis" OR "Lupus Nephritides" OR "Lupus Glomerulonephritides" OR "Central Nervous System Lupus Vasculitis" OR

"Central Nervous System Lupus" OR "Systemic Lupus Erythematosus" OR "Lupus Meningoencephalitis" OR "Lupus Meningoencephalitides" OR "Disseminated Lupus" OR "Erythematodes Visceralis" OR "Lupovisceritis" OR "Lupus Erythematodes Disseminatus" OR "Lupus Erythematosus Visceralis" OR "Malignant Dermatovisceritism" OR "Systemic Lupus Erythematodes" OR "Systemic Lupus Erythematosus" OR "Systemic Lupus Erythematosus") NOT MEDLINE[SB]

Search Report CQ5

I: Review Question

CQ5: What is the most appropriate specific treatment for newborns born to mothers with APS?

II: Search Date

July 19, 2015

III: Limitations for Search

Date/Time: No

Language: No

Document Type: No

Publication Status: Published

IV: Resources and Number of Results

Table 1 Search resources details and number of results

Resource	Time Coverage	Search Interface	# of Hits
CINAHL	1937 – Search Date	EBSCOhost	2
Cochrane Library (Including CDSR, CENTRAL, DARE, HTA, CMR, NHS EED)	Until Search Date	Wiley Online Library	33
EMBASE	1974 – 2015 Week 29	Ovid SP	77
MEDLINE	1946 – Search Date	Ovid SP	297
PubMed [Excluding MEDLINE]	1946 – Search Date	PubMed	2
Subtotal			411
Duplicates			79
Total (for Screening)			332

V: Search Method Section for Paper/Report

Materials and Methods

Search and Selection of Studies

We searched published documents from CINAHL via EBSCOhost, Cochrane Library, PubMed, and EMBASE and MEDLINE via Ovid SP on July 19, 2015 with no date/time, language, and document type. Keywords were collected through experts' opinion, literature review, controlled vocabulary (CINAHL Headings, Medical Subject Headings = MeSH and Excerpta Medica Tree = Emtree), and reviewing the primary search results. Search strategies developed by assistance of a medical information specialist were reported in Appendix 1. Search results were de-duplicated in EndNote X5 and then sent to two researchers for screening. 332 were excluded during screening because they were irrelevant to our research question. No studies selected for full text assessment using inclusion and exclusion criteria. No studies were included in the review for data extraction. Process of selection of studies has been shown in PRISMA flow diagram (Figure 1).

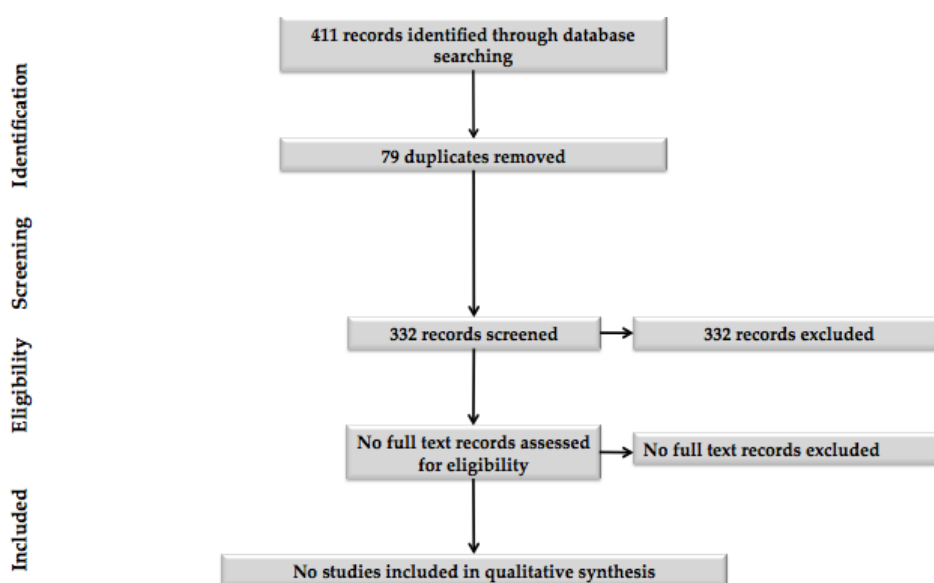


Figure 1 Process of selection of studies for systematic review based on PRISMA flow diagram

Appendix 1: Search Strategies

A. CINAHL

((MH "Antiphospholipid Syndrome") OR TI ("Asherson Syndrome" OR "Ashersons Syndrome" OR "Asherson's Syndrome" OR "Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid

Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies") OR AB ("Asherson Syndrome" OR "Ashersons Syndrome" OR "Asherson's Syndrome" OR "Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies")) AND ((MH "Infant+") OR TI (Babies OR Baby OR Infant* OR Neonat* OR Newborn* OR "Newly Born") OR AB (Babies OR Baby OR Infant* OR Neonat* OR Newborn* OR "Newly Born")) AND (((MH "Crossover Design") OR (MH "Random Assignment") OR (MH "Clinical Trials+") OR (MH "Factorial Design") OR TI (Randomised OR Randomized OR Randomly OR Randomization OR Randomisation OR Placebo OR Trial OR Factorial* OR "Double Blind" OR "Single Blind" OR Assign* OR Allocat* OR "Controlled Study") OR AB (Randomised OR Randomized OR Randomly OR Randomization OR Randomisation OR Placebo OR Trial OR Factorial* OR "Double Blind" OR "Single Blind" OR Assign* OR

Allocat* OR "Controlled Study"))

B. Cochrane Library

#1 MeSH descriptor: [Antiphospholipid Syndrome] explode all trees

#2 MeSH descriptor: [Antibodies, Antiphospholipid] explode all trees

#3 ("Asherson Syndrome" OR "Ashersons Syndrome" OR "Asherson's Syndrome" OR "Hughes Syndrome" or "Hughes Syndromes" or "Antiphospholipid Antibody Syndrome" or "Anti Phospholipid Antibody Syndrome" or "Anti Phospholipid Syndrome" or "Antiphospholipid Syndrome" or "Antiphospholipid Antibody Syndromes" or "Anti Phospholipid Antibody Syndromes" or "Anti Phospholipid Syndromes" or "Antiphospholipid Syndromes" or "Antiphospholipid Antibody" or "Antiphospholipid Antibodies" or "Phospholipid Antiserum" or "Anticardiolipin Antibodies" or "Anticardiolipin Antibody" or "Lupus Coagulation Inhibitor" or "Lupus Coagulation Inhibitors" or "Lupus Anticoagulant" or "Lupus Anticoagulants" or Antiprothrombinase or "Anti Cardiolipin Antibody" or "Anti Cardiolipin Antibodies" or "Anticardiolipin Antibody" or "Anticardiolipin Antibodies" or "Anti Beta2GP1 Antibody" or "Anti Beta2GPI Antibody" or "Beta 2 Glycoprotein 1 Antibody" or "Beta 2 Glycoprotein I Antibody" or "Beta2 Glycoprotein 1 Antibody" or "Beta2 Glycoprotein I Antibody" or "Anti Beta2GP1 Antibodies" or "Anti Beta2GPI Antibodies" or "Beta 2 Glycoprotein 1 Antibodies" or "Beta 2 Glycoprotein I Antibodies" or "Beta2 Glycoprotein 1 Antibodies" or "Beta2 Glycoprotein I Antibodies"):ti,ab

#4 #1 or #2 or #3

#5 MeSH descriptor: [Infant] explode all trees

#6 (Babies OR Baby OR Infant* OR Neonat* OR Newborn* OR "Newly Born"):ti,ab

#7 #5 OR #6

#8 #4 AND #7

C. EMBASE

Antiphospholipid Syndrome/ OR Phospholipid Antibody/ OR Cardiolipin Antibody/ OR Lupus Anticoagulant/ OR Beta2 Glycoprotein 1 Antibody/ OR ("Asherson Syndrome" OR "Ashersons Syndrome" OR "Asherson's Syndrome" OR "Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR

"Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies").ti,ab.

Exp Infant/ OR (Babies OR Baby OR Infant\$ OR Neonat\$ OR Newborn\$ OR "Newly Born").ti,ab.

(random\$ or factorial\$ or crossover\$ or (cross over\$) or cross-over\$ or placebo\$ or (doubl\$ adj blind\$) or (singl\$ adj blind\$) or assign\$ or allocat\$ or volunteer\$).mp. or crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/

exp animals/ OR exp invertebrate/ OR animal experiment/ OR animal model/ OR animal tissue/ OR animal cell/ OR nonhuman/

human/ OR normal human/ OR human cell/

4 and 5

4 not 6

3 not 7

1 and 2 and 8

D. MEDLINE

Anti-Phospholipid Antibody Syndrome/ OR Exp Antibodies, Antiphospholipid/ OR ("Asherson Syndrome" OR "Ashersons Syndrome" OR "Asherson's Syndrome" OR "Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin

Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies").ti,ab.

Exp Infant/ OR (Babies OR Baby OR Infant\$ OR Neonat\$ OR Newborn\$ OR "Newly Born").ti,ab.

(randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or randomly or placebo or trial or groups).ab. or drug therapy.fs. not (animals not (humans and animals)).sh.

1 and 2 and 3

E. PubMed

("Asherson Syndrome" OR "Asherson's Syndrome" OR "Hughes Syndrome" OR "Hughes Syndromes" OR "Antiphospholipid Antibody Syndrome" OR "Anti Phospholipid Antibody Syndrome" OR "Anti Phospholipid Syndrome" OR "Antiphospholipid Syndrome" OR "Antiphospholipid Antibody Syndromes" OR "Anti Phospholipid Antibody Syndromes" OR "Anti Phospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Syndromes" OR "Antiphospholipid Antibody" OR "Antiphospholipid Antibodies" OR "Phospholipid Antiserum" OR "Anticardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Lupus Coagulation Inhibitor" OR "Lupus Coagulation Inhibitors" OR "Lupus Anticoagulant" OR "Lupus Anticoagulants" OR Antiprothrombinase OR "Anti Cardiolipin Antibody" OR "Anti Cardiolipin Antibodies" OR "Anticardiolipin Antibody" OR "Anticardiolipin Antibodies" OR "Anti Beta2GP1 Antibody" OR "Anti Beta2GPI Antibody" OR "Beta 2 Glycoprotein 1 Antibody" OR "Beta 2 Glycoprotein I Antibody" OR "Beta2 Glycoprotein 1 Antibody" OR "Beta2 Glycoprotein I Antibody" OR "Anti Beta2GP1 Antibodies" OR "Anti Beta2GPI Antibodies" OR "Beta 2 Glycoprotein 1 Antibodies" OR "Beta 2 Glycoprotein I Antibodies" OR "Beta2 Glycoprotein 1 Antibodies" OR "Beta2 Glycoprotein I Antibodies") AND (Babies OR Baby OR Infant\$ OR Neonat\$ OR Newborn\$ OR "Newly Born") AND (Randomised OR Randomized OR Randomly OR Randomization OR Randomisation OR Placebo OR Trial OR Groups OR Factorial* OR "Double Blind" OR "Single Blind" OR Assign* OR Allocat* OR Volunteer* OR "Controlled Study") NOT MEDLINE[SB]

Search Report CQ6-1

I: Review Question

CQ6-1: Whether primary prophylaxis is beneficial to prevent obstetric complications during pregnancy in asymptomatic women positive for antiphospholipid antibodies who have no history of recurrent pregnancy loss or intrauterine fetal death?

II: Search Date

from 1950 to Feb 2014.

III: Limitations for Search

Date/Time: No

Language: No

Document Type: No

Publication Status: Published

IV: Search Method Section for Paper/Report

Materials and Methods

Search and Selection of Studies

We searched published documents from Cochrane Library, PubMed, and EMBASE and MEDLINE from 1950 to Feb 2014. Keywords were collected through experts' opinion, literature review, controlled vocabulary, and reviewing the primary search results. Search strategies developed by assistance of a medical information specialist were reported in Appendix 1. In addition, we searched conference abstracts from January 2012 to July 2014 on the official webpages of the American College of Rheumatology, the European League against Rheumatism, the International Society of Thrombosis and Haemostasis, the American College of Obstetricians and Gynaecologists, the European Congress of Obstetrics and Gynaecology and the Royal College of Obstetricians and Gynaecologists World Congress. 247 were excluded during screening because they were irrelevant to our research question. 58 studies selected for full text assessment using inclusion and exclusion criteria. 55 studies were removed because of not fulfilling the criteria. 3 studies were included in the review for data extraction. Process of selection of studies has been shown in PRISMA flow diagram (Figure 1).

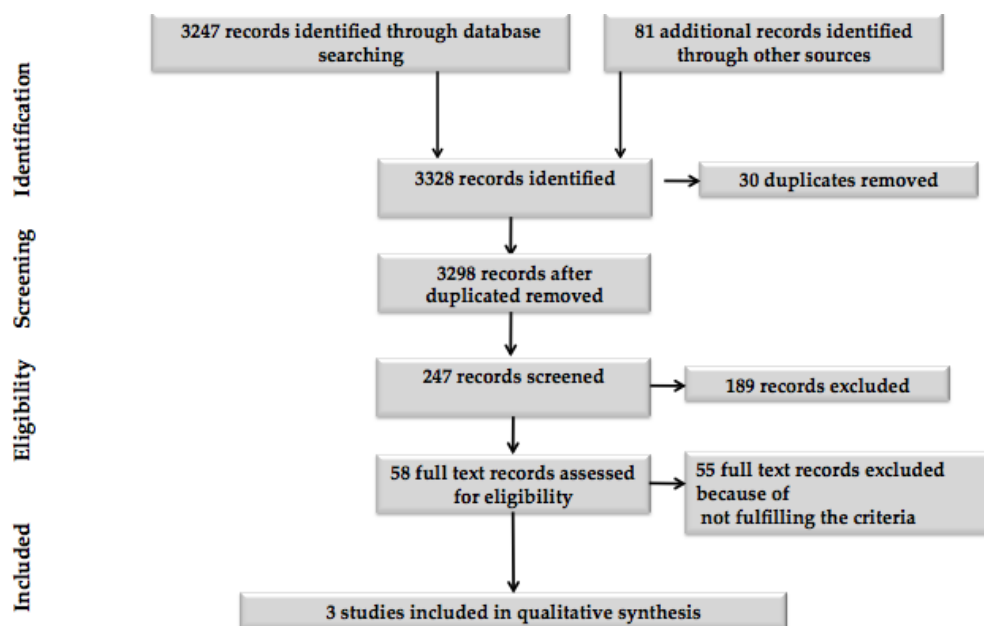


Figure 1 Process of selection of studies for systematic review based on PRISMA flow diagram

Appendix 1: Search Strategies

A. Cochrane Library

Search Name:

Date Run: 27/02/14 17:43:21.684

Description:

ID	Search	Hits
#1	MeSH descriptor: [Antibodies, Antiphospholipid] explode all trees	91
#2	MeSH descriptor: [Antiphospholipid Syndrome] this term only	55
#3	antiphospholipid*	203
#4	anti-phospholipid*	10
#5	aps	196
#6	apls	5
#7	apl	241
#8	anticardiolipin*	94
#9	anti-cardiolipin*	15
#10	lupus coagulation inhibitor*	47
#11	lupus anticoagulant	109
#12	lupus anti-coagulant	5
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	724
#14	MeSH descriptor: [Pregnancy] explode all trees	5585

#15	MeSH descriptor: [Pregnant Women] this term only	80
#16	pregnan*	27152
#17	#14 or #15 or #16	27314
#18	#13 and #17	177
#19	prophylaxis	14761
#20	prevent*	127577
#21	MeSH descriptor: [Primary Prevention] this term only	736
#22	MeSH descriptor: [Heparin] explode all trees	4050
#23	heparin*	8386
#24	ufh	496
#25	lmwh	875
#26	MeSH descriptor: [Aspirin] this term only	4439
#27	aspirin*	8591
#28	MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees	2957
#29	platelet aggregation inhibitor*	3525
#30	antiplatelet	2118
#31	MeSH descriptor: [Anticoagulants] explode all trees	3703
#32	anticoagulant*	5876
#33	anti-coagulant*	109
#34	MeSH descriptor: [Fibrinolytic Agents] explode all trees	1861
#35	fibrinolytic agent*	2400
#36	fibrinolytic drug*	2636
#37	#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36	145864
#38	#18 and #37	160
#39	#38, in Trials	77

B. EMBASE

2014/2/28 Exported HTML | Embase

EMBASE™

Embase Session Results

No. Query Results

#45 #43 NOT #44 1,091

#44 'nonhuman'/de AND [embase]/lim NOT [medline]/lim 742,886

#43 #20 A ND #42 1,131

#42#21OR#22OR#23OR#24OR#25OR#26OR#27OR#28OR#29OR#30OR#31,504,765

OR#32OR#33OR#34OR#35OR#36 OR#37OR#38OR#39 OR#40OR#41
 #41 'fibrinolytic drug':ab,ti AND [embase]/lim NOT [medline]/lim 18
 #40 'fibrinolytic agent':ab,ti AND [embase]/lim NOT [medline]/lim 123
 #39 'fibrinolytic agent'/exp AND [embase]/lim NOT [medline]/lim 24,850
 #38 'anti-coagulant':ab,ti AND [embase]/lim NOT [medline]/lim 516
 #37 anticoagulant*:ab,ti AND [embase]/lim NOT [medline]/lim 16,294
 #36 'anticoagulant agent'/exp AND [embase]/lim NOT [medline]/lim 140,891
 #35 'platelet aggregation inhibitor':ab,ti AND [embase]/lim NOT [medline]/lim 81
 #34 'antithrombocytic agent'/exp AND [embase]/lim NOT [medline]/lim 76,614
 #33 aspirin*:ab,ti AND [embase]/lim NOT [medline]/lim 16,297
 #32 'acetylsalicylic acid'/de AND [embase]/lim NOT [medline]/lim 48,814
 #31 lwmh:ab,ti AND [embase]/lim NOT [medline]/lim 75
 #30 ufh:ab,ti AND [embase]/lim NOT [medline]/lim 888
 #29 heparin*:ab,ti AND [embase]/lim NOT [medline]/lim 20,486
 #28 'heparin'/de AND [embase]/lim NOT [medline]/lim 29,213
 #27 prevent*:ab,ti AND [embase]/lim NOT [medline]/lim 288,003
 #26 'thrombosis prevention'/de AND [embase]/lim NOT [medline]/lim 2,254
 #25 'primary prevention'/de AND [embase]/lim NOT [medline]/lim 8,953
 #24 'prevention'/de AND [embase]/lim NOT [medline]/lim 96,283
 #23 'prevention and control'/de AND [embase]/lim NOT [medline]/lim 1,172
 #22 prophylaxis*:ab,ti AND [embase]/lim NOT [medline]/lim 29,573
 #21 'prophylaxis'/de AND [embase]/lim NOT [medline]/lim 30,786
 #20 #15 A ND #19 1,683
 #19 #16 OR#17 OR #18 141,547
 #18 pregnan*:ab,ti AND [embase]/lim NOT [medline]/lim 106,681
 #17 'pregnant woman'/de AND [embase]/lim NOT [medline]/lim 15,592
 #16 'pregnancy'/exp AND [embase]/lim NOT [medline]/lim 108,163
 #15 #1OR#2OR#3 OR#4OR#5OR#6OR#7OR#8 OR#9OR#10OR#11 OR#12OR 9,784
<https://www.embase.com/search/results>
 #13 OR #14
 #14 'lupus coagulation inhibitor':ab,ti AND [embase]/lim NOT [medline]/lim 1
 #13 'lupus anti-coagulant':ab,ti AND [embase]/lim NOT [medline]/lim 22
 #12 'lupus anticoagulant':ab,ti AND [embase]/lim NOT [medline]/lim 1,380
 #11 'lupus anticoagulant'/de AND [embase]/lim NOT [medline]/lim 1,739
 #10 'anti-cardiolipin':ab,ti AND [embase]/lim NOT [medline]/lim 382
 #9 anticardiolipin*:ab,ti AND [embase]/lim NOT [medline]/lim 1,321

- #8 'cardiolipin antibody'/de AND [embase]/lim NOT [medline]/lim 1,670
- #7 apl:ab,ti AND [embase]/lim NOT [medline]/lim 1,955
- #6 apls:ab,ti AND [embase]/lim NOT [medline]/lim 209
- #5 aps:ab,ti AND [embase]/lim NOT [medline]/lim 3,279
- #4 'anti-phospholipid':ab,ti AND [embase]/lim NOT [medline]/lim 427
- #3 antiphospholipid*:ab,ti AND [embase]/lim NOT [medline]/lim 3,796
- #2 'antiphospholipid syndrome'/de AND [embase]/lim NOT [medline]/lim 2,941
- #1 'phospholipid antibody'/de AND [embase]/lim NOT [medline]/lim 2,872

C. MEDLINE

C1 - Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 26, 2014>, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to Present with Daily Update>Search Strategy:

- 1 exp Antibodies, Antiphospholipid/ (7335)
- 2 Antiphospholipid Syndrome/ (6313)
- 3 antiphospholipid*.tw. (9557)
- 4 anti-phospholipid*.tw. (958)
- 5 aps.tw. (7437)
- 6 apls.tw. (466)
- 7 apl.tw. (5117)
- 8 anticardiolipin*.tw. (4201)
- 9 anti-cardiolipin*.tw. (791)
- 10 lupus coagulation inhibitor*.tw. (6)
- 11 lupus anticoagulant.tw. (3336)
- 12 lupus anti-coagulant.tw. (44)
- 13 or/1-12 (23973)
- 14 exp Pregnancy/ (702513)
- 15 Pregnant Women/ (4986)
- 16 pregnan*.tw. (364348)
- 17 or/14-16 (780855)
- 18 13 and 17 (3571)
- 19 prophylaxis.tw. (69310)
- 20 prevent*.tw. (926017)
- 21 pc.fs. (1000697)
- 22 Primary Prevention/ (13748)
- 23 exp Heparin/ (56068)

24 heparin*.tw. (71136)
25 ufh.tw. (1539)
26 lmwh.tw. (3282)
27 Aspirin/ (37613)
28 aspirin*.tw. (36808)
29 exp Platelet Aggregation Inhibitors/ (89660)
30 platelet aggregation inhibitor*.tw. (733)
31 antiplatelet.tw. (15457)
32 exp Anticoagulants/ (183641)
33 anticoagulant*.tw. (41198)
34 anti-coagulant*.tw. (948)
35 exp Fibrinolytic Agents/ (142806)
36 fibrinolytic agent*.tw. (976)
37 fibrinolytic drug*.tw. (189)
38 or/19-37 (1966868)
39 18 and 38 (2125)
40 (animals not (humans and animals)).sh. (3793523)
41 39 not 40 (2087)
42 remove duplicates from 41 (2079)

Search Report CQ6-2

I: Review Question

CQ6-2: What is the most appropriate treatment for lupus patients with aPL to improve pregnancy related outcome? [Updating Cochrane Review: de Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD004734. DOI: 10.1002/14651858.CD004734.pub4.]

II: Search Date

July 19, 2015

III: Limitations for Search

Date/Time: No

Language: No

Document Type: No

Publication Status: Published

IV: Resources and Number of Results

Table 1 Search resources details and number of results

Resource	Time Coverage	Search Interface	# of Hits
Cochrane Library (Just CENTRAL)	2013 – Until Search Date	Wiley Online Library	4
EMBASE	2013 – 2015 Week 29	Ovid SP	390
MEDLINE	2013 – Search Date	Ovid SP	21
Subtotal	415		
Duplicates	36		
Total (for Screening)	379		

V: Search Method Section for Paper/Report

Materials and Methods

Search and Selection of Studies

We searched published documents from CENTRAL (in Cochrane Library), and EMBASE and MEDLINE via Ovid SP since 2013 to July 19, 2015 with no date/time, language, and document type. Keywords were collected through experts' opinion, literature review, controlled vocabulary (Medical Subject Headings = MeSH and Excerpta Medica Tree = Emtree), and reviewing the primary search results. Search strategies developed by assistance of a medical information specialist were reported in Appendix 1. Search results were de-duplicated in EndNote X5 and then sent to two researchers for screening. 379 were excluded during screening because they were irrelevant to our research question. No studies selected for full text assessment using inclusion and exclusion criteria. No studies were included in the review for data extraction. Process of selection of studies has been shown in PRISMA flow diagram (Figure 1).

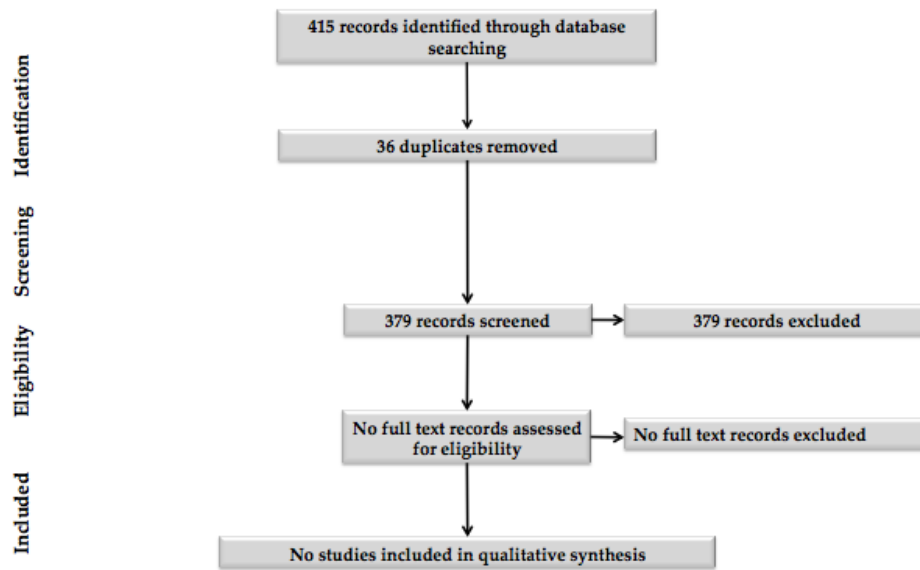


Figure 1 Process of selection of studies for systematic review based on PRISMA flow diagram

Appendix 1: Search Strategies

A. CENTRAL in Cochrane Library

- #1 MeSH descriptor: [Abortion, Spontaneous] explode all trees
- #2 MeSH descriptor: [Abortion, Habitual] explode all trees
- #3 MeSH descriptor: [Fetal Death] explode all trees
- #4 MeSH descriptor: [Fetal Resorption] explode all trees
- #5 (miscarriage* or recurrent miscarriage* or recurrent abortion* or spontaneous pregnancy loss* or recurrent pregnancy loss* or early pregnancy loss* or early pregnancy bleeding* or habitual fetal loss* or stillbirth)
- #6 #1 or #2 or #3 or #4 or #5
- #7 MeSH descriptor: [Aspirin] explode all trees
- #8 MeSH descriptor: [Heparin] explode all trees
- #9 MeSH descriptor: [Heparin, Low-Molecular-Weight] explode all trees
- #10 MeSH descriptor: [Anticoagulants] this term only
- #11 MeSH descriptor: [Anticoagulants] this term only
- #12 antithrombotic*
- #13 #7 or #8 or #9 or #10 or #11 or #12
- #14 #6 and #13 Publication Year from 2013 to 2015, in Trials

B. EMBASE

abortion, spontaneous/ or abortion, habitual/ or fetal death/ or fetal resorption/ or

(miscarriage\$ or recurrent miscarriage\$ or recurrent abortion\$ or spontaneous pregnancy loss\$ or recurrent pregnancy loss\$ or early pregnancy loss\$ or early pregnancy bleeding\$ or habitual fetal loss\$ or stillbirth).tw.

aspirin/ or heparin/ or low-molecular-weight heparin/ or anticoagulants/ or anticoagulant agent/ or antithrombotic\$.tw.

randomized controlled trials/ or random allocation/ or comparative study/ or clinical trials/ or ((clin\$ adj trial\$) or random\$).tw.

1 and 2 and 3

Limit 4 to yr="2013 -Current"

C. MEDLINE

abortion, spontaneous/ or abortion, habitual/ or fetal death/ or fetal resorption/ or (miscarriage\$ or recurrent miscarriage\$ or recurrent abortion\$ or spontaneous pregnancy loss\$ or recurrent pregnancy loss\$ or early pregnancy loss\$ or early pregnancy bleeding\$ or habitual fetal loss\$ or stillbirth).tw.

aspirin/ or heparin/ or low-molecular-weight heparin/ or anticoagulants/ or anticoagulant agent/ or antithrombotic\$.tw.

randomized controlled trials/ or random allocation/ or comparative study/ or clinical trials/ or (randomized controlled trial or controlled clinical trial or clinical trial).pt. or ((clin\$ adj trial\$) or random\$).tw.

1 and 2 and 3

Limit 4 to yr="2013 -Current"

Search Report CQ7

I: Review Question

CQ7: What is the most appropriate anti-coagulate treatment for women with recurrent miscarriage?

II: Search Date

July 19, 2015

III: Limitations for Search

Date/Time: No

Language: No

Document Type: No

Publication Status: Published

IV: Resources and Number of Results

Table 1 Search resources details and number of results

Resource	Time Coverage	Search Interface	# of Hits
CINAHL	1937 – Search Date	EBSCOhost	35
Cochrane Library (Including CDSR, CENTRAL, DARE, HTA, CMR, NHS EED)	Until Search Date	Wiley Online Library	110
EMBASE [Excluding MEDLINE]	1974 – 2015 Week 29	Ovid SP	50
MEDLINE	1946 – Search Date	Ovid SP	724
PubMed [Excluding MEDLINE]	1946 – Search Date	PubMed	15
Subtotal	934		
Duplicates	141		
Total (for Screening)	793		

V: Search Method Section for Paper/Report

Materials and Methods

Search and Selection of Studies

We searched published documents from CINAHL via EBSCOhost, Cochrane Library, PubMed, and EMBASE and MEDLINE via Ovid SP on July 19, 2015 with no date/time, language, and document type. Keywords were collected through experts' opinion, literature review, controlled vocabulary (CINAHL Headings, Medical Subject Headings = MeSH and Excerpta Medica Tree = Emtree), and reviewing the primary search results. Search strategies developed by assistance of a medical information specialist were reported in Appendix 1. Search results were de-duplicated in EndNote X5 and then sent to two researchers for screening. 739 were excluded during screening because they were irrelevant to our research question. 54 studies selected for full text assessment using inclusion and exclusion criteria. 50 studies were removed. 4 studies were included in the review for data extraction. Process of selection of studies has been shown in PRISMA flow diagram (Figure 1).

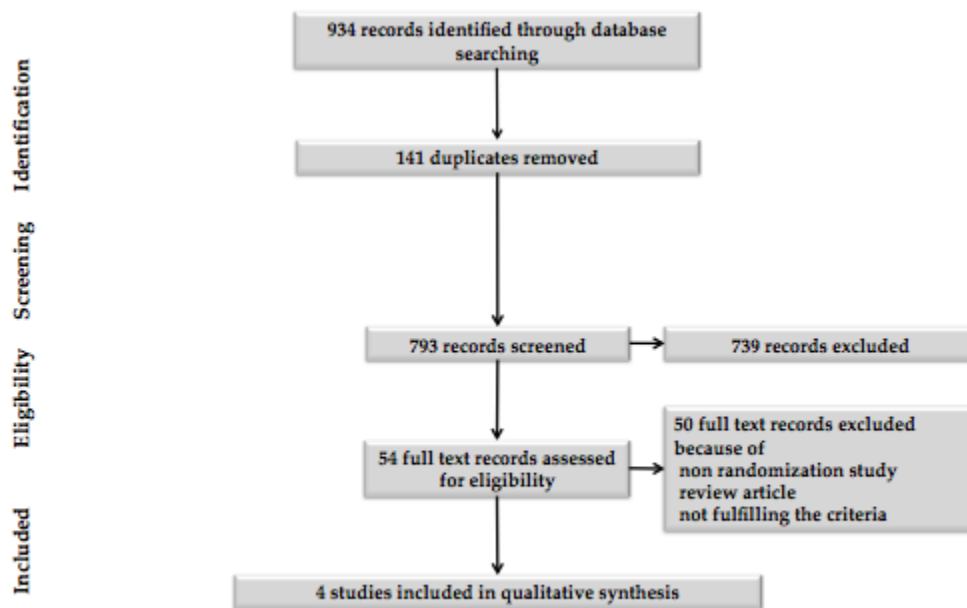


Figure 1 Process of selection of studies for systematic review based on PRISMA flow diagram

Appendix 1: Search Strategies

A. CINHAL

(((MH "Anticoagulants+") OR (MH "Platelet Aggregation Inhibitors+") OR (MH "Aspirin") OR (MH "Heparin+") OR (MH "Warfarin")) OR TI ("Anti Coagulant" OR "Anti Coagulants" OR "Anticoagulant" OR "Anticoagulants" OR "Antiplatelet" OR "Antithrombin" OR "Antithrombins" OR "Antithrombotic" OR "Factor Xa Inhibitor" OR "Factor Xa Inhibitors" OR "Platelet Aggregation Inhibitor" OR "Platelet Aggregation Inhibitors" OR "Platelet Antagonist" OR "Platelet Antagonists" OR "Platelet Antiaggregant" OR "Platelet Antiaggregants" OR "Platelet Inhibitor" OR "Platelet Inhibitors" OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR "Thrombocyte Aggregation Inhibitor" OR "Thrombocyte Aggregation Inhibitors" OR Heparin* OR Warfarin* OR Aldocumar OR Ateroid OR Atheroid OR Clexane OR Coumadin* OR "CY 216" OR "CY216" OR Dalteparin OR "EMT 966" OR "EMT 967" OR "EMT966" OR "EMT967" OR Enoxaparin* OR "FR 860" OR "FR860" OR Fragmin* OR Fraxiparin* OR "Kabi 2165" OR "Kabi2165" OR Liquaemin OR "LMF CY 216" OR "LMF CY216" OR LMWH OR Lovenox OR Marevan OR Nadroparin OR "PK 10,169" OR "PK 10169" OR "PK10,169" OR "PK10169" OR Tedelparin OR Tedicumar OR Warfant OR Aspirin* OR "Acetylsalicylic Acid" OR "Acetyl Salicylic Acid" OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryra OR Solprin OR Solupsan OR

Zorprin) OR AB ("Anti Coagulant" OR "Anti Coagulants" OR "Anticoagulant" OR "Anticoagulants" OR "Antiplatelet" OR "Antithrombin" OR "Antithrombins" OR "Antithrombotic" OR "Factor Xa Inhibitor" OR "Factor Xa Inhibitors" OR "Platelet Aggregation Inhibitor" OR "Platelet Aggregation Inhibitors" OR "Platelet Antagonist" OR "Platelet Antagonists" OR "Platelet Antiaggregant" OR "Platelet Antiaggregants" OR "Platelet Inhibitor" OR "Platelet Inhibitors" OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR "Thrombocyte Aggregation Inhibitor" OR "Thrombocyte Aggregation Inhibitors" OR Heparin* OR Warfarin* OR Aldocumar OR Ateroid OR Atheroid OR Clexane OR Coumadin* OR "CY 216" OR "CY216" OR Dalteparin OR "EMT 966" OR "EMT 967" OR "EMT966" OR "EMT967" OR Enoxaparin* OR "FR 860" OR "FR860" OR Fragmin* OR Fraxiparin* OR "Kabi 2165" OR "Kabi2165" OR Liquaemin OR "LMF CY 216" OR "LMF CY216" OR LMWH OR Lovenox OR Marevan OR Nadroparin OR "PK 10,169" OR "PK 10169" OR "PK10,169" OR "PK10169" OR Tedelparin OR Tedicumar OR Warfant OR Aspirin* OR "Acetylsalicylic Acid" OR "Acetyl Salicylic Acid" OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin)) AND (((MH "Abortion, Spontaneous") OR (MH "Abortion, Habitual")) OR TI ("Habitual Abortion" OR Miscarriage OR "Recurrent Abortion" OR "Repeated Abortion" OR "Spontaneous Abortion" OR "Successive Abortion" OR "Tubal Abortion" OR "Habitual Abortions" OR Miscarriages OR "Recurrent Abortions" OR "Repeated Abortions" OR "Spontaneous Abortions" OR "Successive Abortions" OR "Tubal Abortions") OR AB ("Habitual Abortion" OR Miscarriage OR "Recurrent Abortion" OR "Repeated Abortion" OR "Spontaneous Abortion" OR "Successive Abortion" OR "Tubal Abortion" OR "Habitual Abortions" OR Miscarriages OR "Recurrent Abortions" OR "Repeated Abortions" OR "Spontaneous Abortions" OR "Successive Abortions" OR "Tubal Abortions")) AND (((MH "Crossover Design") OR (MH "Random Assignment") OR (MH "Clinical Trials+") OR (MH "Factorial Design") OR TI (Randomised OR Randomized OR Randomly OR Randomization OR Randomisation OR Placebo OR Trial OR Factorial* OR "Double Blind" OR "Single Blind" OR Assign* OR Allocat* OR "Controlled Study") OR AB (Randomised OR Randomized OR Randomly OR Randomization OR Randomisation OR Placebo OR Trial OR Factorial* OR "Double Blind" OR "Single Blind" OR Assign* OR Allocat* OR "Controlled Study")))

B. Cochrane Library

#1 MeSH descriptor: [Anticoagulants] explode all trees

#2 MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees

#3 MeSH descriptor: [Aspirin] explode all trees
 #4 MeSH descriptor: [Heparin] explode all trees
 #5 MeSH descriptor: [Warfarin] explode all trees
 #6 ("Anti Coagulant" or "Anti Coagulants" or "Anticoagulant" or "Anticoagulants" or "Antiplatelet" or "Antithrombin" or "Antithrombins" or "Antithrombotic" or "Factor Xa Inhibitor" or "Factor Xa Inhibitors" or "Platelet Aggregation Inhibitor" or "Platelet Aggregation Inhibitors" or "Platelet Antagonist" or "Platelet Antagonists" or "Platelet Antiaggregant" or "Platelet Antiaggregants" or "Platelet Inhibitor" or "Platelet Inhibitors" or "Thrombin Inhibitor" or "Thrombin Inhibitors" or "Thrombocyte Aggregation Inhibitor" or "Thrombocyte Aggregation Inhibitors" or Heparin* or Warfarin* or Aldocumar or Ateroid or Atheroid or Clexane or Coumadin* or "CY 216" or "CY216" or Dalteparin or "EMT 966" or "EMT 967" or "EMT966" or "EMT967" or Enoxaparin* or "FR 860" or "FR860" or Fragmin* or Fraxiparin* or "Kabi 2165" or "Kabi2165" or Liquaemin or "LMF CY 216" or "LMF CY216" or LMWH or Lovenox or Marevan or Nadroparin or "PK 10,169" or "PK 10169" or "PK10,169" or "PK10169" or Tedelparin or Tedicumar or Warfant or Aspirin* or "Acetylsalicylic Acid" or "Acetyl Salicylic Acid" or Acetysal or Acylpyrin or Aloxiprimum or Colfarit or Dispril or Easprin or Ecotrin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin):ti,ab
 #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
 #8 MeSH descriptor: [Abortion, Spontaneous] explode all trees
 #9 MeSH descriptor: [Abortion, Habitual] explode all trees
 #10 ("Habitual Abortion" or Miscarriage or "Recurrent Abortion" or "Repeated Abortion" or "Spontaneous Abortion" or "Successive Abortion" or "Tubal Abortion" or "Habitual Abortions" or Miscarriages or "Recurrent Abortions" or "Repeated Abortions" or "Spontaneous Abortions" or "Successive Abortions" or "Tubal Abortions"):ti,ab
 #11 #8 or #9 or #10
 #12 #7 and #11

C. EMBASE

Exp Anticoagulant Agent/ OR Exp Antithrombocytic Agent/ OR Acetylsalicylic Acid/ OR Heparinoid/ OR Heparin/ OR Warfarin/ OR Exp Low Molecular Weight Heparin/ OR ("Anti Coagulant" OR "Anti Coagulants" OR "Anticoagulant" OR "Anticoagulants" OR "Antiplatelet" OR "Antithrombin" OR "Antithrombins" OR "Antithrombotic" OR "Factor Xa Inhibitor" OR "Factor Xa Inhibitors" OR "Platelet Aggregation Inhibitor" OR "Platelet Aggregation Inhibitors" OR "Platelet Antagonist" OR "Platelet Antagonists"

OR "Platelet Antiaggregant" OR "Platelet Antiaggregants" OR "Platelet Inhibitor" OR "Platelet Inhibitors" OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR "Thrombocyte Aggregation Inhibitor" OR "Thrombocyte Aggregation Inhibitors" OR Heparin\$ OR Warfarin\$ OR Aldocumar OR Ateroid OR Atheroid OR Clexane OR Coumadin\$ OR "CY 216" OR "CY216" OR Dalteparin OR "EMT 966" OR "EMT 967" OR "EMT966" OR "EMT967" OR Enoxaparin\$ OR "FR 860" OR "FR860" OR Fragmin\$ OR Fraxiparin\$ OR "Kabi 2165" OR "Kabi2165" OR Liquaemin OR "LMF CY 216" OR "LMF CY216" OR LMWH OR Lovenox OR Marevan OR Nadroparin OR "PK 10,169" OR "PK 10169" OR "PK10,169" OR "PK10169" OR Tedelparin OR Tedicumar OR Warfant OR Aspirin\$ OR "Acetylsalicylic Acid" OR "Acetyl Salicylic Acid" OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin).ti,ab.

Spontaneous Abortion/ OR Recurrent Abortion/ OR ("Habitual Abortion" OR Miscarriage OR "Recurrent Abortion" OR "Repeated Abortion" OR "Spontaneous Abortion" OR "Successive Abortion" OR "Tubal Abortion" OR "Habitual Abortions" OR Miscarriages OR "Recurrent Abortions" OR "Repeated Abortions" OR "Spontaneous Abortions" OR "Successive Abortions" OR "Tubal Abortions").ti,ab.

(random\$ or factorial\$ or crossover\$ or (cross over\$) or cross-over\$ or placebo\$ or (doubl\$ adj blind\$) or (singl\$ adj blind\$) or assign\$ or allocat\$ or volunteer\$).mp. or crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/

exp animals/ OR exp invertebrate/ OR animal experiment/ OR animal model/ OR animal tissue/ OR animal cell/ OR nonhuman/

human/ OR normal human/ OR human cell/

4 and 5

4 not 6

3 not 7

1 and 2 and 8

Limit 9 to Exclude MEDLINE Journals

D. MEDLINE

Exp Anticoagulants/ OR Platelet Aggregation Inhibitors/ OR Aspirin/ OR Exp Heparin/ OR Warfarin/ OR ("Anti Coagulant" OR "Anti Coagulants" OR "Anticoagulant" OR "Anticoagulants" OR "Antiplatelet" OR "Antithrombin" OR "Antithrombins" OR "Antithrombotic" OR "Factor Xa Inhibitor" OR "Factor Xa Inhibitors" OR "Platelet

Aggregation Inhibitor" OR "Platelet Aggregation Inhibitors" OR "Platelet Antagonist" OR "Platelet Antagonists" OR "Platelet Antiaggregant" OR "Platelet Antiaggregants" OR "Platelet Inhibitor" OR "Platelet Inhibitors" OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR "Thrombocyte Aggregation Inhibitor" OR "Thrombocyte Aggregation Inhibitors" OR Heparin\$ OR Warfarin\$ OR Aldocumar OR Ateroid OR Atheroid OR Clexane OR Coumadin\$ OR "CY 216" OR "CY216" OR Dalteparin OR "EMT 966" OR "EMT 967" OR "EMT966" OR "EMT967" OR Enoxaparin\$ OR "FR 860" OR "FR860" OR Fragmin\$ OR Fraxiparin\$ OR "Kabi 2165" OR "Kabi2165" OR Liquaemin OR "LMF CY 216" OR "LMF CY216" OR LMWH OR Lovenox OR Marevan OR Nadroparin OR "PK 10,169" OR "PK 10169" OR "PK10,169" OR "PK10169" OR Tedelparin OR Tedicumar OR Warfant OR Aspirin\$ OR "Acetylsalicylic Acid" OR "Acetyl Salicylic Acid" OR Acetysal OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin).ti,ab.

Abortion, Spontaneous/ OR Abortion, Habitual/ OR ("Habitual Abortion" OR Miscarriage OR "Recurrent Abortion" OR "Repeated Abortion" OR "Spontaneous Abortion" OR "Successive Abortion" OR "Tubal Abortion" OR "Habitual Abortions" OR Miscarriages OR "Recurrent Abortions" OR "Repeated Abortions" OR "Spontaneous Abortions" OR "Successive Abortions" OR "Tubal Abortions").ti,ab.

(randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or randomly or placebo or trial or groups).ab. or drug therapy.fs. not (animals not (humans and animals)).sh.

1 and 2 and 3

E. PubMed

("Anti Coagulant" OR "Anti Coagulants" OR "Anticoagulant" OR "Anticoagulants" OR "Antiplatelet" OR "Antithrombin" OR "Antithrombins" OR "Antithrombotic" OR "Factor Xa Inhibitor" OR "Factor Xa Inhibitors" OR "Platelet Aggregation Inhibitor" OR "Platelet Aggregation Inhibitors" OR "Platelet Antagonist" OR "Platelet Antagonists" OR "Platelet Antiaggregant" OR "Platelet Antiaggregants" OR "Platelet Inhibitor" OR "Platelet Inhibitors" OR "Thrombin Inhibitor" OR "Thrombin Inhibitors" OR "Thrombocyte Aggregation Inhibitor" OR "Thrombocyte Aggregation Inhibitors" OR Heparin* OR Warfarin* OR Aldocumar OR Ateroid OR Atheroid OR Clexane OR Coumadin* OR "CY 216" OR "CY216" OR Dalteparin OR "EMT 966" OR "EMT 967" OR "EMT966" OR "EMT967" OR Enoxaparin* OR "FR 860" OR "FR860" OR Fragmin* OR Fraxiparin* OR "Kabi 2165" OR "Kabi2165" OR Liquaemin OR "LMF CY 216" OR

"LMF CY216" OR LMWH OR Lovenox OR Marevan OR Nadroparin OR "PK 10,169"
OR "PK 10169" OR "PK10,169" OR "PK10169" OR Tedelparin OR Tedicumar OR
Warfant OR Aspirin* OR "Acetylsalicylic Acid" OR "Acetyl Salicylic Acid" OR Acetysal
OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR
Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR
Solupsan OR Zorprin) AND ("Habitual Abortion" OR Miscarriage OR "Recurrent
Abortion" OR "Repeated Abortion" OR "Spontaneous Abortion" OR "Successive
Abortion" OR "Tubal Abortion" OR "Habitual Abortions" OR Miscarriages OR
"Recurrent Abortions" OR "Repeated Abortions" OR "Spontaneous Abortions" OR
"Successive Abortions" OR "Tubal Abortions") AND (Randomised OR Randomized OR
Randomly OR Randomization OR Randomisation OR Placebo OR Trial OR Groups OR
Factorial* OR "Double Blind" OR "Single Blind" OR Assign* OR Allocat* OR Volunteer*
OR "Controlled Study") NOT MEDLINE[SB]

付属資料 2 構造化抄録

CQ3.No.1

A: 書誌情報

タイトル(日本語)	抗リン脂質抗体あるいはループスアンチコアグラント陽性の女性における流産の予防
タイトル(英語)	Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant
著者名	Marianne B E, Marissa Lassere, Jonathan C C, James R S
雑誌名, 巻: 頁	Cochrane Database of Systematic Reviews 2005, Issue 2 CD002859

B: 構造化抄録

目的	抗リン脂質抗体(aPL)あるいはループスアンチコアグラント(LA)陽性の女性における流産の予防目的に低用量アスピリン(LDA)、ヘパリン(低分:LMWH、未分画:UFH)、大量免疫グロブリン療法(IVIg)、プレドニゾン(PSL)などを単独ないし組み合わせて投与することの効果を検討する。
研究デザイン	システマティック・レビュー(ランダム化、準ランダム化試験)
研究施設	大学病院産婦人科、膠原病科
対象患者	流産歴のある抗リン脂質抗体陽性の妊婦
介入	流産歴のある抗リン脂質抗体陽性の妊婦に対して、LDAの使用の効果、あるいは、LDA単剤とLDA+ヘパリンとの比較、LDA+ヘパリンとIVIgの比較。PSL+LDAとLDAの比較あるいは、PSL+LDAと偽薬の比較など。投薬期間などは問わない。
主要評価項目とそれに用いた統計学的手法	主要評価項目は、流産率。母体合併症、児合併症。帝王切開率、出生時体重。
結果	合計 849 人が検討され、13 件の RCT がみつかった。 1, LDA vs. 偽薬 or 通常ケア(3 件,71 人) RR 1.05 [0.66,1.68] 2, ヘパリン(LMWH, UFH)+ LDA vs. LDA or IVIg 2-1 LMWH+LDA vs.LDA(1 件,98 人)RR 0.78[0.39,1.57] 2-2 LMWH+LDA vs.IVIg(1 件,40 人)RR 0.37[0.12,1.16] 2-3 UFH+LDA vs.LDA(2 件,140 人)RR 0.46[0.29,0.71] 3, 高用量ヘパリン+LDA vs. 低用量ヘパリン+LDA(1 件、50 人) RR 0.83[0.29,2.38] 4, PSL+LDA vs. LDA or 偽薬(2 件,122 人) RR 0.85 [0.53, 1.36]

	5, PSL+LDA vs. LDA+へパリン(1件,45人)RR 1.17 [0.47, 2.93] 6, IVIg(±へパリン+LDA)vs.へパリン+LDA or PSL+LDA 6-1, IVIg(±へパリン+LDA)vs.(LMWH or UFH)+LDA(2件, 56人)RR 2.71 [0.86, 8.57] 6-2, IVIg vs. PSL+LDA (1件,82人)RR 0.94[0.42, 2.12]
結論	UFH+LDA は、LDA 単剤に比し有意に流産を減少させた。

C:アブストラクターのコメント

コメント	特記すべきことなし。 後藤美賀子
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CQ3.No.2

A: 書誌情報

タイトル(日本語)	反復する初期流産歴のある抗リン脂質抗体症候群患者におけるベミパリン(低分子へパリン)と低用量アスピリン治療の比較。
タイトル(英語)	Bemiparin versus low dose aspirin for management of recurrent early pregnancy losses due to antiphospholipid antibody syndrome
著者名	Shahla Alalaf
雑誌名, 巻: 頁	Arch Gynecol Obstet. 2012;285:641-647

B: 構造化抄録

目的	流産歴のある抗リン脂質抗体症候群(APS)の女性に対して、低用量アスピリン(LDA)あるいは低分子へパリン(LMWH)のベミパリンの投与をおこない、生児を得る率を検討する。
研究デザイン	ランダム化比較試験
研究施設	大学附属病院
対象患者	2007年から2010年の間に著者の施設を受診した2回以上の連続した20週未満の流産歴のあるAPSの18-42歳の女性。
介入	LDA単剤群は、LDA 100mg/日を36週まで投与。LMWH群は、LMWHのベミパリンを2,500単位/日で妊娠36週まで投与した。
主要評価項目とそれに用いた統計学的手法	主要評価項目は生児率で、産科合併症、児、母胎合併症について検討されている。 カイ2乗検定
結果	研究の対象となったのは141人だった。LDA単剤群には61人、

	LMWH群には80人割り付けられた。生児獲得率は、LDA群で44/61人(72.13%)、LMWH群は69/80人(86.25%)であった。(p=0.045)母児ともに合併症はなかった。
結論	本研究において、LMWH群はLDA単剤群に比し生児獲得率が高かった。

C: アブストラクターのコメント

コメント	LMWHの使用は、現時点では本邦において保険適応外である。 後藤美賀子
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CQ3.No.3

A: 書誌情報

タイトル(日本語)	流産歴のある女性に対する低分子ヘパリンと低用量アスピリンの効果。RCT研究、HepASA
タイトル(英語)	Low Molecular Weight Heparin and Aspirin for Recurrent Pregnancy Loss : Results from the Randomized, Controlled HepASA Trial
著者名	LaskinCA; SpitzerKA; ClarkCA; CrowtherMR; GinsbergJS; HawkerGA; KingdomJC; BarrettJ; GentM
雑誌名, 巻: 頁	The Journal of Rheumatology 2009;36:279-287

B: 構造化抄録

目的	流産歴のある女性に対して、低用量アスピリン(LDA)+低分子ヘパリン(LMWH)あるいはLDA単剤の投与をおこない、効果を検討する。
研究デザイン	ランダム化比較試験(単純無作為化)
研究施設	大学病院産婦人科、生殖医療センター
対象患者	2000年から2004年の4年間の間に著者の施設を受診した2回以上の連続した流産歴のある18-44歳の女性で、下記項目に少なくとも一つは当てはまるもの。抗核抗体陽性、抗リン脂質抗体(aPL)陽性、血栓性素因あり。
介入	LDA単剤群は、LDA81mg/日を投与。LMWH群は、ダルテパリン5,000単位/日+LDA81mg/日で、ダルテパリンは妊娠35週まで投与した。
主要評価項目とそれに 用いた統計学的手法	主要評価項目は生児率で、そのほかは自然流産、子宮外妊娠、児の体重など。
結果	研究の対象となったのは88人だった。LDA単剤群には43人、

	LDA+LMWH 群には 45 人割り付けられた。それぞれ aPL 陽性者は、前者で 20 人、後方で 22 人だった。生児獲得率は、LDA 単剤群は 15/20 人(75%) LDA+LMWH 群で 17/22 人(77.3%)であった。
結論	本研究において、LDA 単剤群と LDA+LMWH 群のいずれも生児獲得率は両群とも比較的高い傾向であった。

C: アブストラクターのコメント

コメント	サンプルサイズが小さく統計学的有意差については解析されていない。 後藤美賀子
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CQ3.No.4

A: 書誌情報

タイトル(日本語)	反復流産歴のある抗リン脂質抗体症候群の妊婦に対し、低分子ヘパリン(エノキサパリン)の 2 つの投与量での効果と安全性の比較
タイトル(英語)	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
著者名	Fouda UM, Sayed AM, Ramadan DI, Fouda IM.
雑誌名, 巻: 頁	J Obstet Gynaecol. 2010;30(8):842-846

B: 構造化抄録

目的	抗リン脂質抗体症候群(APS)で反復流産歴のある妊婦に、低用量アスピリン(LDA)と 2 群で異なる量の低分子ヘパリン(LMWH)、エノキサパリンを投与し、効果と安全性を比較する。
研究デザイン	ランダム化比較試験(単純無作為化)
研究施設	大学病院産婦人科
対象患者	2008 年 12 月から 2010 年 5 月までに著者の施設を受診した 3 回以上の連続した 10 週未満の流産歴のある APS の女性 60 人
介入	いずれの群も LDA75mg を妊娠前より内服し、妊娠 36 週まで継続とした。最初の群は、エノキサパリン 20mg/日、もう一方の群はエノキサパリン 40mg/日の投与をおこなった。いずれも妊娠反応が陽性になり次第開始とした。
主要評価項目とそれに用いた統計学的手法	主要評価項目は生児獲得率で、そのほかは妊娠合併症、子宮内胎児死亡、児の体重、早産率など。 統計学的手法は t 検定、Mann-WhitneyU 検定、カイ 2 乗検定。

結果	それぞれの群に 30 人ずつ割り付けられた。生児獲得率は、エノキサパリン 40mg 群で 23/30 人(76.7%)、エノキサパリン 20mg 群で 21/30 人(70.0%)であった(p=0.56)。
結論	生児獲得率は、両群に差を認めなかった。

C: アブストラクターのコメント

コメント	特記すべきことなし 後藤美賀子
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CQ3.No.5

A: 書誌情報

タイトル(日本語)	反復流産歴のある抗リン脂質抗体症候群(APS)患者に低分子ヘパリンか大量免疫グロブリン療法をおこなうことで生児を得る確率が上がるかのランダム化比較試験
タイトル(英語)	Low-molecular-weight heparin versus intravenous immunoglobulin for recurrent abortion associated with antiphospholipid antibody syndrome
著者名	Dendrinos S, Sakkas E, Makrakis E.
雑誌名, 巻: 頁	Int J Gynaecol Obstet. 2009;104(3):223-225.

B: 構造化抄録

目的	反復流産歴のある抗リン脂質抗体症候群(APS)患者に低用量アスピリン(LDA)+低分子ヘパリン(LMWH)あるいは大量免疫グロブリン療法(IVIg)をおこなうことで生児を得る率は変わるかを検討する。
研究デザイン	ランダム化比較試験(ブロック無作為化)
研究施設	大学病院産婦人科
対象患者	2002年3月から2006年3月までに著者の施設を受診した10週未満の3回以上の連続する流産歴があるAPS患者
介入	LDA+LMWH群では、妊娠判明次第すぐにLDA 75mg/日、LMWH4,500単位/日を開始、LDAは32週までか流産時まで、LMWHは38週までか流産時まで使用。IVIg群では、妊娠判明次第すぐに400mg/kgで投与。28日ごとに32週まで継続しておこなった。
主要評価項目とそれに用いた統計学的手法	生児獲得率、母体の妊娠中・産後合併症(出血、妊娠高血圧症候群、骨折、骨密度、死亡)など t-test および Fisher exact test

結果	LDA+LMWH 群は 40 名、IVIg 群は 38 名であった。生児獲得率は LDA+LMWH 群で 29/40(72.5%)、IVIg 群は 15/38(39.5%)であった(p=0.003)。intent-to-treat 分析では(OR 1.802;95%CI, 1.14-2.84,p=0.007)。早期産や子宮内胎児死亡は差がみられなかった。初期流産は LDA+LMWH 群で 11/40(27.5%)、IVIg 群で 21/38(55.3%)だった(p=0.01)。
結論	今回の研究において、LMWH 群は IVIg 群に比し有意に生児獲得率が高かった。これは intent-to-treat 分析においても有意差が消えなかった。

C: アブストラクターのコメント

コメント	特記すべきことなし 後藤美賀子
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CQ3.No.6

A: 書誌情報

タイトル(日本語)	抗リン脂質抗体症候群による反復流産に対する低分子ヘパリンエノキサパリンと未分画ヘパリンの効果の比較
タイトル(英語)	Enoxaparin versus unfractionated heparin in the management of recurrent abortion secondary to antiphospholipid syndrome
著者名	Usama M. Fouda, Ahmed M. Sayeda, Abdel-Megid A. Abdoua, Dalia I. Ramadanb,
雑誌名, 巻: 頁	Int J Gynaecol Obstet. 2011;112(3):211-215.

B: 構造化抄録

目的	抗リン脂質抗体症候群(APS)で反復流産歴のある妊婦管理には、低用量アスピリン(LDA)+LMWH と LDA+未分画ヘパリン(UFH)のどちらに効果があり安全かを検討する。
研究デザイン	ランダム化比較試験(単純無作為化)
研究施設	大学病院産婦人科
対象患者	3回以上の連続した流産歴のある APS の女性 60 人
介入	いずれの群も LDA75mg を妊娠前より内服し、妊娠 36 週まで継続とした。LMWH 投与群では、エノキサパリン 40mg、1 日 1 回、UFH 投与群はヘパリンカルシウム 5,000 単位、1 日 2 回投与。いずれも妊娠反応が陽性になり次第開始とした。
主要評価項目とそれに用いた統計学	主要評価項目は生児率で、そのほかは出血、妊娠高血圧腎症、続発性骨粗鬆症、子宮内発育遅延、子宮内胎児死亡など。

的手法	統計学的手法は t 検定、Mann-Whitney U 検定、カイ 2 乗検定。
結果	それぞれの群に 30 人ずつ割り付けられた。生児獲得率は、エノキサパリン群で 24/30 人(80.0%)、UFH 群で 20/30 人(66.7%)であった(p=0.244)。
結論	生児獲得率は、LDA+LMWH 群で高い傾向にあるものの、有意差はでなかった。合併症についても両群に有意な差を認めなかった。

C: アブストラクターのコメント

コメント	LDA+LMWH 投与群において生児獲得率が 80%と LDA+UFH 群の 66.7%と比べて、高い傾向にあったものの有意差がつかなかった理由として、サンプルサイズが小さかったことが挙げられる。また、この研究の限界として、両群で投与回数が異なるため、完全に盲検化できないという点がある。 後藤美賀子
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CQ4.No.1

A: 書誌情報

タイトル(日本語)	抗リン脂質抗体陽性患者に血栓予防効果における低用量アスピリンと低用量アスピリン+ワルファリン併用との比較；前向き多施設オープンランダム化比較試験
タイトル(英語)	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)
著者名	Maria J. Cuadrado, Maria L. Bertolaccini, Paul T. Seed, Maria G. Tektonidou, Angeles Aguirre, Luisa Mico, Caroline Gordon, Guillermo Ruiz-Irastorza, Maria V. Egurbide, Antonio Gil, Gerard Espinosa, Frederic Houssiau, Anisur Rahman, Helena Martin, Neil McHugh, Maria Galindo, Mohammed Akil, Mary C. Amigo, Veronica Murru and Munther A. Khamashta
雑誌名, 巻: 頁	Rheumatology 2014;53:275-284

B: 構造化抄録

目的	抗リン脂質抗体(aPL)陽性の SLE 患者または産科的合併症のある患者における低用量アスピリン(LDA)と LDA+ワルファリン併用
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	の血栓症予防に対する有用性と安全性を比較する。
研究デザイン	前向き多施設オープンランダム化比較試験 (観察期間 5 年)
研究施設	大学病院内科
対象患者	aPL 陽性の SLE 患者または産科的合併症のある患者 : 166 人
介入	LDA 群 : LDA(75-125mg/日),併用群 : LDA+ワルファリン(PT-INR 1.3-1.7)
主要評価項目とそれに用いた統計学的手法	主要評価項目は血栓症発症率と副作用(出血)発現率。 統計学的手法 : logrank Test、 regression analysis、 Fisher's exact test
結果	経過観察期間において、全対象患者(166 人)における血栓症発症患者は 8 人(1.8 events/100 persons-years)であった。その内訳は LDA 群(82 人)にて 4 例、 LDA+ワルファリン(84 人)併用群にて 4 例で、両群間で血栓症発症率に統計学的な有意差は認められなかった。また、副作用については出血イベントの発症率が LDA+ワルファリン併用群で有意に高かった(p=0.0007)。
結論	aPL 陽性の SLE 患者または産科的合併症のある患者における血栓症予防効果に、LDA に加えてワルファリンを併用する相乗効果はなく、副作用(出血)の発現率が増加した。

C: アブストラクターのコメント

コメント	特記すべきことなし。 野澤和久
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CQ.6-1

A: 書誌情報

タイトル(日本語)	無症候性の抗リン脂質抗体陽性女性の妊娠合併症予防(システマティックレビュー)
タイトル(英語)	Primary prophylaxis to prevent obstetric complications in asymptomatic women with antiphospholipid antibodies: systematic review
著者名	Amengual O, Fujita D, Ota E, Carmona L, Oku K, Sugiura-Ogasawara M, Murashima A, Atsumi T.
雑誌名, 巻: 頁	Lupus. 2015 ;24:1135-1142.

B: 構造化抄録

目的	無症候性の抗リン脂質抗体陽性女性において一次予防は妊娠合併症を回避させることができるか
研究デザイン	3論文のメタアナリシス(2RCT+1Retrospective)
研究施設	日本の大学病院
対象患者	無症候性妊娠中の抗リン脂質抗体陽性女性
介入	LDA 単剤対偽薬ないしは通常のケア
主要評価項目とそれに用いた統計学的手法	流産と生産。胎児仮死、生下時体重、34週未満の早産、子癩前症
結果	治療群と非治療群における生産、早産、低出生体重、妊娠合併症のリスス比はそれぞれ 1.14 (95% confidence interval CI : 0.18-7.31); 1.71 (0.32-8.98); 0.98 (0.07-13.54) and 2.15 (0.63-7.33)であった。
結論	LDA 単剤対偽薬ないしは通常のケア群間での差は認められなかった

C: アブストラクターのコメント

コメント	特記すべきことなし。 奥 健志
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CQ7.No.1

A: 書誌情報

タイトル(日本語)	遺伝性血栓形成傾向を問わない、原因不明の不育症女性に対するアスピリン and/or ヘパリン投与について
タイトル(英語)	Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia
著者名	S. Kaandorp, M. Di Nisio, M. Goddijn and S. Middeldorp
雑誌名, 巻: 頁	Cochrane Database of Systematic Reviews 2014; 7:

B: 構造化抄録

目的	2回以上原因不明の流産歴がある女性における(遺伝性の血栓形成傾向は問わない)、低用量アスピリン(LDA)やヘパリンなどの抗血小板・抗凝固療法の有効性と安全性を評価すること
研究デザイン	Cochrane Pregnancy and Childbirth Group's Trials Register (1October 2013) and scanned bibliographies of all located articles for any unidentified articles.

研究施設	コクランレビュー
対象患者	2回以上原因不明流産歴がある女性(遺伝性の血栓形成傾向の有無は問わない)
介入	LDA、ヘパリン等の抗血小板・抗凝固療法
主要評価項目とそれに用いた統計学的手法	生児獲得率
結果	<p>2回以上原因不明の流産歴がある女性における(遺伝性の血栓形成傾向は問わない)に用量が様々な低分子ヘパリン(LMWH)またはLDA単剤、または両者併用の影響を調べた9つの研究(1228人の女性のデータを含む)をレビューした。</p> <p>全体として研究デザインと治療レジメンに関して heterogeneous で、3つの研究はバイアスのリスクが高いとみなした。バイアスが高い研究3つのうち2つは、1つの治療法が他よりも有効であることを示したが、感度分析では、抗血小板・抗凝固薬はいずれも生児獲得率に対して有効でなかった(LDA単剤対プラセボの生産のリスク比 0.94, (95%信頼区間 0.80 to 1.11, n = 256)、LMWH 対 LDA のリスク比 1.08 (95% CI 0.93 to 1.26, n = 239)、LDA 対無治療のリスク比 1.01 (95% CI 0.87 to 1.16) n = 322)。早産、子癩前症、子宮内発育不全、先天奇形のような産科合併症は、どの治療レジメンにも有意な影響を受けなかった。含まれた研究において、LDAは出血のリスクを増さなかったが、1つの研究でLWHMとLDA併用が出血リスクを有意に増加させた。同じ研究で患者のほぼ40%にLMWH注射に対する局所皮膚反応(痛み、かゆみ、腫脹)が報告された。</p>
結論	<p>研究の数は限定される。9つの研究の質は様々で、異なる治療が研究されており、バイアスのリスクが低い研究の中で偽薬対照は1つだけであった。バイアスのリスクが低い研究では、抗凝固薬の有益性はみとめられなかった。バイアスの低リスクの研究の抗凝固薬の薬効は、見つからなかった。したがって、本レビューは原因不明の反復流産女性の抗凝固薬使用を指示しない。</p>

C: アブストラクターのコメント

コメント	<p>原因不明の反復流産で、遺伝性の血栓傾向を持つ女性における抗凝固薬の影響については、さらなるランダム化比較試験で評価する必要がある。現時点では薬効の証拠がない。渡邊央美</p>
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CQ7.No.2

A: 書誌情報

タイトル(日本語)	原因不明の不育症女性のための低分子量ヘパリン：最小化ランダム化方式による多施設試験
タイトル(英語)	Low-molecular-weight heparin for women with unexplained recurrent pregnancy loss: a multicenter trial with a minimization randomization scheme
著者名	Schleussner, G. Kamin, G. Seliger, N. Rogenhofer, S. Ebner, B. Toth, M. Schenk, M. Henes, M. K. Bohlmann, T. Fischer, O. Brosteanu, R. Bauersachs and D. Petroff
雑誌名, 巻: 頁	Annals of Internal Medicine 2015; 9: 601-609

B: 構造化抄録

目的	低分子ヘパリン(LMWH)が原因不明の不育症患者における妊娠継続と生児獲得率を増加させるかどうかを決定する。
研究デザイン	最小化を利用したランダム化の対照化多施設試験
研究施設	ドイツとオーストリアの大学病院と産科 14 施設
対象患者	2 回以上連続して妊娠 12 週未満の流産に終わったか、後期流産、または死産の経験が 1 回以上ある単胎妊娠の女性 449 人が、超音波で胎児心拍確認後、妊娠 5-8 週時組み入れられた。
介入	対照群はマルチビタミン錠剤、介入群はビタミンとダルテパリンナトリウム 5,000IU を妊娠 24 週まで投与された。
主要評価項目とそれに用いた統計学的手法	主要転帰 妊娠 24 週時の妊娠継続 二次転帰 生児獲得率と後期妊娠合併症 ランダム化 妊娠週数と遺伝性血栓傾向で層別化
結果	1, 妊娠 24 週時妊娠継続率 介入群 191/220 (86.8%),対照群 188/214 (87.9%) (絶対差, -1.1 パーcentageポイント [95% CI, -7.4 to 5.3 パーcentageポイント]) 2, 生児獲得率 介入群 185/215 (86.0%),対照群 183/211 (86.7%) (絶対差, -0.7 パーcentageポイント[CI, -7.3 to 5.9 パーcentageポイント]). 3, その他 3 例子宮内胎児死亡(1 人は LMWH),9 例子癩前症または HELLP 症候群(3 人は LMWH),11 例胎児発育不全または胎盤機能不全(5 人は LMWH)

結論	LMWH 連日注射によって、不育症女性の妊娠継続や生児獲得率は増加しない。注射の負担があるので、流産・死産予防のために推奨されない。
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C: アブストラクターのコメント

コメント	プラセボ注射を使用しておらず、試験スタッフも患者も盲検化されていない。 ETHIG II study に 2013 年学会発表 渡邊央美
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CQ7.No.3

A: 書誌情報

タイトル(日本語)	原因不明の不育症予防に対するエノキサパリン: 多施設無作為二重盲検偽薬対照試験
タイトル(英語)	Enoxaparin for prevention of unexplained recurrent miscarriage: A multicenter randomized double-blind placebo-controlled trial
著者名	E. Pasquier, L. Saint Martin, C. Bohec, C. Chauleur, F. Bretelle, G. Marhic, G. Gal, V. Debarge, F. Lecomte, C. Denoual-Ziad, V. Lejeune-Saada, S. Douvier, M. Heisert and D. Mottier
雑誌名, 巻: 頁	Blood 2015; 14: 2200-2205

B: 構造化抄録

目的	原因不明の不育症予防に対するエノキサパリンの効果を調べる
研究デザイン	多施設無作為二重盲検偽薬対照試験
研究施設	フランスの病院センター13 施設
対象患者	同一パートナーとの間に妊娠 15 週より前の原因不明流産歴が 2 回以上ありその後生産に至っていない血栓形成傾向精密検査陰性の妊婦 258 人を妊娠反応陽性担った後妊娠 5 週以前に組み入れ
介入	エノキサパリン 40mg/日 vs. 偽薬(生食) 初回受診 24 時間以内から妊娠 35 週まで自己注射
主要評価項目とそれに用いた統計学的手法	主要転帰 生児獲得率 二次転帰 流産・死産率、産科合併症発生率、母体血小板減少症発生率、出血エピソード、皮膚反応

結果	256人を組み入れた。 生児獲得率は、エノキサパリン群 138人中 66.6%、偽薬群 118人中 72.9% 絶対差は-6% (95% CI, -17.1 to 5.1)で、エノキサパリン群における生児獲得率 10%増加を除外した(P 5.34)。
結論	エノキサパリン 40mg/日は、原因不明不育症の血栓形成傾向でない女性における生児獲得率を改善しない。

C: アブストラクターのコメント

コメント	特記すべきことなし。 渡邊央美
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CQ7.No.4

A: 書誌情報

タイトル(日本語)	リビアの不育症妊婦の治療における低用量アスピリンと低分子ヘパリン
タイトル(英語)	Low dose aspirin and low-molecular-weight heparin in the treatment of pregnant Libyan women with recurrent miscarriage
著者名	M. O. Elmahashi, A. M. Elbareg, F. M. Essadi, B. M. Ashur and I. Adam
雑誌名, 巻: 頁	BMC research notes 2014; 7: 23

B: 構造化抄録

目的	不育症妊婦の治療における低用量アスピリン(LDA)と低分子ヘパリン(LMWH)の効果
研究デザイン	無作為比較対照試験
研究施設	リビア
対象患者	3回以上連続流産歴のある女性
介入	LDA単剤またはLDA+LMWH併用。 胎児心拍確認後75mg/日のLDAを開始、併用群はエノキサパリン0.4mL/日自己注射も開始。流産・死産または妊娠34週まで継続。
主要評価項目とそれに用いた統計学的手法	流産と生産。

結果	併用群は、単剤群と比較して、流産率が低く(22/75 [29%] 対 43/75 [47%]、 $P < 0.001$)、生児獲得率が高かった(53/75 [71%] 対 32/75 [42%]、 $P < 0.001$)。
結論	第1三半期反復流産歴がある女性において、LDAとLMWH併用は、LDA単剤と比較して妊娠維持に有用である。

C: アブストラクターのコメント

コメント	特記すべきことなし。 渡邊央美
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付属資料 3 デルファイ法による総意形成のまとめ

デルファイ法とは

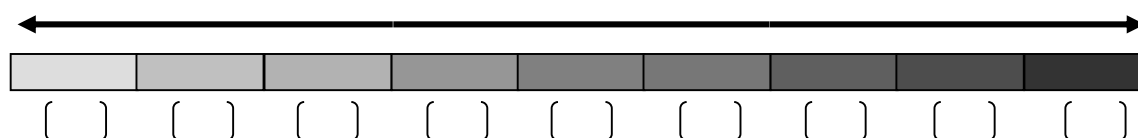
CQ に対して作成された推奨文を医師、助産師、患者、社会医学(医療経済学も含む)などのパネリストが独立して投票し、意見がまとまるまで、その結果を公表しながら繰り返して行うことで、直観的意見や経験的判断を、集約・洗練していき総意形成を図る技法である。本ガイドライン作成においては以下のような形式で、メールないしは郵便を用いて行った。

1. 9 段階の中から適切なものを選択して下さい。その際に、コメント等ありましたら、 欄にご記載下さい。
2. 事務局で結果を集計し、中央値が 7 以上あるいは 3 以下であれば、総意形成の成立と判断します。意見が分かれる場合や、コメントの内容によっては、事務局で文言を修正したのち、再度お考えを伺います。

適切でない

どちらとも言えない

適切である



CQ1. どのような状況において抗リン脂質抗体を測定するのか？

産婦人科医 16 名、内科医 1 名、社会医学系研究者 1 名、助産師 1 名、患者 1 名から成る組織構成で 3 回にわたって意見を求め統合した。以下、各回の質問内容と結果について示す。

1 回目

- Q1 妊娠 10 週以降の原因不明子宮内胎児死亡の既往の場合には抗リン脂質抗体検査を行う 中央値=9
- Q2 子癇、重症妊娠高血圧腎症や胎盤機能不全による妊娠 34 週未満の早産の既往の場合には抗リン脂質抗体検査を行う 中央値=8.5
- Q3 子癇や重症妊娠高血圧腎症の既往の場合には発症時期に関わらず抗リン脂質抗体検査を行う 中央値=6.5
- Q4 敬称妊娠高血圧腎症の既往の場合には発症時期に関わらず抗リン脂質抗体検査を行う 中央値=5
- Q5 HELLP 症候群の既往の場合には抗リン脂質抗体検査を行う 中央値=5.5
- Q6 胎盤早期剥離の既往の場合には抗リン脂質抗体検査を行う 中央値=7
- Q7 胎児発育不全の既往の場合には抗リン脂質抗体検査を行う 中央値=7

- Q8 3回以上の連続した妊娠10週未満の原因不明流産の既往の場合には抗リン脂質抗体検査を行う 中央値=9
- Q9 2回の連続した妊娠10週未満の原因不明流産の既往の場合には抗リン脂質抗体検査を行う 中央値=8
- Q10 生化学的妊娠を繰り返す場合には抗リン脂質抗体検査を行う 中央値=6.5
- Q11 原因不明不妊症の場合には抗リン脂質抗体検査を行う 中央値=3.5
- Q12 体外授精で反復着床障害の場合には抗リン脂質抗体検査を行う 中央値=4
- Q13 血栓症の既往の場合には抗リン脂質抗体検査を行う 中央値=9
- Q14 膠原病(主にSLE)合併の場合には抗リン脂質抗体検査を行う 中央値=9
- Q15 妊娠時検査で血小板低値の場合には抗リン脂質抗体検査を行う 中央値=6.5
- Q16 妊娠時検査で梅毒反応が生物学的疑陽性の場合には抗リン脂質抗体検査を行う 中央値=7.5

2回目

- Q3 早発型の子癇や重症妊娠高血圧腎症の既往の場合には抗リン脂質抗体検査を行う 中央値=7.5
- Q4 軽症であっても妊娠高血圧腎症の既往がある場合には抗リン脂質抗体検査を行う 中央値=6
- Q5 妊娠高血圧症候群やFGRを伴うHELLP症候群の既往の場合には抗リン脂質抗体検査を行う 中央値=7
- Q10 生化学的妊娠を2回以上繰り返す場合には抗リン脂質抗体検査を行う 中央値=5.5
- Q11 (不育症ではなく)不妊症の場合には抗リン脂質抗体検査は推奨されない 中央値=7
- Q12 体外授精で反復着床障害の場合には抗リン脂質抗体検査を行う 中央値=4
- Q15 妊娠時検査で血小板低値(10万以下)の場合には抗リン脂質抗体検査を行う 中央値=6.5
- Q17 (APSの家族性は証明されていないため)臨床症状がなく、APSの家族歴のみ有する場合には抗リン脂質抗体検査は推奨されない 中央値=7

3回目

- Q4 軽症であってもFGRを伴う早発型妊娠高血圧腎症の既往がある場合には抗リン脂質抗体検査を行う 中央値=7
- Q15 妊娠時初発で血小板減少を認めた場合は(ITPや妊娠性血小板減少症の診断は除外診断であるため)、症例により抗リン脂質抗体検査を行う 中央値=7

以下の2つの推奨文については、2回デルファイ法を施行した結果を事務局で協議しました。その結果、現時点で総意形成は難しく、保留とするのが適切と考えています。それで

よろしいかお答えください。

Q10 生化学的妊娠を2回以上繰り返す場合には抗リン脂質抗体検査を行う

はい 19

いいえ 1

Q12 体外受精で反復着床障害の場合には抗リン脂質抗体検査を行う

はい 19

いいえ 1

デルファイ法より導いた推奨文

1. 抗リン脂質抗体を測定することが妥当と判断される状況

- 2回以上の連続した妊娠10週未満の原因不明流産の既往

Q：2回の連続した妊娠10週未満の原因不明流産の既往の場合には抗リン脂質抗体検査を行う 中央値=8

Q：3回以上の連続した妊娠10週未満の原因不明流産の既往の場合には抗リン脂質抗体検査を行う 中央値=9

Q：妊娠10週以降の原因不明子宮内胎児死亡の既往の場合には抗リン脂質抗体検査を行う 中央値=9

- 子癇、重症妊娠高血圧腎症(特に早発型)や胎盤機能不全(胎児発育不全)の既往

Q：子癇、重症妊娠高血圧腎症や胎盤機能不全による妊娠34週未満の早産の既往の場合には抗リン脂質抗体検査を行う 中央値=8.5

Q：早発型の子癇や重症妊娠高血圧腎症の既往の場合には抗リン脂質抗体検査を行う 中央値=7.5

Q：妊娠高血圧症候群やFGRを伴うHELLP症候群の既往の場合には抗リン脂質抗体検査を行う 中央値=7

Q：軽症であってもFGRを伴う早発型妊娠高血圧腎症の既往がある場合には抗リン脂質抗体検査を行う 中央値=7

Q：胎児発育不全の既往の場合には抗リン脂質抗体検査を行う 中央値=7

- 血栓症の既往

Q：血栓症の既往の場合には抗リン脂質抗体検査を行う 中央値=9

- 膠原病(主にSLE)合併の場合

Q：膠原病(主にSLE)合併の場合には抗リン脂質抗体検査を行う 中央値=9

- 妊娠検査で梅毒反応の生物学的疑陽性、あるいは血小板減少を認めた場合

Q：妊娠時検査で梅毒反応が生物学的疑陽性の場合には、抗リン脂質抗体検査を行う 中央値=7.5

Q：妊娠時初発で血小板減少を認めた場合は(ITP や妊娠性血小板減少症の診断は除外診断であるため)、症例により抗リン脂質抗体検査を行う 中央値=7

- 胎盤早期剥離の既往

Q：胎盤早期剥離の既往の場合には抗リン脂質抗体検査を行う 中央値=7

2. 抗リン脂質抗体を測定すべきではないと考えられる状況

- 不妊症の場合

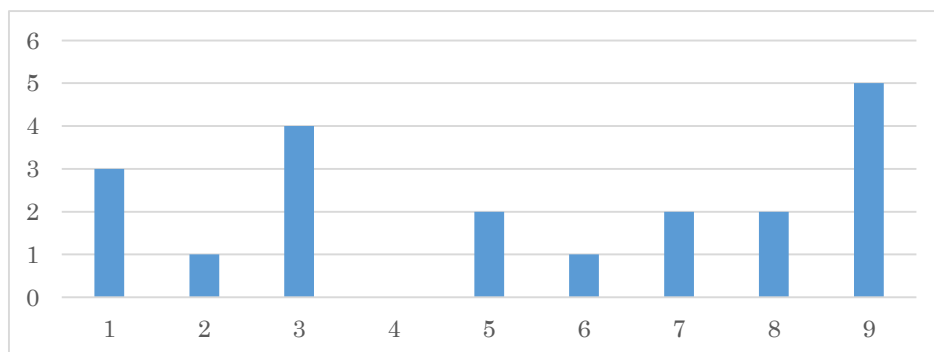
Q：(不育症ではなく)不妊症の場合には抗リン脂質抗体検査は推奨されない 中央値=7

- 臨床症状がなく、抗リン脂質抗体症候群(APS)の家族歴のみ有する場合

Q：(APS の家族性は証明されていないため)臨床症状がなく、APS の家族歴のみ有する場合には抗リン脂質抗体検査は推奨されない 中央値=7

3. 抗リン脂質抗体の測定に関して賛否両論がある状況

- 生化学的妊娠を 2 回以上繰り返す場合 中央値=5.5



寄せられたコメント(コメント者の評価点)

・化学流産と APS の関連についてエビデンスがあれば施行します。現時点ではエビデンス(-)と考えております。(1)

・着床障害群と不育症群の抗体陽性頻度は類似しており、陽性者はいると思うが、アスピリン、ヘパリンは有用ではなく、治療法が確立するまでは研究として行うべき。(6)

・不育症と考えれば当然の検査であると思います。(9)

・医学的には 2 回とすると、検査必要な方が多すぎて困った状況になると思いますが、たび重なる場合には不育症としての検査が必要かと思います。(5)

・35 歳以上で 2 回以上繰り返す場合には検査したほうがいいと思う。(9)

反復生化学的妊娠症例では抗カルジオリピン IgG 陽性例が有意に多かったというデータを

得ている。(7)

・化学妊娠の定義が曖昧だから。患者自身は初期流産と化学流産を厳密に区別できていないから。問診での既往歴の化学妊娠は信頼性が低いので、初期流産として診療上扱うのが妥当である。(9)

・日本産科婦人科学会でも化学流産を妊娠回数に数えないとしているのに、流産としてカウントし化学流産を2回反復したら反復流産として精査・加療の対象とするのは、ミスリーディングです。医療費の無駄にもつながります。ある意味、慎むべきでしょう。(3)

・そもそも化学流産のみでは、APSの診断基準を満たさないで調べることは適切でないと思います。(3)

・化学流産は間違いで生化学的妊娠が正しい用語です。たとえAPSであっても、ヘパリン+LDAの有効性は全く証明されていないため。(3)

・化学流産は不妊治療の人などは結構な確率で起こっている。流産とは分けて考えるべき。(3)

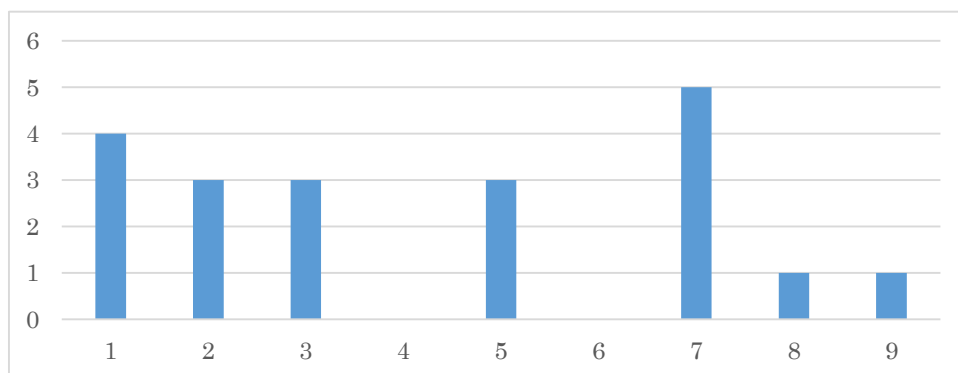
・化学流産は妊娠の60%という報告もあり、胎芽染色体異常が推定される(確認はできない)。「化学流産は流産に含めない」というのが根本の定義であり、研究が十分されていない。臨床的におこなうべきではない。ART施設が測定をおこなっているが、患者の負担が増加するばかりだ。(1)

・分類基準にも全く含まれず、エビデンスもないことから、あくまで研究として行うべきである。(1)

・化学流産とAPSの関連については否定されているということについては(抗リン脂質抗体陽性も含めて)十分なエビデンスがあると考えています。(2)

・学術的な取扱い、また医療費の適切な分配という観点からは不適切なのかもしれませんが、患者さんの苦しみは深く、また年齢も若くない場合が多いと思いますので私のほうからは勧めませんが、検査を希望されるようであればそれにこたえています。(8)

● 体外受精で反復着床障害の場合 中央値=4



寄せられたコメント(コメント者の評価点)

・反復着床障害とAPSの関連性についてエビデンスがあれば行います。現時点ではエビデ

ンス(-)と考えております。(1)

・陽性でも病原性が疑わしい。治療もない。エビデンスのない治療を行う口実となり、不適切。(3)

・反復着床障害であれば実施してみる価値はあると思います。(7)

・体外受精は費用も高額で心身共に負担もかかるので反復着床障害の場合には検査したほうがよいと思う。(7)

・そのような症例に抗リン脂質抗体検査を行ったことがない。(5)

・不妊症との関連としてエビデンスがない。不妊治療施設での抗リン脂質抗体の自費測定とヘパリンの過剰治療は、目に余り、危険であるときえ言える。戒めのためにも、推奨しない。(1)

・EBMがあるのでしょうか？まだ、研究レベルではないのでしょうか。(5)

・抗リン脂質抗体症候群と着床障害との関連が強くないため抗リン脂質抗体を測定することは適切でないと思います。(2)

・APSが着床障害となるエビデンスが全くないため。(3)

・陽性に出る可能性は高いが、鑑別のために妊娠に至らない場合は行う。(7)

・コンセンサスは得られていない。良好胚でもPGSをすれば異常は多い。(1)

・分類基準にも全く含まれず、エビデンスもないことから、あくまで研究として行うべきである。(1)

・対象となる症例が非常に多いと思いますが、その割には確立された関係性とは言えないという気がします。現時点では全国的に推奨する診療行為では無いように思いました。(2)

・化学流産を2回以上繰り返す場合と同様に着床障害とAPSの関係は否定されていると考えます。(2)

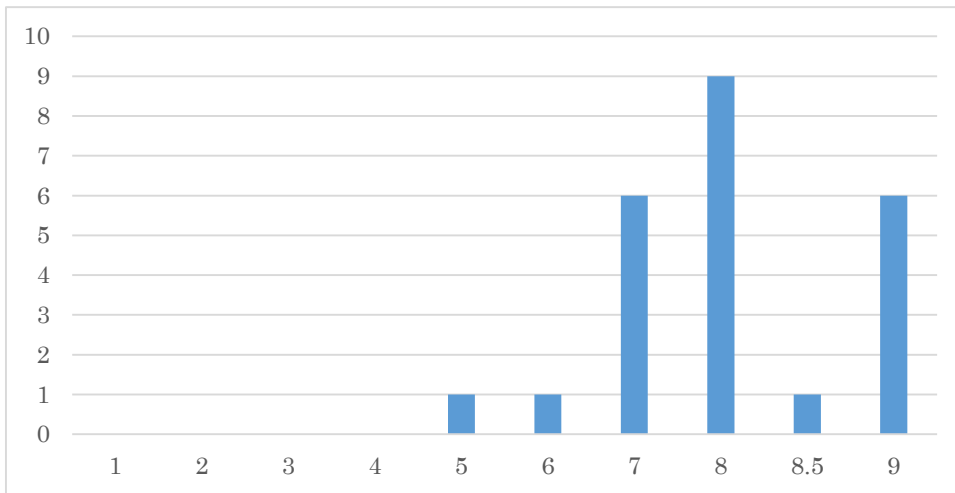
・学術的な取扱い、また医療費の適切な分配という観点からは不適切なのかもしれませんが、患者さんの苦しみは深く、また年齢も若くない場合が多いと思いますので私のほうからは勧めませんが、検査を希望されるようであればそれにこたえています。(7)

CQ2. 産科的APSのリスクの評価方法は？

内科系医師14名、産科系医師7名、社会医学系研究者1名、助産師1名、患者1名から成る組織構成で意見を求め統合した。以下、各推奨文に対する賛成度の集計結果について示す。

[推奨文]確立された産科的APSのリスクの評価方法はない。しかし、死産歴を有する例、PIHの既往例、血栓症の既往例、抗リン脂質抗体複数陽性例、抗リン脂質抗体高値陽性例、LA陽性例、APTT延長例では周産期予後が悪くなるという報告を参考とする。

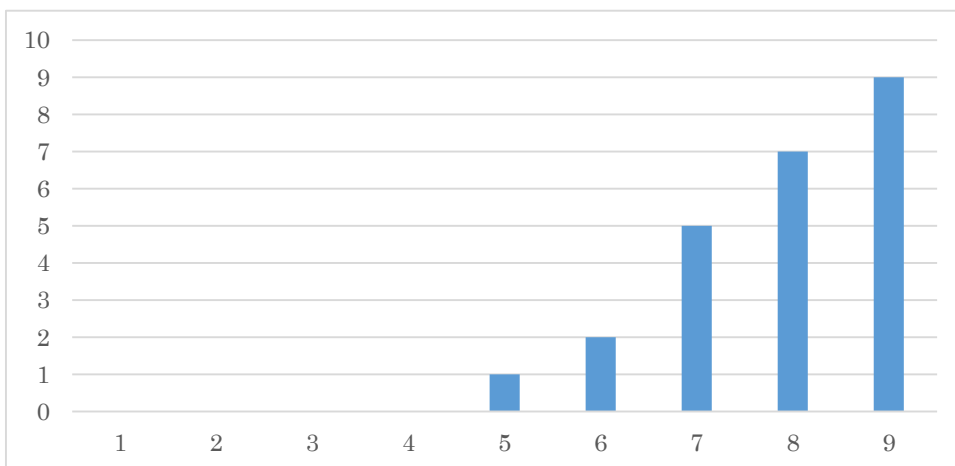
中央値=8



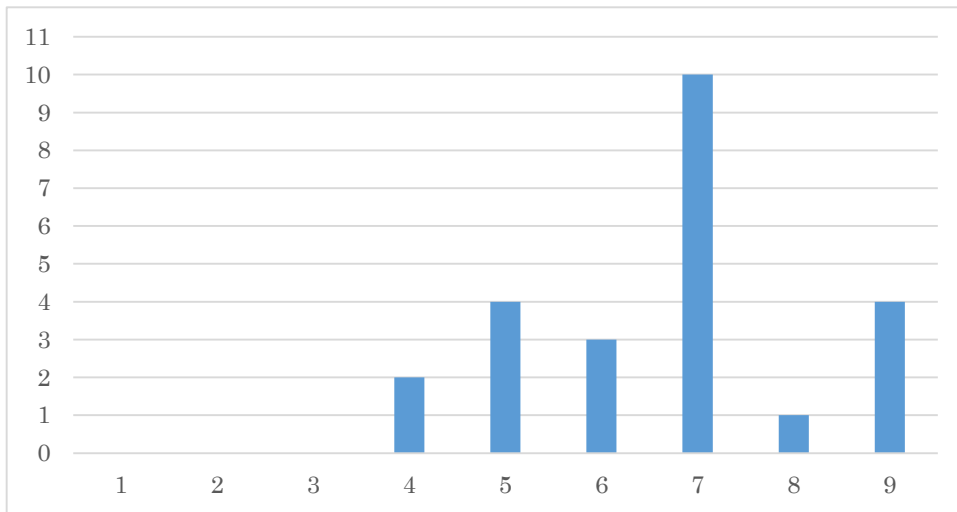
CQ3. 産科的 APS のリスクにあった治療方法は？

内科系医師 14 名、産科系医師 7 名、社会医学系研究者 1 名、助産師 1 名、患者 1 名から成る組織構成で意見を求め統合した。以下、各推奨文に対する賛成度の集計結果について示す。

[推奨文]1. APS 合併妊娠の基本的治療は、妊娠初期からの低用量アスピリンおよび未分画ヘパリンの併用療法である。中央値=8



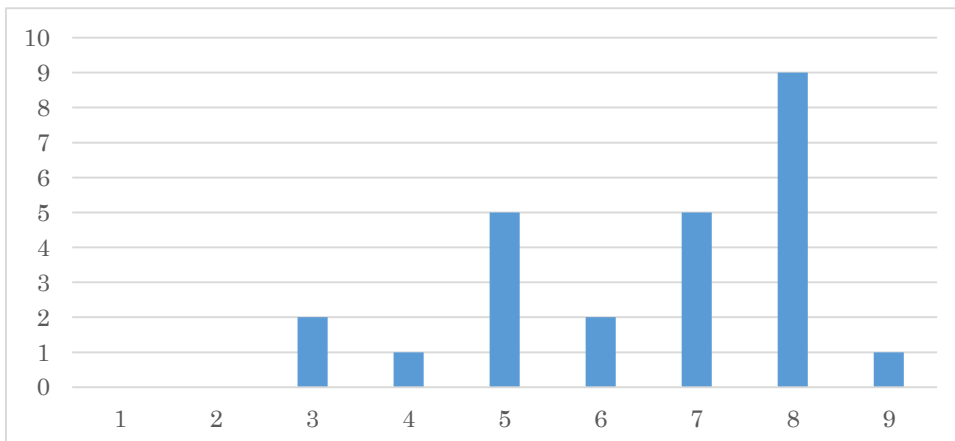
[推奨文]2. CQ2 のリスク評価でハイリスクと判断される例や、基本的治療を行っても生児が得られなかった例では、基本的治療に加えて IVIg や PSL の追加を考慮してよい。中央値=7



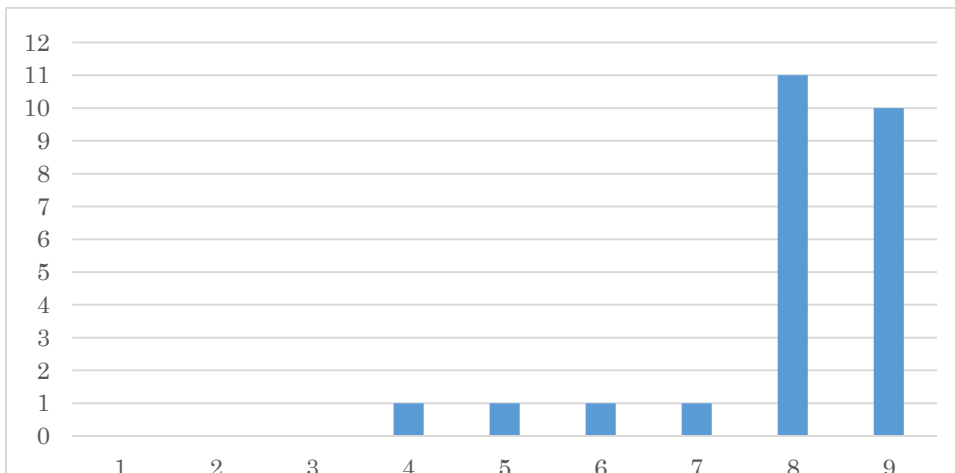
CQ4. 産科的 APS 母体の産後のフォローはどうするか？

内科系医師 15 名、産科系医師 7 名、社会医学系研究者 1 名、助産師 1 名、患者 1 名から成る組織構成で意見を求め統合した。以下、各推奨文に対する賛成度の集計結果について示す。

[推奨文]1. (過去に血栓症有さない)産科的 APS の患者の出産後のフォローアップにおいては、2 種類以上の抗リン脂質抗体が陽性または SLE の合併があるならば抗血小板療法を行なう。中央値=7



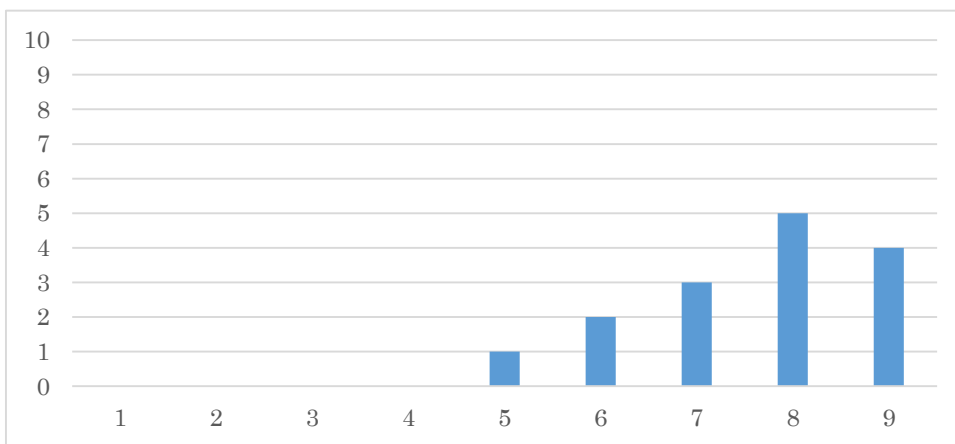
[推奨文]2. 産科的 APS 患者(原発性 APS 患者の場合)であっても、抗核抗体陽性や補体低下などの免疫学的異常がある場合には、将来的に SLE を発症する可能性が高いので内科的なフォローアップを行う。中央値=8



CQ5. APS 母体から出生した児に対する特別な治療は必要か？

内科系医師 4 名、産科系医師 6 名、新生児科医 2 名、社会医学系研究者 1 名、助産師 1 名、患者 1 名から成る組織構成で意見を求め統合した。以下、各推奨文に対する賛成度の集計結果について示す。

[推奨文]APS 母体から出生した児に対する治療において、早産児・低出生体重児としての対応以外に一定の推奨はない。中央値=8

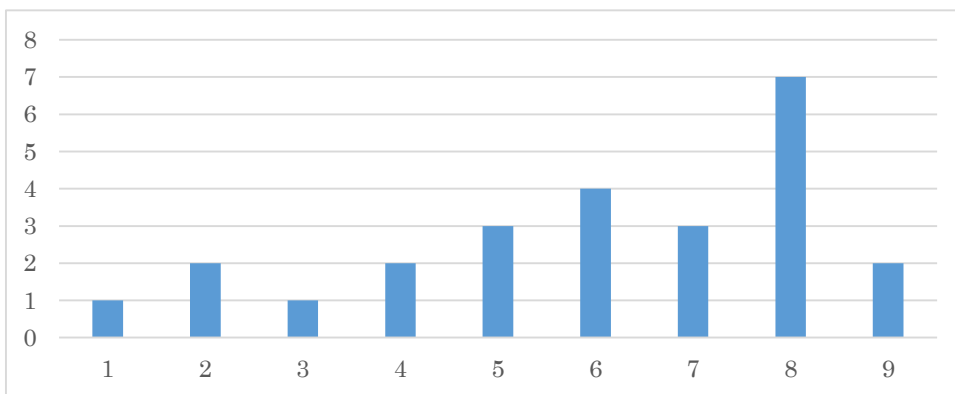


CQ6. 臨床所見のない抗リン脂質抗体陽性者における治療方針は？

CQ6-1 SLE を有しない場合

内科系医師 15 名、産科系医師 7 名、社会医学研究者 1 名、助産師 1 名、患者 1 名から成る組織構成で意見を求め統合した。以下、各推奨文に対する賛成度の集計結果について示す。

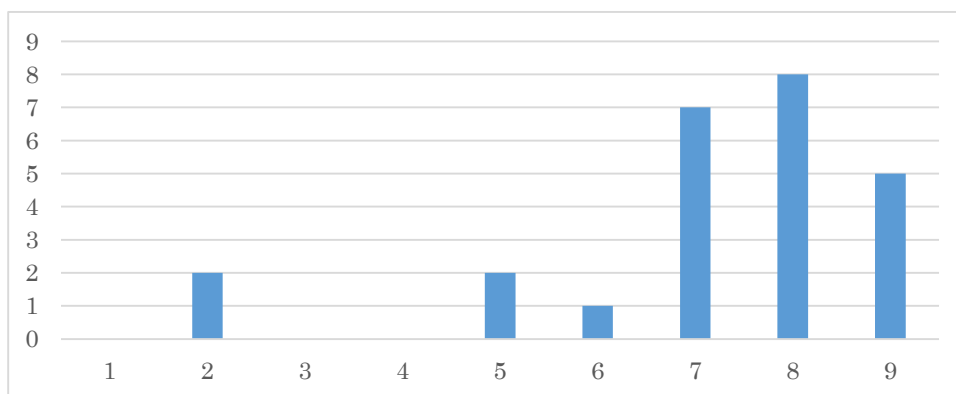
[1 回目推奨文] 基礎疾患として SLE をもたない場合、妊娠中産科的 APS の発症予防を目的として低用量アスピリンやヘパリンによる治療を行うことは推奨されない。中央値=6



寄せられたコメント(コメント者の評価点)

- ・「抗リン脂質抗体陽性のみ妊婦への安易な LDA 療法」は慎むべきだと思います。(8)
- ・まだ、どうしたら良いか悩んでいます。SLE をもたない場合でも Hep+LDA を通常行っていますし、予後の悪い人も経験しています。この推奨文は流産歴がない場合だと適切ですが、流産歴があれば賛同できません。(5)
- ・下記の論文(メタアナリシス)がある。この論文では LDA の予防効果に関する論文であるので、ヘパリンの記載はどうか。(6)
- ・当調査研究班から発表されたシステマティックレビューの結果を尊重します。(8)
- ・無症候性の APS 患者が年間の血栓症を発症するリスクは 0-3.8%と報告されており、これはアスピリンによる出血を来した割合とほぼ同等である。しかしながら、すべての APS 陽性患者にアスピリンが有効でないと判断するには十分なサンプルサイズが得られたランダム化コントロールスタディーが少ないと思われる。aPL プロファイルで血栓症リスクが高い患者(持続的な LA 陽性、aCL : 中～高等度陽性、または抗 β_2 GPI+LA or aCL の場合)は低容量アスピリンを考慮しても良い。(5)

[2回目推奨文] 臨床症状(血栓症や妊娠合併症の既往)がなく、SLE を合併していない、抗リン脂質抗体陽性者の妊娠において、産科的 APS の発症予防を目的の低用量アスピリン(LDA)やヘパリンによる治療は必ずしも推奨されない。中央値=7.5

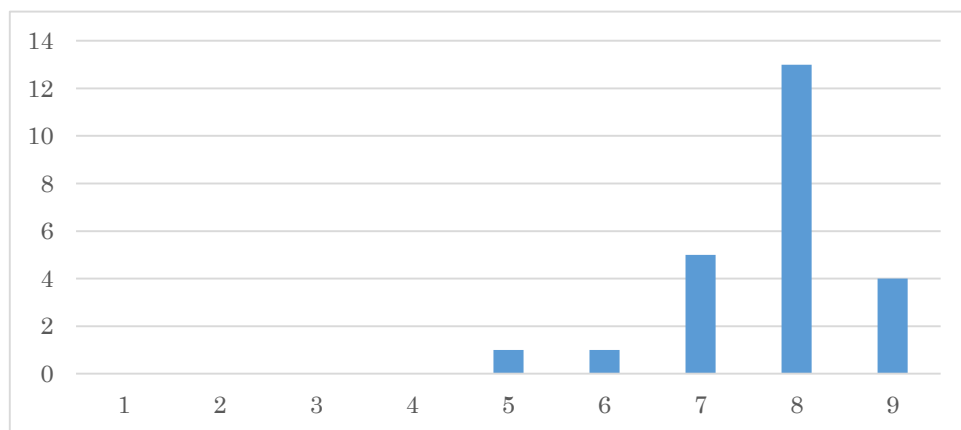


CQ6-2 SLE を有する場合

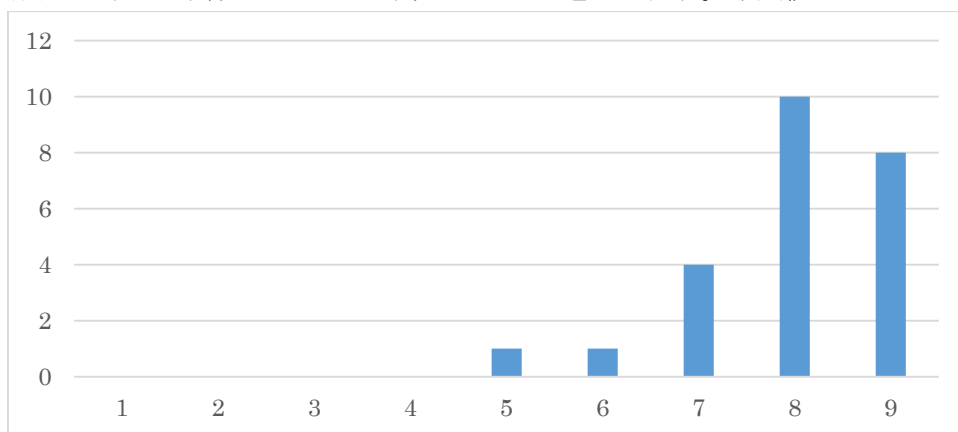
内科系医師 14 名、産科系医師 7 名、社会医学系研究者 1 名、助産師 1 名、患者 1 名から成る組織構成で意見を求め統合した。以下、各推奨文に対する賛成度の集計結果について示す。

[推奨文]基礎疾患として **SLE をもつ症例**で、LAC 陽性あるいは LAC 陽性に加えて抗カルジオリピン抗体(古典法*または β_2 GPI 依存性抗カルジオリピン抗体)高値**の場合

1. 産科的 APS の発症予防を目的とした妊娠中の薬物治療としては、他のリスクおよび患者の背景を考慮した上で LDA とヘパリン(予防量:10,000 単位/日前後)による治療を行うことが容認される。中央値=8



2. 産後は産科ガイドラインに則り、以下のリスク因子を有している場合には分娩後抗凝固療法(通常 3 日間以上)あるいは間欠的空気圧迫法を行う。中央値=8



CQ7. 原因不明の不育症に対する抗凝固・抗血小板療法の考え方は？

産婦人科医 16 名、内科医 1 名、社会医学系研究者 1 名、助産師 1 名、患者 1 名から成る組織構成で意見を求め統合した。以下、各推奨文に対する賛成度の集計結果について示す。

[推奨文] 原因不明の不育症に対して、ルーチンに抗血小板薬やヘパリンによる治療は行わない。中央値=8

