Trombofilia y Embarazo

Dr. Ramón Serra Tagle
Ginecólogo Obstetra
Hospital Naval de Punta Arenas

Dr. Juan Carlos Zúñiga Armijo,
Becado Ginecología Obstetricia,
Hospital Barros Luco Trudeau

Temario

- Definiciones.
- Epidemiología.
- Manifestaciones clínicas.
- Prevención de TVP.
- Vigilancia materna.
- Prevención de complicaciones obstétricas.

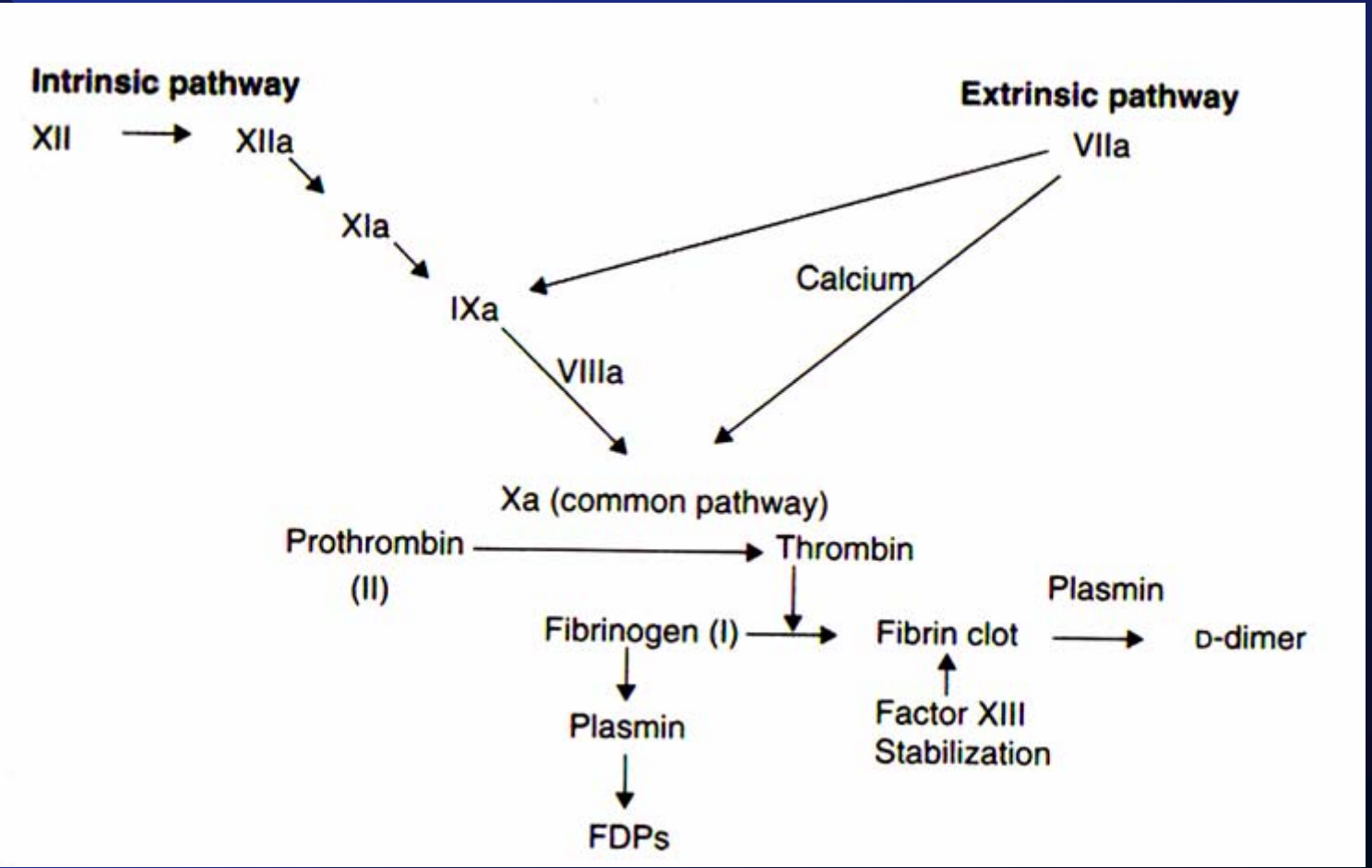
Definiciones

- **Hemostasia:**
  - **Tapón plaquetario.**
  - **Activación cascada de la coagulación.**
  - **Regulación de la coagulación:**
    - **Mecanismos antitrombóticos.**
  - **Remoción del coagulo (fibrinolosis).**

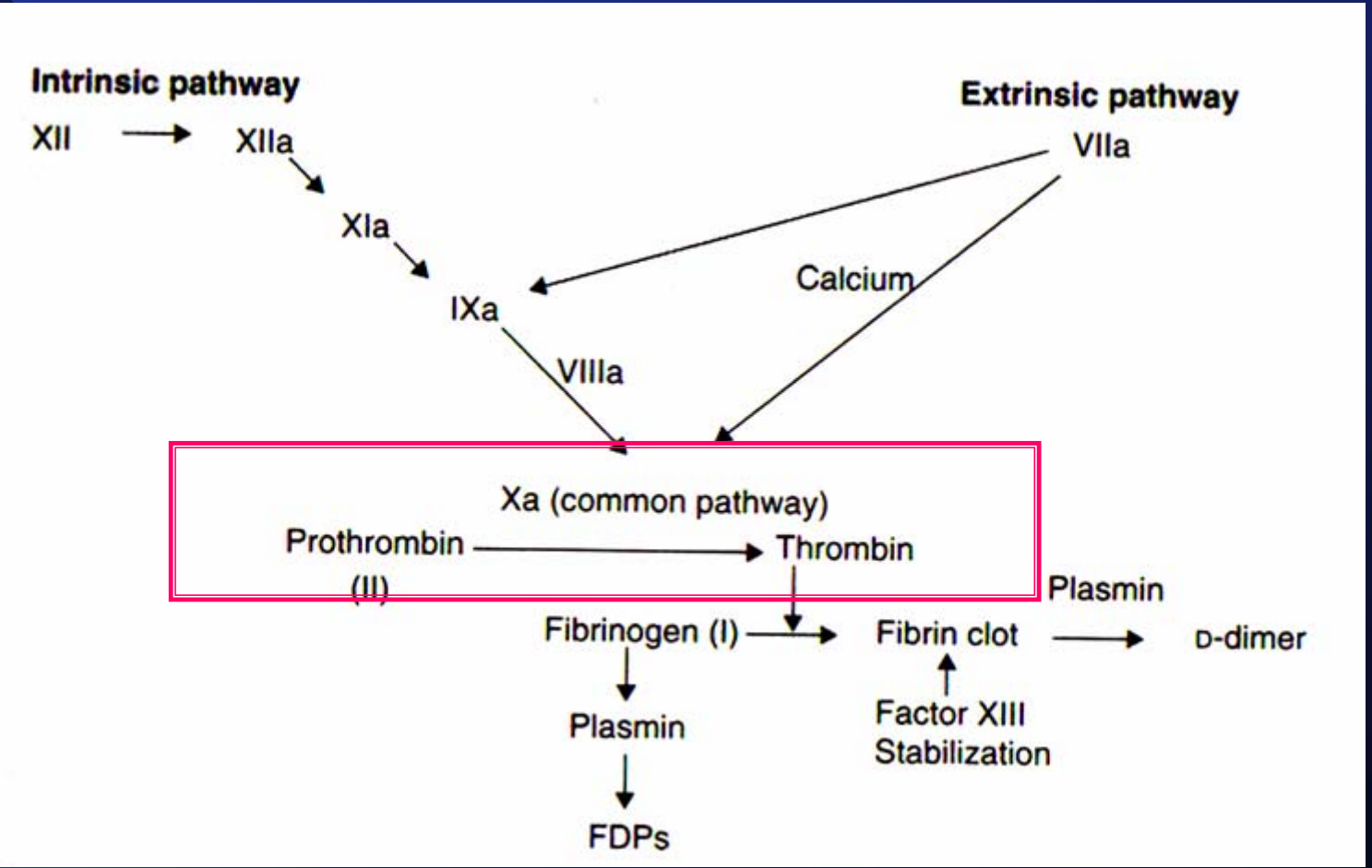
Definiciones

- **Tapón plaquetario:**
  - **Adhesión.**
  - **Agregación.**
  - **Secreción.**
  - **Actividad procoagulante.**

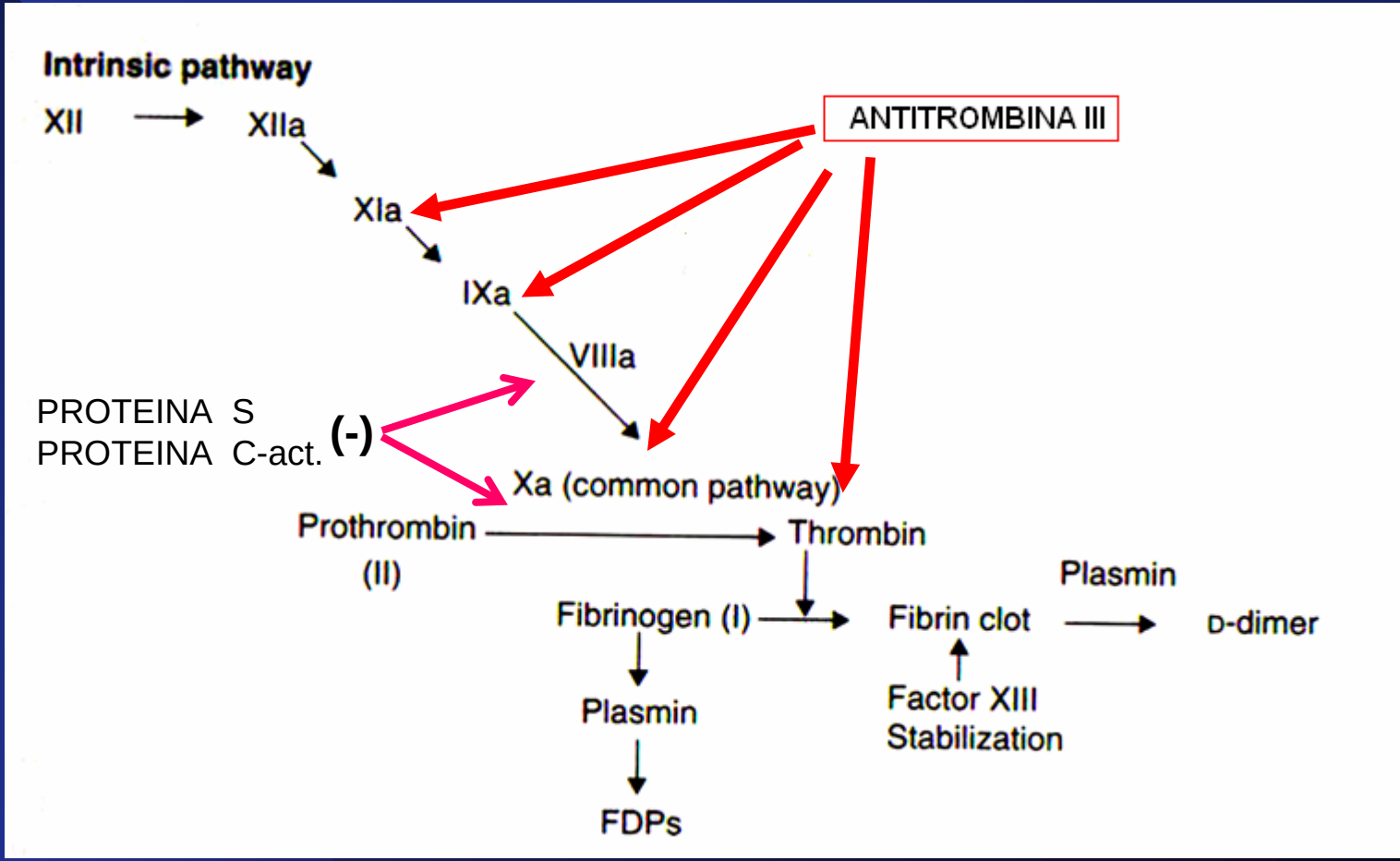
Definiciones



Definiciones



Definiciones



Definiciones

- Coagulación y embarazo:
  - Resistencia a Proteína C.
  - Disminuye actividad de Proteína S.
  - Aumenta el Fibrinogens y los Factores II, VII, VIII y X.
  - Aumentan los niveles y actividad de inhibidores de la fibrinolisis:
    - TAFI (Thrombin activatable fibrinolytic inhibitor)
    - PAI-1 y PAI-2 (plasminogen activator inhibitor type 1 and 2.

Definiciones

- **Trombofilia:**
  - **Condiciones genéticas o adquiridas que aumentan el riesgo de enfermedad tromboembólica.**

Hereditarias:

Déficit de anti trombina III.
Déficit de proteína C.
Déficit de proteína S.
Factor V de Leiden.
Mutación G20210A.
Disfibrogenemia.

Adquiridas:

SAF.

Complejas:

Alza del factor VIII.
Hiperhomocisteinemia

Epidemiología

	Prevalence in general population (percent)	Percentage of all VTE in pregnancy
Factor V Leiden heterozygote	1-15	40
Factor V Leiden homozygote	<1	2
Prothrombin gene heterozygote	2-5	17
Prothrombin gene homozygote	<1	0.5
Factor V Leiden/prothrombin double heterozygote	0.01	1-3
Antithrombin III activity	0.02	1
Protein C activity	0.2-0.4	14
Protein S free antigen	0.03-0.13	3

References:

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9. *Dykes AC, Walker ID, McMahon AD, Islam SI, Tait RC. A study of Protein S antigen levels in 3788 healthy volunteers: influence of age, sex and hormone use, and estimate for prevalence of deficiency state. Br J Haematol. 2001; 113:636-41. (Level II-3)*
10. *Goodwin AJ, Rosendaal FR, Kottke-Marchant K, Bovill EG. A review of the technical, diagnostic, and epidemiologic considerations for protein S assays. Arch Pathol Lab Med 2002; 126:1349-66. (Level III)*

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Manifestaciones clínicas

- TVP materna:

	VTE risk per pregnancy (women with *no history of VTE*) (percent)	VTE risk per pregnancy (women with *previous history of VTE*) (percent)
Factor V Leiden heterozygote	<0.3	10
Factor V Leiden homozygote	1.5	17
Prothrombin gene heterozygote	<0.5	>10
Prothrombin gene homozygote	2.8	>17
Factor V Leiden/prothrombin double heterozygote	4.7	>20
Antithrombin III activity	3-7	40
Protein C activity	0.1-0.8	4-17
Protein S free antigen	0.1	0-22

The relationship of the factor V Lieden mutation and pregnancy outcomes for mother and fetus. Obstet Gynecol. 2005 Sep ; 106 (3) :517 -24

- Objetivo: estimar frecuencia de eventos tromboembólicos en embarazadas portadoras de la mutación del factor V.

- Resultados:

  - 4885 embarazadas evaluadas, 134 portadoras (2.7%).

  - Eventos tromboembólicos:
    - Mutación FVL : 0
    - Control: 3 TEP y 1 TEP se produjo.

  - Otras conclusiones:
    - La mutación FVL no se asoció con aumento de abortos, preeclampsia, desprendimiento de la placenta, o RCIU.

Manifestaciones clinicas

- **Obstétricas:**
  - **Preeclampsia.**
  - **DPPNI**
  - **RCIU.**
  - **Aborto recurrente.**
  - **Muerte fetal**

Thrombophilic disorders and fetal loss: a meta-analysis

Evelyne Rey, Susan R Kahn, Michèle David, Ian Shrier *Lancet* 2003; **361:** 901–08

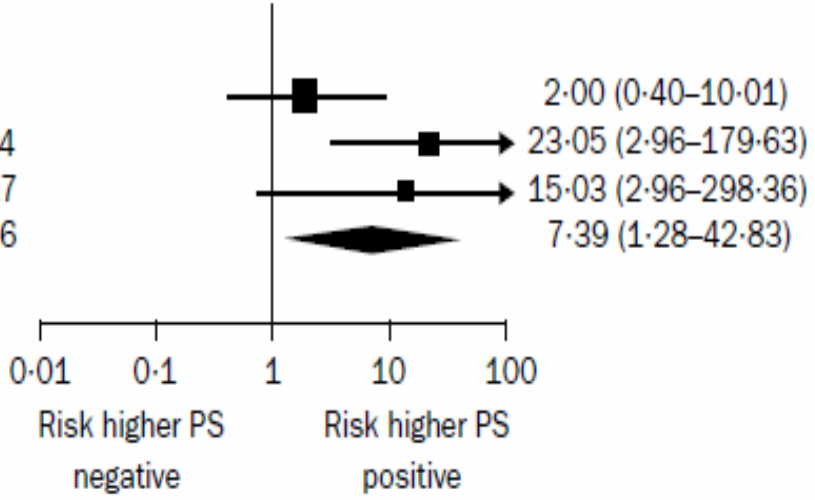
Study	FVL positive n/N	FVL negative n/N	Odds ratio (95% CI)	Odds ratio (95% CI)
FVL and recurrent fetal loss before 13 weeks				
Balasch[8]	1/2	54/103		0·91 (0·06–14·90)
Fatin[9]	6/8	53/121		3·85 (0·75–19·85)
Foka[10]	9/13	52/148		4·15 (1·22–14·14)
Grandone[11]	2/7	25/138		1·81 (0·33–9·86)
Rai[20]	59/71	845/983		0·80 (0·42–1·53)
Reznikoff[22]	27/38	233/462		2·41 (1·17–4·98)
Younis[25]	6/14	31/162		3·17 (1·03–9·80)
Subtotal (95% CI)	110/153	1293/2117		2·01 (1·13–3·58)
Test for heterogeneity p=0·11				
Test for overall effect p=0·02				

Study	PTm positive n/N	PTm negative n/N	Odds ratio (95% CI)	Odds ratio (95% CI)
PTm and recurrent fetal loss				
Fatini[9]	1/2	58/127		1·19 (0·07–19·44)
Foka[10]	7/9	73/171		4·70 (0·95–23·28)
Gris[27]	1/5	88/547		1·04 (0·12–9·04)
Kutteh[15]	1/2	49/98		1·00 (0·06–16·44)
Pickering[18]	4/7	118/181		0·71 (0·15–3·28)
Pihusch[19]	5/6	97/224		6·55 (0·75–56·95)
Raziel[21]	2/3	34/73		2·29 (0·20–26·43)
Reznikoff[22]	20/27	240/473		2·77 (1·15–6·68)
Wramsby[24]	3/6	59/125		1·12 (0·22–5·76)
Subtotal (95% CI)	44/68	816/2019		2·05 (1·18–3·54)
Test for heterogeneity p=0·67				
Test for overall effect p=0·01				

Thrombophilic disorders and fetal loss: a meta-analysis

Evelyne Rey, Susan R Kahn, Michèle David, Ian Shrier *Lancet* 2003; **361:** 901–08

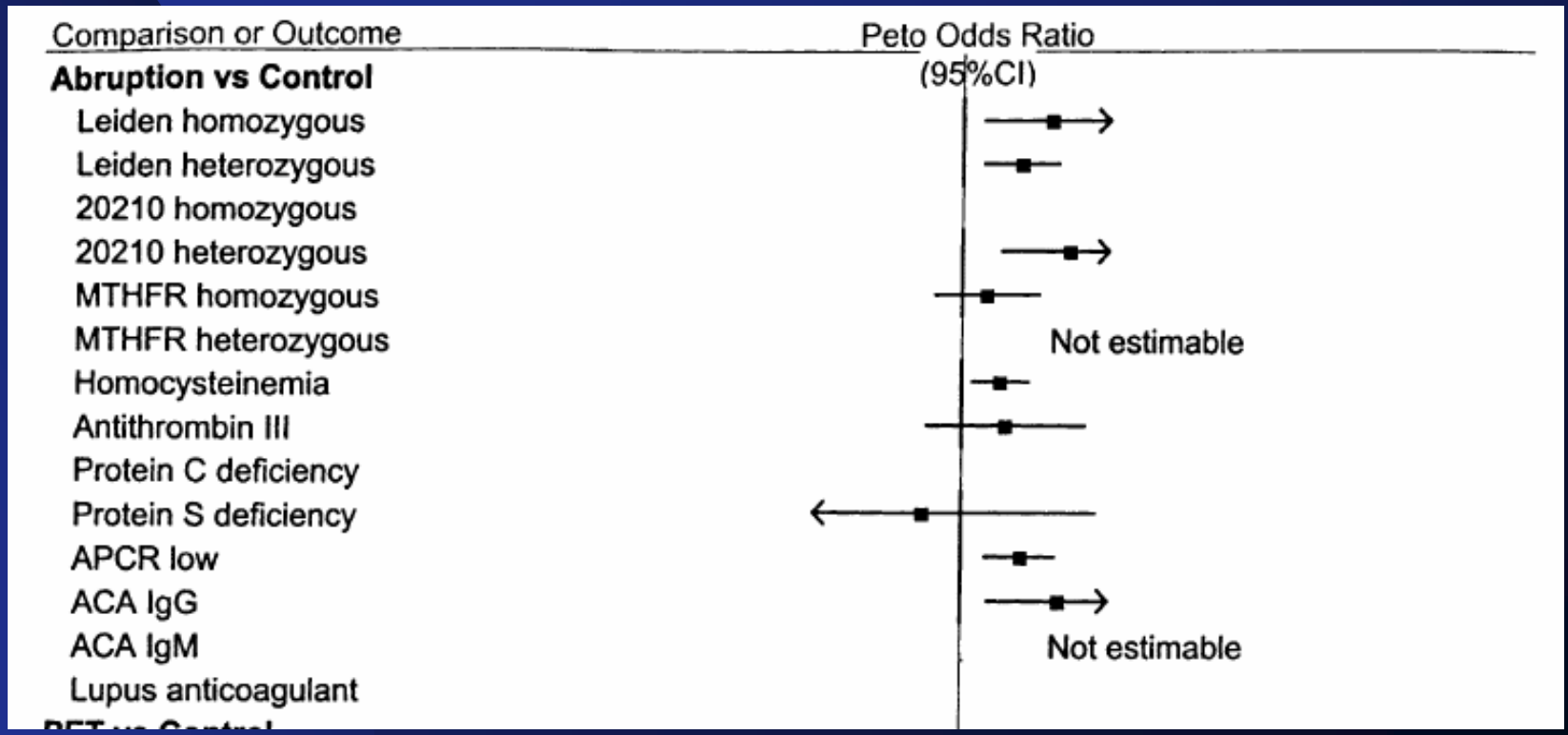
Study	PS positive n/N	PS negative n/N	Odds ratio (95% CI)	Odds ratio (95%CI)
Protein S deficiency and non-recurrent fetal loss				
Alfirevic[30]	3/7	15/55		2·00 (0·40–10·01)
Gris[27]	11/12	221/684		23·05 (2·96–179·63)
Many[34]	3/3	37/117		15·03 (2·96–298·36)
Subtotal (95% CI)	17/22	273/856		7·39 (1·28–42·83)
Test for heterogeneity p=0·13				
Test for overall effect p=0·03				



Review

How strong is the association between maternal thrombophilia and adverse pregnancy outcome? A systematic review

Zarko Alfirevic[a,*], Devender Roberts[a], Vanessa Martlew[b]



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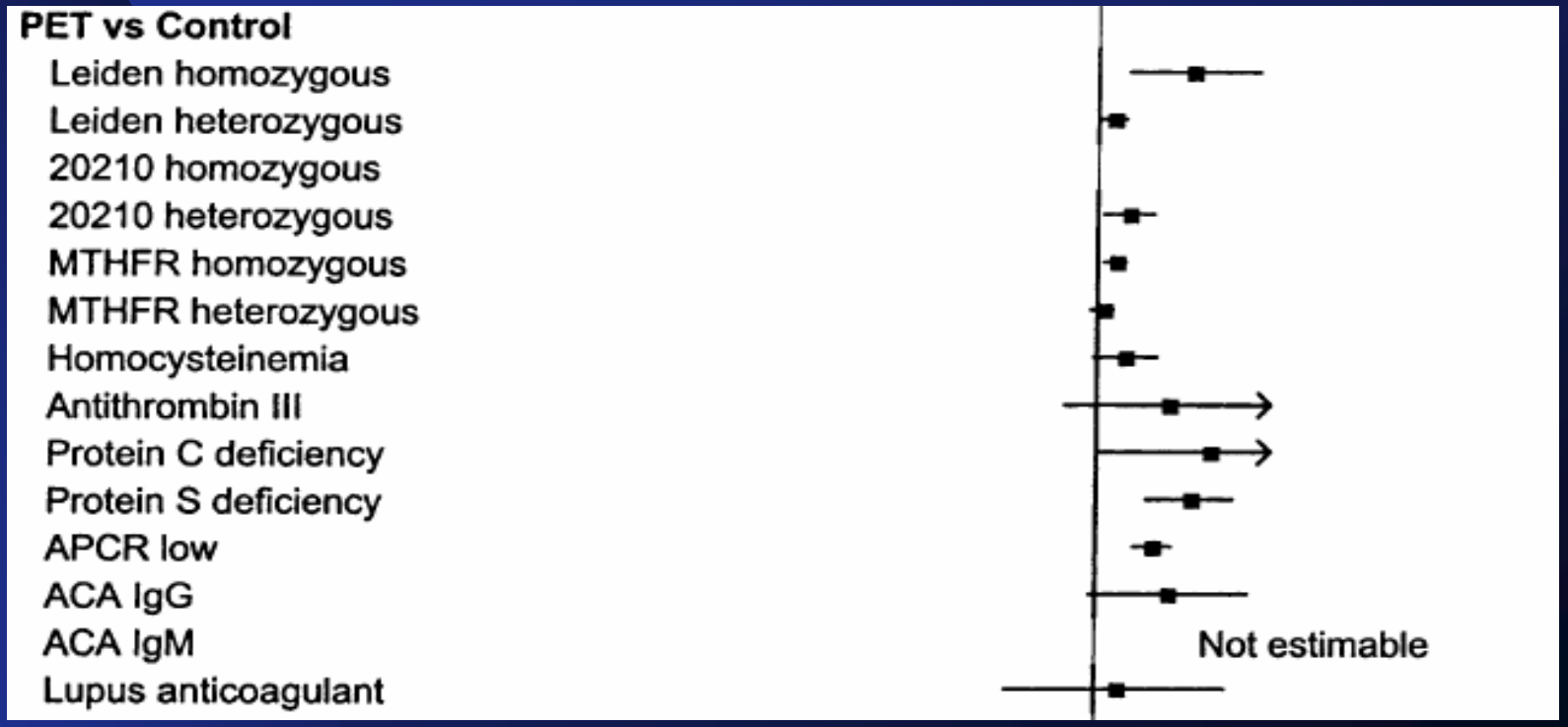

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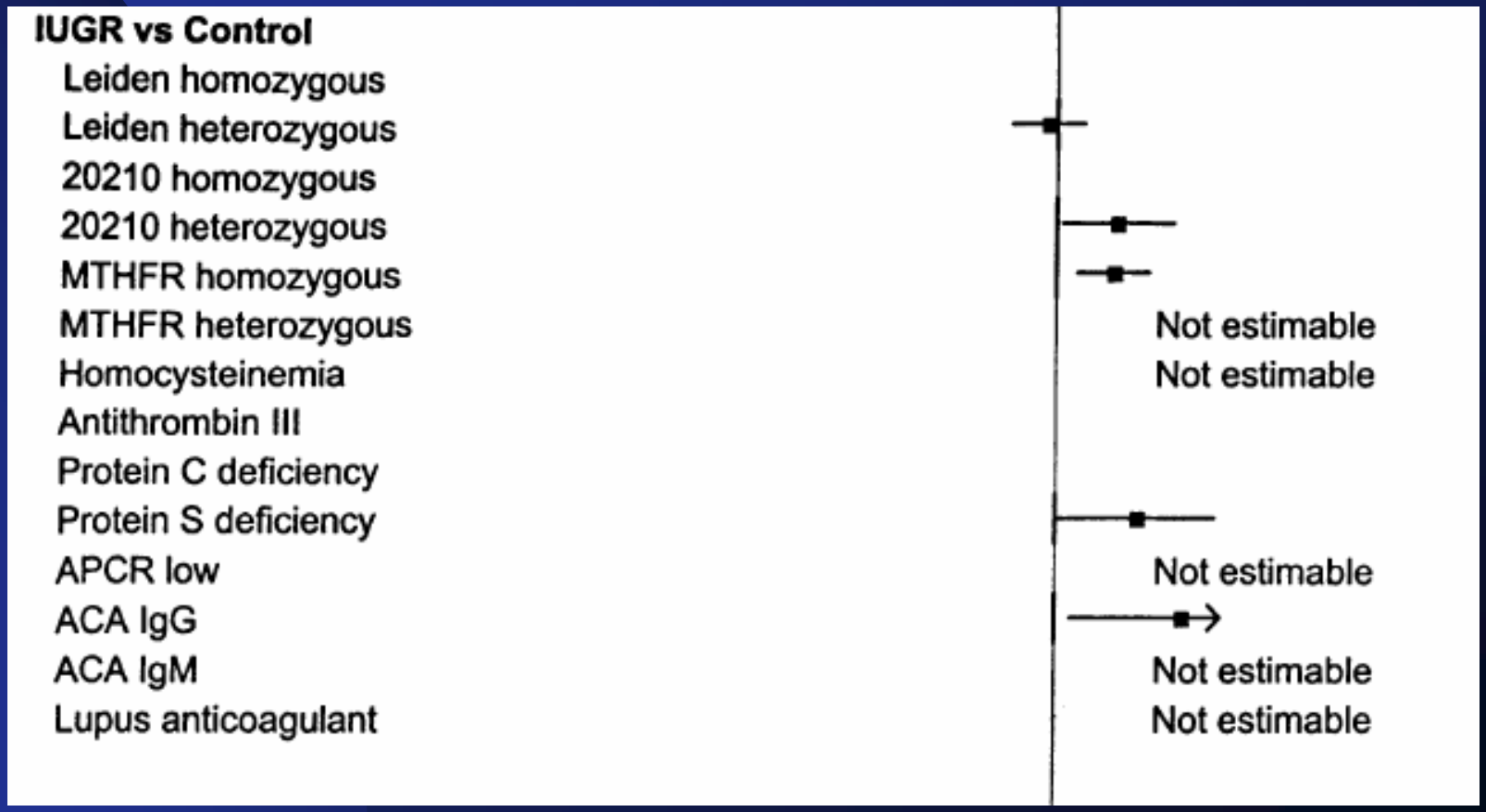


Tratamiento

- Mejorar el resultado perinatal.
- Disminuir la tasa de abortos.
- Disminuir la frecuencia de SHE, PES, RCF, insuficiencia placentaria y prematurez.
- Disminuir el riesgo de muerte fetal.
- Disminuir el riesgo de fenómenos trombóticos maternos.

Heparin for pregnant women with acquired or inherited thrombophilias (Review)

Walker MC, Ferguson SE, Allen VM

THE COCHRANE COLLABORATION®

Authors' conclusions

There are no completed trials to determine the effects of heparin on pregnancy outcomes for women with a thrombophilia.

Tratamiento

- Profiláctico:
  - **Para mujeres que no han tenido fenómenos trombóticos.**
  - **Portadoras de trombofilias de bajo riesgo de trombosis.**
- Anticoagulante:
  - **Para mujeres con historia de eventos trombóticos venosos o arteriales.**
  - **Portadoras de trombofilias de alto riesgo de trombosis.**

Tratamiento

- **Trombofilias de bajo riesgo:**
  - **Factor V Leiden heterocigoto.**
  - ***G20210A* heterocigoto.**
  - **Déficit de proteína C.**
  - **Déficit de proteína S.**
- **Trombofilias de alto riesgo:**
  - **Déficit de antitrombina III.**
  - **Doble heterocigoto para *G20210A* y factor V de Leiden.**
  - **Factor V Leiden homocigoto.**
  - ***G20210A homocigoto*.**

Tratamiento

Clinical scenario	Postpartum management
Low-risk thrombophilia* without previous VTE	Surveillance without anticoagulation therapy or postpartum anticoagulation therapy if the patient has additional risks factors[Δ]
Low-risk thrombophilia* with a single previous episode of VTE - not receiving long-term anticoagulation therapy	Postpartum anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia[◇] without previous VTE	Postpartum anticoagulation therapy
High-risk thrombophilia[◇] with a single previous episode of VTE - not receiving long-term anticoagulation therapy	Postpartum anticoagulation therapy or intermediate- or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be at least as high as antepartum treatment)

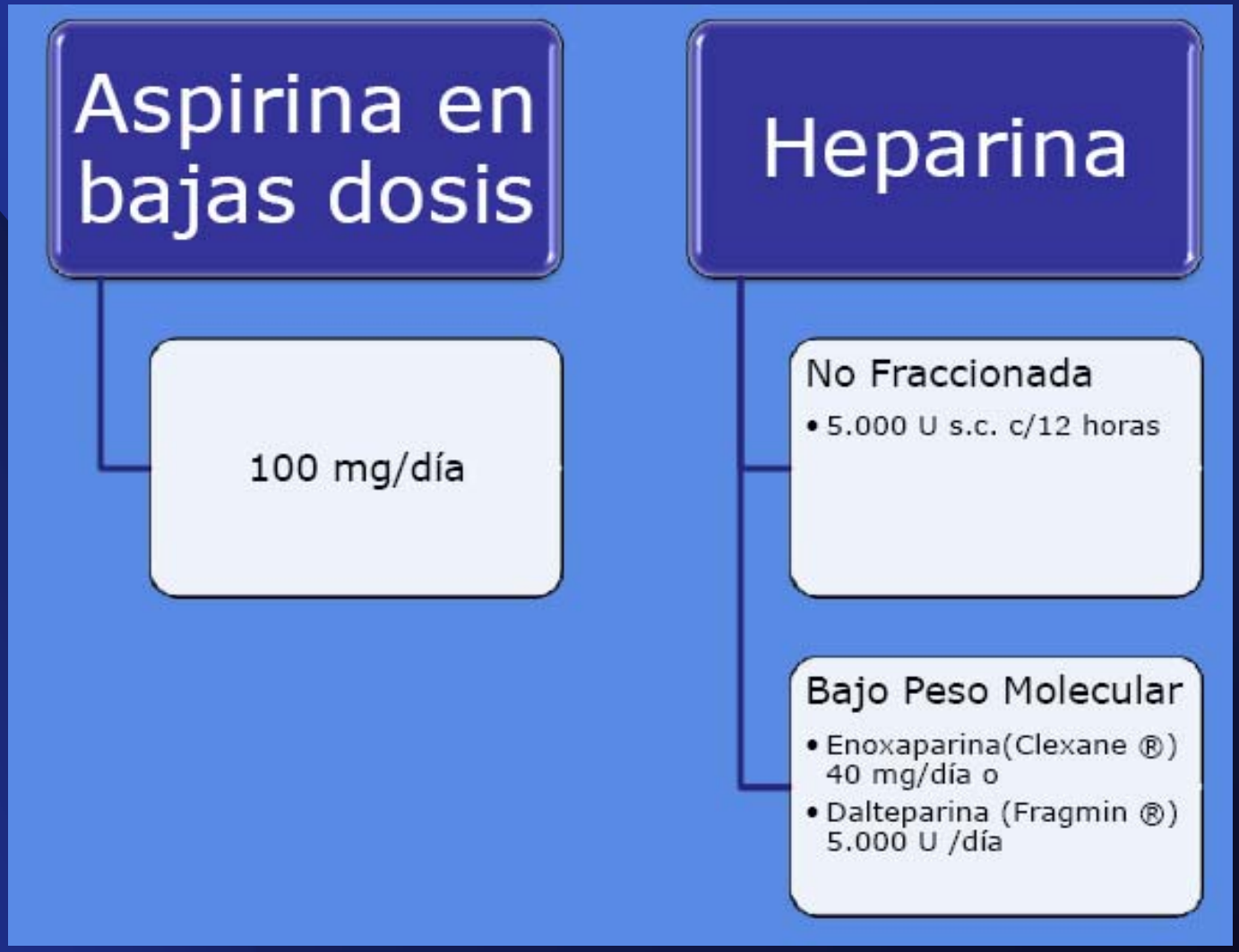
ACOG Practice Bulletin #123. Thromboembolism in pregnancy. Obstet Gynecol 2011; 118:718.

Tratamiento

Clinical scenario	Postpartum management
Low-risk thrombophilia* without previous VTE	Surveillance without anticoagulation therapy or postpartum anticoagulation therapy if the patient has additional risks factors[Δ]
Low-risk thrombophilia* with a single previous episode of VTE - not receiving long-term anticoagulation therapy	Postpartum anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia[◊] without previous VTE	Postpartum anticoagulation therapy
High-risk thrombophilia[◊] with a single previous episode of VTE - not receiving long-term anticoagulation therapy	Postpartum anticoagulation therapy or intermediate- or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be at least as high as antepartum treatment)

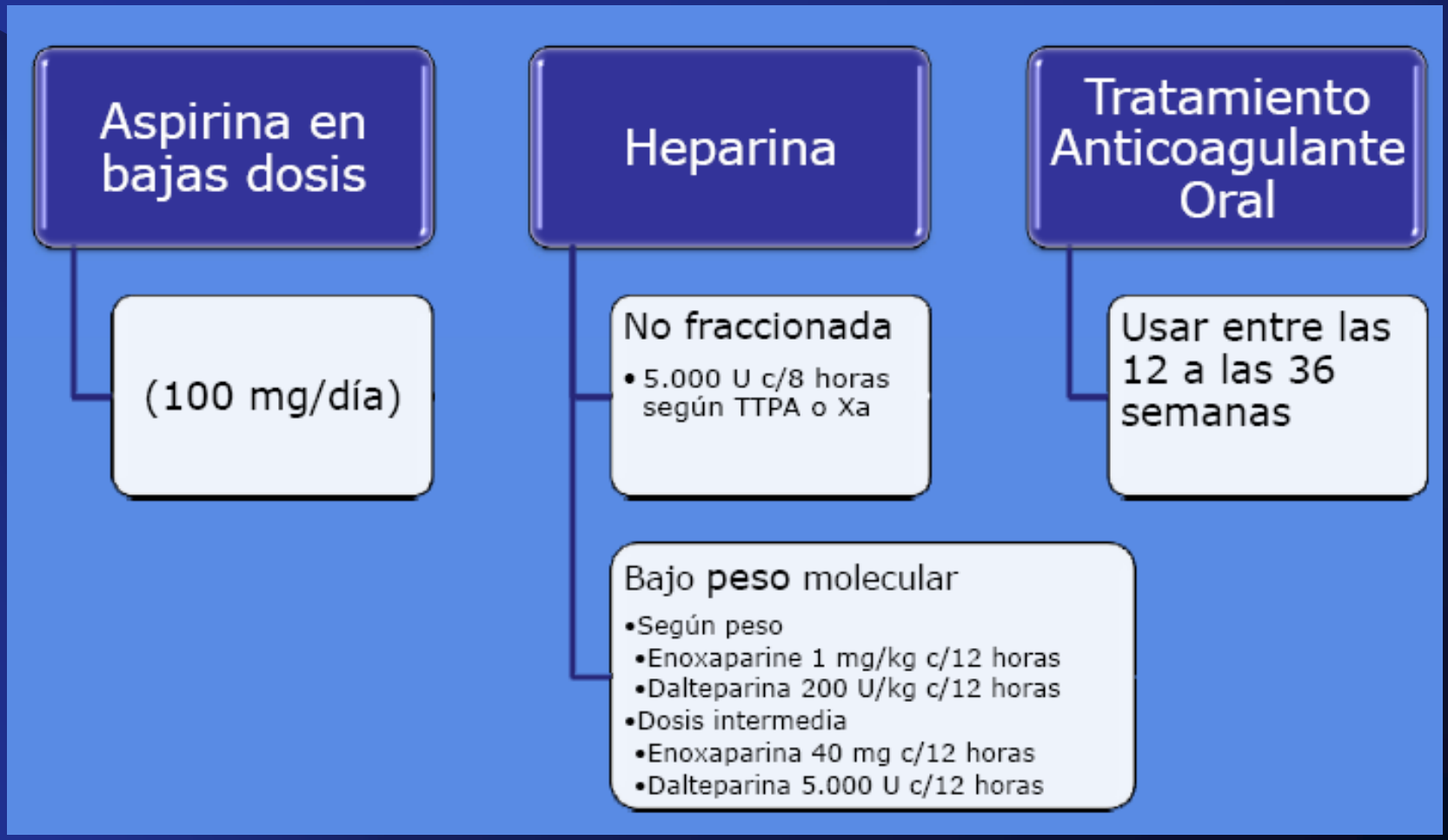
ACOG Practice Bulletin #123. Thromboembolism in pregnancy. Obstet Gynecol 2011; 118:718.

Esquema profiláctico



Dr. Jorge A. Carvajal C. PhD. (PUC)

Esquema Terapéutico



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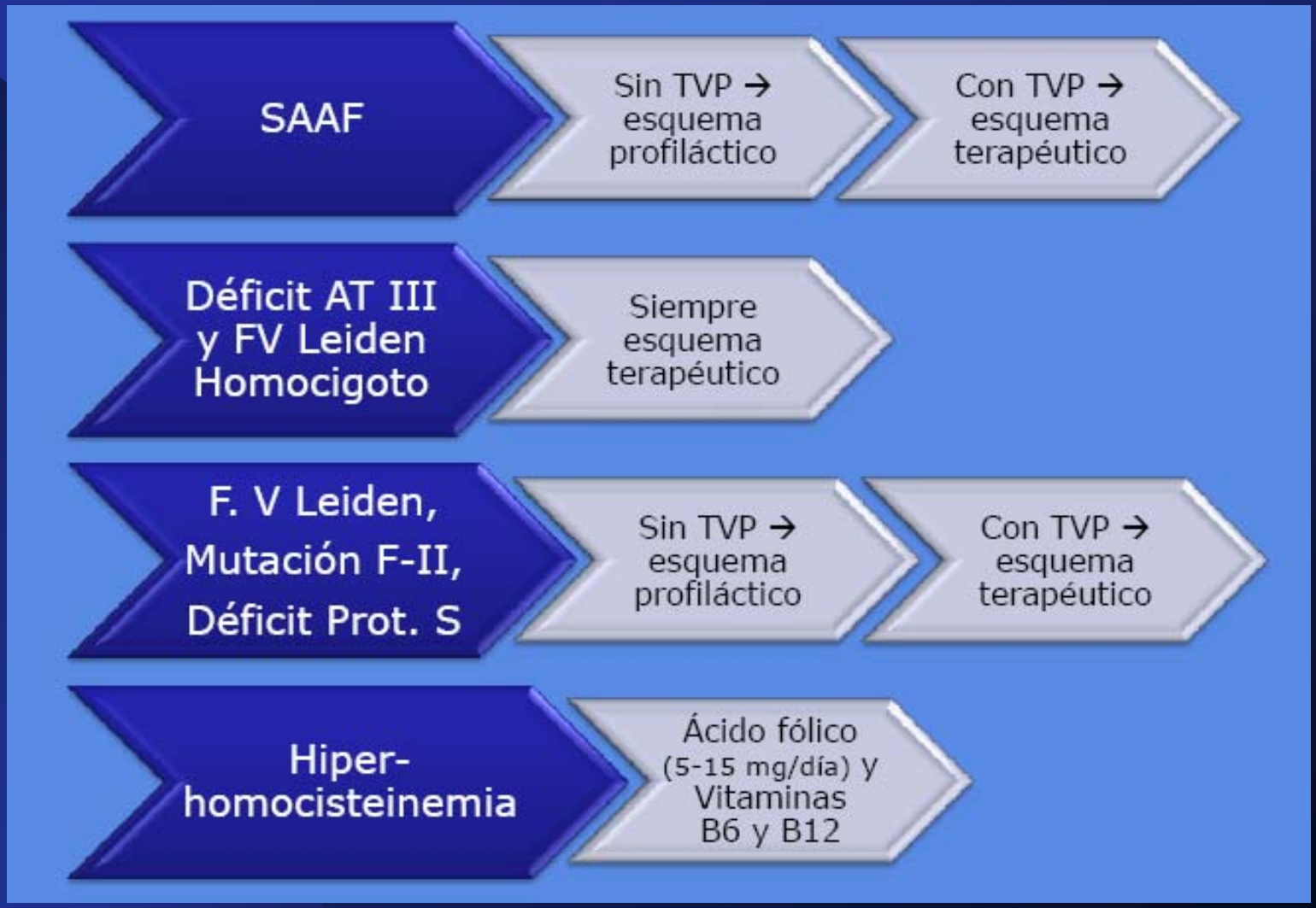
Esquema UC



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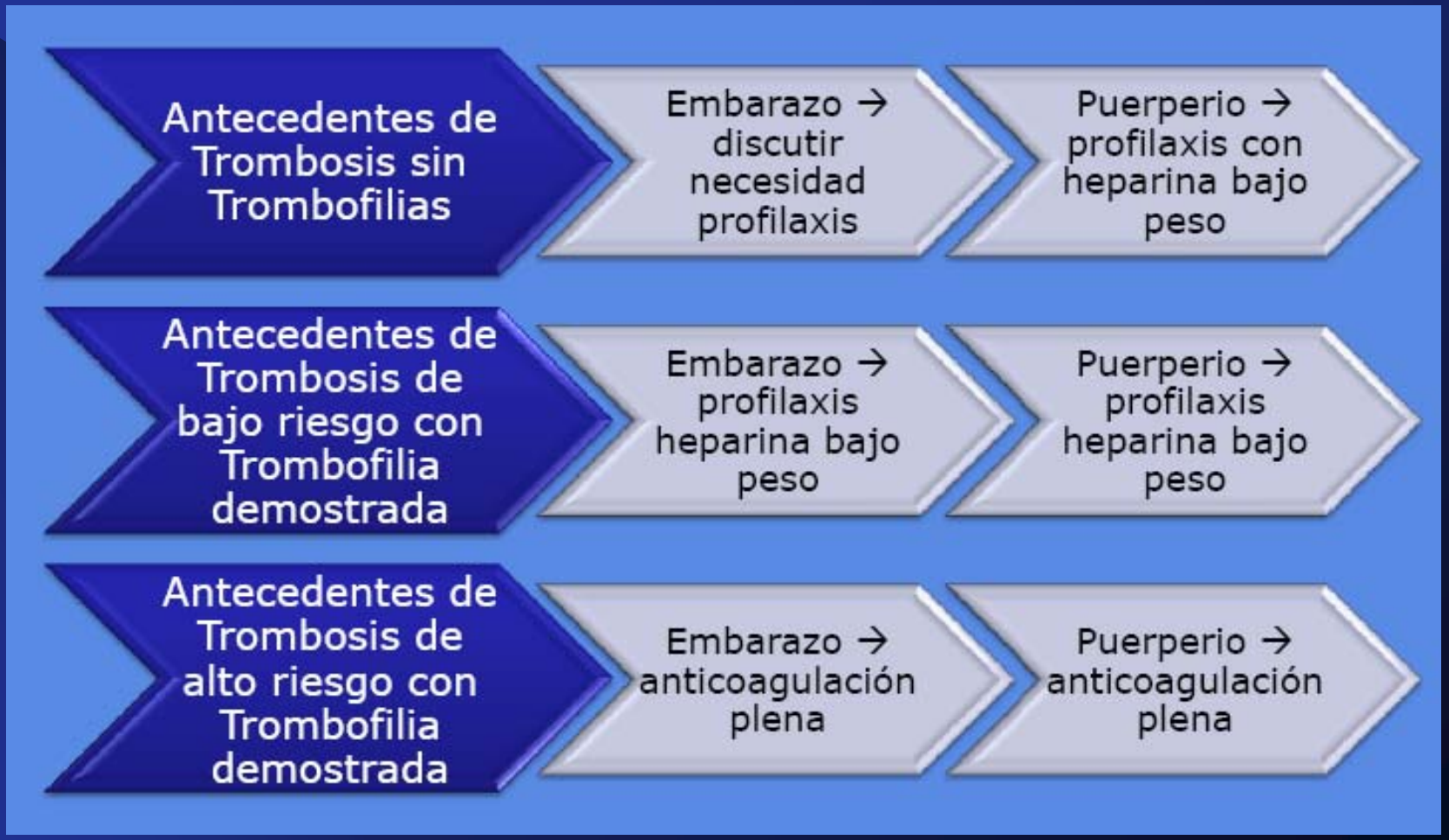


Dr. Jorge A. Carvajal C. PhD. (PUC)

Síndrome Antifosfolipidos

- **Criterios clínicos:**
  - **Trombosis Vascular**
  - **Morbilidad Gestacional:**
    - **Una o más muertes fetales > 10 semanas con feto anatómicamente normal.**
    - **Uno o más partos prematuros < 34 semanas debidos:**
      - **PES–Eclampsia**
      - **Insuficiencia Placentaria (RBNE; Doppler (FDA o FDR); OHA; RCIU**
      - **Tres o más abortos espontáneos < 10 semanas sin causa demostrada. Pero descartando causas genéticas, hormonales y anatómicas.**

Síndrome Antifosfolipidos

- **Criterios de laboratorio:**
  - **Anticoagulante Lúpico: Criterios específicos de International Society on Thrombosis and Haemostasis.**

  _ Anticuerpos Anticardiolipinas:
    - **IgG//IgM: Títulos Medianos o Altos(> 40GPL o MPL)**
  - **Anticuerpos Anti β2 – Glicoproteína I:**
    - **IgM o IgG: Títulos mayores a pc. 99**
- **El test debe ser positivo en dos ocasiones con al menos 12 semanas y menos de 5 años de diferencia.**

International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4: 295–306.

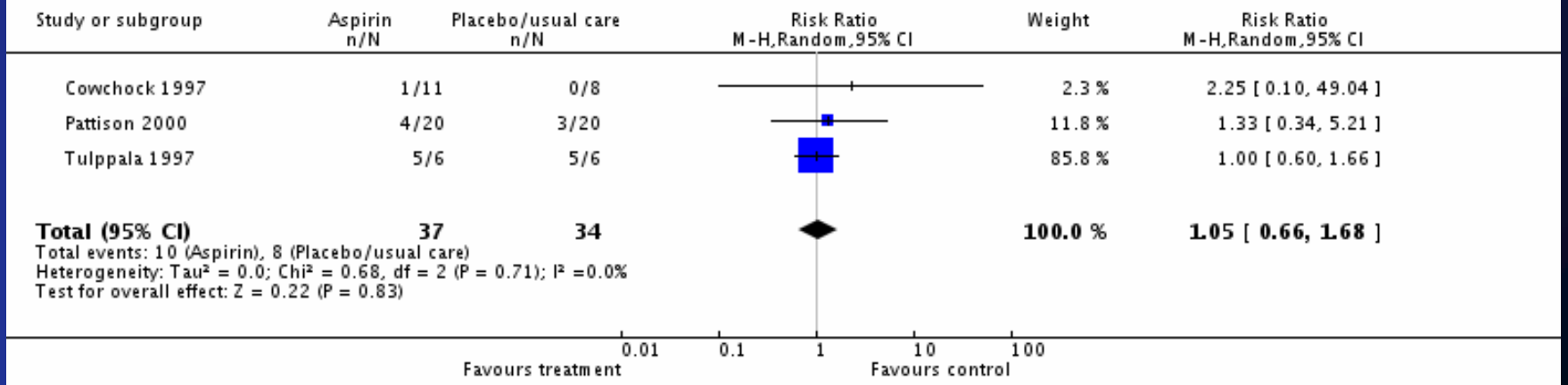
Síndrome Antifosfolipidos

PREVENTION OF RECURRENT MISCARRIAGE FOR WOMEN WITH ANTIPHOSPHOLIPID ANTIBODY OR LUPUS ANTICOAGULANT

Empson Marianne B, Lassere Marissa, Craig Jonathan C, Scott James R

THE COCHRANE COLLABORATION®

Review: Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant
Comparison: 1 All interventions - pregnancy loss
Outcome: 1 Aspirin versus placebo or usual care



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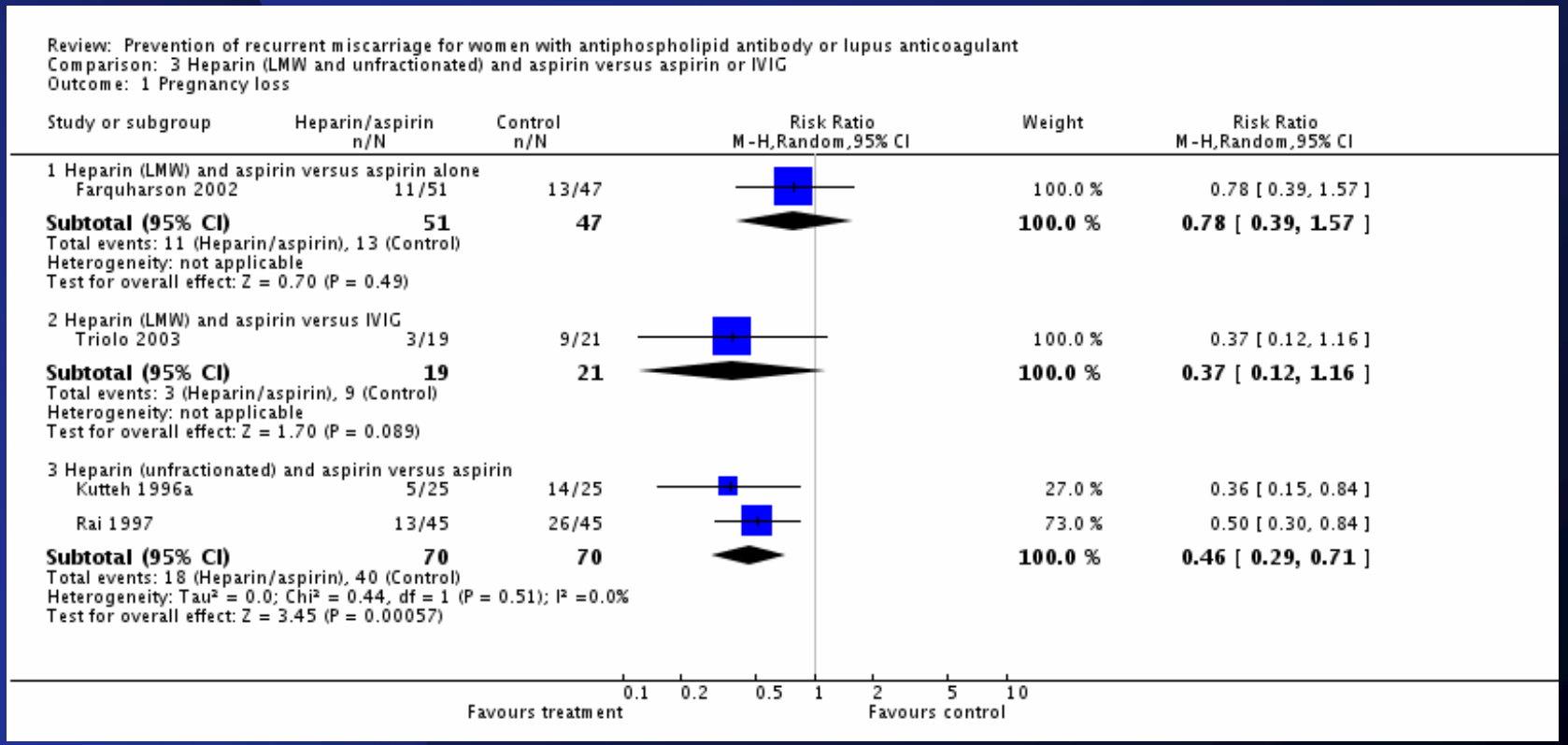
Review: Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant
Comparison: 3 Heparin (LMW and unfractionated) and aspirin versus aspirin or IVIG
Outcome: 1 Pregnancy loss

Study or subgroup	Heparin/aspirin n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Heparin (LMW) and aspirin versus aspirin alone					
Farquharson 2002	11/51	13/47		100.0 %	0.78 [0.39, 1.57]
Subtotal (95% CI)	**51**	**47**		**100.0 %**	**0.78 [0.39, 1.57]**
Total events: 11 (Heparin/aspirin), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.49)					
2 Heparin (LMW) and aspirin versus IVIG					
Triolo 2003	3/19	9/21		100.0 %	0.37 [0.12, 1.16]
Subtotal (95% CI)	**19**	**21**		**100.0 %**	**0.37 [0.12, 1.16]**
Total events: 3 (Heparin/aspirin), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.70 (P = 0.089)					
3 Heparin (unfractionated) and aspirin versus aspirin					
Kutteh 1996a	5/25	14/25		27.0 %	0.36 [0.15, 0.84]
Rai 1997	13/45	26/45		73.0 %	0.50 [0.30, 0.84]
Subtotal (95% CI)	**70**	**70**		**100.0 %**	**0.46 [0.29, 0.71]**
Total events: 18 (Heparin/aspirin), 40 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.44, df = 1 (P = 0.51); I² =0.0%					
Test for overall effect: Z = 3.45 (P = 0.00057)					



FIN

Becados Pasantes CERPO.
Junio 2012.

MUCHAS GRACIAS

Dr. Ramón Serra Tagle
Dr. Juan Carlos Zúñiga Armijo