Trombofilia y abortos de repetición. Actualización

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1. Evolución Concepto de Trombosis y de Aborto de repetición
2. Evolución en el test de trombofilia en Aborto de repetición: ¿Dónde estamos?
3. Importancia del Aborto de repetición como enfermedad cardiovascular
4. Tratamiento hematológico a la Mujer con Aborto de repetición.

TROMBOFILIAS y Complicaciones Obstétricas

- En los años noventa comenzaron a publicarse los primeros estudios sobre la posible asociación de la trombofilia con las CVG. Aunque no queda claro si la trombofilia en esta patología es asociativa o causal, lo que sí se ha demostrado es el aumento de riesgo de presentar CVG en mujeres con diferentes trombofilias y el registro TREATS estudió dicho riesgo:

Tabla 1. Riesgo de CVG asociado a la presencia de trombofilia según registro TREATS (x)

Complicaciones vasculares gestacionales	*OR (IC 95%)*
Abruptio placentae	3,26 (2,10-5,06)
Preeclampsia	1,91 (1,60-2,28)
Pérdida fetal antes de la semana gestacional 24	2,22 (1,70-2,91)
Pérdida fetal tras la semana gestacional 24	2,31 (1,66-3,21)
Retraso de crecimiento intraútero	2 (1,49-3,40)

haematologica/edición española | 2009; 94 (Extra 1) | 29 |

Wu et al. Health Technology Assessment 2006; Vol. 10: No. 11

trombofilia y abortos 1º y 2º trimestre

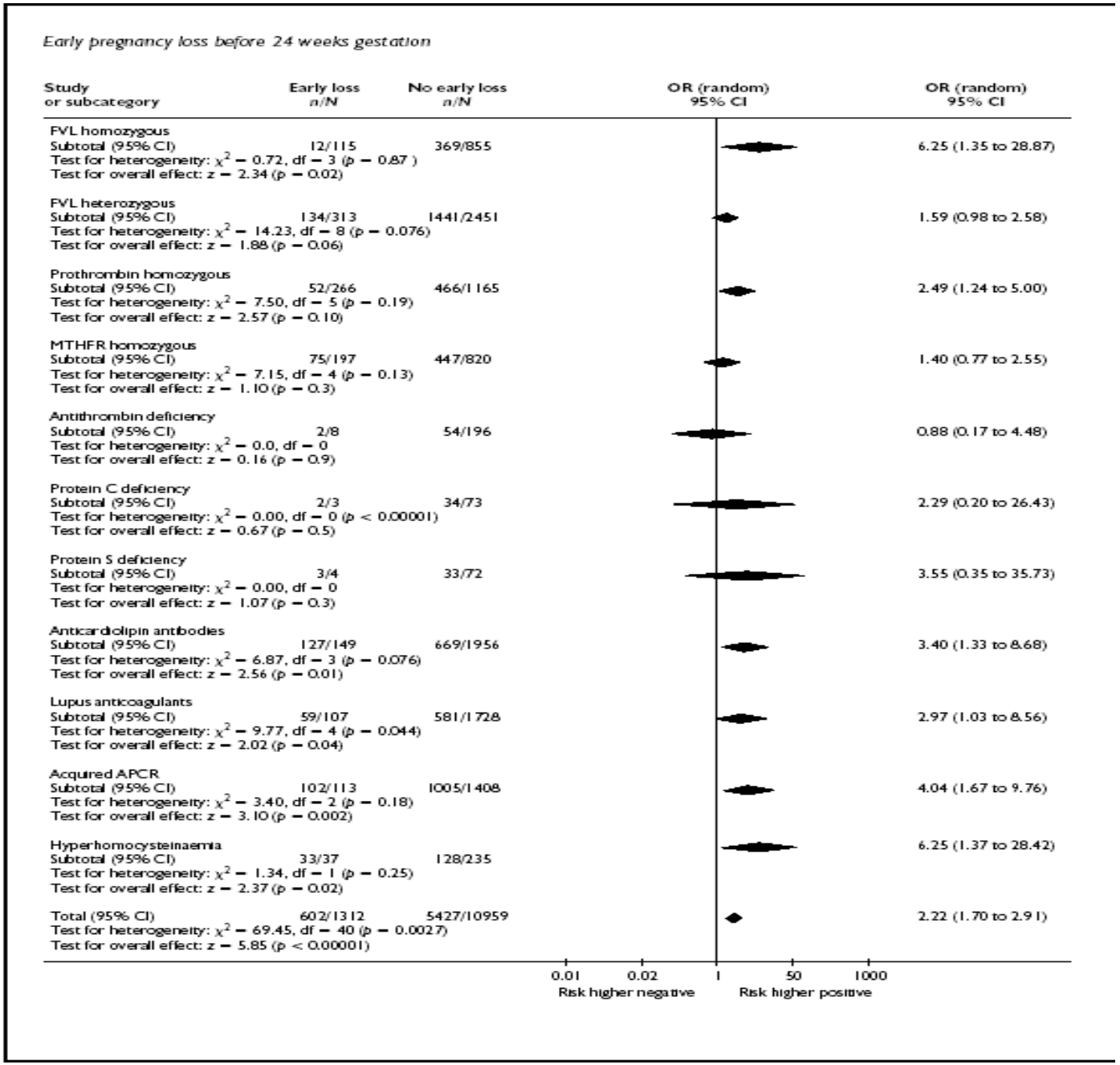
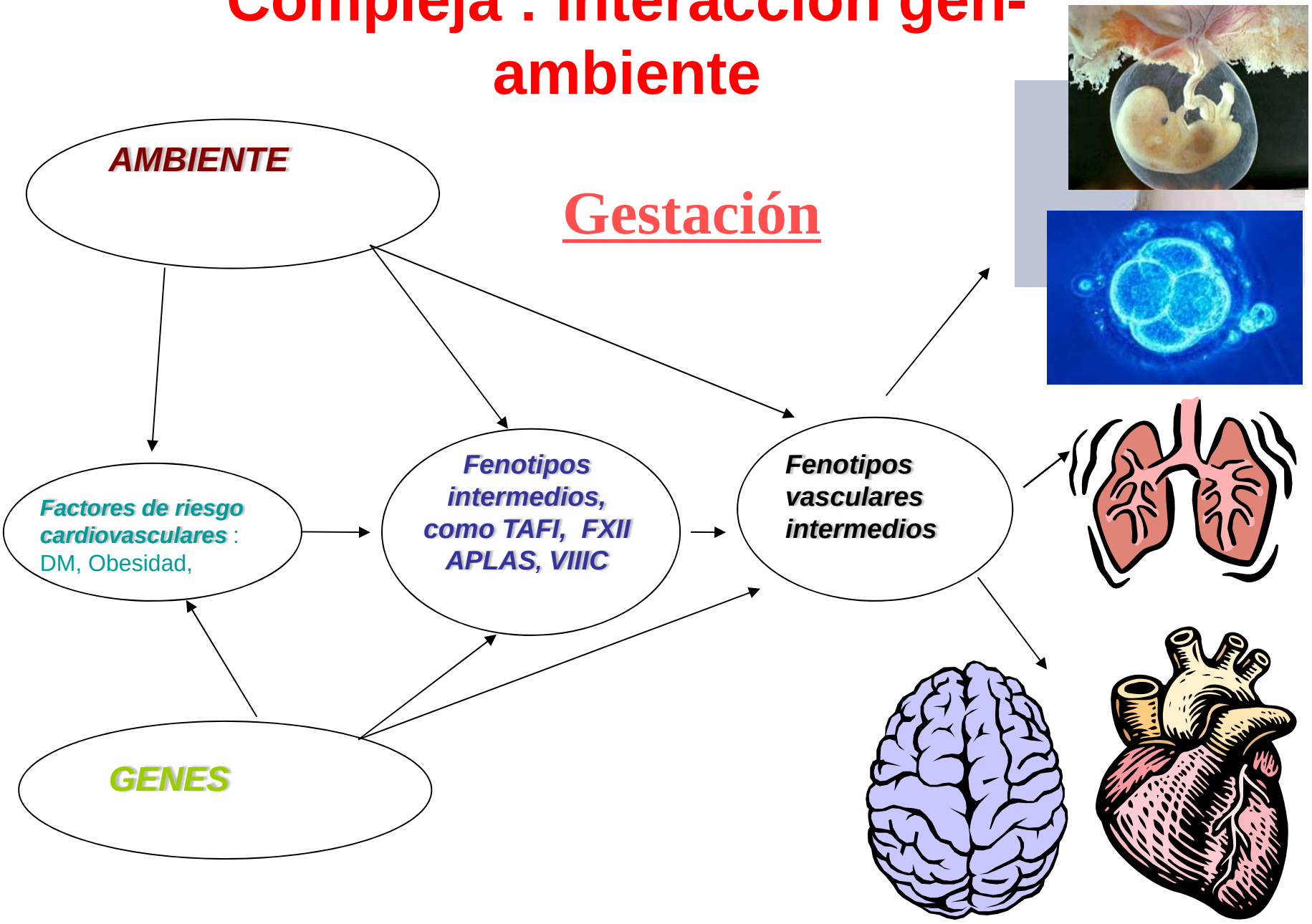
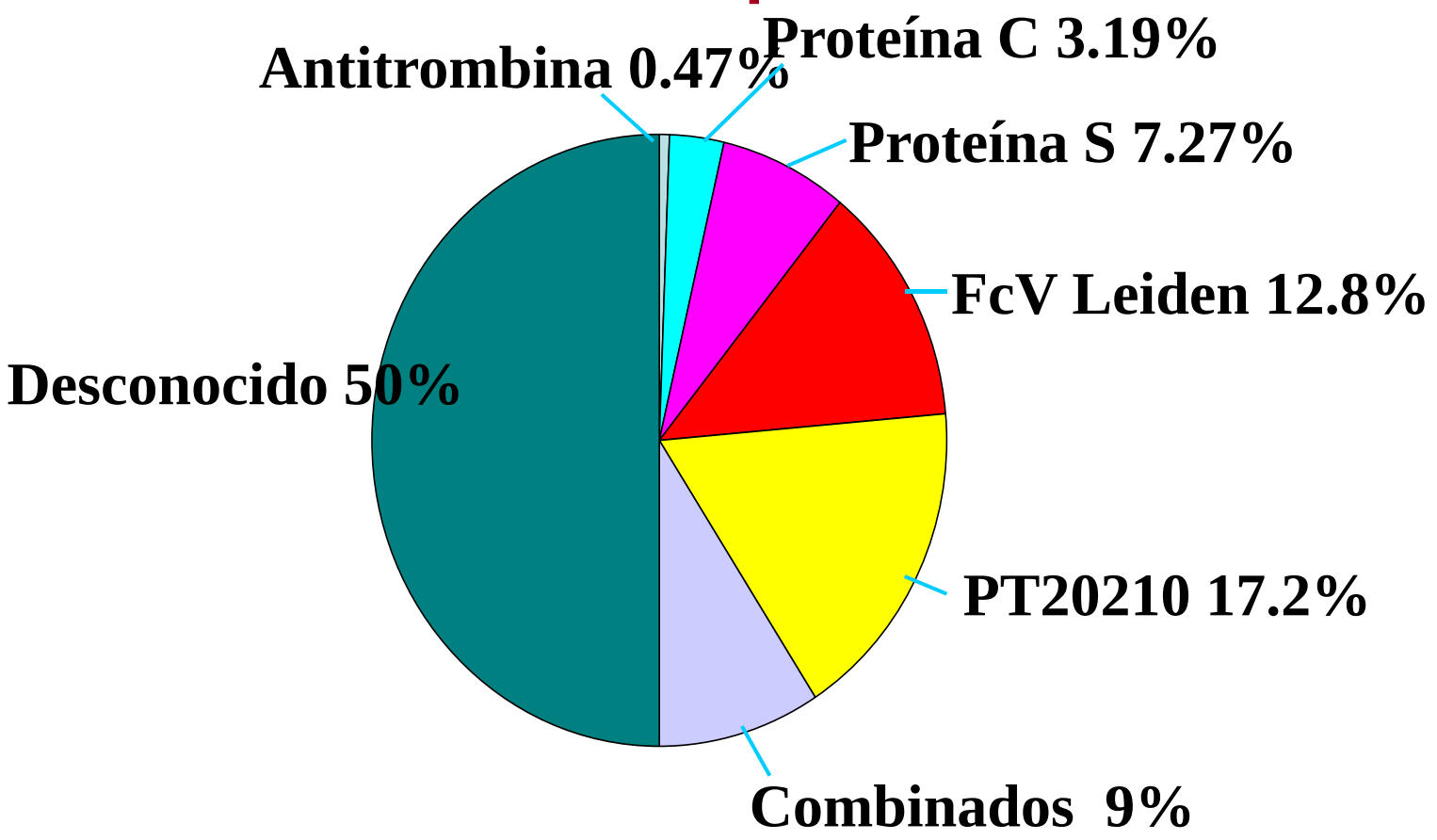


FIGURE 7 Odds ratios for selected thrombophilias and risk of pregnancy loss

Trombosis:Enfermedad Compleja : interacción gen-ambiente



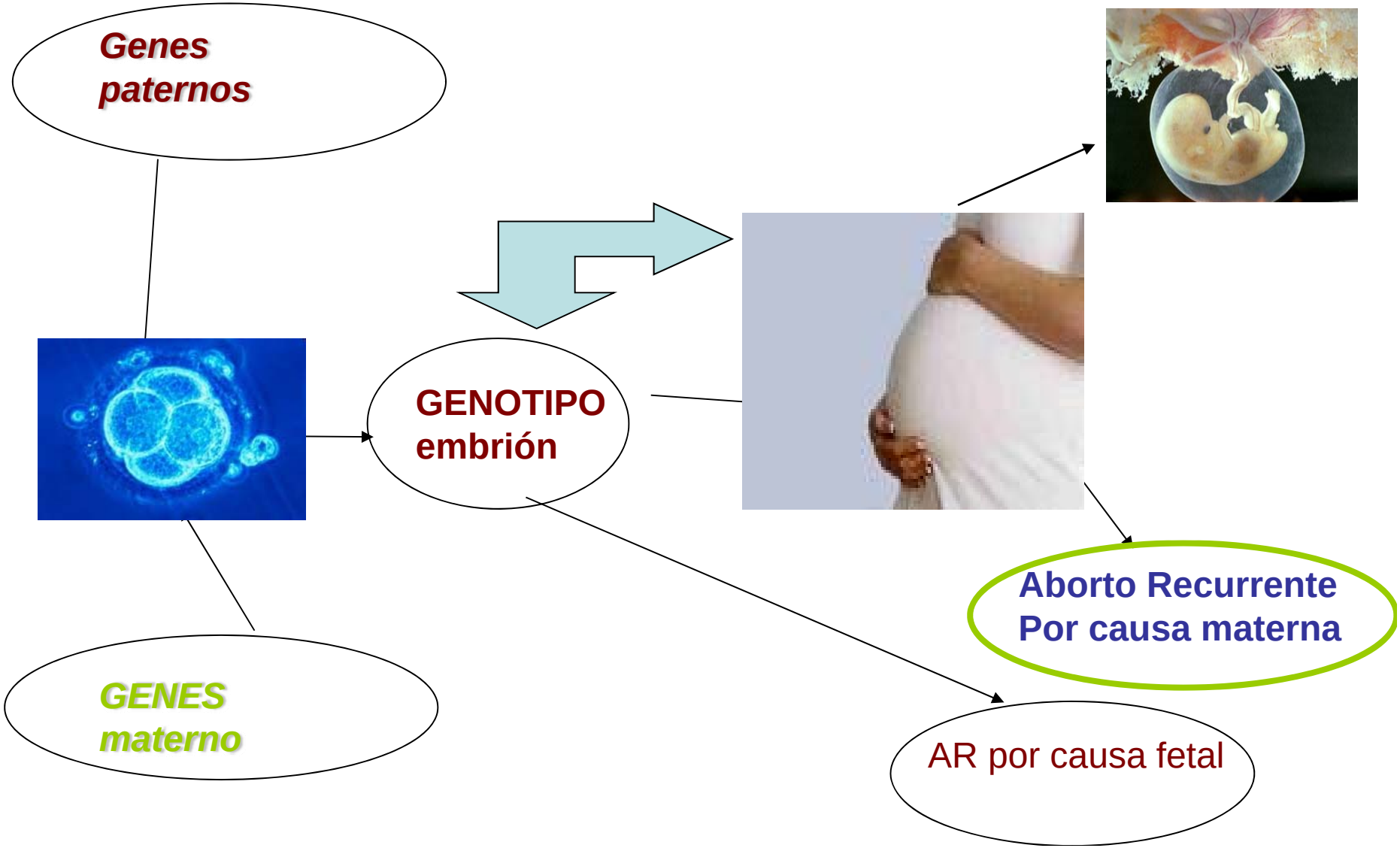
Modelo de TARTA: NO es aplicable.
Causas biológicas de trombosis
Población española



Mateo et.al *Throm Haemost* 77:444.1997

Mateo et.al *Blood Coal Fibrinol* 9:71.1998

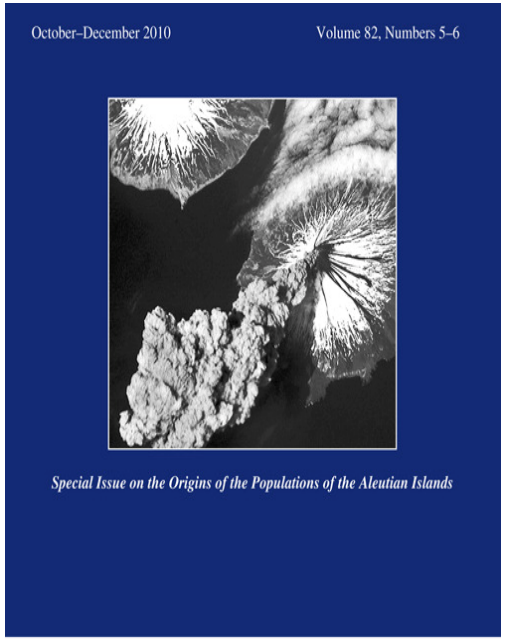
AR: enfermedad compleja :
interacción gen-ambiente



TROMBOSIS : ESTUDIOS GENOME-WIDE DE LIGAMIENTO FAMILIAS O HERMANOS

Quantitative Trait Locus on Chromosome 12q14.1 Influences Variation in Plasma Plasminogen Levels in the San Antonio Family Heart Study

A. SANTAMARÍA,[1,2] V. P. DIEGO,[1] L. ALMASY,[1] D. L. RAINWATER,[1] M. C. MAHANEY,[1] A. G. COMUZZIE,[1] S. A. COLE,[1] T. D. DYER,[1] R. P. TRACY,[3] M. P. STERN,[4] J. W. MACCLUER,[1] AND J. BLANGERO[1]



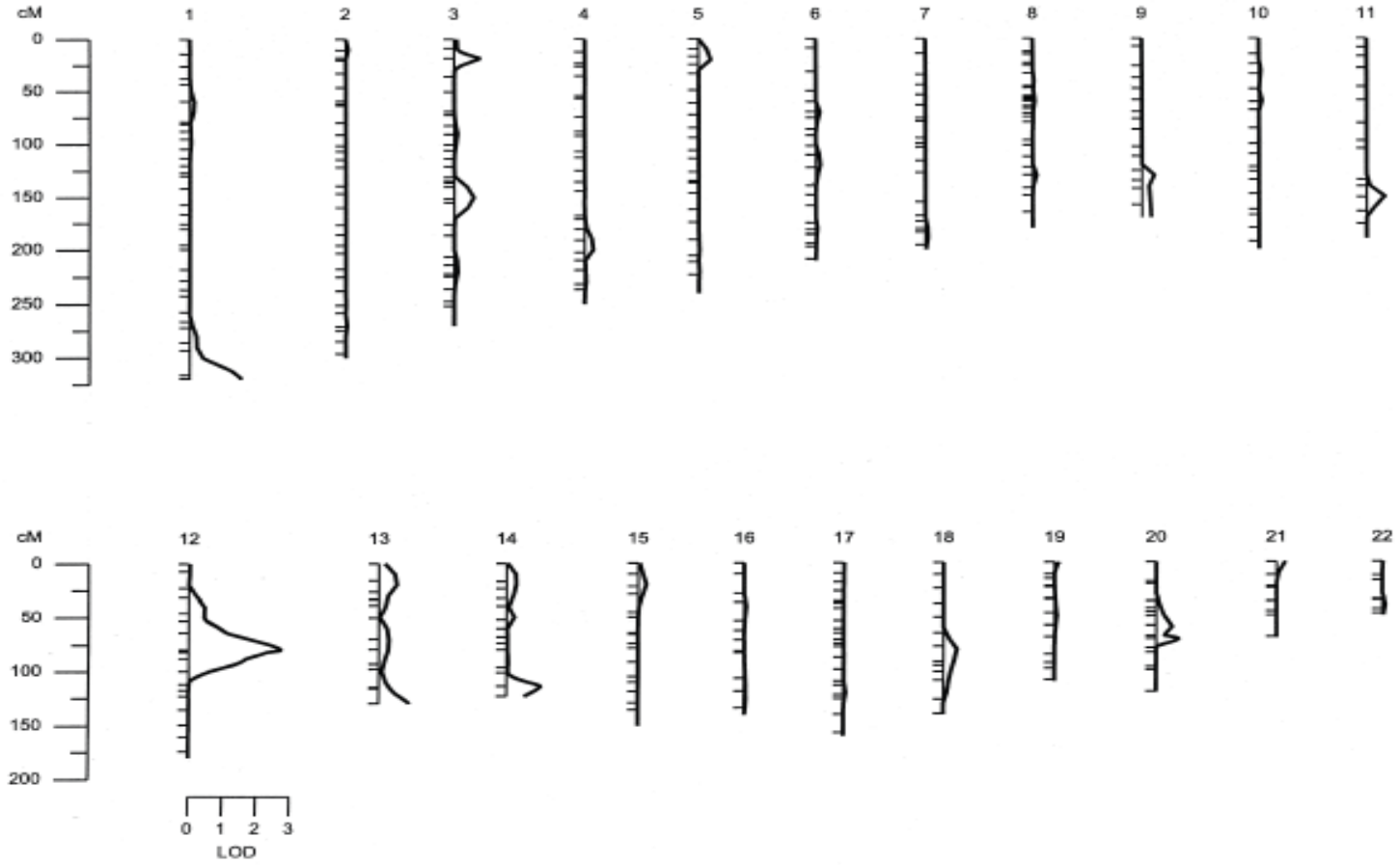


Figure 1. Results from the autosomal multipoint genome scan. LOD scales are shown for all chromosomes having LOD scores exceeding 1. Hatch marks along chromosomes indicate marker positions.

Discussion

We have identified a region on chromosome 12q14.1 that harbors a QTL implicated in the quantitative variation in plasminogen plasma levels in the first whole-genome linkage screen of plasminogen, using data from 26 pedigrees in the SAFHS. At this locus we observed a QTL-specific heritability of 0.24. However,

Metodología:
GWAS y
GW-family studies

21. Editorial. Freely associating. *Nat Genet*. 1999;22:1–2.
22. Cooper DN, Nussabaum RL, Krawczak M. Proposed guidelines for papers describing DNA polymorphism-disease associations. *Hum Genet*. 2002;110:207–208.

1.Encontrar SNPs.

2 Reproducir en cohortes de gran tamaño los SNPs encontrados y ver si se demuestra que está asociado con la enfermedad en población general.(sin diferencias étnicas, etc)

A Quantitative-Trait Locus in the Human Factor XII Gene Influences Both Plasma Factor XII Levels and Susceptibility to Thrombotic Disease

José Manuel Soria,[1] Laura Almasy,[2] Juan Carlos Souto,[1] Delphine Bacq,[3] Alfonso Buil,[1] Alexandra Faure,[3] Elisabeth Martínez-Marchán,[1] José Mateo,[1] Montserrat Borrell,[1] William Stone,[2] Mark Lathrop,[3] Jordi Fontcuberta,[1] and John Blangero[2]

Homozygosity of the *T* Allele of the 46 C→T Polymorphism in the *F12* Gene Is a Risk Factor for Ischemic Stroke in the Spanish Population

Amparo Saumoaria, MD; José Mateo, MD, PhD; Isabel Tirado, PharmD; Arturo Oliver, MD; Roberto Belvis, MD; Joan Martí-Fábregas, MD, PhD; Rosa Felices; José Manuel Soria, MD, PhD; Juan Carlos Souto, MD, PhD; Jordi Fontcuberta, MD, PhD

Thrombosis

Homozygosity of the *T* allele of the 46 C→T polymorphism in the *F12* gene is a risk factor for acute coronary artery disease in the Spanish population

Following new guidelines that contain recommendations on the desirable features of a genetic association study, we performed a case-control study to establish the risk of acute coronary artery disease (CAD) related to the polymorphism (46 C→T) in the *F12* gene. We found a 6-fold higher risk of acute CAD associated with the homozygosity of the *T* allele of the *F12*, *46C→T* polymorphism in the Spanish population.

haematologica 2004; 89:878-879
(http://www.haematologica.org/2004/7/878)

GWAS en AR

A genome-wide scan in affected sibling pairs with idiopathic recurrent miscarriage suggests genetic linkage

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Submitted on October 19, 2010; resubmitted on January 11, 2011; accepted on January 17, 2011

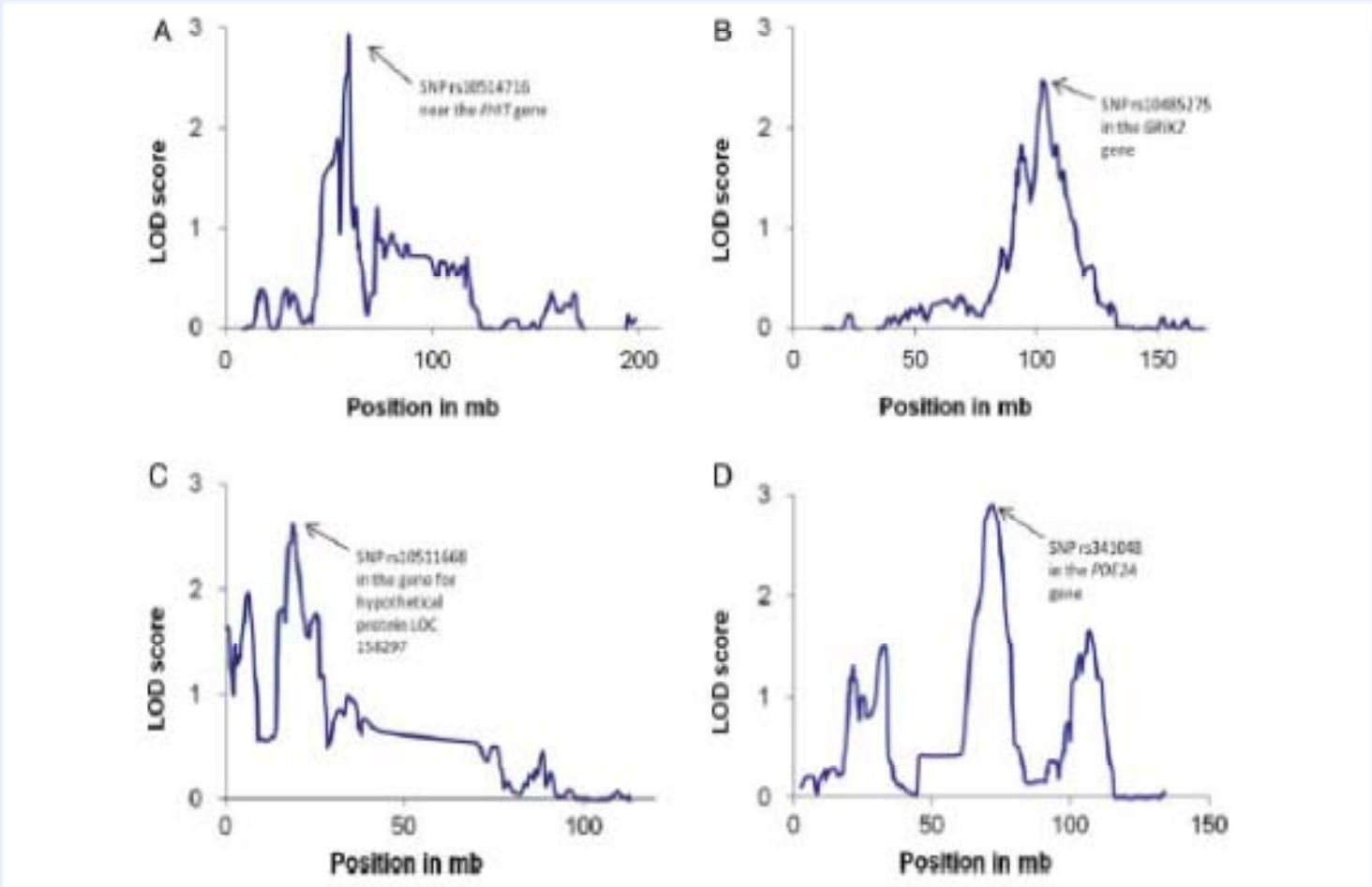

Figure 2 The four chromosomes in which peaks with LOD score >2.5 was identified in subgroups.

ABSTRACT: Previously, siblings of patients with idiopathic recurrent miscarriage (IRM) have been shown to have a higher risk of miscarriage. This study comprises two parts: (i) an epidemiological part, in which we introduce data on the frequency of miscarriage among 268 siblings of 244 patients with IRM and (ii) a genetic part presenting data from a genome-wide linkage study of 38 affected sibling pairs with IRM. All IRM patients (probands) had experienced three or more miscarriages and affected siblings two or more miscarriages. The sibling pairs were genotyped by the Affymetrix GeneChip 50K Xba [illegible] and non-parametric linkage analysis was performed via the software package Merlin. We find that siblings of IRM patients exhibit a higher frequency of miscarriage than population controls regardless of age at the time of pregnancy. We identify chromosomal regions with LOD scores between 2.5 and 3.0 in subgroups of affected sibling pairs. Maximum LOD scores were identified in four occurrences: for rs10514716 (3p14.2) when analyzing sister-pairs only; for rs10511668 (9p22.1) and rs341048 (11q13.4) when only analyzing families where the probands have had four or more miscarriages; and for rs10485275 (6q16.3) when analyzing one sibling pair from each family only. We identify two founder mutations. Concluding, our results imply that IRM patients and their siblings share factors which increase the risk of miscarriage. In the first genome-wide linkage study of affected sibling pairs with IRM, we identify regions on chromosomes 3, 6, 9 and 11 which warrant further investigation in order to elucidate their putative roles in the genesis of IRM.

Key words: recurrent miscarriage / affected sibling pair analysis / risk of miscarriage / epidemiology / genome-wide linkage study

Modelo de AR como enfermedad compleja

Christiansen *et al*. Gynecol Obstet Invest 2008.

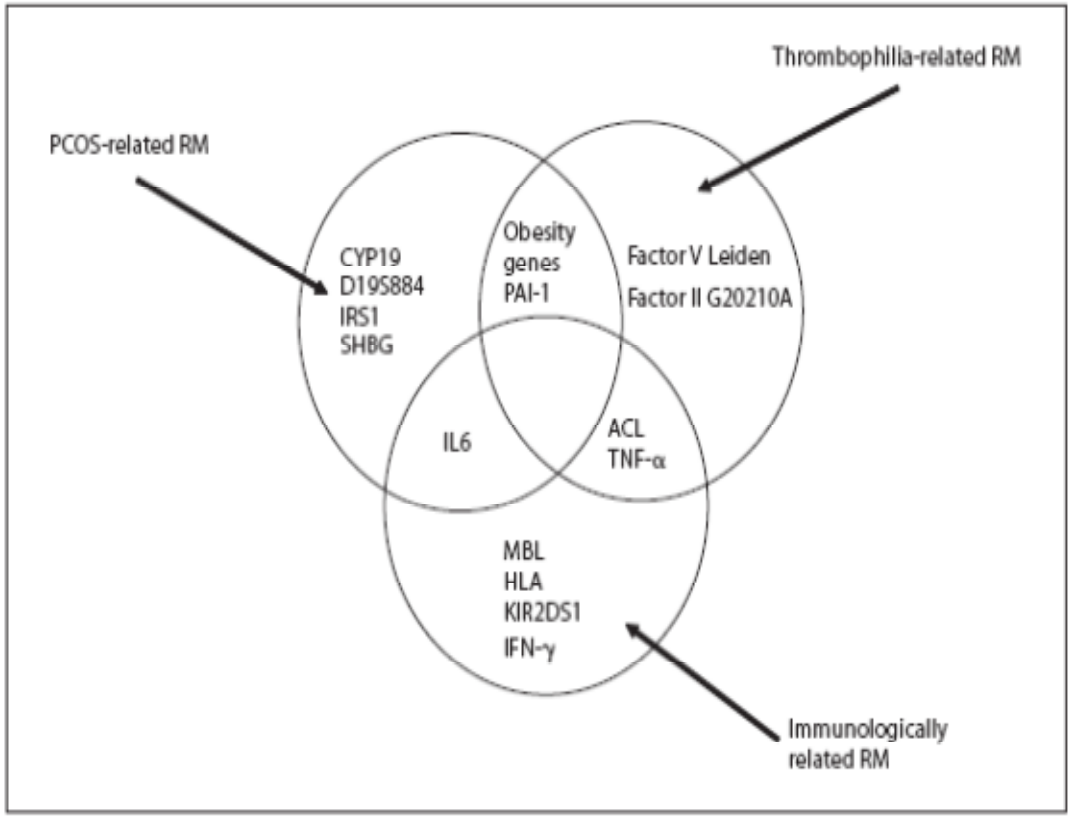

Fig. 1. The proposed three multifactorially determined entities of recurrent miscarriage (RM) characterized by a clustering of genetic biomarkers for polycystic ovary syndrome (PCOS), thrombophilia and immunological dysfunction, respectively. The PCOS-related biomarkers are those suggested to be the most promising candidate genes so far [38, 59, 60] plus genes predisposing to obesity. CYP19 = Aromatase gene; D19S884 = microsatellite in fibrillin-3 gene; IL6 = interleukin-6 gene; IRS1 = insulin receptor substrate 1 gene; SHBG = sex hormone-binding globulin gene; PAI-1 = plasminogen activator inhibitor-1 gene; ACL = anticardiolipin antibody.

Table 2. Prevalence of a series of autoimmune and thromboembolic disorders in patients with RM and age-matched Danish female controls

Disorder	RM (n = 328)	Controls	OR (95% CI)	p
Systemic lupus erythematosus	1.2%	0.03%	41.0 (4.1–332)	<0.001
Thromboembolism	2.7%	0.8%	3.4 (1.3–9.1)	<0.05
Hyper/hypothyreosis	4.5%	2.0%	2.3 (1.2–4.6)	<0.05
Type 1 diabetes mellitus	1.2%	0.4%	3.0 (0.8–12.4)	NS
Inflammatory bowel disease	1.5%	0.2%	7.6 (1.5–40.0)	<0.05

Table 3. Prevalence of a series of genetic biomarkers in the background population and their associations RM

Genetic polymorphism	Population prevalence	RM in carriers OR (95% CI)	Subsets of RM in carriers* OR (95% CI)
Factor II G20210A mutation	3%	2.1 (1.2–3.5)	
Factor V Leiden mutation	7%	2.0 (1.1–3.6)	
HLA-DR3	21%	1.4 (1.1–1.9)	1.8 (1.3–2.5)
HLA-G 14bp+/14bp+**	11%	2.7 (1.1–6.5)	
MBL O/O or LX/O***	13%	1.3 (0.6–2.8)	2.1 (1.0–5.1)
INF-γ T/T	16%	1.9 (1.0–3.6)	
IL-10 G/G	17%	1.8 (1.1–2.9)	
KIR2DS1	41%	2.2 (1.1–4.3)	

In the future, the association of more genetic bio
narkers with RM will be discovered but it might still b
lifficult to infer with certainty in the individual cas
vhether the cause of RM is mainly immunologic, throm
ophilic or PCOS-related. To complicate matters, genet
c biomarkers for immunity and thrombophilia inher
ted from the partner are also expected to play a role i
he overall genetic background for RM. We still posses
ery limited information about genes from the fathe
hat contribute to *maternally caused RM*, which indee
nay prove to be a misnomer. The optimal future sce
ario is, in our view, the situation where for every cou
le, we can enter information about screening for 50-
00 validated genetic biomarkers, their individua
trengths of association with RM and their degree o
pistatic interaction together with information abou
elevant clinical [illegible] based algo
ith [illegible]. Subsequently, the proportions of the causal [illegible]
round (the so-called etiological fraction) that are im
nunological, thrombophilic, endocrine or fetal are cal
lated. This knowledge will provide the clinician wit
he opt[illegible]l means of providing the treatment [illegible] ha
been proven to be most efficient in placebo-controlle
rials in adequately selected patients as discussed previ
ously.

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TEST TROMBOFILIA OBSTETRICO

Thrombophilic defect	Recurrent pregnancy loss before 13 weeks	Non-recurrent pregnancy loss	Non-recurrent pregnancy loss after 19 weeks
Antithrombin deficiency	0.88	1.54	Not analyzed
Protein C deficiency	1.57	1.41	Not analyzed
Protein S deficiency	14.72	7.39	Not analyzed
Factor V Leiden	2.01	1.73	3.26
Prothrombin G20210A	2.05	2.32	2.3

TEST TROMBOFILICO-INFLAMATORIO OBSTÉTRICO

- Ac estandar
- AC ANTIPROTEINA Z
- AC ANTI ANEXINA V
- SINTAXIN-BINDING 5 y 7
- FACTOR VIIIC
- GENOTIPO ABO
- POLIMORFISMO 46 C/T FACTOR 12
- PAI-2
- homocisteina
- …..

- Descartar otras causas no trombofílicas:

- Sindrome mieloproliperativos
- Enf.von Willebrand.

- The time has come to consider first trimester miscarriage not a trivial incident but a profound adverse life event.

- Building on evidence-based approach in management and counselling, future research will allow a more comprehensive treatment of women who experience miscarriage.

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Pregnancy loss and risk of cardiovascular disease: a prospective population-based cohort study (EPIC-Heidelberg. *Heart rt.2010*

Objectives To examine whether pregnancy loss (miscarriage, abortion or stillbirth) is associated with a higher risk of myocardial infarction (MI) and stroke.

Design Population-based prospective cohort study.

Setting The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort in Heidelberg, Germany (mean follow-up 10.8 years).

All 11.518 women who had ever been pregnant (aged 35–66).

Recurrent miscarriage (>3) was associated with about nine times higher risk of MI (age-adjusted HR=8.90, 95% CI 3.18 to 24.90; fully adjusted HR 5.06, 95% CI 1.26 to 20.29).

Conclusions These results suggest that women who experience spontaneous pregnancy loss are at a substantially higher risk of MI later in life. **Recurrent miscarriage and stillbirth are strong sex-specific predictors for MI and thus should be considered as important indicators for cardiovascular risk factors monitoring and preventive measures.** Further research is suggested to elucidate underlying risk factors of pregnancy loss that at the same time strongly predispose to cardiovascular disease.

SAFO y Riesgo Cardiovascular

Risk of thromboembolic events after recurrent spontaneous abortion in antiphospholipid syndrome: a case–control study

Maria Angeles Martinez-Zamora,[1] Sara Peralta,[1] Montserrat Creus,[1] Dolors Tassies,[2] Juan Carlos Reverter,[2] Gerard Espinosa,[3] Ricard Cervera,[3] Francisco Carmona,[1] Juan Balasch[1]

OR : 15 (IC: 3,2-70)

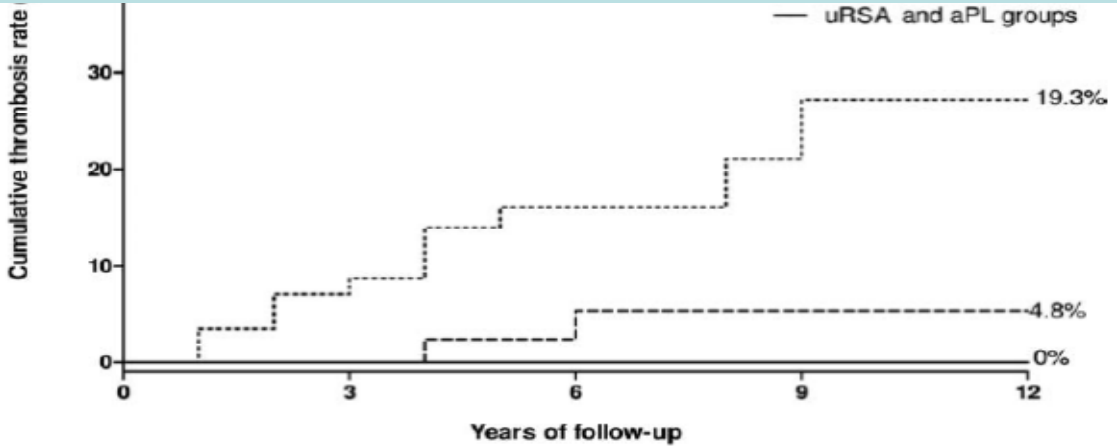

Figure 1 Kaplan–Meier curves of 12-year cumulative incidence of thrombotic events in the four groups studied. aPL group, patients with positive tests for antiphospholipid antibodies (aPL) without pregnancy or thrombotic morbidity (laboratory testing for aPL was performed at the time of patients attending our hospital; APS–RSA group, antiphospholipid syndrome patients with recurrent spontaneous abortion; tRSA group, patients with recurrent spontaneous abortion without aPL but with other known thrombophilias; uRSA group, patients with recurrent spontaneous abortion without aPL or other known thrombophilias.

Ann Rheum Dis 2012;**71**:61–66. doi:10.1136/ard.2011.153817

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EFECTOS NO-ANTITROMBÓTICOS DE LAS HBPM EN OBSTETRICIA

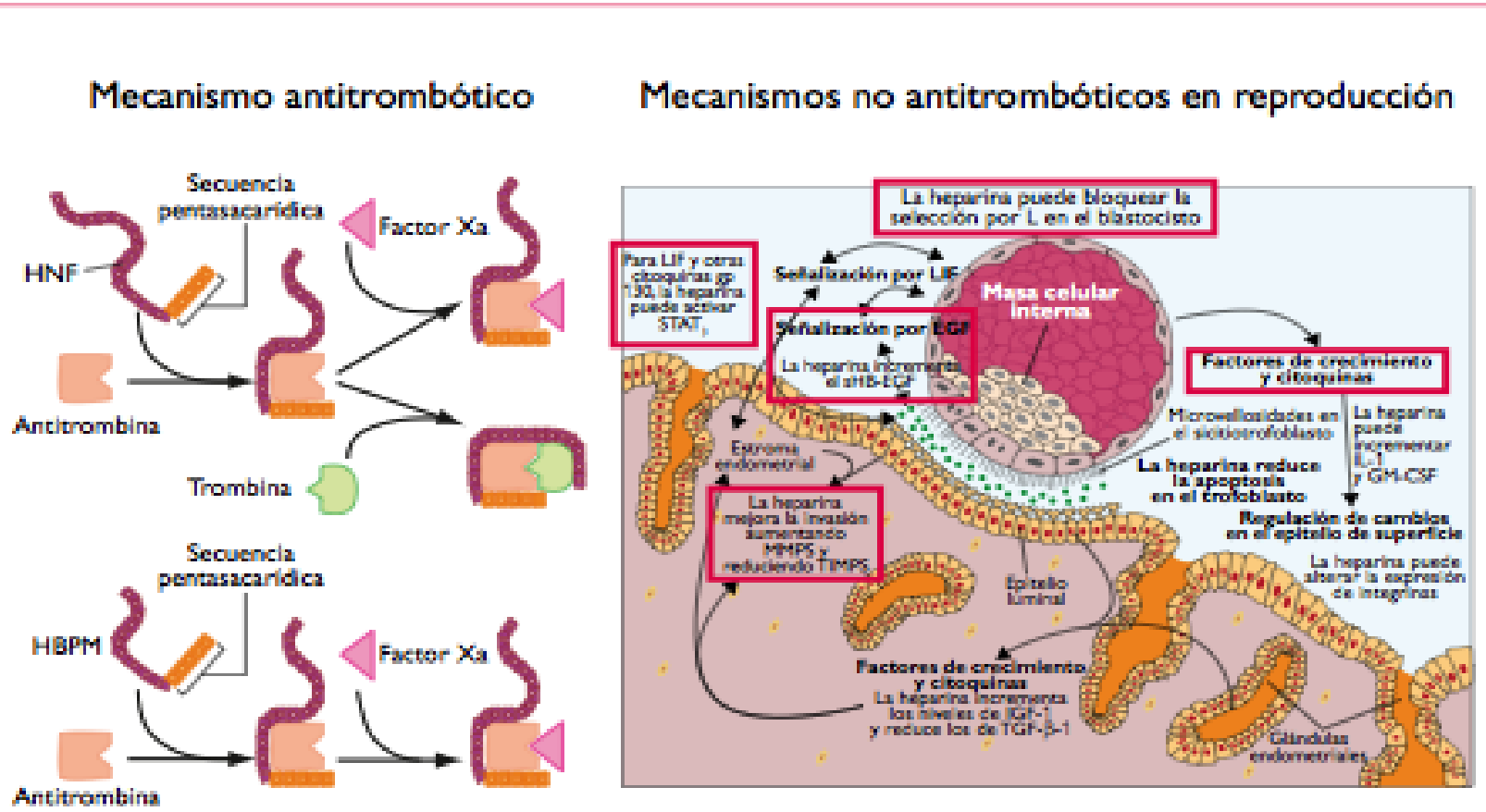


Figura 1. Mecanismos de acción de la HBPM.

LOW- MOLECULAR- WEIGHT- HEPARIN IN OBSTETRIC CARE: A REVIEW OF THE LITERATURE

SILVIA D'IPPOLITO, MD, AMPARO SANTAMARIA ORTIZ,PHD, AND NICOLETTA DI SIMONE, MD, PHD

REPROD SCI. 2011 JUL;18(7):602-13.

Estudios de HBPM en complicaciones del embarazo y trombofilia (I)

Table 2. Studies of Heparin in Pregnancy Complications Associated with Thrombophilic Disorders.

Reference	Study Design	Treatment	Study Population	Outcome	Results
Brenner et al,[26] Thromb Haemost	Uncontrolled series.	Enoxaparin 40 mg (single thrombophilic defect) vs enoxaparin 80-120 mg (combined thrombophilic defect).	50 women with thrombophilia and RPL.	Live birth rate.	Enoxaparin is safe and effective in prevention of pregnancy loss in women with inherited and acquired thrombophilia.
Bar et al,[32] Thromb Res	Uncontrolled series.	Low dose aspirin (100 mg/day) plus LMWH (40 mg/day) in patients with evidence of thrombophilia, Low dose aspirin alone for the remainder.	65 patients with a history of RPL, IUFD, IUGR and severe early-onset PE.	Fetal and maternal Doppler flow parameters.	Thromboprophylactic therapy transiently improves maternal circulation parameters in patients with thrombophilia at risk of fetal loss or other gestational complications. Large prospective trials are warranted.
Kupferminc et al,[27] Hypert Pregnancy	Uncontrolled series.	LMWH (40 mg/day) started at 8-12 weeks' gestation until 6 weeks post partum plus aspirin 100 mg from 8-12 weeks' gestation until 37-38 weeks' gestation.	33 women carriers of thrombophilia with previous severe pregnancy complications (PE, abruption placentae, IUGR, IUFD.	Haemorrhagic events Recurrence rate of PE, abruption placentae, IUGR, IUFD.	Administration of LMWH combined with aspirin was safe, well tolerated, and was not associated with any significant haemorrhagic events. The mean gestational age and birth weight improved significantly in the treated pregnancies and the rate of pregnancy complications was only of 9.1%.
Carp et al,[28] J Thromb Haemost	Cohort study.	Enoxaparin 40 mg (37 patients) vs no treatment (48 patients).	85 women with thrombophilic disorder and RPL.	Subsequent live birth rate.	70.2% of treated pregnancies resulted in live birth compared with 43.8% in untreated pts. The beneficial effect was seen mainly in primary aborters. However the benefit was not statistically significant, probably due to the small number of patients.
Grandone et al,[31] Fertil Steril	Uncontrolled series.	UFH 5000 IU twice a day or enoxaparin 4000 IU/d (22 patients) vs aspirin 100 mg/d (3patients).	25 women with Factor V Leiden and/or Factor II mutation and obstetrics complications.	Live birth.	Heparin prophylaxis at fixed low doses and possibly aspirin could be efficacious in preventing adverse outcomes in women carrying inherited thrombophilia with previous poor obstetric outcomes.

(continued)

D'Ippolito et al. 2011. Reproductive Sciences 18:602-613.

Estudios de HBPM en complicaciones del embaraz( )

De 9 estudios en pacientes con trombofilia:
7 con enoxaparina, 2 con dalteparina

Table 2 (continued)

Reference	Study Design	Treatment	Study Population	Outcome	Results
Gris et al,[30] Blood	Randomized prospective controlled trial.	LMWH (enoxaparin 40 mg) vs aspirin alone (100 mg/die) at the beginning of the 8th week of amenorrhea after a positive pregnancy test.	Women with one single previous unexplained fetal loss from the 10 week of amenorrhea and no explained pregnancy losses associated with Factor V Leiden, F II mutation, protein S deficiency.	Live birth.	Marked improvement in live birth rates as compared to aspirin following a single late pregnancy loss in women with thrombophilic disorders.
Brenner et al, J Thromb Haemost[33]	Multicenter prospective randomized open-label trial. LIVE-ENOX STUDY: it is not an investigation of the effect of enoxaparin in the prevention of RPL, for it assumes its efficacy is already evident! The study compares the efficacy and safety of two different doses of enoxaparin.	LMWH (enoxaparin 40 mg/die) vs LMWH (enoxaparin 40 mg bid /die) at 5-10 weeks of pregnancy, continuing throughout pregnancy and up to 6 week postpartum.	Patients with thrompophilia and history of RPL.	Primary endpoint: Delivery of a live healthy infant. Safety endpoint: Maternal thrombocytopenia and any drug related adverse events throughout the study.	Pregnancy outcomes were similar whether 40 mg or 80 mg /day enoxaparin regimens were used. Enoxaparin 80 mg did not increase either bleeding complications or heparin induced thrombocytopenia compared with 80 mg. The lower dosage of enoxaparin (40 mg/day) might suffice for thrombophilic risk while a higher dosage of enoxaparin (80 mg/day) might be beneficial and equally safe in women with a particularly high thrombophilic risk.
Leduc et al,[36] J Obstet Gynaecol Can	Cohort study.	43 patients: anticoagulant prophylaxis was administered using dalteparin (3500-7500 IU twice/day) in 13 patients; aspirin (80 mg/day) plus dalteparin in 26 patients and aspirin alone (80 mg/day) in 11patients.	Women who had at least 1 pregnancy complicated by severe early onset PE, placental abruption, FGR or fetal death, and inherited thrombophilias.	Recurrence rate of obstetrical complications.	ASA alone and dalteparin alone equivalent effects in preventing PE and FGR. Combined dalteparin and aspirin significantly decreased risk of PE by 20% and FGR by 30% in women with inherited thrombophilias.
Abou-Nassar et al,[37] Thromb Haemost 2007	Randomized controlled trial.	Dalteparin (5000 IU/day until 20 weeks and then 5000 IU/12H until 37 weeks) vs no treatment.	91 patients at high risk of pregnancy complications with confirmed thrombophilia.	Coagulation activation: levels of thrombin-antithrombin complexes (TAT), prothrombin fragments, D-dimer anti-Xa activity	Dalteparin did not reduce coagulation activation in high risk thrombophilic women during pregnancy.

Abbreviations: LMWH, low molecular weight heparin; IUFD, intrauterine fetal death; RPL, recurrent pregnancy loss; PE, preeclampsia; UFH unfractionated heparin; IUGR: intrauterine fetal growth restriction.

D'Ippolito et al. 2011. Reproductive Sciences 18:602-613.

Estudios de HBPM

ABORTOS DE REPETICIÓN (con y sin trombofilia)

41 estudios: 23 enoxaparina, 4 dalteparina, 2 nadroparina, 2 seleparina, 2 tinzaparina, 1 bemiparina, 6 HBPM sin detallar, 1 HNF

Otras CVG (con y sin trombofilia)

11 estudios: 6 dalteparina, 5 enoxaparina y 1 nadroparina/seleparina

Mejora de implante en técnicas de reproducción asistida **(con y sin trombofilia)**

7 estudios: 5 enoxaparina, 1 bemiparina, 1 dalteparina y 1 fraxiparina

LOW MOLECULAR WEIGHT HEPARIN FOR THE SECONDARY PREVENTION OF PLACENTAL-MEDIATED PREGNANCY COMPLICATIONS: A SYSTEMATIC REVIEW AND META ANALYSIS

Rodger, Gris, Rey, Carrier, Le gal.

State of the Art, ISTH , Japan 2011

We performed a systematic review and meta-analysis of **randomized controlled trials** (RCTs) comparing low molecular weight heparin (LMWH) versus no LMWH treatment for secondary prevention of placenta mediated pregnancy complications.

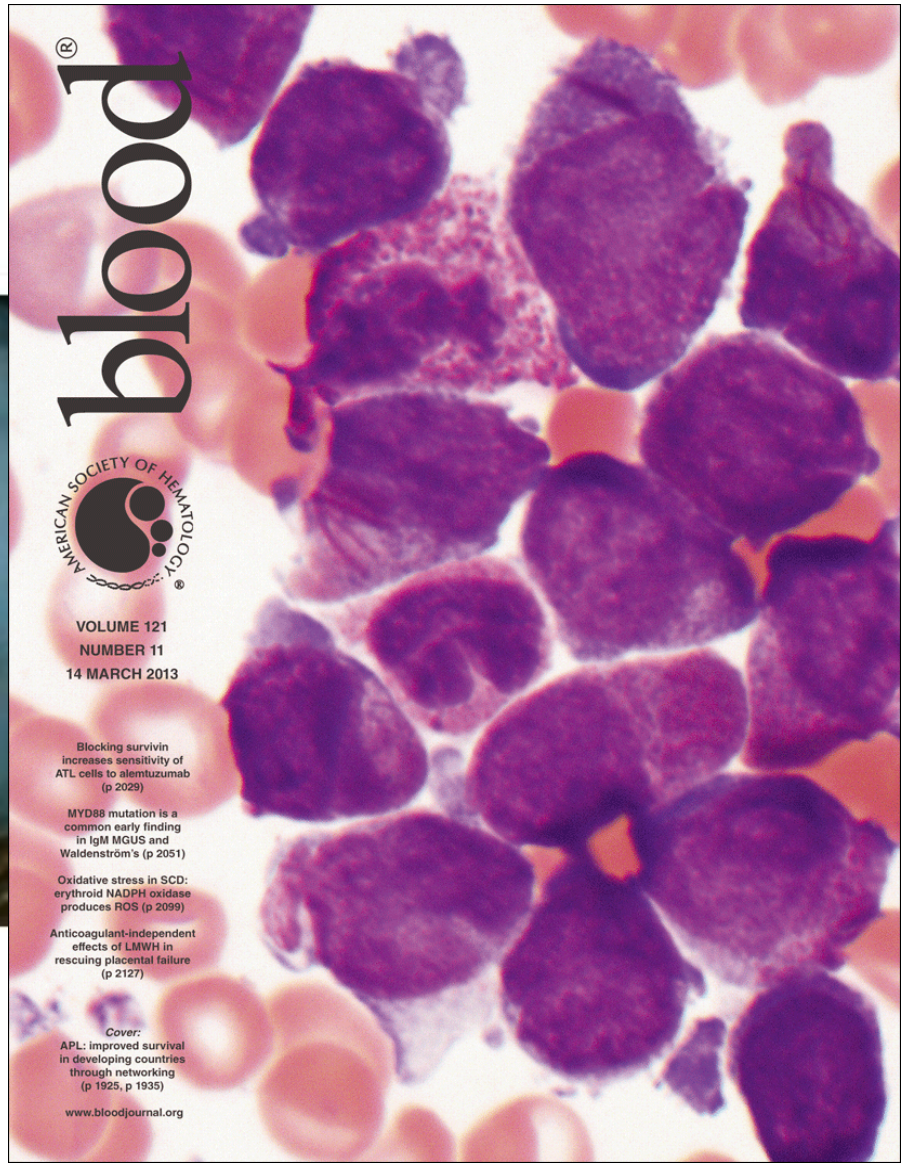
Results.

574 women with either prior pre-eclampsia, fetal growth restriction (<10th percentile), major abruption or stillbirth >20 weeks. Overall, 21/288 (7%) women on LMWH had recurrent severe placenta-mediated pregnancy complications, as compared with 85/286 (29%) women with no LMWH: ***absolute risk reduction 22%,*** (Figure).

Habemus

VATICANO Segundo día de votaciones

Fumata blanca



blood
Leading the world in reporting basic and applied hematology research
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Heparin–not only thinning the blood

An et al showed elegantly that thrombin-mediated maternal platelet activation is central in the mechanism of placental failure. Although these data are very intriguing, ideally, glycol-split heparin (chemically modified heparin without the AT site) should be included in future studies to show whether the beneficial pregnancy-related effects of heparin are solely based on the heparan sulfate proteoglycan backbone and are independent of the AT site. Chemical alterations to the backbone size might provide additional information about the molecular actions of heparin.

As outlined, heparins are widely used in pregnancy; yet, beyond the classic effects on coagulation, there is still a vast lack of knowledge on how heparin contributes to improved pregnancy outcomes. Work by An et al[1] demonstrates new concepts supporting the clinical importance of this drug and its noncoagulation-dependent aspects, opening the way to a renaissance of heparin and its use in clinical practice.

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Heparin rescues factor V Leiden–associated placental failure independent of anticoagulation in a murine high-risk pregnancy model

+ Author Affiliations

Key Points

Abstract

Low molecular weight heparin (LMWH) is being tested as an experimental drug for improving pregnancy outcome in women with inherited thrombophilia and placenta-mediated pregnancy complications, such as recurrent pregnancy loss. The role of thrombotic processes in these disorders remains unproven, and the issue of antithrombotic prophylaxis is intensely debated. Using a murine model of factor V Leiden–associated placental failure, we show that treatment of the mother with LMWH allows placental development to proceed and affords significant protection from fetal loss. Nonetheless, the therapeutic effect of LMWH is not replicated by anticoagulation; fondaparinux and a direct Xa inhibitor, C921-78, achieve anticoagulation similar to LMWH but produce little or no improvement in pregnancy outcome. Genetic attenuation of maternal platelet aggregation is similarly ineffective. In contrast, even a partial loss of thrombin sensitivity of maternal platelets protects pregnancies. Neonates born from these pregnancies are growth retarded, suggesting that placental function is only partially restored. The placentae are smaller but do not reveal any evidence of thrombosis. Our data demonstrate an anticoagulation-independent role of LMWH in protecting pregnancies and provide evidence against the involvement of thrombotic processes in thrombophilia-associated placental failure. Importantly, thrombin-mediated maternal platelet activation remains central in the mechanism of placental failure.

CONCLUSIONES

1. Aborto de Repetición como emfermedad compleja.
2. Aborto como factor de riesgo cardiovascular
3. La HBPM como opción terapéutica en las mujeres con factor trombofílico-inflamatorio (conocido o no).
4. Test trombofílico más personalizado

TEST TROMBOLICO OBSTETRICO

PERSONALIZADO: TAILORED