TEKRARLAYAN GEBELIK KAYBI – HEPARIN

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Akdeniz Üniversitesi Tıp Fakültesi Perinatoloji Bilim Dalı

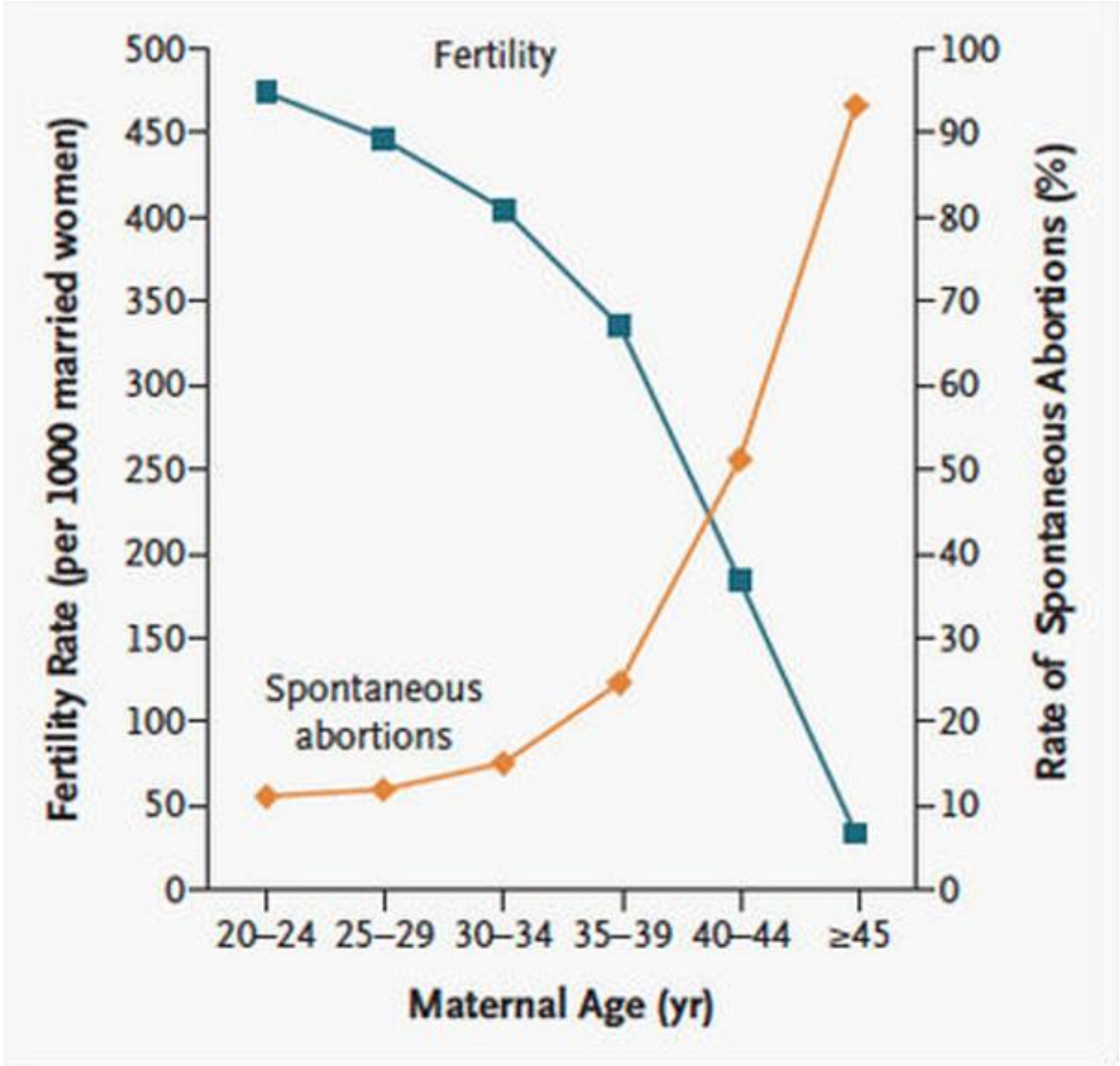
CANLI DOĞUM ŞANSI

- Fertilize ovum'un canlı doğum ile sonuçlanma şansı : %30.

- Klinik olarak saptanan gebeligin canlı doğum ile sonuçlanma şansı : % 80 – 85.

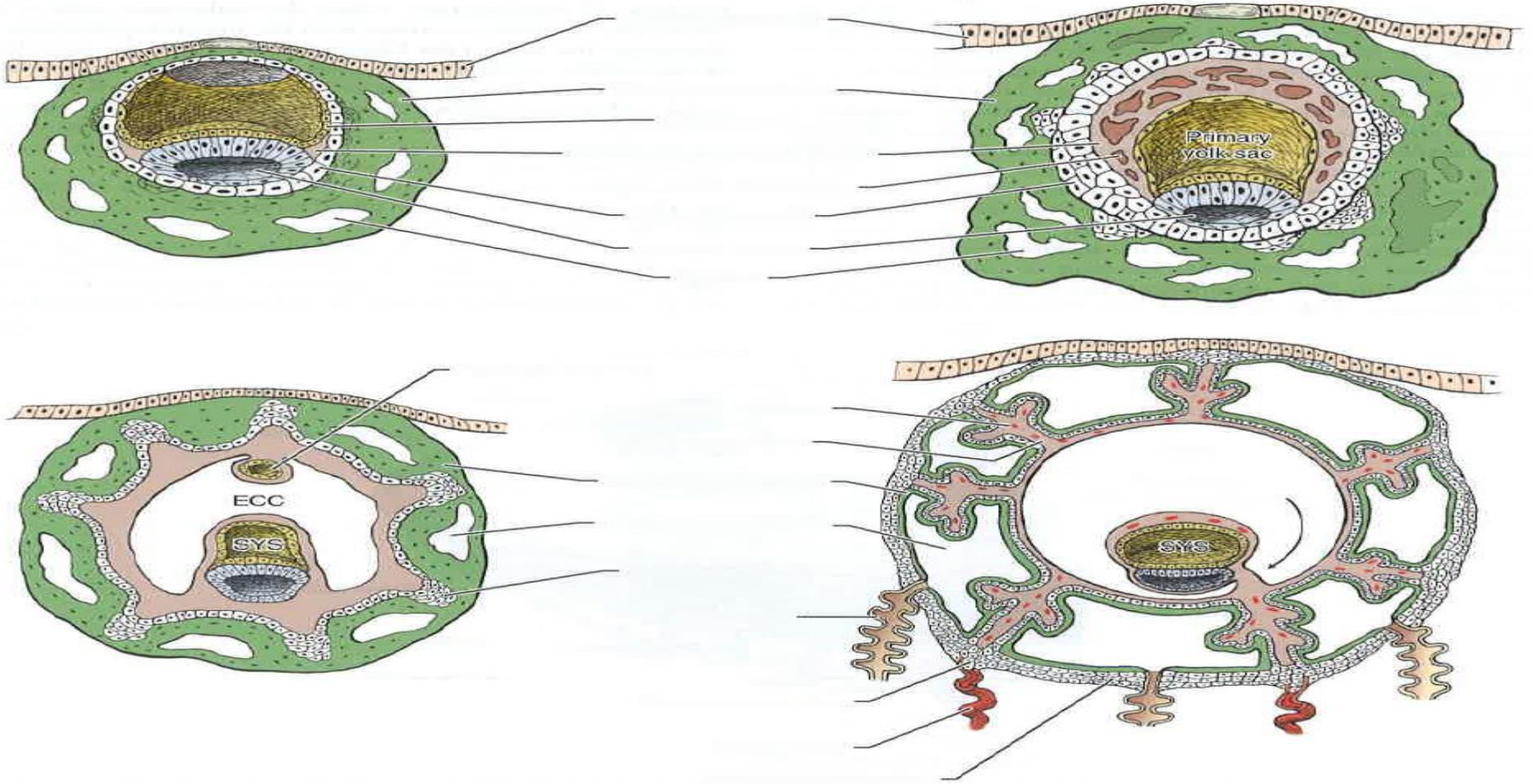
- Gebeliğin kendisi de protrombotik bir durumdur.

EDMONDS DK, LINDSAY KS, MILLER JF, ET AL. EARLY EMBRYONIC MORTALITY IN WOMEN. *FERTIL STERIL.* 1982;38(4):447–453.


Fertility
Spontaneous abortions
Fertility Rate (per 1000 married women)
Rate of Spontaneous Abortions (%)
Maternal Age (yr)
500
450
400
350
300
250
200
150
100
50
0
100
90
80
70
60
50
40
30
20
10
0
20–24
25–29
30–34
35–39
40–44
≥45

YAŞ	YAŞ'A BAĞLI GEBELİK KAYIP RİSKİ
12-19	% 13
20-24	% 11
25-29	% 12
30-34	% 15
35-39	% 25
40-44	% 51
≥ 45	% 93

DE LA ROCHEBROCHARD E,THONNEAU P. PATERNAL AGE AND MATERNAL AGE ARE RISK FACTORS FOR MISCARRIAGE; RESULTS OF A MULTICENTRE EUROPEAN STUDY.HUM REPROD 2002;17:1649–56

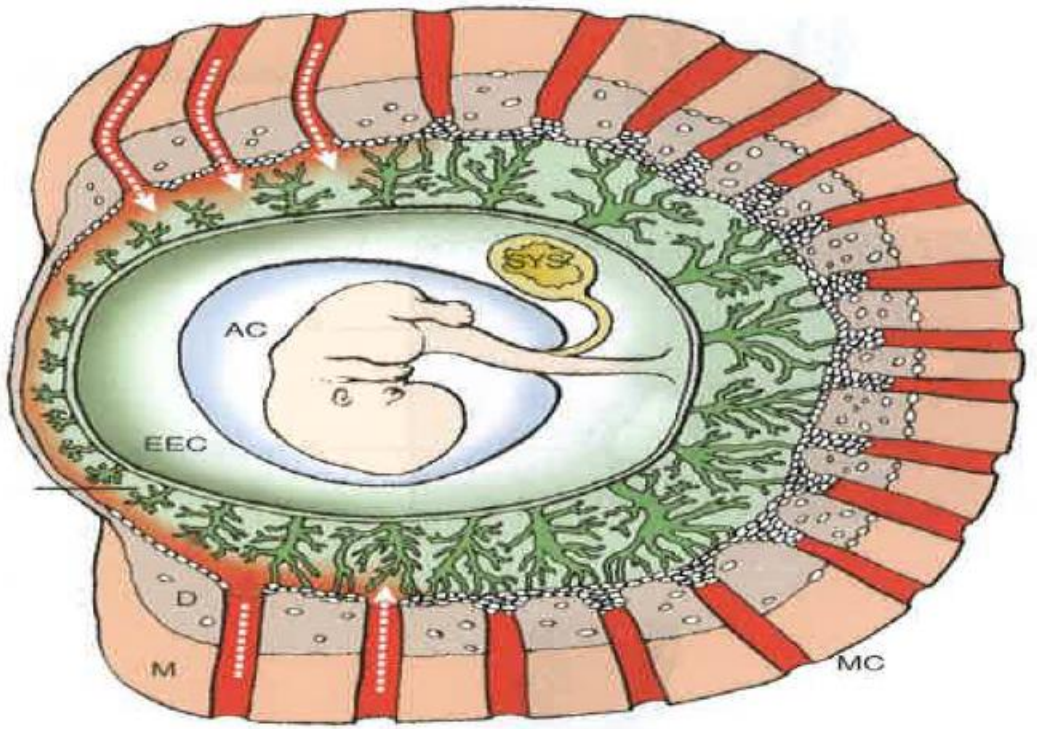


- Fertilizasyondan sonraki 9 -16. günler.

- Intervillöz boşluğa doğrudan yapılan histeroskopi, anne kanından ziyade şeffaf bir sıvı olduğunu göstermiştir.

- Histerektomi yapılacak gebe uteruslara yapılan perfüzyon çalışmaları IVS'ye anlamlı kan akımının olmadığını ortaya koymuştur.

- IVS'de ki oksijen konsantrasyonu < 20 mmHg, ancak 10 – 12. gestasyonel haftadan sonra artar.



TEKRARLAYAN GEBELIK KAYBI

- ≥ 2 adet ultrasonografi veya histopatolojik inceleme ile ortaya konan gebelik kaybı

- ≥ 3 ardışık gebelik kaybı (biokimyasal gebelik, yeri bilinmeyen gebelik, vs.)

PRACTICE COMMITTEE OF AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE.
GREENTOP GUIDELINE 17. RECURRENT MISCARRIAGE, INVESTIGATION AND TREATMENT OF COUPLES. ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS,

- 12. gebelik haftasından daha önce , ≥ 3 ardışık gebelik kaybı olan 587 olgunun incelendiği retrospektif kohort çalışmasına göre biokimyasal gebelikler ve yeri bilinmeyen gebeliklerin gelecekteki gebelikler üzerine kötü etkileri vardır ve bu etkiler intrauterin kayıp gebelikleri ile benzerdir.

KOLTE A, VAN OPPENRAAIJ R, QUENBY S, ET AL. NONVISUALIZED PREGNANCY LOSSES ARE PROGNOSTICALLY IMPORTANT FOR UNEXPLAINED RECURRENT MISCARRIAGE. HUM REPROD. 2014;29:931–937.

Table 1
Theoretical incidence of recurrent pregnancy loss (RPL) according to the number of miscarriages used in the definition

No. of Miscarriages Required to Diagnose RPL	Incidence ≥
2	1/45
3	1/300
4	1/2000
5	1/13,000
6	1/90,000
7	1/600,000
8	1/4,000,000

Estimates based on a mean sporadic miscarriage rate of 15%.

Incidences calculated as $I = \mu^{\text{number of miscarriages}}$ (where μ = sporadic miscarriage rate of 15%).

Incidences may be underestimated, as the true incidence of RPL is thought to be more than the theoretical incidence.

SARAVELOS SH, REGAN L. UNEXPLAINED RECURRENT PREGNANCY LOSS. OBSTET GYNECOL CLIN NORTH AM. 2014 MAR;41(1):157-66

Table 2
Theoretical incidence of RPL (2 pregnancy losses) according to maternal age

Maternal Age	Incidence of RPL ≥
20	1/85
25	1/70
30	1/45
35	1/16
40	1/4
45	1/2

Estimates based on a sporadic miscarriage rates according to maternal age.

Incidences calculated as $I = \mu^2$ (where μ = sporadic miscarriage rates for age).

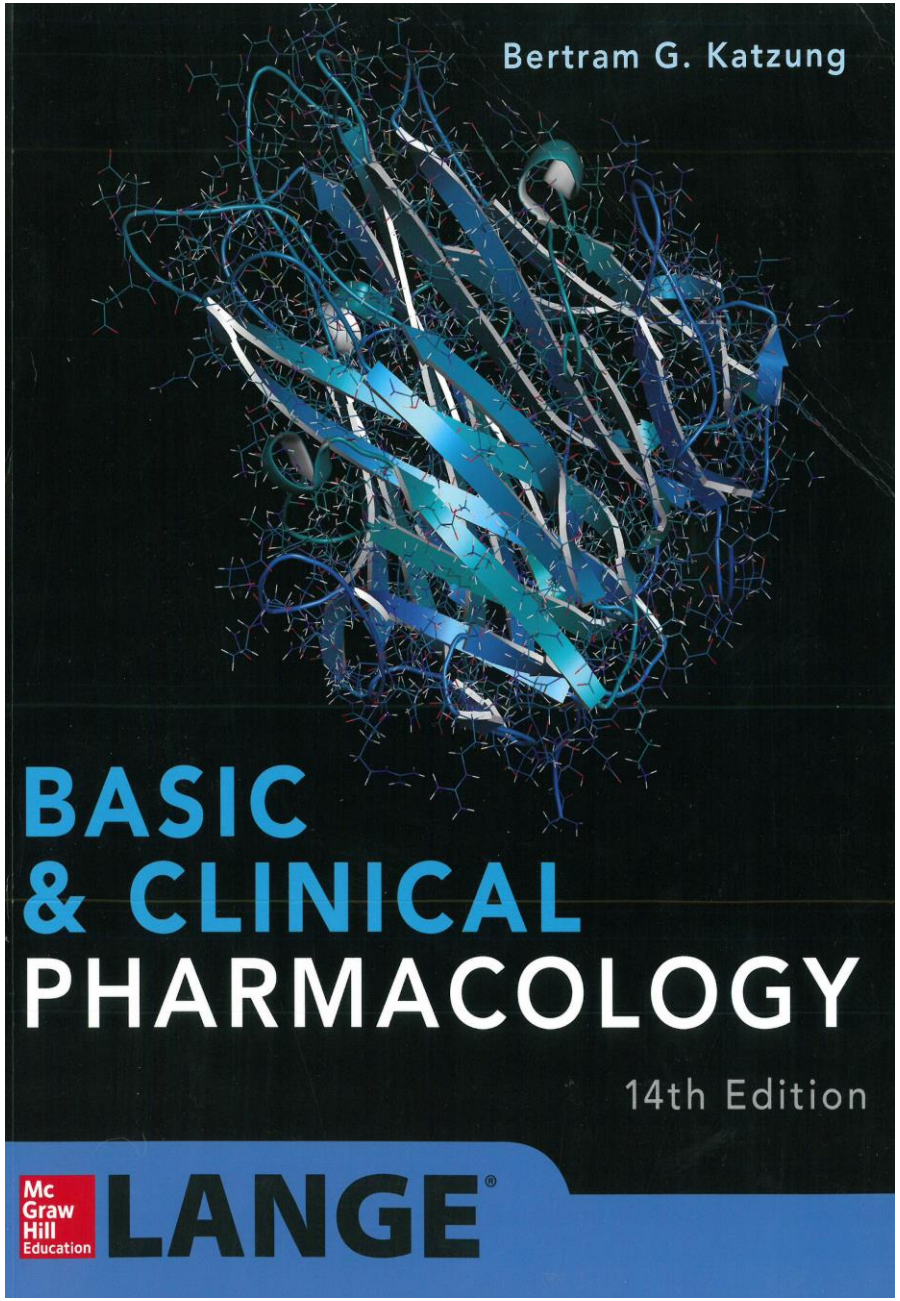
Incidences may be underestimated, as the true incidence of RPL is thought to be more than the theoretical incidence.

SARAVELOS SH, REGAN L. UNEXPLAINED RECURRENT PREGNANCY LOSS. OBSTET GYNECOL CLIN NORTH AM. 2014 MAR;41(1):157-66

TABLE 27-1 APPROXIMATE RECURRENCE RISK FIGURES USEFUL FOR COUNSELING WOMEN WITH REPEATED SPONTANEOUS ABORTIONS

	PRIOR SPONTANEOUS ABORTIONS	RISK (%)
Women with liveborn infant	0	5-10
	1	20-25
	2	25
	3	30
	4	30
Women without liveborn infant	3	30-40

Data from Regan L. A prospective study on spontaneous abortion. In: Beard RW, Sharp F (eds). *Early Pregnancy Loss: Mechanisms and Treatment.* London: Springer-Verlag; 1988, p 22; Warburton D, Fraser FC. Spontaneous abortion risks in man: data from reproductive histories collected in a medical genetic unit. *Am J Hum Genet.* 1964;16:1; and Poland BJ, Miller JR, Jones DC, et al. Reproductive counseling in patients who have had a spontaneous abortion. *Am J Obstet Gynecol.* 1977;127:685.
Recurrence risks are slightly higher for older women.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PHARMACOLOGY
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Mc Graw Hill Education
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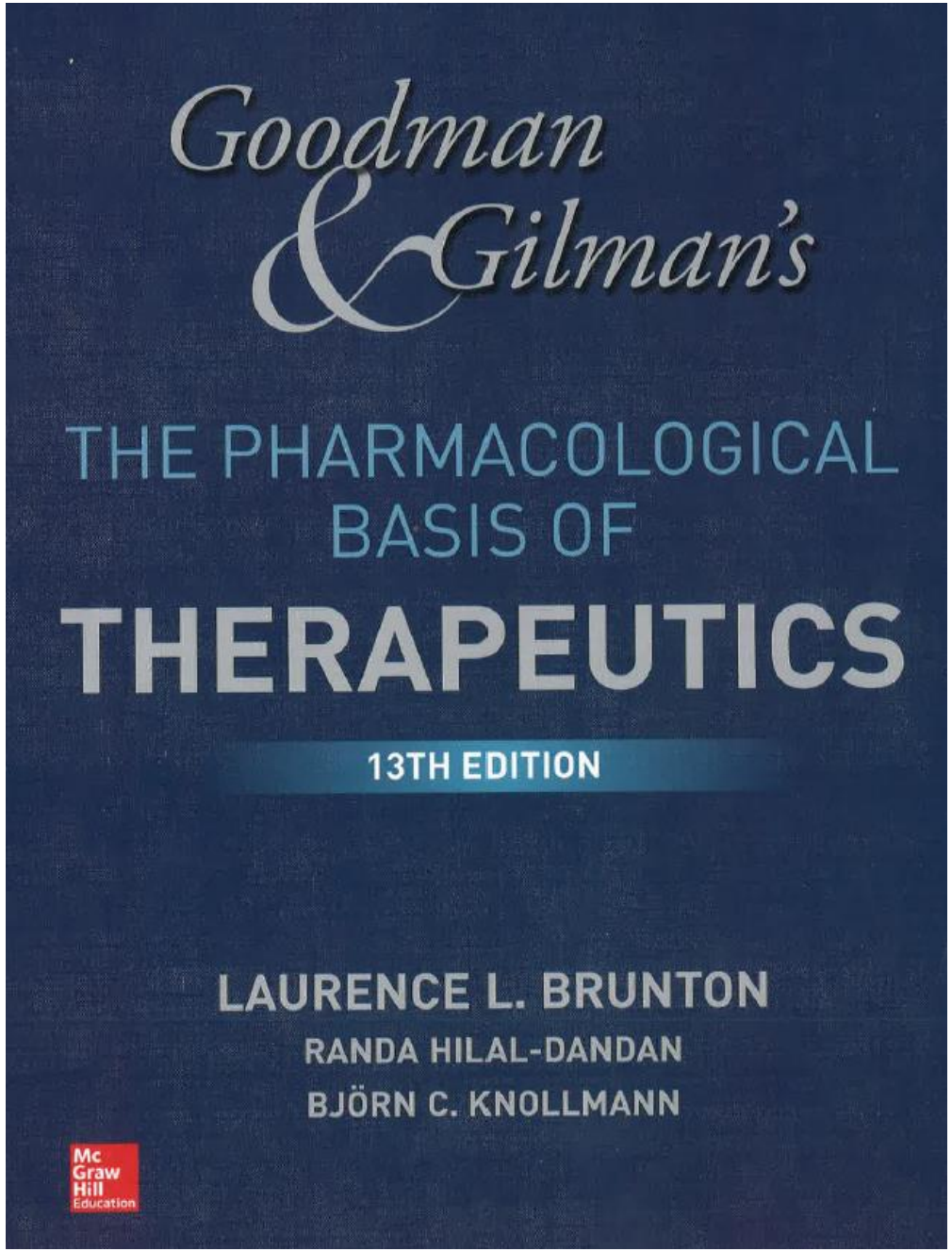
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& Gilman's
THE PHARMACOLOGICAL BASIS OF
THERAPEUTICS
13TH EDITION
LAURENCE L. BRUNTON
RANDA HILAL-DANDAN
BJÖRN C. KNOLLMANN
Mc Graw Hill Education

HEPARIN ÖZELLIKLERI

- Sülfatlı mukopolisakkaridlerin heterojen bir bileşimidir.

- İndirekt trombin inhibitörüdür.

- Endotelyal hücrelerin yüzeylerine ve birçok plazma proteinine bağlanır.

- Biolojik aktivitesini endojen bir antikoagülan olan antitrombin üzerinden gerçekleştirir.

- Antitrombin faktör 2a, 9a ve 10a'yı, bunlarla stabil eş-molar kompleksler oluşturarak, inhibe eder.

- Heparin yokluğunda bu yavaş bir süreçken, heparin ortamda olduğu zaman 1000 kat hızlı reaksiyonlar gerçekleşir.

TABLE 32–1 ■ COMPARISON OF THE FEATURES OF SUBCUTANEOUS HEPARIN, LOW-MOLECULAR-WEIGHT HEPARIN, AND FONDAPARINUX

FEATURES	HEPARIN	LMWH	FONDAPARINUX
Source	Biological	Biological	Synthetic
Mean molecular weight (Da)	15,000	5000	1500
Target	Xa and IIa	Xa and IIa	Xa
Subcutaneous			
Bioavailability (%)	30 (at low doses)	90	100
$t_{1/2}$ (h)	1–8[a]	4	17
Renal excretion	No	Yes	Yes
Antidote effect	Complete	Partial	None
Thrombocytopenia	<5%	<1%	<0.1%

[a]Half-life $t_{1/2}$ is dose dependent; half-life is 1 h with 5000 units given subcutaneously and can extend to 8 h with higher doses.

YMAH VE DMAH

- DMAH'in avantajları; yüksek bioyararlanım, daha az doz ihtiyacı ile benzer etkinlik.
- Tekrarlayan gebelik kaybına yönelik aPTT veya anti-Faktör 10a takip önerisi yok.
- Yan etkiler; kanama ve heparin-induced trombositopeni'dir.

HEPARIN - KONTRENDIKASYONLAR

- Heparin-induced trombositopeni
- Hipersensitivite
- Aktif kanama
- Hemofili
- Belirgin trombositopeni
- İntrakranial hemoraji
- İnfektif endokardit
- Aktif tüberkükloz
- GIS ülseri
- İleri karaciğer hastalığı, böbrek hastalığı
- Düşük tehdidi

The anti-inflammatory effects of heparin and related compounds

Edward Young *

Thrombosis Research (2008) 122, 743–752

Potential mechanisms

Heparin-binding proteins

inflammatory activity. The mechanisms responsible for the anticoagulant effects of heparin are well understood; those underlying its anti-inflammatory activity are not. The mechanisms behind the antico-

More than 100 heparin-binding proteins have been identified and the list is growing [41]. It is not response. Heparin has been shown to bind acute phase [42] and complement proteins [43] and this property may contribute to the anti-inflammatory activity of heparin.

Heparin and related glycosaminoglycans such as heparan sulfate play an important role in the immune system because of their ability to interact with pro-inflammatory cytokines and chemokines. It

Heparin and selectin-mediated cell adhesion

There is accumulating evidence that heparin interferes with the adhesion of leukocytes to the endothelium. Heparin has been shown to inhibit f-met-leu-phe-activated (fMLP) neutrophil adherence to resting endothelial cells [49] while another study demonstrated that heparin and partially desulphated derivatives were able to inhibit nonactivated neutrophils to platelet activating factor (PAF) stimulated endothelial cells [50]. Low molecular weight heparin has also been reported to inhibit adhesion of neutrophils to endothelial cells [51].

Clinical evidence

The potential of heparin as an anti-inflammatory drug is supported by several modestly sized clinical trials in various models of inflammatory disease. Heparin and related compounds have been shown to benefit patients with bronchial asthma, ulcerative colitis and burns.

Heparin and nuclear factor kappa B (NF-κB)

At the molecular level, there is evidence that heparin and related compounds may exert its anti-

inflammatory effects through the transcription factor NF-κB. Inflammation is associated with the coordinated action of a series of cytokine and adhesion molecule genes. The regulation of these genes involves nuclear factor κB (NF-κB), a ubiquitous inducible transcription factor. NF-κB is activated by a vast number of agents including cytokines, lipopolysaccharide (LPS), UV irradiation, growth factors, free radicals, oxidative stress and viral infection [68]. The genes regulated by NF-κB

Heparin and apoptosis

- Bazı in vitro - hayvan çalışmaları, heparinin terapotik etkisinin, antikoagülan özelliklerinden bağımsız, lokal aksiyonlar ile olduğunu ortaya koymuştur.

- Heparin, trofoblastlara antikor bağlanmasını inhibe edebilir, kompleman aktivasyonunu önleyebilir ve trofoblastik invazyonun derinleşmesine katkı sağlayabilir.

KUTTEH WH, HINOTE CD. ANTIPHOSPHOLIPID ANTIBODY SYNDROME. OBSTET GYNECOL CLIN NORTH AM. 2014;41(1):113-32

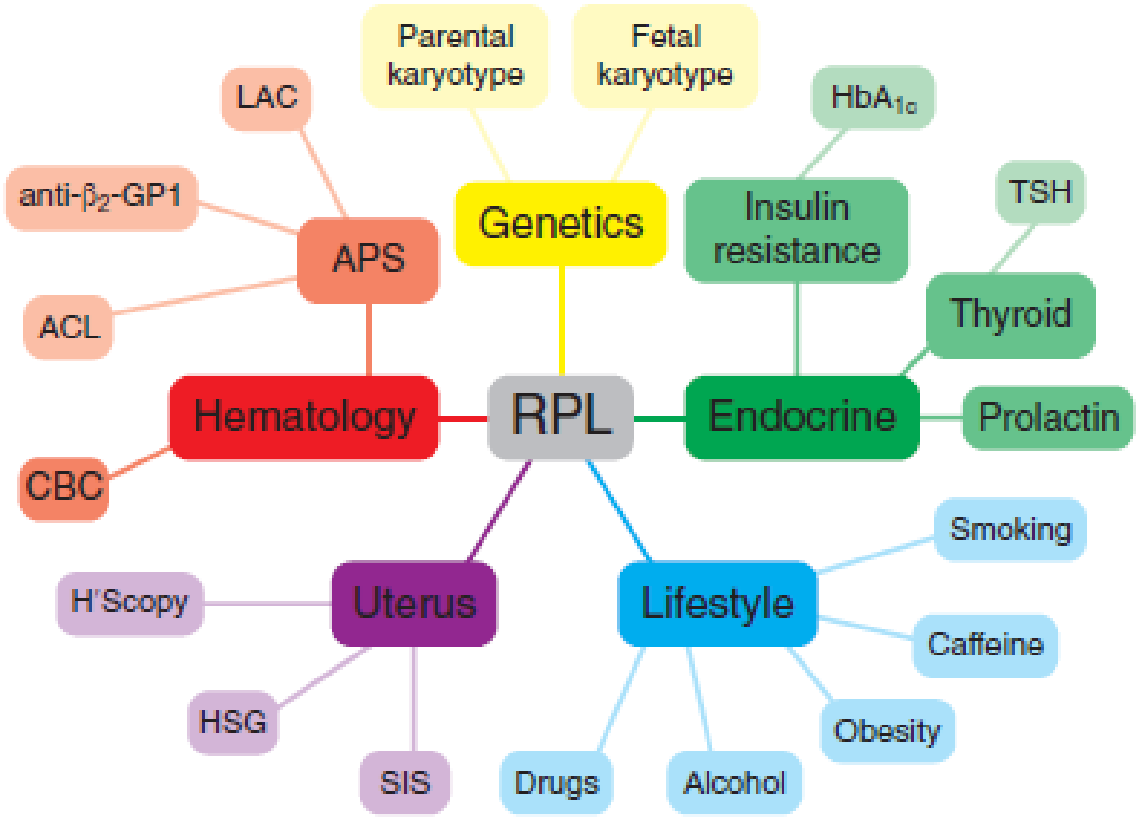
NE ZAMAN ARAŞTıRALıM ? 2 VS 3

- 2 kayıp sonrasında, gebelik kayıp riski : % 24 - 29

- 3 kayıp sonrasında, gebelik kayıp riski : % 31 - 33

EL HACHEM H, ET AL. RECURRENT PREGNANCY LOSS: CURRENT PERSPECTIVES. INT J WOMENS HEALTH. 2017 MAY 17;9:331-345.

TEKRARLAYAN GEBELIK KAYBI ILE ILIŞKILI FAKTORLER



KALITSAL TROMBOFiLiLER

- Kalıtsal trombofililer ile trombojenik olaylar arasındaki ilişki nettir.

- Kalıtsal trombofililer ile gebelik kayıplarının da içinde bulunduğu kötü gebelik sonuçları (preeklampsi, iugg, ablasyo plasenta) arasındaki ilişki halen tartışmalıdır.

Table 1. Risk of Venous Thromboembolism With Different Inherited Thrombophilias

	Prevalence in General Population (%)	VTE Risk Per Pregnancy (No History) (%)	VTE Risk Per Pregnancy (Previous VTE) (%)	Percentage of All VTE
Factor V Leiden heterozygote	1–15	0.5–3.1	10	40
Factor V Leiden homozygote	<1	2.2–14.0	17	2
Prothrombin gene heterozygote	2–5	0.4–2.6	>10	17
Prothrombin gene homozygote	<1	2–4	>17	0.5
Factor V Leiden/ prothrombin double heterozygote	0.01	4–8.2	>20	1–3
Antithrombin deficiency	0.02	0.2–11.6	40	1
Protein C deficiency	0.2–0.4	0.1–1.7	4–17	14
Protein S deficiency	0.03–0.13	0.3–6.6	0–22	3

ACOG PRACTICE BULLETIN 2018

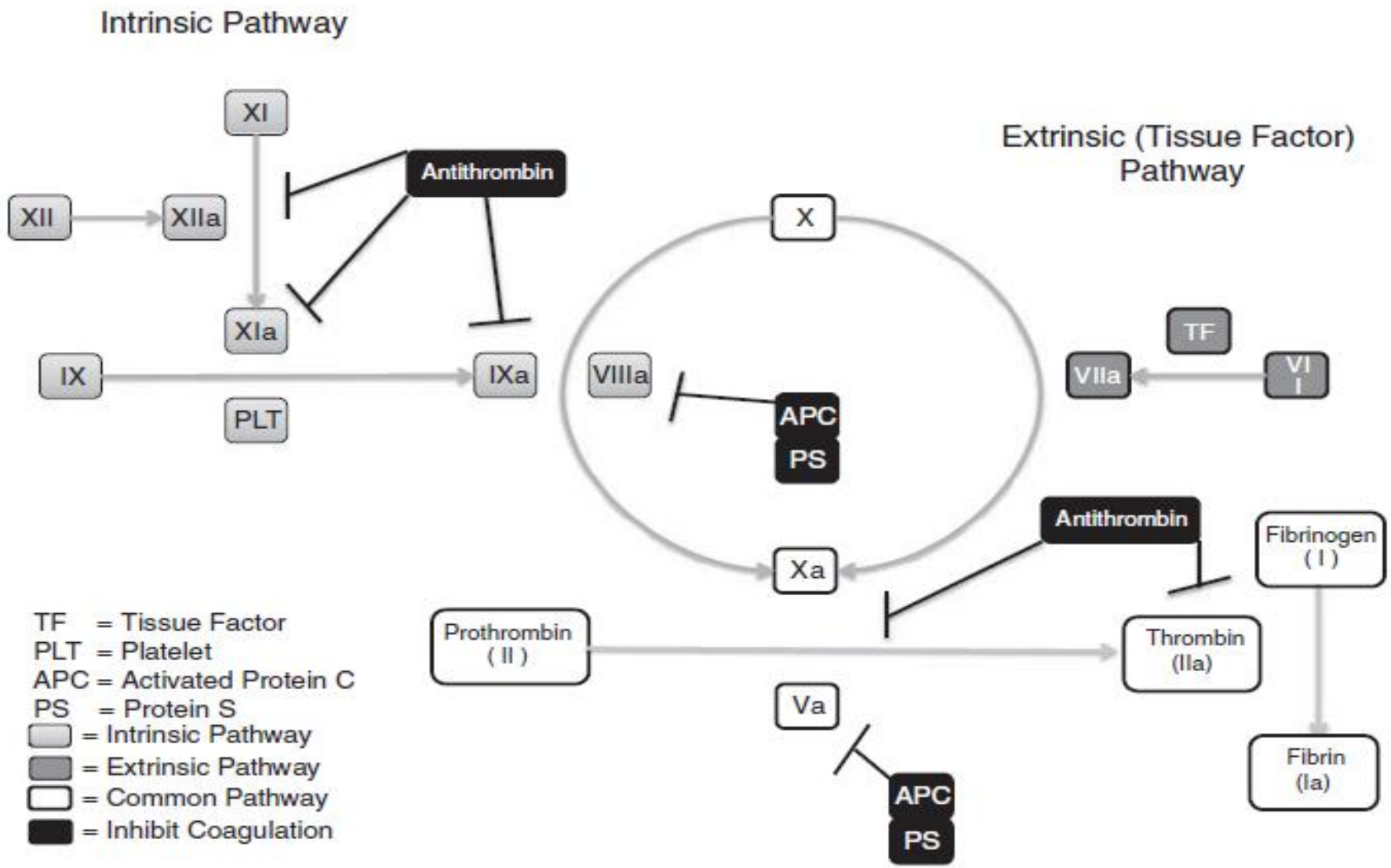


FIGURE 1. Important factors of the coagulation system.

FAKTÖR 5 LEıDEN MUTASYONU

- Normalde Faktör 5a'nın görevi protrombini, trombine çevirmektir.

- Aktive protein C, Faktör 5'i inaktive ederek kan pıhtılarının çok fazla büyümesini önler.

- Kromozom 1q23 nokta mutasyonu sonucunda, sentezlenen proteinin 506. pozisyonundaki arjinin glutamin ile yer değiştirir.

- Bu tek değişiklik protein C klivaj hattında distorsiyon yaratarak, Faktör 5a'nın Protein C tarafından inaktive edilmesine rezistans oluşturur.

- Benzer şekilde, Faktör 8'inde protein C tarafından regülasyonu bozulur.

PROTROMBIN GEN MUTASYONU

- Protrombin G20210A mutasyonu, genin okunmayan 3’ uçundaki guanin’in adenin ile yer değiştirmesi sonucunda oluşur.

- Net etki, artmış protrombin okunması ve dolaşımda artmış kan seviyeleridir.

PAI-1 VE FAKTÖR 13

- Tekrarlayan gebelik kaybı ile ilişkili gibi görünen kalıtsal bir diğer bozukluk, bozuk plazmin aracılı proteoliz gibi görülmektedir.

- Bu durum trofoblastik invazyon esnasındaki maternal doku remodelling'ini bozarak düzgün plasenta oluşumunu etkileyebilir.

- Öne sürülen 2 adet polimorfizim vardır;

    - Faktör 13 Val34Leu ve

    - Plazminojen aktivatör inhibitör 1 (PAI-1) 4G/5G

DOSSENBACH-GLANINGER A, VAN TROTSENBURG M, DOSSENBACH M, ET AL. PLASMINOGEN ACTIVATOR INHIBITOR 1 4G/5G POLYMORPHISM AND COAGULATION FACTOR XIII VAL34LEU POLYMORPHISM: IMPAIRED FIBRINOLYSIS AND EARLY PREGNANCY LOSS. *CLIN CHEM*. 2003;49(7):1081–1086.

- Günümüzde 10 adet PAI gen polimorfizmi tanımlanmıştır ancak çok azı plazmadaki inhibitör seviyesini etkilemektedir.

- Transkripsiyona başlanan kısımdan itibaren 675. sıradaki baz sırasında, o kısma bir adet guanozin insersiyonu/delesyonu 4G/5G polimorfizmi ile sonuçlanmaktadır.

- Faktör 13 Val34Leu allel taşıyıcıları + fibrinogen < 300 mg/dL → RPL, OR: 2.9

- Metformin → PAI-1 düzeylerini düşürür ve fibrinolitik sorunu olanlarda potansiyel tedavi adayı olarak gösterilmiştir.

VELAZQUEZ EM, MENDOZA SG, WANG P, ET AL. METFORMIN THERAPY IS ASSOCIATED WITH A DECREASE IN PLASMA PLASMINOGEN ACTIVATOR INHIBITOR-1, LIPOPROTEIN(A), AND IMMUNOREACTIVE INSULIN LEVELS IN PATIENTS WITH THE POLYCYSTIC OVARY SYNDROME. *METABOLISM*. 1997;46(4):454–457

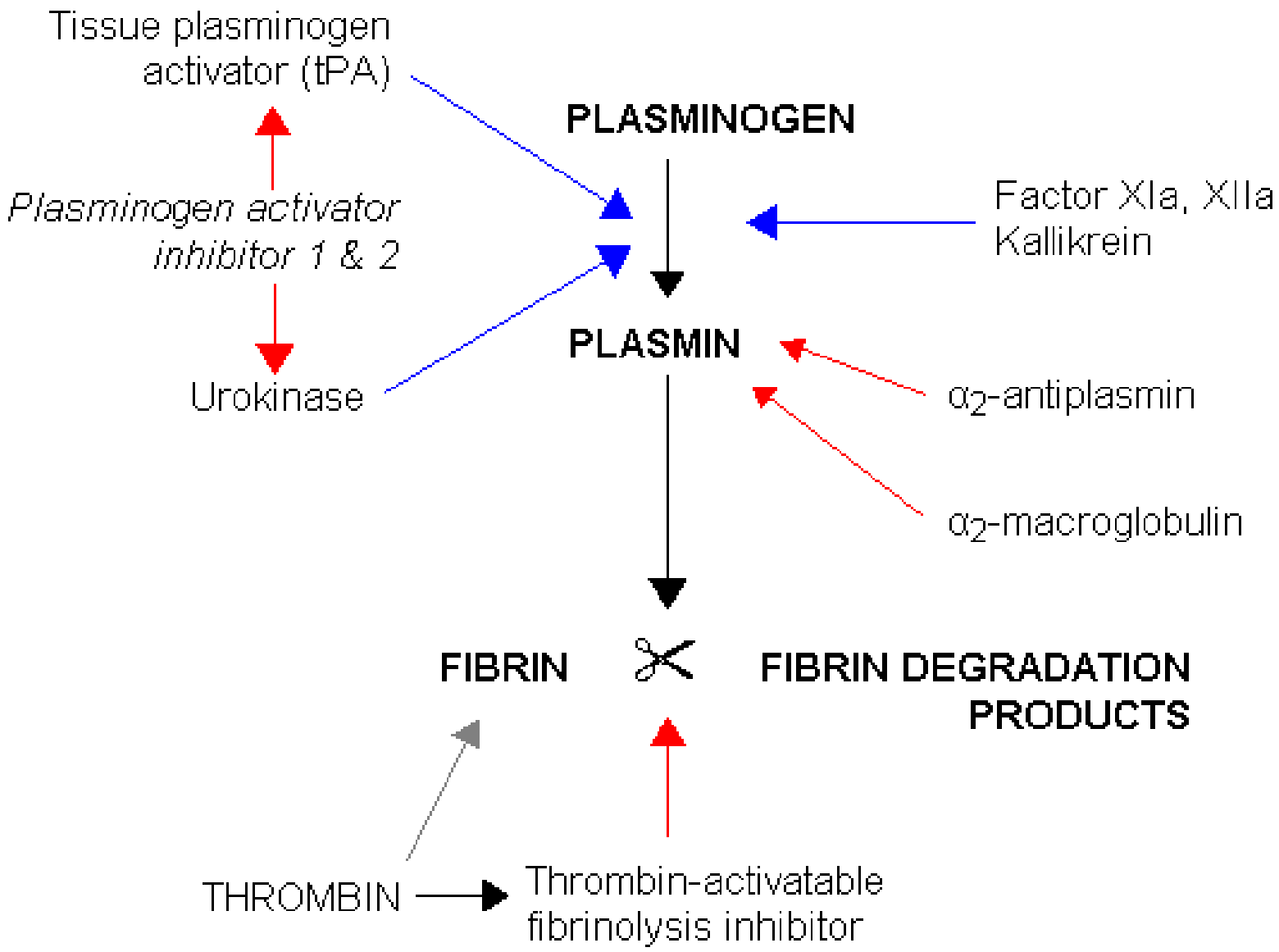
- Ürokinaz ve onun reseptörü olan PAI-1, proteoliz ve trofoblastik invazyon ile maternal doku re-modellinginden sorumlu gibi gözükmektedirler.

- Diğer taraftan Nitabuch fibrinoid tabakasının oluşumunda desidual damarların duvarlarında fibrin birikimii maternal prokoagulan kaskadın aktivasyonu ile oluşur.

- Komplike olmayan gebeliklerde denge korunur ancak düşüklerde intravenöz kan pıhtılıları ve artmış intervillöz doku fibrini, hemostazda bir bozukluk olabileceğine işaret eder.

- Bu durum, fibrine kovalent olarak bağlanan faktör 13 ve fibrinolitik sistemde merkezi bir rolü olan PAI-1'e dikkatleri çekmektedir.

CRAVEN CM, CHEDWICK LR, WARD K. PLACENTAL BASAL PLATE FORMATION IS ASSOCIATED WITH FIBRIN DEPOSITION IN DECIDUAL VEINS AT SITES OF TROPHOBLAST CELL INVASION. AM J OBSTET GYNECOL 2002;186:291–6. 18. KUTTEH WH, PARK VM, DEITCHER SR. HYPERCOAGULABLE STATE MUTATION ANALYSIS IN WHITE PATIENTS WITH EARLY FIRST-TRIMESTER RECURRENT PREGNANCY LOSS. FERTIL STERIL 1999;71:1048–53.


Tissue plasminogen activator (tPA)
PLASMINOGEN
Plasminogen activator inhibitor 1 & 2
Factor XIa, XIIa Kallikrein
PLASMIN
Urokinase
α2-antiplasmin
α2-macroglobulin
FIBRIN
FIBRIN DEGRADATION PRODUCTS
THROMBIN
Thrombin-activatable fibrinolysis inhibitor

The PAI-1 gene 4G/5G Polymorphism and Deep Vein Thrombosis in Patients with Inherited Thrombophilia

Maria Teresa Sartori, MD, Cristina Danesin, MD, Graziella Saggiorato, PhD,

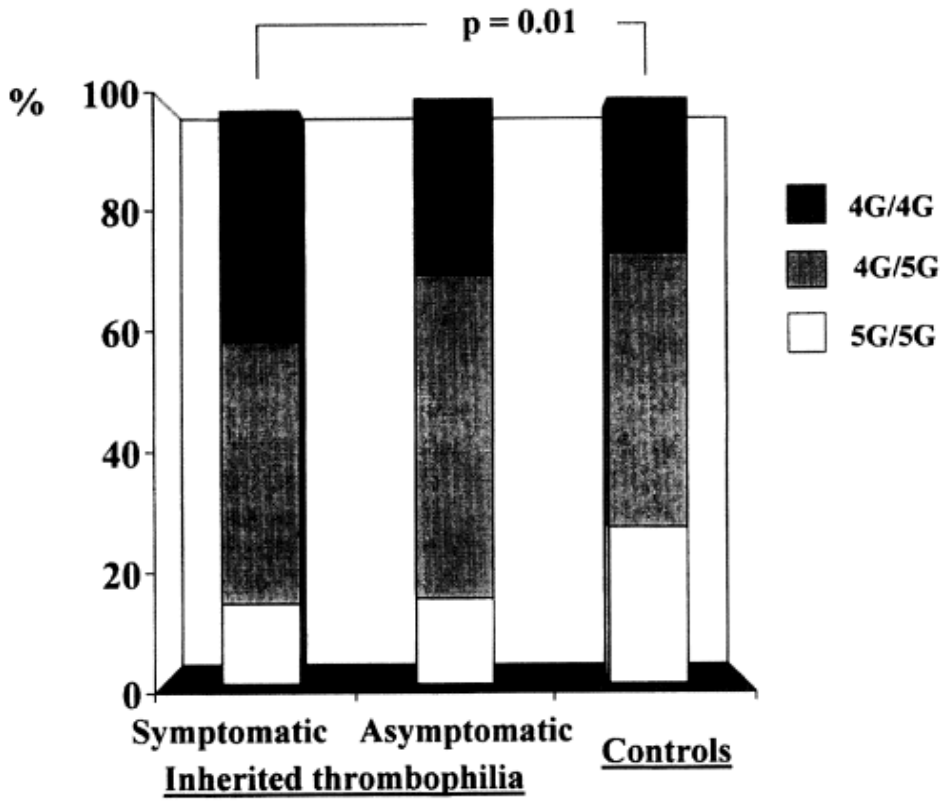


FIG. 1. Genotype distribution of PAI-1 4G/5G polymorphism in patients with inherited thrombophilia symptomatic and asymptomatic for DVT and in healthy controls. The different prevalence of 4G/4G and 5G/5G carriers observed in symptomatic thrombophilia patients vs. controls was significant ($\chi^2 = 6.53$, $p = 0.01$).

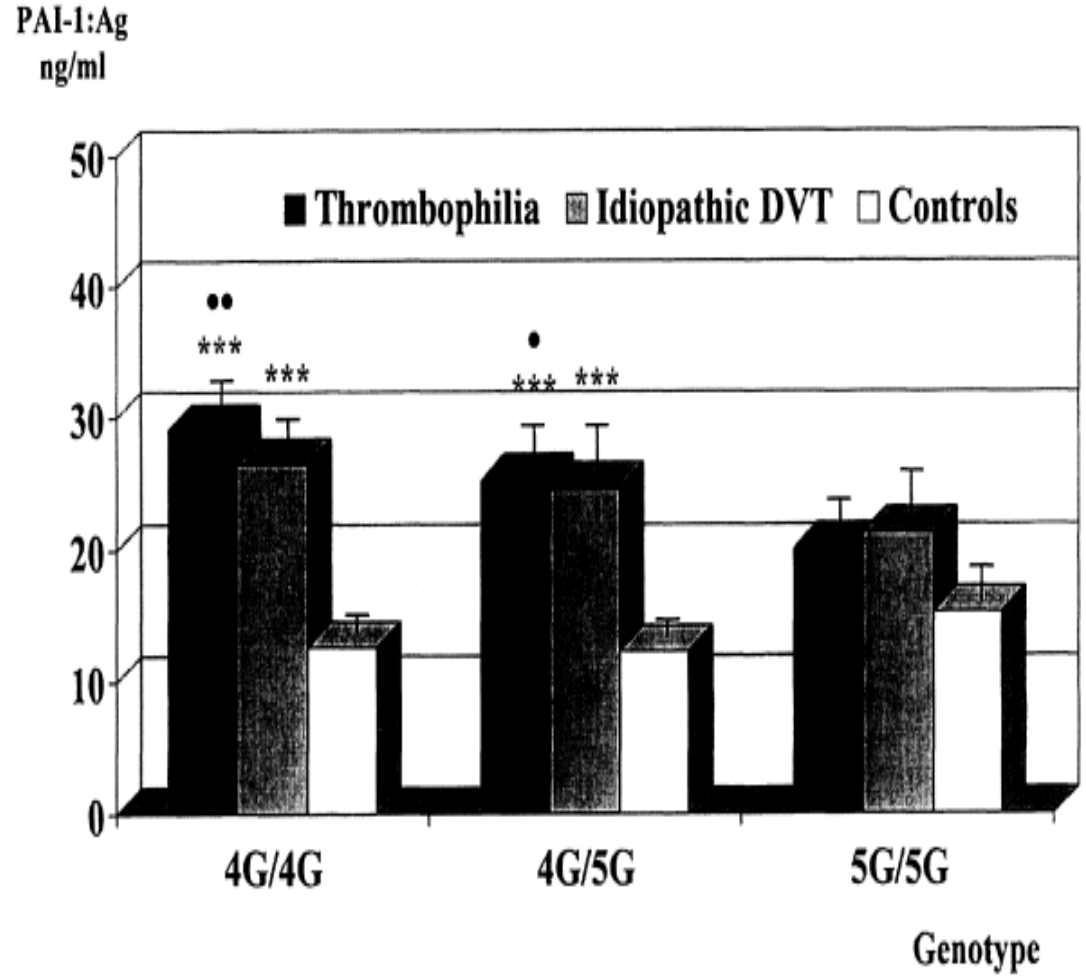


FIG. 2. Mean (± SEM) PAI-1 antigen levels in inherited thrombophilia patients, in idiopathic DVT patients, and in healthy controls according to PAI-1 4G/5G polymorphism genotype. ***$p < 0.001$, patients vs. controls. ••$p = 0.01$, 4G/4G vs. 5G/5G thrombophilia patients; •$p = 0.04$, 4G/5G vs. 5G/5G thrombophilia patients.

Clin Exp Obstet Gynecol. 2011;38(4):347-50.

Effects of inherited thrombophilia in women with recurrent pregnancy loss.

Habibovic Z[1], Zeybek B, Sanhal C, Eroglu Z, Karaca E, Ulukus M.

Author information

Abstract

PURPOSE OF INVESTIGATION: To evaluate the prevalence and effects of inherited thrombophilia caused by factor V Leiden, prothrombin G20210A and methylenetetrahydrofolate reductase (MTHFR) C677T mutations in women with recurrent pregnancy loss.

METHODS: A study group of 97 women with recurrent miscarriages and a control group of 71 healthy pregnant women were included in the study. Genotype analyses for factor V Leiden, prothrombin G20210A and MTHFR C677T polymorphisms were performed by real-time polymerase chain reaction (RT-PCR).

RESULTS: The frequency of factor V Leiden, prothrombin G20210A and MTHFR C677T mutations were similar in both the study and control group. There were eight patients (8.2%) who had more than one gene mutation in the study group and one patient in the control group (1.4%). This difference was not statistically significant. Study group patients (n = 97) were compared in terms of the number of miscarriages and the abortion week, in addition to being a carrier of factor V Leiden and MTHFR C677T gene mutations. No statistically significant correlation was found between being a factor V Leiden and MTHFR C677T mutation carrier with either the number of miscarriages or the abortion week.

CONCLUSION: Factor V Leiden, prothrombin G20210A and MTHFR C677T gene mutations are not individually related with recurrent pregnancy loss. However, combined gene mutation status may be associated with recurrent miscarriages.

SYSTEMS BIOLOGY IN REPRODUCTIVE MEDICINE, 2018
https://doi.org/10.1080/19396368.2018.1456576

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MOLECULAR DIAGNOSTICS

Association between thrombophilia gene polymorphisms and recurrent pregnancy loss risk in the Iranian population

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[a]Research and Development Laboratory, Javid Biotechnology Institute, Tehran, Iran; [b]Mehr General Laboratories, Tehran, Iran; [c]Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Table 3. The different genotypic frequencies of the ten thrombophilia gene mutations in case and control groups.

	Case (n = 200)			Control (n = 200)			
Polymorphisms	Normal (%)	Heterozygote (%)	Homozygote (%)	Normal (%)	Heterozygote (%)	Homozygote (%)	*p-Value*
PAI-1(−675 I/D, 5G/4G)	70 (35)	112 (56)	18 (9)	150 (75)	43 (21.5)	7 (3.5)	$p < 0.0001$
FII (G20210A)	192 (96)	6 (3)	2 (1)	199 (99.5)	1 (0.5)	0	0.0579
FV Leiden	150 (75)	30 (15)	20 (10)	192 (96)	8 (4)	0	$p < 0.0001$
FV (A5279G)	129 (64.5)	25 (12.5)	23 (11.5)	187 (93.5)	7 (3.5)	6 (3)	$p < 0.0001$
FV (A4070G)	186 (93)	12 (6)	2 (1)	196 (98)	4 (2)	0	0.6721
FXIII (Val34Leu)	121 (60.5)	72 (36)	7 (3.5)	146 (73)	49 (24.5)	5 (2.5)	0.0295
ITGB3 (1565T/C)	171 (85.5)	16 (8)	13 (6.5)	110 (55)	67 (26)	23 (19)	$p < 0.0001$
MTHFR (677C/T)	91 (45.5)	76 (38)	33 (16.5)	136 (68)	58 (29)	6 (3)	$p < 0.0001$
MTHFR (1298 A/C)	142 (71)	48 (24)	10 (5)	171 (85.5)	28 (14)	1 (0.5)	0.0005
BF (−455 G/A)	131 (65.5)	59 (29.5)	10 (5)	163 (81.5)	36 (18)	1 (0.5)	0.0003

MTHFR: methylenetetrahydrofolate reductase; BF: beta fibrinogen; ITGB3: integrin beta 3, FXIII Val34Leu coagulation factor XIII, FV factor V, F II, prothrombin; FVL: Factor V Leiden and PAI-1: plasminogen activator inhibitor type 1 polymorphisms.

*Some patients had more than one thrombophilia mutation.

Int J Lab Hematol. 2017 Dec;39(6):590-595. doi: 10.1111/ijlh.12703. Epub 2017 Jun 12.

Thrombophilic gene polymorphisms and recurrent pregnancy loss in Greek women.

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Author information

Abstract

INTRODUCTION: Recurrent pregnancy loss (RPL) is a multifactorial disorder. The aim of this study was the detection of various genetic polymorphisms and their correlation to RPL, in Greek women.

METHODS: The impact of 12 thrombophilic polymorphisms was evaluated, among 48 Greek women with a history of RPL, vs 27 healthy parous women. Multiplex PCR and in situ hybridization on nitrocellulose films were performed, to investigate 12 genetic polymorphisms previously reported as risk factors for RPL.

RESULTS: Heterozygous FV Leiden, homozygous PAI-1 4G/4G, heterozygous MTHFR C677T, homozygous MTHFR A1298C, as much as the combined thrombophilic genotypes MTHFR 677T + ACE I/D, MTHFR 677T/1298C + ACE D/D, ACE I/D + b-fibrinogen -455 G/A, FV HR2 + b-fibrinogen -455 G/A showed a correlation as risk factors for RPL, whereas the rest of the investigated polymorphisms and their combinations did not render statistically significant differences between the two groups in study.

CONCLUSION: The results of this study, as well as those of similar studies, concerning the detection of genetic, environmental, and physiological factors underlying RPL, will prove of critical significance in the investigation and treatment of thrombophilic predisposition, in cases of RPL.

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Thrombophilia and Recurrent Pregnancy Loss: The Enigma Continues

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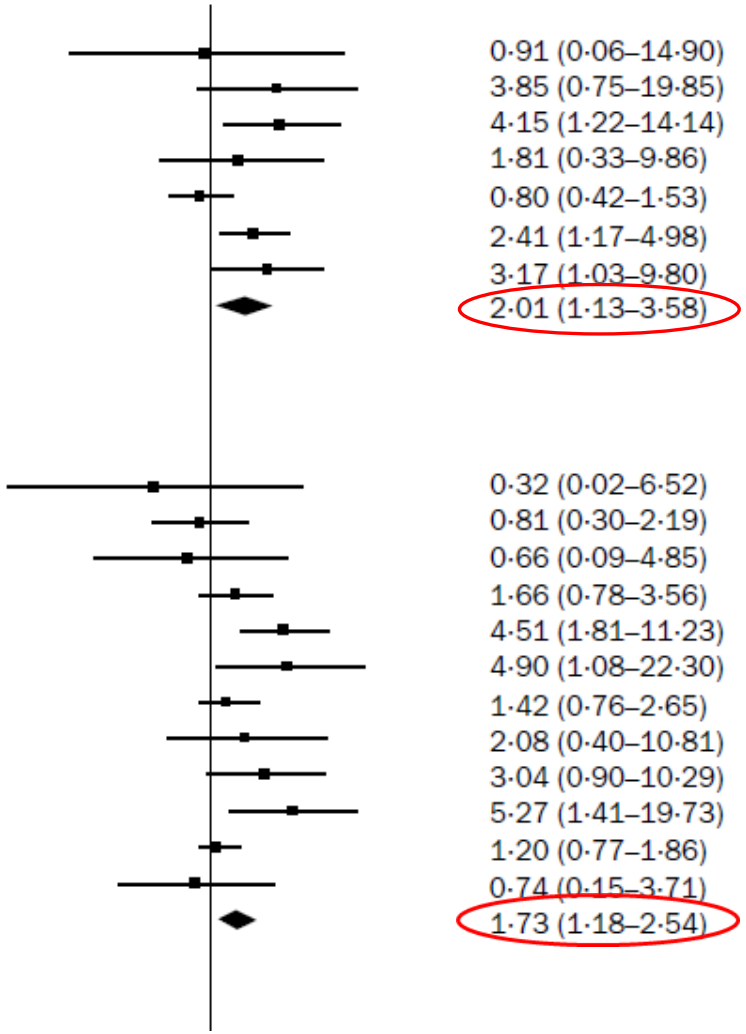
Table 5. Comparison of demographic data and analysis of the patients with mutation between women with two miscarriages and women with three or more miscarriages.

Parameter	Two (n=1695)	Three or more (n=226)	p-Value
Age	(19–37) [26.36±3.44]	(20–37) [27.40±3.95]	**0.000**
Weight	(58–70) [64.81±4.25]	(58–70) [65.14±4.17]	0.339
Height	(1.69–1.75) [170.76±1.85]	(1.50–1.75) [170.74±2.38]	0.911
Number of abortus	(2–2) [2.00±0.00]	(3–6) [3.28±0.596]	**0.000**
f2(Prothrombin) G20210A homozygous	43 (4.0%)	12 (6.5%)	0.127
f2(Prothrombin) G20210A heterozygous	87 (8.1%)	35 (18.9%)	**0.000**
MTHFR C677T homozygous	142 (13.2%)	23 (12.4%)	0.769
MTHFR C677T heterozygous	186 (17.3%)	29 (15.7%)	0.583
Factor V Leiden H1299R homozygous	12 (1.1%)	3 (1.6%)	0.473
Factor V Leiden H1299R heterozygous	152 (14.2%)	46 (24.9%)	**0.000**
MTHFR A1298C homozygous	203 (18.9%)	24 (13.0%)	0.503
MTHFR A1298C heterozygous	179 (16.7%)	37 (20.0%)	0.267
PAI-1 4G/5G	123 (11.5%)	45 (24.3%)	**0.000**
PAI-1 4G/4G	121 (11.3%)	44 (23.8%)	**0.000**

Thrombophilic disorders and fetal loss: a meta-analysis

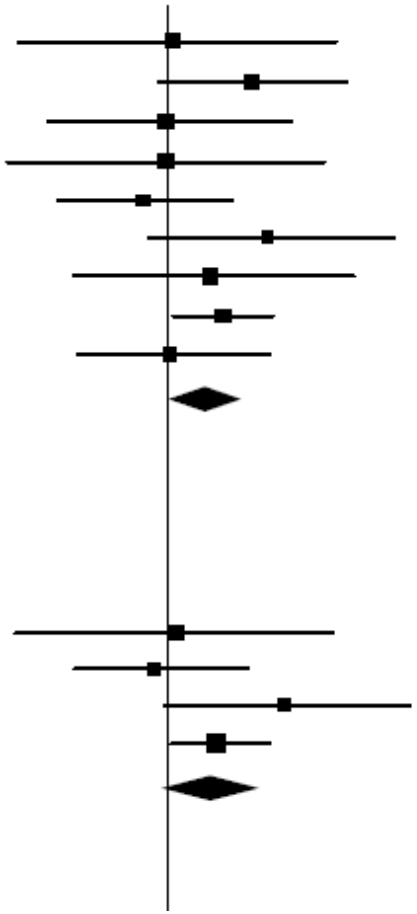
Study	FVL positive n/N	FVL negative n/N	Odds ratio (95% CI)	Odds ratio (95% CI)
FVL and recurrent fetal loss before 13 weeks				
Balasch[8]	1/2	54/103		0·91 (0·06–14·90)
Fatin[9]	6/8	53/121		3·85 (0·75–19·85)
Foka[10]	9/13	52/148		4·15 (1·22–14·14)
Grandone[11]	2/7	25/138		1·81 (0·33–9·86)
Rai[20]	59/71	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				
FVL and non-recurrent fetal loss				
Alfirevic[30]	0/3	18/59		0·32 (0·02–6·52)
Bare[26]	5/128	18/461		0·81 (0·30–2·19)
Clark[31]	1/59	42/1645		0·66 (0·09–4·85)
Dizon-Townson[32]	12/29	164/550		1·66 (0·78–3·56)
Gris[27]	15/22	217/674		4·51 (1·81–11·23)
Kupferminc[4]	3/10	9/112		4·90 (1·08–22·30)
Lindqvist[33]	12/269	70/2197		1·42 (0·76–2·65)
Many[34]	3/6	37/114		2·08 (0·40–10·81)
Martinelli[35]	5/11	62/288		3·04 (0·90–10·29)
Murphy[28]	3/16	24/572		5·27 (1·41–19·73)
Preston[36]	38/141	93/395		1·20 (0·77–1·86)
Tal[29]	2/9	45/162		0·74 (0·15–3·71)
Subtotal (95% CI)	99/703	803/7229		1·73 (1·18–2·54)
Test for heterogeneity p=0·086				
Test for overall effect p=0·005				



REY E, KAHN SR, DAVID M, ET AL. THROMBOPHILIC DISORDERS AND FETAL LOSS: A META-ANALYSIS. *LANCET*. 2003;361(9361):901–908.

Thrombophilic disorders and fetal loss: a meta-analysis

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				
PTm and recurrent fetal loss before 13 weeks				
Fatini[9]	1/2	58/127		1·19 (0·07–19·44)
Pickering[18]	4/7	87/150		0·97 (0·21–4·47)
Pihusch[19]	5/6	70/197		9·07 (1·04–79·20)
Reznikoff[22]	20/27	240/463		2·65 (1·10–6·40)
Subtotal (95% CI)	30/42	455/937		2·32 (1·12–4·79)
Test for heterogeneity p=0·38				
Test for overall effect p=0·02				



Thrombophilic disorders and fetal loss: a meta-analysis

Findings We included 31 studies. Factor V Leiden was associated with early (OR 2·01, 95% CI 1·13–3·58) and late (7·83, 2·83–21·67) recurrent fetal loss, and late non-recurrent fetal loss (3·26, 1·82–5·83). Exclusion of women with other pathologies that could explain fetal loss strengthened the association between Factor V Leiden and recurrent fetal loss. Activated protein C resistance was associated with early recurrent fetal loss (3·48, 1·58–7·69), and prothrombin G20210A mutation with early recurrent (2·56, 1·04–6·29) and late non-recurrent (2·30, 1·09–4·87) fetal loss. Protein S deficiency was associated with recurrent fetal loss (14·72, 0·99–218·01) and late non-recurrent fetal loss (7·39, 1·28–42·63). Methylenetetrahydrofolate mutation, protein C, and antithrombin deficiencies were not significantly associated with fetal loss.

The Relationship of the Factor V Leiden Mutation and Pregnancy Outcomes for Mother and Fetus

VOL. 106, NO. 3, SEPTEMBER 2005 Dizon-Townson et al

Donna Dizon-Townson, MD, Connie Miller, PhD, Baha Sibai, MD, Catherine Y. Spong, MD,

Methods: Women with a singleton pregnancy and no history of thromboembolism were recruited at 13 clinical centers before 14 weeks of gestation from April 2000 to August 2001. Each was tested for the FVL mutation, as was

Table 2. Adverse Pregnancy Outcome in Maternal Carriers of the Factor V Leiden Mutation Compared With Noncarriers

	FVL Carriers	FVL Noncarriers	Relative Risk (95% CI)	*P*
Pregnancy loss	8/134 (6.0)	264/4,751 (5.6)	1.1 (0.5–2.2)	.84
Preeclampsia	5/134 (3.7)	141/4,751 (3.0)	1.3 (0.4–2.8)	.60
Abruption	0	31/4,751 (0.7)	0	1.00
SGA < 5th percentile*	6/124 (4.8)	173/4,428 (3.9)	1.2 (0.5–2.6)	.64
SGA < 10th percentile*	10/124 (8.1)	403/4,428 (9.1)	0.9 (0.5–1.7)	.69

FVL, factor V Leiden mutation; CI, confidence interval; SGA, birth weight small for gestational age.
Data are presented as n/N (%) or relative risk (95% confidence interval).
* Based on live-born singletons.

Table 3. Association Between Conceptus Factor V Leiden Mutation Carrier Status and Adverse Pregnancy Outcomes

	FVL Carriers	FVL Noncarriers	Relative Risk (95% CI)	*P*
Preeclampsia	8/121 (6.6)	121/3,912 (3.1)	2.1 (1.0–4.1)	.06
Pregnancy loss	0/121 (0)	35/3,912 (0.9)	0	.63
Abruption	2/121 (1.7)	22/3,912 (0.6)	2.9 (0.3–10.7)	.16
SGA < 10th percentile*	10/20 (8.3)	352/3,857 (9.1)	0.9 (0.5–1.6)	.77

FVL, factor V Leiden mutation; CI, confidence interval; SGA, birth weight small for gestational age.
Data are presented as n/N (%) or relative risk (95% confidence interval).
* Based on live-born singletons.

Prothrombin Gene *G20210A* Mutation and Obstetric Complications

VOL. 115, NO. 1, JANUARY 2010

*Robert M. Silver, MD, Yuan Zhao, MS, Catherine Y. Spong, MD, Baha Sibai, MD, George Wendel Jr, MD, Katharine Wenstrom, MD, Philip Samuels, MD, Steve N. Caritis, MD, Yoram Sorokin, MD, Menachem Miodovnik, MD, Mary J. O'Sullivan, MD, Deborah Conway, MD, and Ronald J. Wapner, MD, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (NICHD MFMU) Network**

Table 2. Adverse Pregnancy Outcomes in Maternal Carriers of the Prothrombin Gene *G20210A* Mutation Compared With Noncarriers (Univariable Analysis)

	Carrier (n=157)	Noncarrier (n=4,010)	RR	95% CI	*P*
Pregnancy loss	9 (5.7)	238 (6.0)	0.96	0.50–1.84	.907
Preeclampsia	6 (3.8)	123 (3.1)	1.25	0.56–2.78	.487*
SGA 5%	8 (5.4)	151 (4.0)	1.35	0.68–2.70	.394
SGA 10%	17 (11.6)	338 (9.0)	1.28	0.81–2.03	.291
Abruption	2 (1.27)	24 (0.6)	2.13	0.51–8.93	.257*
Oligohydramnios	8 (5.1)	177 (4.4)	1.15	0.58–2.30	.684
Preterm delivery	23 (15.3)	458 (12.1)	1.27	0.86–1.86	.239
GA at delivery	39.0 (37.5–40.0)	39.0 (37.0–40.0)	—	—	.424†

RR, relative risk; CI, confidence interval; SGA, small for gestational age; GA, gestational age.
Data are n (%) or median (interquartile range) or unless otherwise specified.
* Fisher's exact test.
† Wilcoxon test.

Table 3. Adverse Pregnancy Outcomes in Maternal Carriers of the Prothrombin Gene *G20210A* Mutation Compared With Noncarriers

	Odds Ratio	95% CI	*P*
Pregnancy loss	0.98	0.49–1.95	.951
Preeclampsia	1.30	0.56–3.02	.536
SGA 5%	1.39	0.67–2.89	.377
SGA 10%	1.34	0.80–2.25	.267
Abruption	2.23	0.52–9.58	.280
Oligohydramnios	1.18	0.57–2.44	.659
Preterm delivery	1.39	0.87–2.21	.165
GA at delivery	—	—	.941

CI, confidence interval; SGA, small for gestational age; GA, gestational age.
Multivariable analysis adjusted for maternal age, race, parity, prior pregnancy loss, prior SGA neonates, and family history of thromboembolism.

The PAI-1 4G/5G and ACE I/D Polymorphisms and Risk of Recurrent Pregnancy Loss: A Case–Control Study

Jin Ju Kim[1,2], Young Min Choi[2,3], Sung Ki Lee[4], Kwang Moon Yang[5], Eun Chan Paik[6], Hyeon Jeong Jeong[7], Jong Kwan Jun[3], Ae Ra Han[8], Min A Hong[3]

Table II Plasminogen activator inhibitor type 1 (PAI-1) 4G/5G and angiotensin converting enzyme (ACE) I/D polymorphisms in recurrent pregnancy loss (RPL) patients and controls

	PAI-1 4G/5G					ACE I/D			
Genotype	*n*	4G/4G (%)	4G/5G (%)	5G/5G (%)	*P* value	I/I (%)	I/D (%)	D/D (%)	*P* value
Control	304	102 (33.6)	154 (50.7)	48 (15.8)		104 (34.2)	148 (48.7)	52 (17.1)	
Whole RPL patients	227	73 (32.2)	123 (54.2)	31 (13.7)	0.676	83 (36.6)	110 (48.5)	34 (15.0)	0.784
≥3[a]	143	47 (32.9)	74 (51.7)	22 (15.4)	0.977	51 (35.7)	71 (49.7)	21 (14.7)	0.819

Calculated with chi-square test, and *P* values are indicated for each RPL groups and the controls.
[a]Number of pregnancy losses.

study. Am J Reprod Immunol 2014; 72: 571–576

Genetic association studies of ACE and PAI-1 genes in women with recurrent pregnancy loss

A systematic review and meta-analysis

doi:10.1160/TH12-08-0584
Thromb Haemost 2013; 109: 8–15

Mei-Tsz Su[1]; Sheng-Hsiang Lin[2]; Yi-Chi Chen[3]; Pao-Lin Kuo[1]

[1]Department of Obstetrics and Gynecology, National Cheng Kung University Hospital, College of Medicine, Tainan, Taiwan; [2]Graduate Institute of Clinical Medicine, National Cheng Kung U

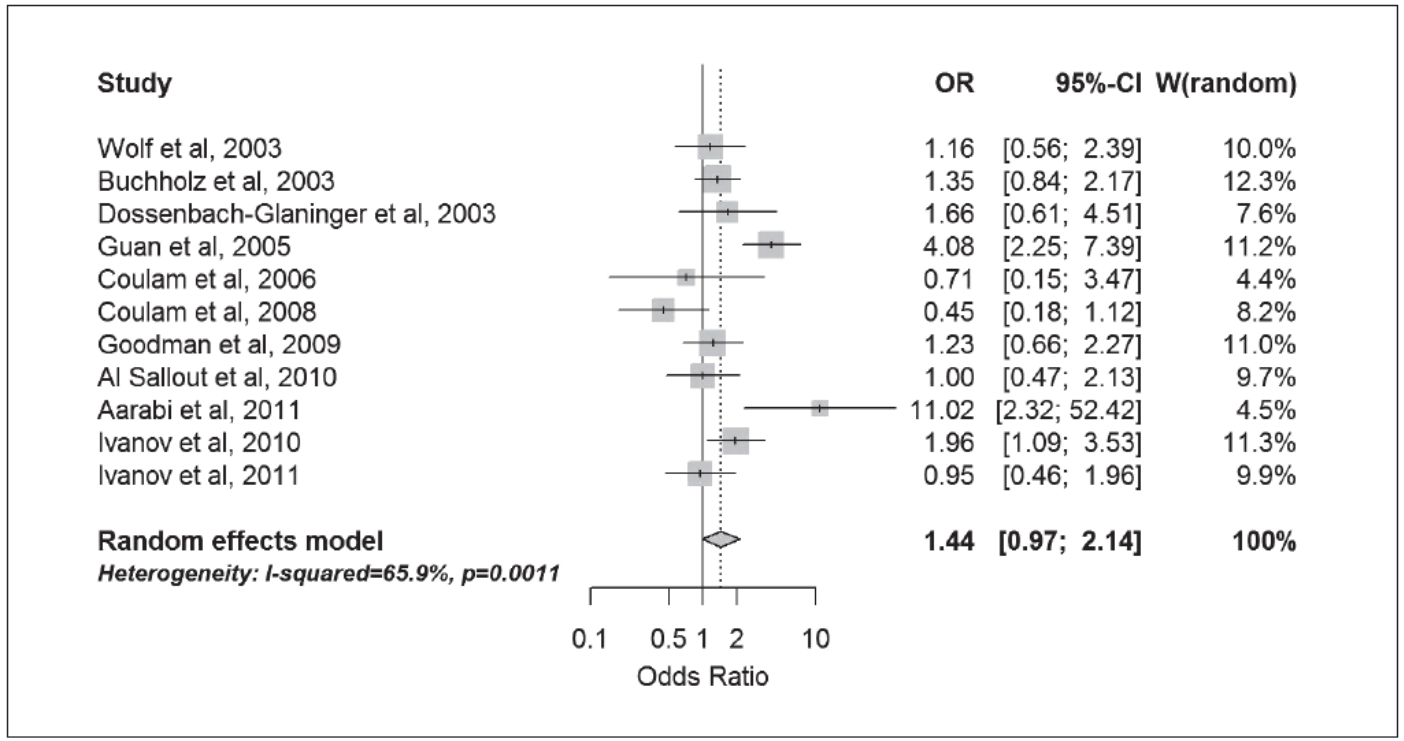


Figure 2: Association of PAI-1 polymorphism and RPL (more than two miscarriages) under a recessive genetic model. Results of individual and summary odds ratio (OR) estimates, 95% confidence interval (CI) and weights (W) of each study are shown. Horizontal lines represent 95%CI and dotted vertical lines represent the value of the summary OR.

Acta Inform Med. 2018 Oct;26(3):156-159. doi: 10.5455/aim.2018.26.156-159.

Association Between - 675 ID, 4G/5G PAI-1 Gene Polymorphism and Pregnancy Loss: A Systematic Review.

Adler G[1], Mahmutbegovic E[2], Valjevac A[3], Adler MA[4], Mahmutbegovic N[5], Safranow K[6], Czerska E[7], Pawinska-Matecka A[7], Ciechanowicz I[8], Marjanovic D[9,10].

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Abstract

INTRODUCTION: Several analysis for different population conclude that endothelial plasminogen activator inhibitor 1 gene polymorphism, -675 ID, 4G/5G *PAI-1* (ref SNP ID: rs1799889, also described as rs34857375, has merged into rs1799762) may increase risk of **pregnancy loss** (PL). However, there is a disagreement as to the association 4G allele with **pregnancy loss**.

AIM: Therefore, we decided to investigate the -675 ID, 4G/5G *PAI-1* as a potential genetic factor linked to PL in European and worldwide populations. A systematic review of the scientific literature was conducted with the use of the PubMed and Scopus electronic databases (1991-present), using the following search terms: **pregnancy loss**, miscarriage, genetic risk of thrombophilia, rs1799889 *PAI*-1 gen, 4G/5G *PAI-1* gene polymorphism, *PAI-1* gene locus 4G/5G polymorphism.

RESULTS: Among European populations, the statistically significant association between 4G allele and **recurrent** PL only in Czechs and Bulgarian women was found ($p<0.002$ and $p=0.018$, respectively); while, among populations outside Europe in Iranian, Tunisian and Turkish women (each $p<0.001$).

CONCLUSIONS: We concluded, that both in Europe and elsewhere in the world, the high frequency of 4G allele in population, is not unambiguously linked with the risk of **pregnancy loss**.

Search results

Items: 10

Showing results for ***rodger recurrent pregnancy loss***. Your search for *rodger recurrrent pregnancy loss* retrieved no results.

1. Anticoagulants to prevent **recurrent** placenta-mediated **pregnancy** complications: Is it time to put the needles away?
   Skeith L, **Rodger** M.
   Thromb Res. 2017 Mar;151 Suppl 1:S38-S42. doi: 10.1016/S0049-3848(17)30065-8. Review.
   PMID: 28262232

2. Low-molecular-weight heparin and **recurrent** placenta-mediated **pregnancy** complications: a meta-analysis of individual patient data from randomised controlled trials.
   Rodger MA, Gris JC, de Vries JIP, Martinelli I, Rey É, Schleussner E, Middeldorp S, Kaaja R, Langlois NJ, Ramsay T, Mallick R, Bates SM, Abheiden CNH, Perna A, Petroff D, de Jong P, van Hoorn ME, Bezemer PD, Mayhew AD; Low-Molecular-Weight Heparin for Placenta-Mediated **Pregnancy** Complications Study Group.
   Lancet. 2016 Nov 26;388(10060):2629-2641. doi: 10.1016/S0140-6736(16)31139-4. Epub 2016 Oct 6.
   PMID: 27720497

3. A meta-analysis of low-molecular-weight heparin to prevent **pregnancy loss** in women with inherited thrombophilia.
   Skeith L, Carrier M, Kaaja R, Martinelli I, Petroff D, Schleußner E, Laskin CA, **Rodger** MA.
   Blood. 2016 Mar 31;127(13):1650-5. doi: 10.1182/blood-2015-12-626739. Epub 2016 Feb 2. Review.
   PMID: 26837697 **Free Article**

4. **Recurrent pregnancy loss**: drop the heparin needles....
   Rodger MA.
   Blood. 2015 Apr 2;125(14):2179-80. doi: 10.1182/blood-2015-02-626457. No abstract available.
   PMID: 25838275 **Free Article**

5. LMWH to prevent placenta-mediated **pregnancy** complications: an update.
   Duffett L, **Rodger** M.
   Br J Haematol. 2015 Mar;168(5):619-38. doi: 10.1111/bjh.13209. Epub 2014 Nov 15. Review.
   PMID: 25399526

6. Low-molecular-weight heparin for prevention of placenta-mediated **pregnancy** complications: protocol for a systematic review and individual patient data meta-analysis (AFFIRM).
   Rodger MA, Langlois NJ, de Vries JI, Rey E, Gris JC, Martinelli I, Schleussner E, Ramsay T, Mallick R, Skidmore B, Middeldorp S, Bates S, Petroff D, Bezemer D, van Hoorn ME, Abheiden CN, Perna A, de Jong P, Kaaja R.
   Syst Rev. 2014 Jun 26;3:69. doi: 10.1186/2046-4053-3-69.
   PMID: 24969227 **Free PMC Article**

7. Meta-analysis of low-molecular-weight heparin to prevent **recurrent** placenta-mediated **pregnancy** complications.
   Rodger MA, Carrier M, Le Gal G, Martinelli I, Perna A, Rey E, de Vries JI, Gris JC; Low-Molecular-Weight Heparin for Placenta-Mediated **Pregnancy** Complications Study Group.
   Blood. 2014 Feb 6;123(6):822-8. doi: 10.1182/blood-2013-01-478958. Epub 2013 Dec 19. Review.

PMID: 24357725 **Free Article**

8. An update on thrombophilia and placenta mediated **pregnancy** complications: what should we tell our patients?
   Rodger MA.
   Thromb Res. 2013 Jan;131 Suppl 1:S25-7. doi: 10.1016/S0049-3848(13)70015-X. Review.
   PMID: 23452735

9. Tinzaparin use in **pregnancy**: an international, retrospective study of the safety and efficacy profile.
   Nelson-Piercy C, Powrie R, Borg JY, **Rodger** M, Talbot DJ, Stinson J, Greer IA.
   Eur J Obstet Gynecol Reprod Biol. 2011 Dec;159(2):293-9. doi: 10.1016/j.ejogrb.2011.08.005. Epub 2011 Sep 25.
   PMID: 21945573

10. The management of thrombophilia during **pregnancy**: a Canadian survey.
    Rodger MA, Carrier M, Keely E, Karovitch A, Nimrod C, Walker M, Wells PS.
    J Obstet Gynaecol Can. 2002 Dec;24(12):946-52.
    PMID: 12464993

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A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia

Leslie Skeith,[1,2] Marc Carrier,[1-3] Risto Kaaja,[4] Ida Martinelli,[5] David Petroff,[6] Ekkehard Schleußner,[7] Carl A. Laskin,[8-10] and Marc A. Rodger[1-3,11]

We performed a meta-analysis of randomized controlled trials comparing low-molecular-weight heparin (LMWH) vs no LMWH in women with inherited thrombophilia and prior late (≥10 weeks) or recurrent early (<10 weeks) pregnancy loss. Eight trials and 483 patients met our inclusion criteria. There was no significant difference in livebirth rates with the use of LMWH compared with no LMWH (relative risk, 0.81; 95% confidence interval, 0.55-1.19; $P = .28$), suggesting no benefit of LMWH in preventing recurrent pregnancy loss in women with inherited thrombophilia. (*Blood*. 2016;127(13):1650-1655)

A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia

Leslie Skeith,[1,2] Marc Carrier,[1-3] Risto Kaaja,[4] Ida Martinelli,[5] David Petroff,[6] Ekkehard Schleußner,[7] Carl A. Laskin,[8-10] and Marc A. Rodger[1-3,11]

BLOOD, 31 MARCH 2016 • VOLUME 127, NUMBER 13

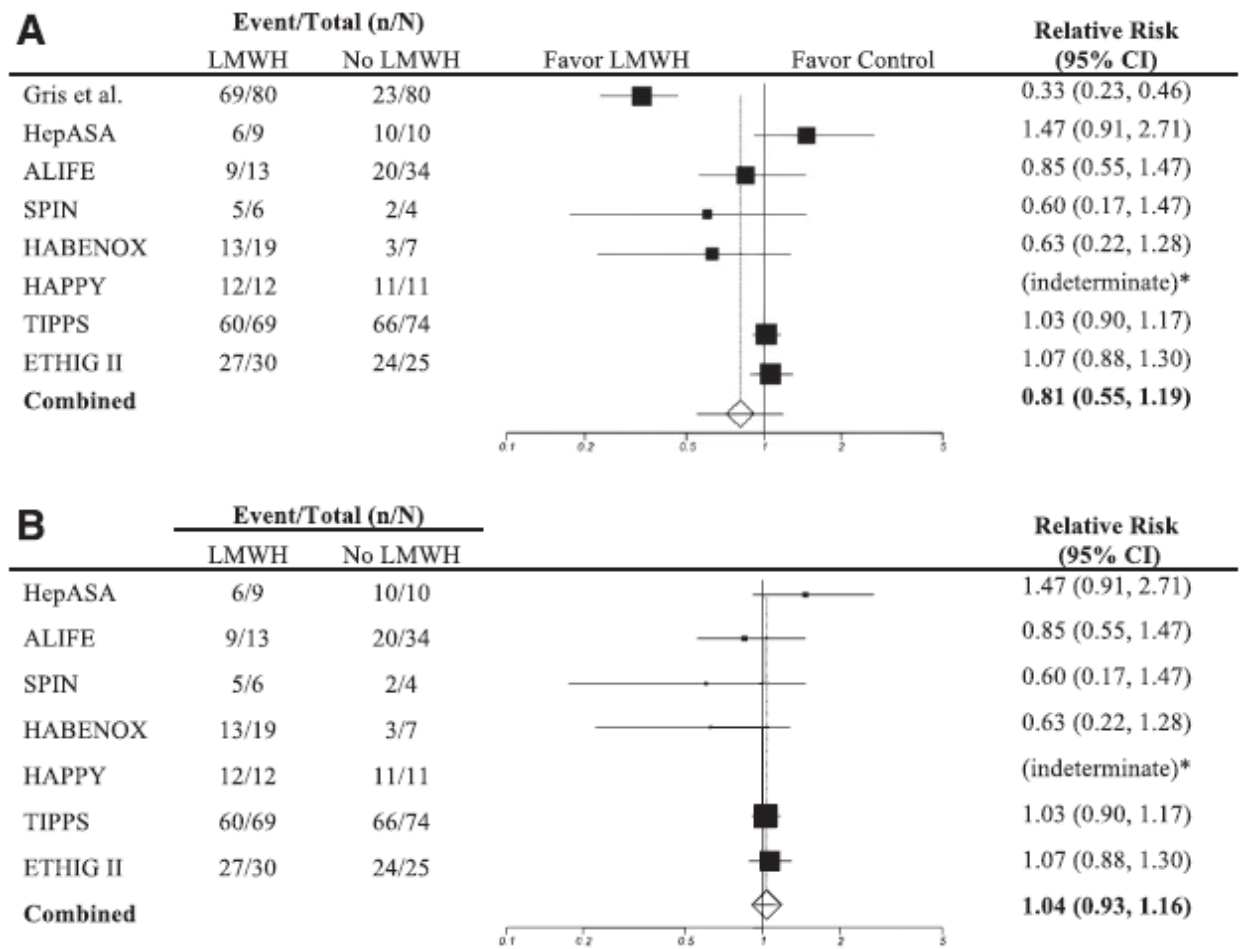


Figure 2. Forest plot of the relative risk of pregnancy loss comparing LMWH vs no LMWH. (A) All trials are included. (B) Multicenter trials only are included. "Favor LMWH" suggests a benefit of LMWH in preventing pregnancy loss; "Favor Control" suggests a benefit of no LMWH in preventing pregnancy loss; * denotes an indeterminate RR because there were no pregnancy losses among the 23 women from the HAPPY trial.[24]

A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia

Leslie Skeith,[1,2] Marc Carrier,[1-3] Risto Kaaja,[4] Ida Martinelli,[5] David Petroff,[6] Ekkehard Schleußner,[7] Carl A. Laskin,[8-10] and Marc A. Rodger[1-3,11]

Table 3. Results of a meta-analysis of eligible trials comparing LMWH vs no LMWH in preventing future pregnancy loss in women with inherited thrombophilia

	Proportion with outcome in the treatment group		Proportion with outcome in the control group					
	%	n/N	%	n/N	RR	95% CI	*P*	I^2, %
Primary outcome								
Livebirth rate	84.5	201/238	64.9	159/245*	0.81	0.55-1.19	.28	91.9
Livebirth rate (multicenter trials)	83.5	132/158	82.4	136/165*	1.04	0.93-1.16	.52	12.9
Prior late loss†								
Livebirth rate	84.2	128/152	59.0	92/156	0.81	0.38-1.72	.58	95.3
Livebirth rate (multicenter trials)	81.9	59/72	90.8	69/76	1.12	0.97-1.30	.13	0.0
Prior recurrent early loss‡								
Livebirth rate§	86.5	32/37	86.2	25/29	0.97	0.80-1.19	.79	N/A

N/A, not applicable; n/N, number (n) with outcome/number (N) in treatment group.
*One participant in the control group (aspirin alone) had a twin pregnancy with 1 livebirth and 1 stillbirth.
†Late loss is defined as 1 loss ≥10 wk.
‡Recurrent early loss is defined as 2 losses <10 wk.
§All trials included were multicenter trials.

A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia

Leslie Skeith,[1,2] Marc Carrier,[1-3] Risto Kaaja,[4] Ida Martinelli,[5] David Petroff,[6] Ekkehard Schleußner,[7] Carl A. Laskin,[8-10] and Marc A. Rodger[1-3,11]

Case presentation

Case 1. A 34-year-old woman with 3 consecutive unexplained miscarriages wants to get pregnant again. Would she benefit from thrombophilia testing?

Case 2. A 25-year-old woman with 1 unexplained pregnancy loss at 16 weeks' gestation is found to be heterozygote for the factor V Leiden mutation. She has no personal history of thrombosis. She asks whether taking low-molecular-weight heparin (LMWH) could prevent a second pregnancy loss.

Cases revisited

Case 1

We would advise against testing for inherited thrombophilia.

Case 2

We would not recommend the use of LMWH to prevent future pregnancy loss.

Cochrane Library

Cochrane Database of Systematic Reviews

Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia (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.

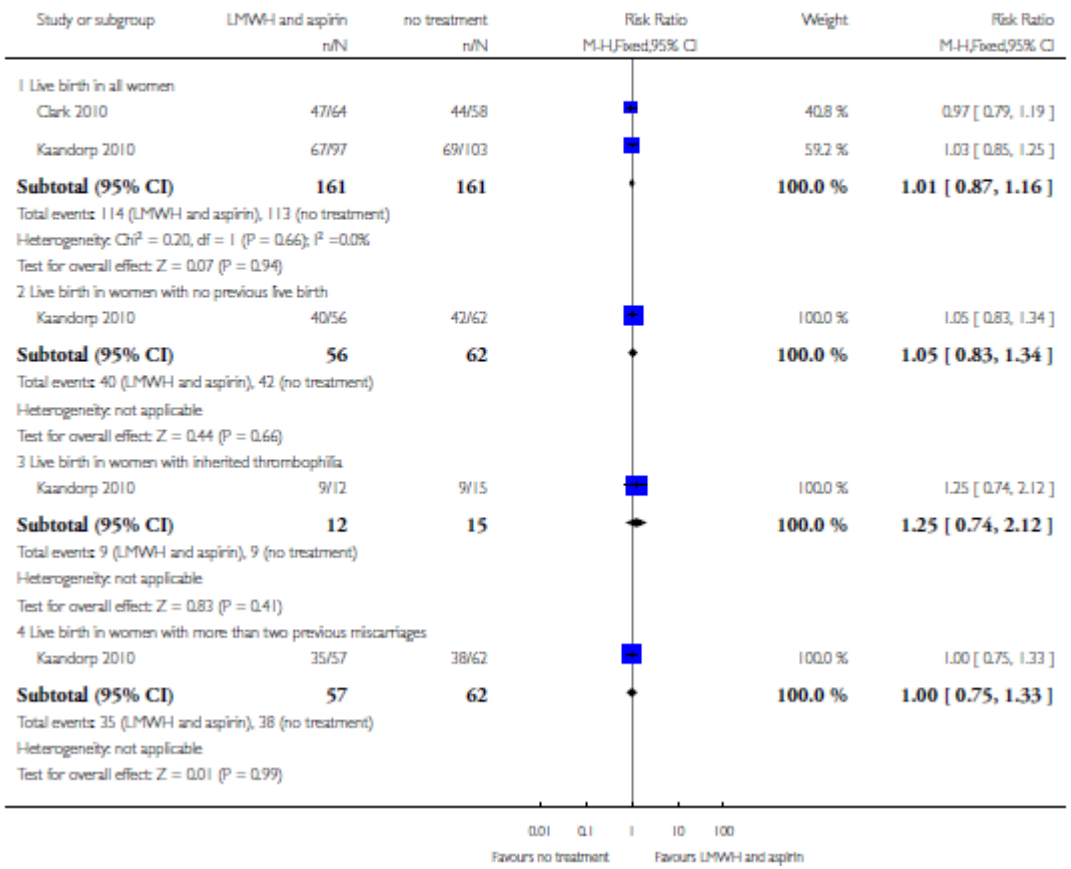
Analysis 6.1. Comparison 6 LMWH and aspirin versus no treatment, Outcome 1 Live birth.

Review: Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia

Comparison: 6 LMWH and aspirin versus no treatment

Outcome: 1 Live birth

Study or subgroup	LMWH and aspirin n/N	no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Live birth in all women					
Clark 2010	47/64	44/58		40.8 %	0.97 [0.79, 1.19]
Kaandorp 2010	67/97	69/103		59.2 %	1.03 [0.85, 1.25]
Subtotal (95% CI)	**161**	**161**		**100.0 %**	**1.01 [0.87, 1.16]**
Total events: 114 (LMWH and aspirin), 113 (no treatment)					
Heterogeneity: Chi^2 = 0.20, df = 1 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 0.07 (P = 0.94)					
2 Live birth in women with no previous live birth					
Kaandorp 2010	40/56	42/62		100.0 %	1.05 [0.83, 1.34]
Subtotal (95% CI)	**56**	**62**		**100.0 %**	**1.05 [0.83, 1.34]**
Total events: 40 (LMWH and aspirin), 42 (no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					
3 Live birth in women with inherited thrombophilia					
Kaandorp 2010	9/12	9/15		100.0 %	1.25 [0.74, 2.12]
Subtotal (95% CI)	**12**	**15**		**100.0 %**	**1.25 [0.74, 2.12]**
Total events: 9 (LMWH and aspirin), 9 (no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.83 (P = 0.41)					
4 Live birth in women with more than two previous miscarriages					
Kaandorp 2010	35/57	38/62		100.0 %	1.00 [0.75, 1.33]
Subtotal (95% CI)	**57**	**62**		**100.0 %**	**1.00 [0.75, 1.33]**
Total events: 35 (LMWH and aspirin), 38 (no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					



MAIN RESULTS: Nine studies, including data of 1228 **women**, were included in the review evaluating the effect of either LMWH (enoxaparin or nadroparin in varying doses) or **aspirin** or a combination of both, on the chance of live birth in **women** with **recurrent miscarriage**, with or without **inherited thrombophilia**. Studies were heterogeneous with regard to study design and treatment regimen and three studies were considered to be at high risk of bias. Two of these three studies at high risk of bias showed a benefit of one treatment over the other, but in sensitivity analyses (in which studies at high risk of bias were excluded) anticoagulants did not have a beneficial effect on live birth, regardless of which anticoagulant was evaluated (risk ratio (RR) for live birth in **women** who received **aspirin** compared to placebo 0.94, (95% confidence interval (CI) 0.80 to 1.11, n = 256), in **women** who received LMWH compared to **aspirin** RR 1.08 (95% CI 0.93 to 1.26, n = 239), and in **women** who received LMWH and **aspirin** compared to no-treatment RR 1.01 (95% CI 0.87 to 1.16) n = 322).Obstetric complications such as preterm delivery, pre-eclampsia, intrauterine growth restriction and congenital malformations were not significantly affected by any treatment regimen. In included studies, **aspirin** did not increase the risk of bleeding, but treatment with LWMH and **aspirin** increased the risk of bleeding significantly in one study. Local skin reactions (pain, itching, swelling) to injection of LMWH were reported in almost 40% of patients in the same study.

Outcomes of threatened abortions after anticoagulation treatment to prevent recurrent pregnancy loss

Amihai Rottenstreich [a], *Hagai Amsalem* [b], *Geffen Kleinstern* [c,d], *Yosef Kalish* [a,*]

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[c] *H*
[d]

Table 2 – Patient outcomes in relation to the management of low-molecular weight heparin after threatened abortion.[a]

	All patients (n = 114)	Discontinued LMWH (n = 47)	Continued LMWH (n = 67)	P-value
No other bleeding episodes after discharge, n (%)	63 (55.3)	34 (72.3)	29 (43.3)	0.002
Miscarriage, n (%)	47 (41.2)	6 (12.8)	41 (61.3)	<0.0001
Gestational age at miscarriage, weeks	12 [9–16] (12.7)	12 [9–17] (13.1)	11 [9–18] (12.6)	NS
Time elapsed from threatened abortion, weeks	3 [1–4] (2.8)	3 [1–3] (3.4)	3 [1–4] (2.6)	NS
Miscarriage ≥10 weeks of gestation n (%)[b]	32 (68.1)	4 (66.7%)	28 (68.2)	NS
Live birth, n (%)	67 (58.8)	41 (87.2)	26 (38.8)	<0.0001
Gestational age at delivery, weeks	37 [37–38] (37)	38 [37–38] (37.3)	37 [37–38] (36.6)	NS
Birth weight, g	2960 [2500–3200] (2795)	2980 [2502–3240] (2829)	2894 [2424–3174] (2741)	NS
Mode of delivery, n (%)[c]				NS
Vaginal delivery	22 (32.8)	15 (36.6)	7 (26.9)	
Caesarean section	45 (67.2)	26 (63.4)	19 (73.1)	
Pregnancy complications, n (%)[c]				
Preeclampsia	3 (4.5)	2 (4.9)	1 (3.8)	NS
PPROM	4 (6.0)	2 (4.9)	2 (7.7)	NS
Placental abruption	0	0	0	
Intrauterine fetal death	0	0	0	
Small for gestation age (10th percentile)	9 (13.4%)	6 (14.6)	3 (11.5)	NS
Premature delivery[c]	11 (16.4%)	5 (12.2)	6 (23.1)	NS
≥24 to <28 weeks, n	2	1	1	
≥28 to <32 weeks, n	0	0	0	
≥32 to <37 weeks, n	9	4	5	

[a] All continuous variables are expressed as medians [interquartile range] (mean).
[b] Denominator is the number of women who experienced miscarriage.
[c] Denominators are the number of women with live birth.
LMWH, low-molecular weight heparin; NS, not statistically significant; PPROM, preterm premature rupture of membranes.

Outcomes of threatened abortions after anticoagulation treatment to prevent recurrent pregnancy loss

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ABSTRACT

We aimed to determine the outcome of threatened abortion in women treated with low-molecular weight heparin (LMWH) for recurrent pregnancy loss (RPL). Data of women with RPL who experienced threatened abortion while taking LMWH between 2007 and 2016 were retrospectively reviewed. All patients received the LMWH, enoxaparin (40 mg). Thrombophilia was present in 38 (33.3%) women, including 11 (9.6%) with antiphospholipid syndrome (APLS). The overall live birth rate was 58.8% (67/114). Live birth rates were 87.2% (41/47 patients) and 38.8% (26/67 patients) among those who discontinued versus those who continued LMWH treatment, respectively ($P < 0.0001$). Among APLS patients, live births resulted in eight of the nine women who continued LMWH. In multivariate analysis, discontinuation of LMWH was the only significant predictor of live birth outcome ($P < 0.0001$). Thrombophilia, presence of subchorionic haematoma, and severity of bleeding were not found to be associated with live birth outcomes. For women with threatened abortions, continuation of LMWH indicated to prevent RPL was negatively associated with live birth rates. Therefore, we support its discontinuation in this setting. Among women with APLS, LMWH continuation resulted in a relatively high live birth rate; we advocate against its withdrawal in this subset of patients.

Res Pract Thromb Haemost. 2018 Feb 9;2(2):357-365. doi: 10.1002/rth2.12081. eCollection 2018 A PMC Full text

Antigenic binding sites of anti-protein S autoantibodies in patients with recurrent pregnancy loss.

Sato Y[1], Sugi T[1], Sakai R[1].

Author information

Abstract

BACKGROUND: Protein S (PS) deficiency is a risk factor for adverse **pregnancy** outcomes including **recurrent pregnancy loss**. Several studies have shown that the presence of anti-PS autoantibodies (anti-PS) leads to an acquired PS deficiency. Hence, an epitope mapping study was conducted to know the pathogenesis of anti-PS in patients with **recurrent pregnancy loss**.

METHODS: PS was treated with thrombin to divide the protein into γ-carboxyglutamic acid (Gla) domain and Gla-domain free PS. For the preparation of fragments of epidermal growth factor (EGF)-like domains (EGF1-4), PS was subjected to proteolysis using lysyl endopeptidase. The epitopes were identified in immunoblot. Whether anti-PS recognized EGF family proteins in anti-PS-positive patients was also examined.

RESULTS: Anti-PS recognized Gla-domain free PS, especially the three fragments of EGF-like domains, EGF1-2, EGF3-4, and EGF1-4. Anti-PS recognized recombinant human EGF. Anti-PS and polyclonal antibodies to recombinant human EGF recognized PS in the absence of Ca^{2+} but not in the presence of Ca^{2+}. In competitive inhibition studies, polyclonal antibodies to recombinant mouse EGF blocked anti-PS binding to PS in a concentration-dependent manner.

CONCLUSIONS: These results suggest that anti-PS in patients with **recurrent pregnancy loss** recognize EGF-like domains in PS. Interestingly, anti-PS also recognized EGF family proteins. Anti-PS in patients with **recurrent pregnancy loss** may be associated with not only thrombophilia but also the disruption of the EGF system.

Inherited Thrombophilias and Adverse Pregnancy Outcomes

A Review of Screening Patterns and Recommendations

Obstet Gynecol Clin N Am 41 (2014) 133–144

Table 2
Candidates for thrombophilia evaluation

	ALL MDs[a] (%)	OB/GYN (%)	REI (%)	*P*
≥3 RPL	173/185 (94)	72/77 (94)	101/108 (94)	.57
≥2 RPL	141/185 (76)	55/77 (71)	86/108 (80)	.13
ART failed attempt	29/104 (28)	N/A	29/104 (28)	—
ART new attempt	2/102 (2)	N/A	2/102 (2)	—
Personal history thrombosis	181/186 (97)	75/78 (96)	106/108 (98)	.44
Family history thrombosis	150/183 (82)	61/77 (79)	89/106 (84)	.59
Stillbirth or IUFD >20 wk	164/183 (90)	66/78 (85)	98/105 (93)	.35
Spontaneous pregnancy loss[b]	81/176 (46)	31/76 (41)	50/100 (50)	.72
Prior IUGR	76/181 (42)	33/77 (43)	43/104 (41)	.64
Abruption, demise	112/181 (62)	50/75 (67)	62/106 (58)	.69
Abruption, live birth	65/177 (37)	27/73 (37)	38/104 (37)	.59
Personal history thrombophilia	161/183 (88)	63/77 (82)	98/106 (92)	.06
Prior baby with NTD	32/182 (18)	7/76 (9)	25/106 (24)	.01[c]
Sister with baby with NTD	23/181 (13)	5/76 (7)	18/105 (17)	.03[c]

Abbreviations: ART, assisted reproductive technology; GYN, gynecologist; IUFD, intrauterine fetal demise; N/A, not applicable.

[a] Not all participants answered all survey questions, so the numbers are not equal to the total number of respondents.

[b] Spontaneous pregnancy loss defined as less than 20 weeks.

[c] Significantly different results between OB/GYNs and REIs.

Table 3
Thrombophilia testing routinely being ordered by physicians

	ALL MDs[a] (%)	OB/GYN (%)	REI (%)	*P*
Anticardiolipin antibody	181/185 (98)	75/78 (96)	106/107 (99)	.72
Lupus anticoagulant antibody	180/186 (97)	74/78 (95)	106/108 (98)	.25
Antiphospholipid panel	147/183 (80)	67/78 (86)	80/105 (76)	.02[b]
Factor V Leiden G1691A	166/185 (90)	71/78 (91)	95/107 (89)	.41
Activated protein C resistance	98/182 (54)	33/77 (43)	65/105 (62)	.04[b]
Prothrombin G20210A	140/184 (76)	53/77 (69)	87/107 (81)	.07
MTHFR	75/178 (42)	20/73 (27)	56/105 (53)	<.01[b]

[a] Not all participants answered all survey questions, so the numbers are not equal to the total number of respondents.

[b] Significantly different results between OB/GYNs and REIs.

Table 4
Treatment patterns for thrombophilias (all physicians)[a]

	n[b]	Heparin[c] and/or Aspirin		Aspirin Only		Vitamin B and/or Folic Acid	
Anticardiolipin antibody	135	109	81%	19	14%	8	6%
Lupus anticoagulant antibody	128	107	84%	16	13%	7	5%
Antiphospholipid panel	107	86	81%	14	13%	8	7%
Factor V Leiden	121	108	89%	3	2%	8	7%
Activated protein C resistance	52	41	79%	5	10%	7	13%
Prothrombin mutation	78	70	90%	5	6%	4	5%
MTHFR C677T	61	12	20%	1	2%	59	97%
PCD	71	59	83%	8	11%	6	8%
PSD	67	54	81%	7	10%	7	10%
Antithrombin deficiency	47	41	87%	1	2%	4	9%
Anti-B2 glycoprotein	18	13	72%	2	11%	3	18%
Hyperhomocysteinemia	51	5	10%	1	2%	37	73%

[a] The numerator is equal to the number of physicians who treated the patient with the indicated treatment modality, and the denominator is equal to the number of physicians who both treated the indicated thrombophilia and answered the question concerning treatment modality. Not all participants answered all survey questions, so the numbers are not equal to the total number of respondents.

[b] Not all participants answered all survey questions, so the numbers are not equal to total number of respondents.

[c] Heparin includes both low-molecular-weight heparin and unfractionated heparin in either prophylactic or therapeutic doses.

ANTI FOSFOLIPID ANTIKOR SENDROMU

- İlk zamanlarda kardiolipin gibi anyonik fosfolipidlerle reaksiyon gösteren antikorlar olduğu düşünülse de; sonraki veriler AFA'larının çoğunun hücre membranı gibi uygun bir yüzeyin üzerinde eksprese olan veya bu yüzeylere bağlanan fosfolipid-bağlayıcı proteinlere karşı oluşan antikorlar oldularını ortaya koymuştur.

- Birçok AFA olsa da esas obstetrik komplikasyonlardan sorumlu olanlar tanıda kullanılanlardır.

Table 1 Diagnostic criteria for APS according to "the International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome"

International consensus classification criteria for the APS	
At least 1 clinical and 1 laboratory criteria must be present for definite APS	
Clinical criteria	
I – Vascular thrombosis	One or more clinical episodes of an arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathologic confirmation, thrombosis should be without significant evidence of inflammation in the vessel wall.
II – Obstetric morbidity	1) One or more unexplained demise of a morphologically normal fetus at or beyond 10 weeks of gestation, with normal fetal morphology documented by ultrasound or by direct examination, or 2) One or more premature births of a morphologically normal neonate before the 34th week of gestation, because of a) eclampsia or severe preeclampsia or b) placental insufficiency, or 3) Three or more unexplained consecutive miscarriages of <10 weeks of gestation. Known factors associated with recurrent miscarriage, including parental genetic, anatomic, and endocrinologic factors should be ruled out.
Laboratory criteria	I – aCL (IgG and/or IgM) in the blood, present in medium or high titers (> 40 GPL or MPL or >99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA. II – Anti-β2GP1 antibody of IgG and/or IgM isotype in the blood (>99th percentile) on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA. III – Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis.

Notes: Anti-β2GP1: anti-β2 glycoprotein-I. Reproduced from Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4(2):295–306, with permission from John Wiley and Sons, copyright 2006.[24]
Abbreviations: APS, antiphospholipid syndrome; aCL, anticardiolipin antibody; ELISA, enzyme-linked immunosorbent assay.

Revised classification criteria for the antiphospholipid syndrome

Antiphospholipid syndrome is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met*
Clinical criteria
1. Vascular thrombosis¶ One or more clinical episodesΔ of arterial, venous, or small vessel thrombosis◇, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (ie, unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity a. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus; or b. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency§; or c. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded. In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.
Laboratory criteria¥
1. LA present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies).
2. aCL of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (ie, >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA.
3. Anti-beta-2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

LA: lupus anticoagulant; aCL: anticardiolipin antibody; Ig: immunoglobulin; ELISA: enzyme-linked immunosorbent assay; APS: antiphospholipid syndrome; aPL: antiphospholipid antibodies; LDL: low-density lipoprotein; HDL: high-density lipoprotein; GFR: glomerular filtration rate.

* Classification of APS should be avoided if less than 12 weeks or more than five years separate the positive aPL test and the clinical manifestation.

¶ Coexisting inherited or acquired factors for thrombosis are not reasons for excluding patients from APS trials. However, two subgroups of APS patients should be recognized, according to: (a) the presence; and (b) the absence of additional risk factors for thrombosis. Indicative (but not exhaustive) cases include: age (>55 in men and >65 in women) and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes mellitus, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index ≥30 kg m^{-2}, microalbuminuria, estimated GFR <60 mL $minute^{-1}$), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, and surgery. Thus, patients who fulfill criteria should be stratified according to contributing causes of thrombosis.

Δ A thrombotic episode in the past could be considered as a clinical criterion, provided that thrombosis is proved by appropriate diagnostic means and that no alternative diagnosis or cause of thrombosis is found.

◇ Superficial venous thrombosis is not included in the clinical criteria.

§ Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance test(s), eg, a non-reactive non-stress test, suggestive of fetal hypoxemia; (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, eg, absent end-diastolic flow in the umbilical artery; (iii) oligohydramnios, eg, an amniotic fluid index of 5 cm or less; or (iv) a postnatal birth weight less than the 10th percentile for the gestational age.

¥ Investigators are strongly advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL antibody present alone; IIc, anti-beta-2 glycoprotein-I antibody present alone.

From: Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4:295. http://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2006.01753.x/abstract. Copyright © 2006 International Society on Thrombosis and Haemostasis. Reproduced with permission of John Wiley & Sons, Inc. This image has been provided by or is owned by Wiley. Further permission is needed before it can be downloaded to PowerPoint, printed, shared, or emailed. Please contact Wiley's Permissions Department either via email: permissions@wiley.com or use the RightsLink service by clicking on the Request Permission link accompanying this article on Wiley Online Library (www.onlinelibrary.wiley.com).

AFAS - PATOGENEZ

- Doalşımda beta2 glikoprotein I'nın sirküler formunun daha hakim olması
- Prot C'nin doğal anti-koagulan özelliğinin inhibe olması
- Anti-trombin'in aktivasyon ve heparin bağlama özelliğinin inhibe olması
- vWF – bağımlı trombosit agregasyonunda bozulma
- Kompleman aktivasyonu
- Faktör 11'in serbest aktif thiol formunda artış
- Endotelyal hücreler, monositler, nötrofiller, ve plateletlerin dahil olduğu vasküler hücrelerde aktivasyon
- Bozulmuş trofoblastik invazyon, azalmış sinsityotrofoblast invazyonu

DIAGNOSIS AND MANAGEMENT OF THE ANTIPHOSPHOLIPID SYNDROME
CHATURVEDI S, MCCRAE K. BLOOD REV. 2017; 31(6): 406–417

AFAS – OBSTETRIK KOMPLIKASYONLAR

- Plasental inflamasyon
- Plasental tromboz
- Plasental enfarkt
- Anormal plasentasyon

MERONI PL, TEDESCO F, LOCATI M, ET AL. ANTI-PHOSPHOLIPID ANTIBODY MEDIATED FETAL LOSS: STILL AN OPEN QUESTION FROM A PATHOGENIC POINT OF VIEW. ///P//S 2010;19(4):453–456.

ANTI FOSFOLIPID ANTIKOR SENDROMU

- Tekrarlayan gebelik kaybı olan hastalardaki AFAS varlığı → % 5 – 20

- AFAS vs. kontrol, gebelik kaybı → % 50 - 90 vs. % 10 - 15

ANDREOLı ET AL. ESTIMATED FREQUENCY OF ANTIPHOSPHOLIPID ANTIBODIES IN PATIENTS WITH PREGNANCY MORBIDITY, STROKE, MYOCARDIAL INFARCTION, AND DEEP VEIN THROMBOSIS: A CRITICAL REVIEW OF THE LITERATÜRE. ARTHRITIS CARE RES (HOBOKEN). 2013 NOV;65(11):1869-73
OSHIRO BT, SILVER RM, SCOTT JR, ET AL. ANTIPHOSPHOLIPID. ANTIBODIES AND FETAL DEATH. OBSTET GYNECOL. 1996;87(4):489–493..

AFAS'TA HEPARIN + ASPIRIN

- Yeni gelişecek gebelik kaybında → % 50 azalma (Meta – analiz)
- Tedavi alan vs. almayanlarda canlı doğum → % 88 vs. % 44

- Heparin + Aspirin vs. Aspirin canlı doğum oranı → % 71 vs. % 42

EMPSON M, LASSERE M, CRAIG JC, ET AL. RECURRENT PREGNANCY LOSS WITH ANTIPHOSPHOLIPID ANTIBODY: A SYSTEMATIC REVIEW OF THERAPEUTIC TRIALS. *OBSTET GYNECOL*. 2002;99(1):135–144

KUTTEH WH. ANTIPHOSPHOLIPID ANTIBODY-ASSOCIATED RECURRENT PREGNANCY LOSS: TREATMENT WITH HEPARIN AND LOW-DOSE ASPIRIN IS SUPERIOR TO LOW-DOSE ASPIRIN ALONE. *AM J OBSTET GYNECOL*. 1996;174(5):1584–1589.

RAI R, COHEN H, DAVE M, ET AL. RANDOMISED CONTROLLED TRIAL OF ASPIRIN AND ASPIRIN PLUS HEPARIN IN PREGNANT WOMEN WITH RECURRENT MISCARRIAGE ASSOCIATED WITH PHOSPHOLIPID ANTIBODIES (OR ANTIPHOSPHOLIPI

Approach to treatment of pregnant and postpartum women with APS or aPL

	Antepartum	Postpartum
APS with prior arterial or venous thrombosis, with or without APS-defining pregnancy morbidity	Therapeutic-dose LMWH and low-dose ASA	Warfarin for an indefinite period of time.
APS based on laboratory criteria for aPL and APS-defining pregnancy morbidity of ≥1 fetal losses ≥10 weeks of gestation or ≥3 unexplained consecutive spontaneous pregnancy losses <10 weeks of gestation and NO history of arterial or venous thrombosis	Prophylactic-dose LMWH and low-dose ASA	Prophylactic-dose LMWH and low-dose ASA for six weeks regardless of route of delivery.
APS based on laboratory criteria for aPL and APS-defining pregnancy morbidity of ≥1 preterm deliveries of a morphologically normal infant before 34 weeks of gestation due to severe preeclampsia, eclampsia, or other findings consistent with placental insufficiency and NO history of arterial or venous thrombosis	Most cases: Low-dose ASA	Vaginal delivery: Intermittent pneumatic compression and low-dose ASA while in the hospital. Graduated compression stockings and low-dose ASA for six weeks. Cesarean delivery: Prophylactic-dose LMWH and low-dose ASA for six weeks.
	In cases of ASA failure or when placental examination shows extensive decidual inflammation and vasculopathy and/or thrombosis, prophylactic-dose LMWH with low-dose ASA	Prophylactic-dose LMWH and low-dose ASA for six weeks regardless of route of delivery.
Laboratory criteria for APS but NO clinical criteria for APS (ie, NO history of venous or arterial thrombosis and NO history of APS-defining obstetric morbidity)	Low-dose ASA	Vaginal delivery: Intermittent pneumatic compression and low-dose ASA while in the hospital. Graduated compression stockings and low-dose ASA for six weeks. Cesarean delivery: Prophylactic-dose LMWH and low-dose ASA for six weeks.

Examples of therapeutic LMWH (also referred to as weight-adjusted, full-treatment dose): enoxaparin 1 mg/kg every 12 hours, dalteparin 200 units/kg once daily, tinzaparin 175 units/kg once daily, dalteparin 100 units/kg every 12 hours.
Examples of prophylactic LMWH: enoxaparin 40 mg SC once daily, dalteparin 5000 units SC once daily, tinzaparin 4500 units SC once daily. These doses may need to be modified at extremes of body weight.
Anticoagulation can generally be resumed four to six hours after vaginal delivery or 6 to 12 hours after cesarean delivery, unless there is significant bleeding or risk for significant bleeding. Previous neuraxial anesthesia is also a consideration (eg, anticoagulation may be resumed 4 or more hours after catheter removal unless traumatic placement).
NOTE: Tinzaparin is not available in the United States. The role and frequency of anti-Xa testing for management of therapeutic dosing of LMWH in pregnancy are reviewed in the UpToDate topic on anticoagulation in pregnancy.

APS: antiphospholipid syndrome; LMWH: low molecular weight heparin; ASA: aspirin; aPL: antiphospholipid antibodies; SC: subcutaneous.

UpToDate®

Table 2 Brief overview of current evaluation of treatment options for recurrent pregnancy loss (RPL)†

Treatment option	Recommended (Yes/No)	Quality of the evidence
Preimplantation genetic testing	No	VL
Anticoagulant therapy for RPL plus hereditary thrombophilia	No	L
Anticoagulant therapy for RPL plus APS	Yes	L
Prednisolone for RPL plus thrombophilia	No	VL
IVIG for RPL plus thrombophilia	No	VL
Levothyroxine for RPL plus subclinical hypothyroidism	Yes	VL
hCG for RPL	No	L
Antioxidants for sperm DNA damage	No	VL
Immunotherapy (paternal-donor) for RPL	No	M
IVIG for RPL	No	L
Prednisolone for RPL	No	VL
Anticoagulant for RPL without thrombophilia	No	M
Progesterone for RPL	No	M
G-CSF for RPL	No	VL
Chinese herbal medicine for RPL	No	VL
Intralipid therapy for RPL	No	L

†The summary is based on current ESHRE guidelines.[2] APS, antiphospholipid syndrome; G-CSF, granulocyte-colony stimulating factor; hCG, human chorionic gonadotropin; IVIG, intravenous immunoglobulin; L, low; M, moderate; VL, very low.

NEW INSIGHTS INTO THE MECHANISMS UNDERLYING RECURRENT PREGNANCY LOSS. EWINGTON LJ, TEWARY S, BROSENS JJ. OBSTET GYNAECOL RES. 2019;45(2):258-265

DERNEK GÖRÜŞLERİ

ACOG - FAQ

- Tanı: ≥2 adet düşük,
- ≥3 araştırma yapılır

- İlişkili durumlar;
    - genetik (translokasyon vs.)
    - uterin konjenital anomaliler – adezyonlar
    - AFAS
    - diabet

ACOG 2016

Royal College of Obstetricians & Gynaecologists

The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage

Green-top Guideline No. 17
April 2011

5. What are the recommended investigations of couples with recurrent first-trimester miscarriage and second-trimester miscarriage?

5.1 Antiphospholipid antibodies

All women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriage should be screened before pregnancy for antiphospholipid antibodies. D

To diagnose antiphospholipid syndrome it is mandatory that the woman has two positive tests at least 12 weeks apart for either lupus anticoagulant or anticardiolipin antibodies of immunoglobulin G and/or immunoglobulin M class present in a medium or high titre over 40 g/l or ml/l, or above the 99th percentile).

5.2 Karyotyping

Cytogenetic analysis should be performed on products of conception of the third and subsequent consecutive miscarriage(s).

D

Parental peripheral blood karyotyping of both partners should be performed in couples with recurrent miscarriage where testing of products of conception reports an unbalanced structural chromosomal abnormality.

D

5.3 Anatomical factors

All women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriages should have a pelvic ultrasound to assess uterine anatomy.

✓

Suspected uterine anomalies may require further investigations to confirm the diagnosis, using hysteroscopy, laparoscopy or three-dimensional pelvic ultrasound.

✓

5.4 Thrombophilias

Women with second-trimester miscarriage should be screened for inherited thrombophilias including factor V Leiden, factor II (prothrombin) gene mutation and protein S.

D

A meta-analysis[68] of retrospective studies has reported a strong association between second-trimester miscarriage and inherited thrombophilias: factor V Leiden, factor II (prothrombin) gene mutation and protein S deficiency.

Evidence level 2++

6. Treatment options for recurrent miscarriage

6.1 What are the treatment options for recurrent first trimester and second trimester miscarriage?

Women with recurrent miscarriage should be offered referral to a specialist clinic. ✓

6.2 Antiphospholipid syndrome

Pregnant women with antiphospholipid syndrome should be considered for treatment with low-dose aspirin plus heparin to prevent further miscarriage. B

Neither corticosteroids nor intravenous immunoglobulin therapy improve the live birth rate of women with recurrent miscarriage associated with antiphospholipid antibodies compared with other treatment modalities; their use may provoke significant maternal and fetal morbidity. A

6.3 Genetic factors

The finding of an abnormal parental karyotype should prompt referral to a clinical geneticist. D

Preimplantation genetic diagnosis has been proposed as a treatment option for translocation carriers.[89,90] Since preimplantation genetic diagnosis necessitates that the couple undergo in vitro fertilisation to produce embryos, couples with proven fertility need to be aware of the financial cost as well as implantation and live birth rates per cycle following in vitro fertilisation/preimplantation genetic diagnosis. Furthermore, they should be informed that they have a higher (50–70%) chance of a healthy live birth in future untreated pregnancies following natural conception[37,38,91] than is currently achieved after preimplantation genetic diagnosis/in vitro fertilisation (approximately 30%).[92]

Evidence level 4

Preimplantation genetic screening with in vitro fertilisation treatment in women with unexplained recurrent miscarriage does not improve live birth rates. C

Preimplantation genetic screening in conjunction with in vitro fertilisation has been advocated as a treatment option for women with recurrent miscarriage, the rationale being that the identification and transfer of what are thought to be genetically normal embryos will lead to a live birth. The live birth rate of women with unexplained recurrent miscarriage who conceive naturally is significantly higher than currently achieved after preimplantation genetic screening/in vitro fertilisation (20–30%).[92-95]

Evidence level 2+

6.4.1 Congenital uterine malformations

There is insufficient evidence to assess the effect of uterine septum resection in women with recurrent miscarriage and uterine septum to prevent further miscarriage. C

6.4.2 Cervical weakness and cervical cerclage

Cervical cerclage is associated with potential hazards related to the surgery and the risk of stimulating uterine contractions and hence should be considered only in women who are likely to benefit. A

Women with a history of second-trimester miscarriage and suspected cervical weakness who have not undergone a history-indicated cerclage may be offered serial cervical sonographic surveillance. B

In women with a singleton pregnancy and a history of one second-trimester miscarriage attributable to cervical factors, an ultrasound-indicated cerclage should be offered if a cervical length of 25 mm or less is detected by transvaginal scan before 24 weeks of gestation. B

6.5 Endocrine factors

There is insufficient evidence to evaluate the effect of progesterone supplementation in pregnancy to prevent a miscarriage in women with recurrent miscarriage. B

There is insufficient evidence to evaluate the effect of human chorionic gonadotrophin supplementation in pregnancy to prevent a miscarriage in women with recurrent miscarriage. B

Suppression of high luteinising hormone levels among ovulatory women with recurrent miscarriage and polycystic ovaries does not improve the live birth rate. A

There is insufficient evidence to evaluate the effect of metformin supplementation in pregnancy to prevent a miscarriage in women with recurrent miscarriage. C

6.6 Immunotherapy

Paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and intravenous immunoglobulin in women with previous unexplained recurrent miscarriage does not improve the live birth rate. A

6.7 Inherited thrombophilias

There is insufficient evidence to evaluate the effect of heparin in pregnancy to prevent a miscarriage in women with recurrent first-trimester miscarriage associated with inherited thrombophilia. C

Heparin therapy during pregnancy may improve the live birth rate of women with second-trimester miscarriage associated with inherited thrombophilias. A

6.8 Unexplained recurrent miscarriage

Women with unexplained recurrent miscarriage have an excellent prognosis for future pregnancy outcome without pharmacological intervention if offered supportive care alone in the setting of a dedicated early pregnancy assessment unit. B

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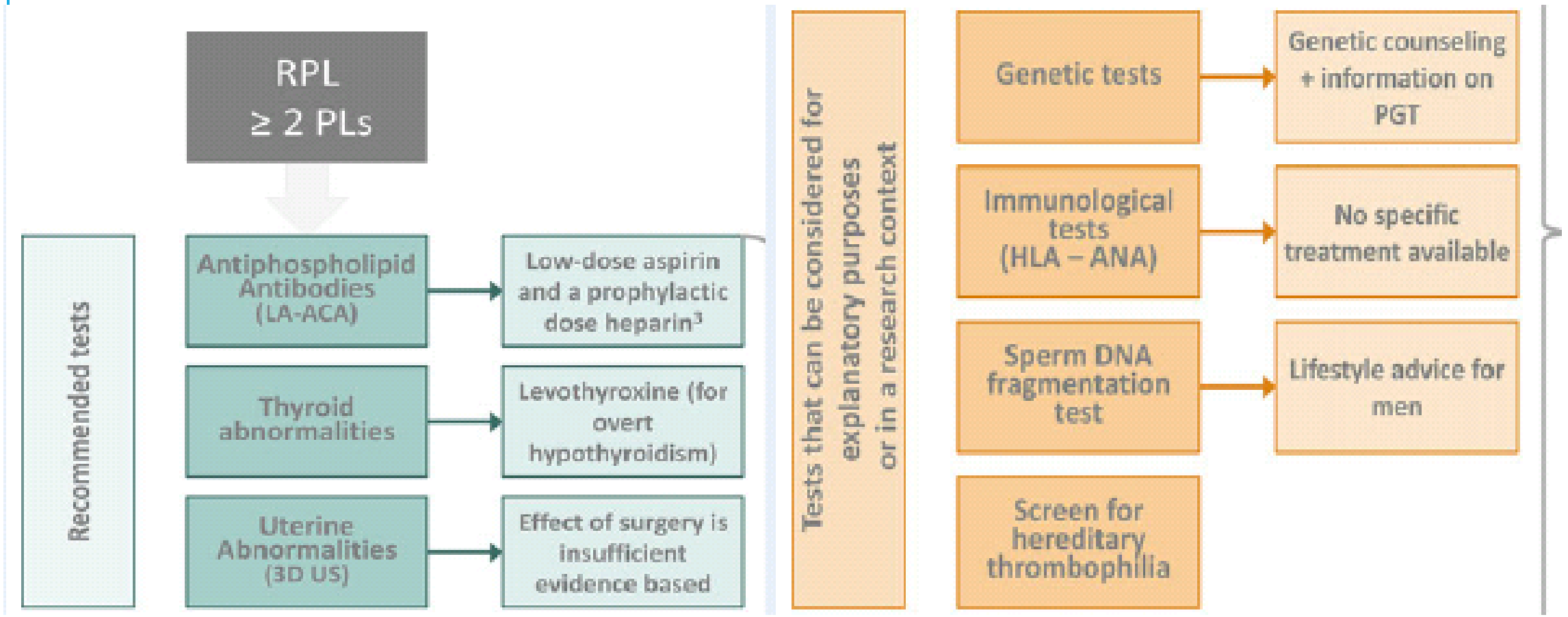
doi:10.1093/hropen/hoy004

human reproduction open

ESHRE PAGES

ESHRE guideline: recurrent pregnancy loss

- Gebelik kaybı : < 24 hafta (viabilite)
- ≥ 2 gebelik kaybı, ardışık olması şart değil !!!
- Özelleşmiş tekrarlayan gebelik kaybı polikliniği, duygusal destek de önemli



3: Low-dose aspirin and heparin are recommended after three or more pregnancy losses, or in the context of a clinical trial.


Non-recommended tests
Other immunological tests[1]
Metabolic or hormonal tests[2]
Lifestyle advice
TLC
Prophylactic vitamin D

What is the value of thrombophilia screening in women with RPL?

For women with RPL, we suggest not to screen for hereditary thrombophilia unless in the context of research, or in women with additional risk factors for thrombophilia (Bradley *et al.*, 2012).

Conditional
⊕⊕⊕◯

For women with RPL, we recommend screening for antiphospholipid antibodies (lupus anticoagulant [LA], and anticardiolipin antibodies [ACA IgG and IgM]), after two pregnancy losses (Miyakis *et al.*, 2006; Opatrny *et al.*, 2006).

Strong
⊕⊕◯◯

For women with RPL, screening for β2 glycoprotein I antibodies (aβ2GPI) can be considered after two pregnancy losses.

GPP

Which therapeutic interventions should be offered to couples with RPL and thrombophilia to increase the chance of a live birth?

For women with hereditary thrombophilia and a history of RPL, we suggest not to use antithrombotic prophylaxis unless in the context of research, or if indicated for venous thromboembolism (VTE) prevention (Skeith *et al.*, 2016).	Conditional ⊕⊕◯◯
For women who fulfil the laboratory criteria of antiphospholipid syndrome (APS) and have a history of three or more pregnancy losses, we suggest administration with low dose aspirin (75–100 mg/day), starting before conception, and a prophylactic dose heparin (unfractionated heparin [UFH] or low molecular weight heparin [LMWH]) starting at date of a positive pregnancy test, over no treatment (Empson *et al.*, 2005; Mak *et al.*, 2010; Ziakas *et al.*, 2010).	Conditional ⊕◯◯◯
The guideline development group (GDG) suggests offering anticoagulant treatment for women with two pregnancy losses and antiphospholipid syndrome (APS), only in the context of clinical research.	GPP

Heparin or low dose aspirin are not recommended, as there is evidence that they do not improve live birth rate in women with unexplained RPL (de Jong *et al.*, 2014).

Strong
⊕⊕⊕○

Evaluation and treatment of recurrent pregnancy loss: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Birmingham, Alabama

TABLE 1

Suspected causes of recurrent pregnancy loss.

Cause	Contribution to RPL (%)	Recommended screening	Supportive scientific evidence	Controversial scientific evidence	Not recommended
Cytogenetic	2–5	Balanced reciprocal translocations			
aPL syndrome	8–42 (mean, 15)	Lupus anticoagulant, anticardiolipin IgG or IgM antibody, anti-β_2-glycoprotein I	IgG and IgM antibodies, aPL testing for other phospholipids and β_2 glycoprotein I	IgG or IgM anti-annexin A5, anti-factor XII, anti-prothrombin, IgA aPLs	ANA, antithyroid antibodies
Anatomic	1.8–37.6 (mean, 12.6)	Hysterosalpingography Sonohysterography	Congenital uterine abnormalities	Uterine fibroids, polyps	Cervical incompetence
Hormonal or metabolic		Prolactin TSH Hemoglobin A1c	Uncontrolled diabetes or thyroid disease, prolactin	Polycystic ovary syndrome and insulin resistance, luteal phase progesterone	
Infectious		None		Bacterial vaginosis, endocervical infections	
Male factor		None		Abnormal sperm DNA	
Psychological		None		Psychological effects on uterine receptivity	
Alloimmune		None		Mucosal CD16− NK cells, embryotoxic factor, cytokine profiles, blocking antibodies, HLA typing, anti-paternal leukocyte antibodies, circulating CD16− NK cells	Circulating CD16− NK cells
Environmental, occupational, or personal habits		History			Not related to recurrent pregnancy loss

Note: ANA = antinuclear antibodies; aPL = antiphospholipid.

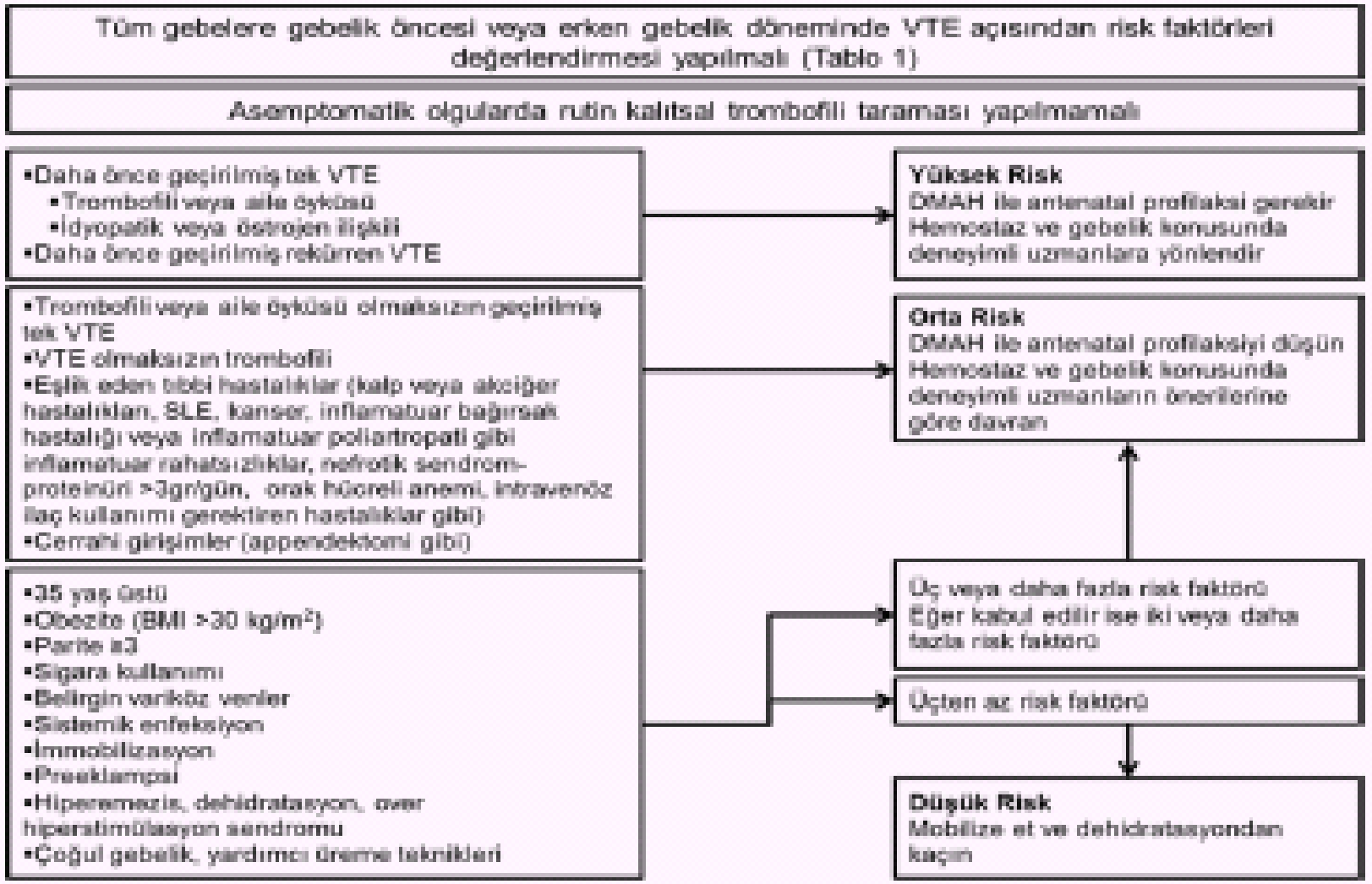
Practice Committee. Recurrent pregnancy loss. Fertil Steril 2012

Table 2 Etiologies of recurrent pregnancy loss, recommended tests for diagnosis, and treatment options

Etiology	Tests for diagnosis	Treatment options
Uterine factor	3D ultrasonography, sonohysterography, hysterosalpingography, hysteroscopy	Hysteroscopic resection of septum
		Myomectomy, hysteroscopic removal of polyps
	Magnetic resonance imaging	Adhesiolysis
Antiphospholipid syndrome	aCL, Anti-β2GP1, lupus anticoagulant	Heparin + aspirin
Endocrine abnormality	Thyroid-stimulating hormone	Levothyroxine
	Prolactin	Bromocriptine
	Fasting glucose or HbA_{1c}	Diabetes control (weight loss, nutrition, metformin)
Genetic	Karyotype of product of conception	Genetic counseling
	Parental karyotype	Preimplantation genetic diagnosis for balanced translocation
Environmental factors	Screen for smoking, drug use, excessive alcohol and caffeine intake	Eliminate environmental toxins
Psychological		Psychological support in a specialized setting
Unexplained		Progesterone supplementation (no consensus)
		Immunomodulating treatments (no consensus)
		Preimplantation genetic screening (no consensus)
Other (no consensus)		
Luteal phase deficiency	Mid-luteal progesterone, endometrial biopsy	Progesterone supplementation
Chronic endometritis	Endometrial biopsy	Antibiotic treatment
Other infections	Cultures	Appropriate treatment
Male factor	DNA fragmentation test on sperm	Lifestyle modifications, multivitamins, donor sperm

Note: Anti-β2GP1: anti-β2 glycoprotein-I.
Abbreviations: aCL, anticardiolipin; 3D, three-dimensional.

AKIS SEMASI-2: GEBELİKTE VENÖZ TROMBOPROFİLAKSİ İÇİN ANTENATAL DEĞERLENDİRME



AKIŞ ŞEMASI-3: GEBELİKTE VENÖZ TROMBOPROFİLAKSİ İÇİN POSTNATAL DEĞERLENDİRME