

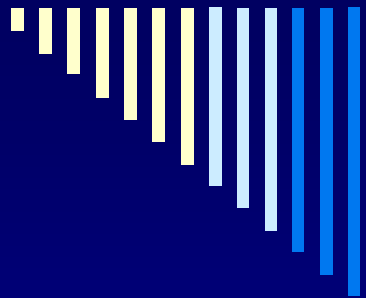
IVF BAŞARISIZLIĞI VE GEBELİK KAYBINDA DÜŞÜK MOLEKÜL AĞIRLIKLIL HEPARİNİN YERİ



ÜREME TIBBI VE CERRAHİSİ DERNEĞİ

Doç. Dr. M. Tuncay ÖZGÜN

**Erciyes Üniversitesi Tıp Fakültesi,
Kadın Hastalıkları ve Doğum AD**



Trombofili

- Kalitsal
- Edinsel



Yüksek riskli trombofililer

- Antitrombin eksikliği
- Heterozigot Protrombin gen mutasyonu+heterozigot FV leiden
- Homozigot FV Leiden
- Homozigot Protrombin gen mutasyonu
- Kombine defektler



Düşük Riskli Trombofililer

- Heterozigot FV Leiden
- Heterozigot Protrombin gen mutasyonu
- Protein C
- Protein S eksikliği



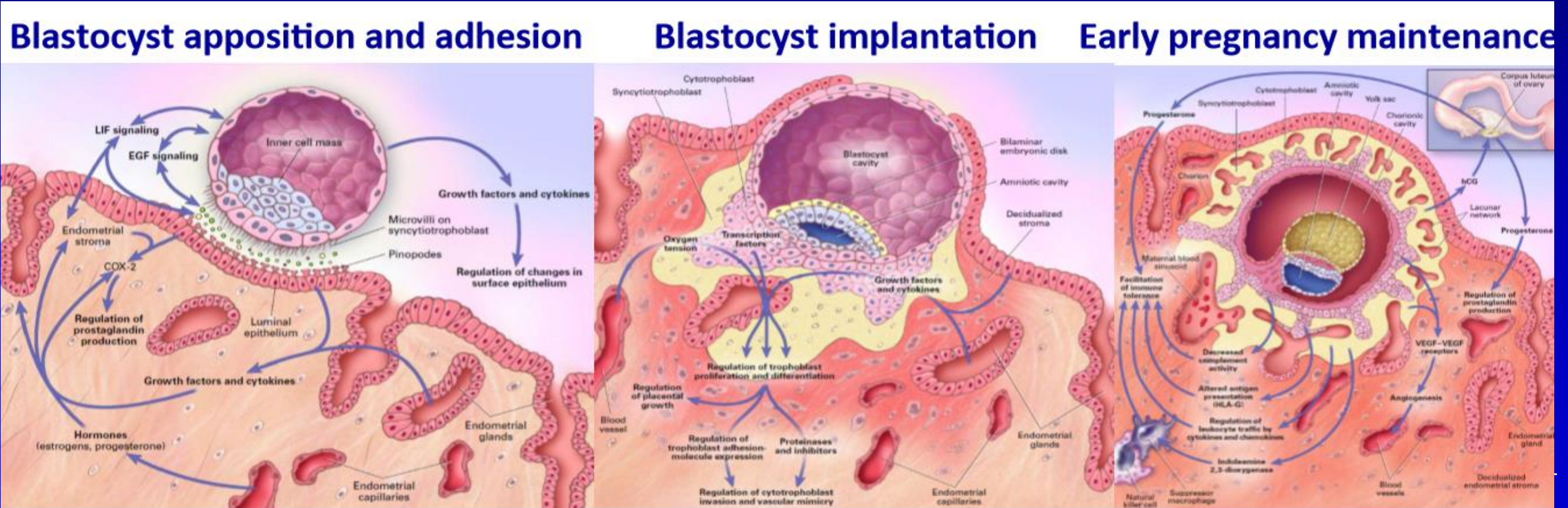
Antifosfolipid sendrom (APS)

TANI: En az bir klinik veya bir laboratuvar kriter

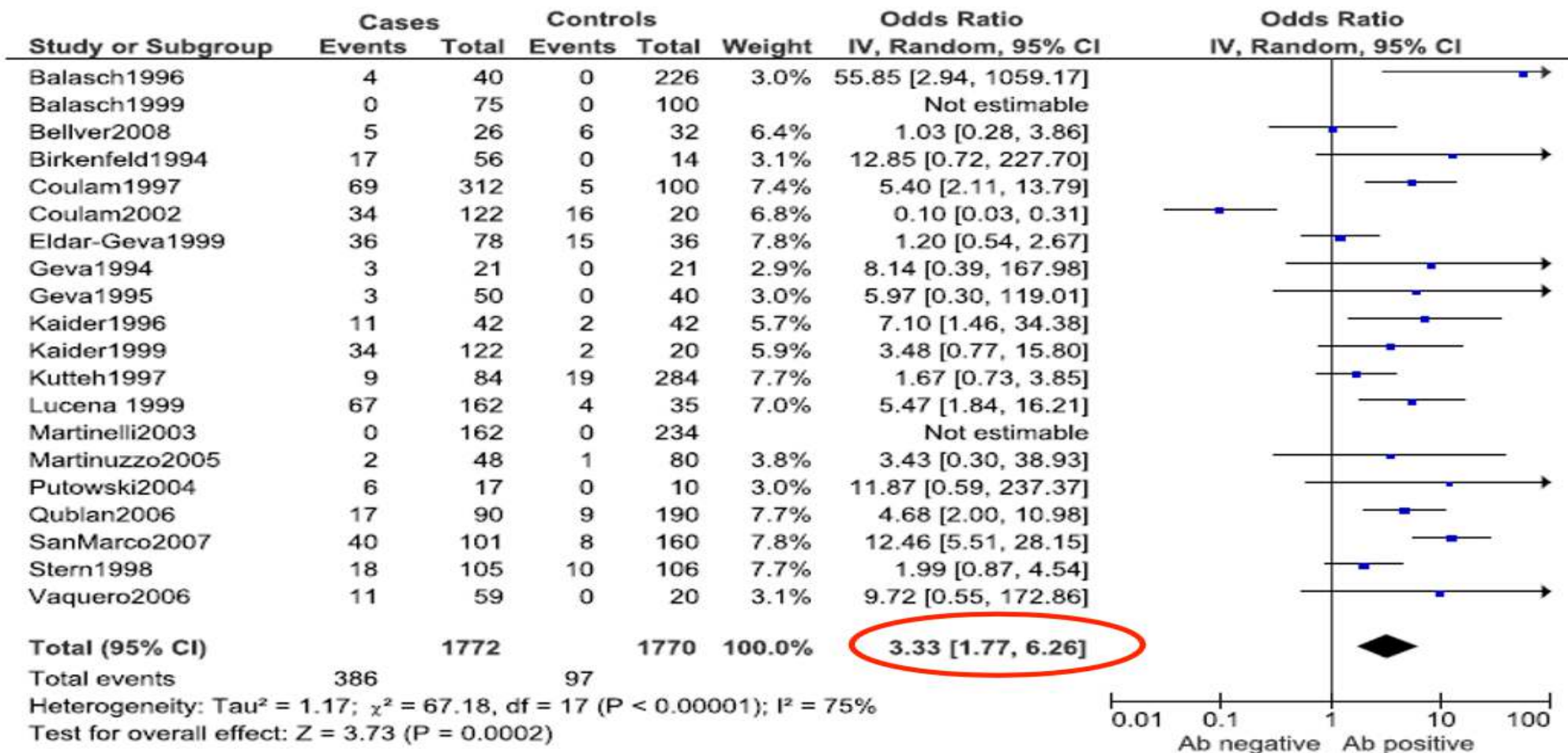
- Revised Sapporo classification (2006)

Clinical		Laboratory	
Thrombosis	≥ 1 documented episodes of: <ul style="list-style-type: none"> • Arterial • Venous and/or • Small vessel thrombosis 	ACA	ACA of IgG and/or IgM isotype in medium/high titre (> 40 IU) or $>99^{\text{th}}$ percentile
Pregnancy morbidity	≥ 1 unexplained fetal deaths of ≥ 10 weeks POA (morphologically normal fetus)	LA	Detected
	≥ 1 premature births of $\leq 34^{\text{th}}$ week POA d/t: Severe PE or Placental insufficiency (IUGR) (morphologically normal neonate)	Anti-beta2-glyco protein	$>99^{\text{th}}$ percentile
	≥ 3 unexplained consecutive spontaneous abortions < 10 week POA		* On 2 or more occasions At least 12 weeks apart

İmplantasyon hormonal olarak hazırlanmış olan uterus ile blastokist arasındaki kompleks olaylar sonucu olur



Antiphospholipid antibodies: prevalence in IVF failures

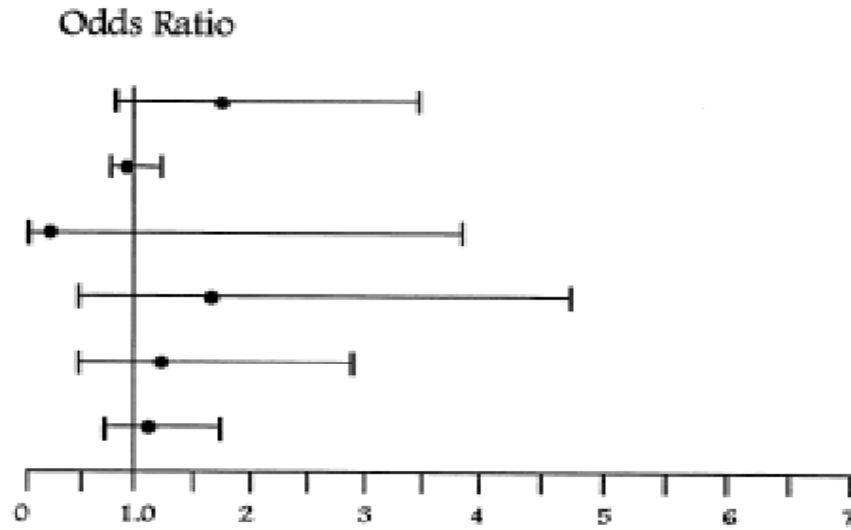


- Higher prevalence of antiphospholipid antibodies in women with ART failures

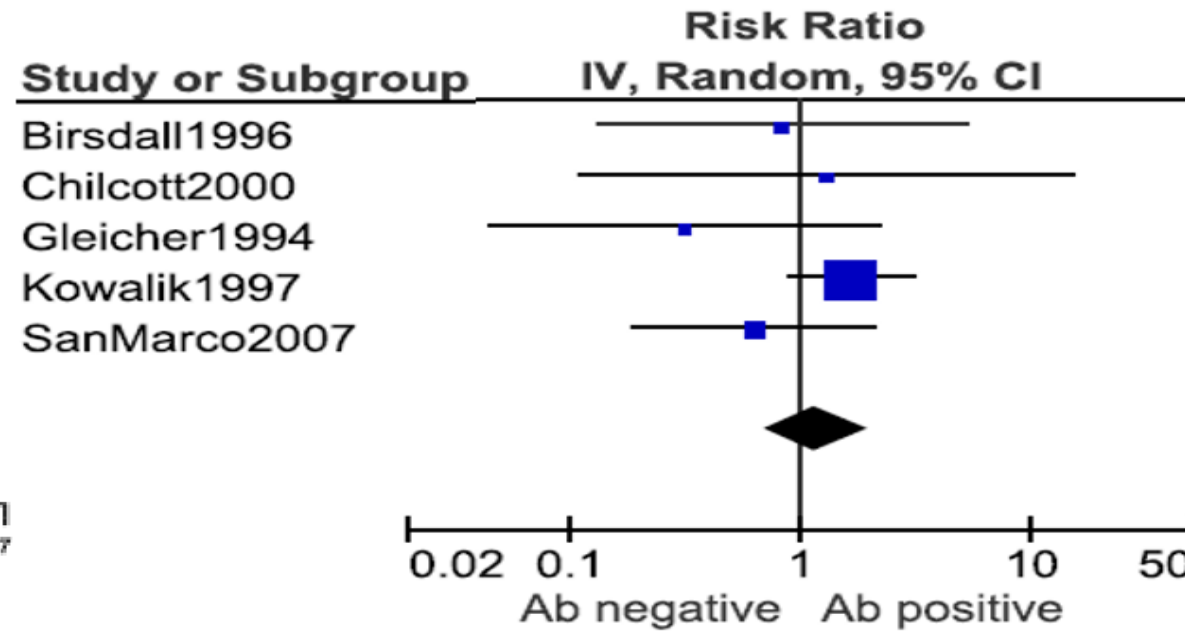
Antiphospholipid antibodies: IVF outcome

Hornstein al., Fertil Steril 2001

Di Nisio et al., Blood 2011

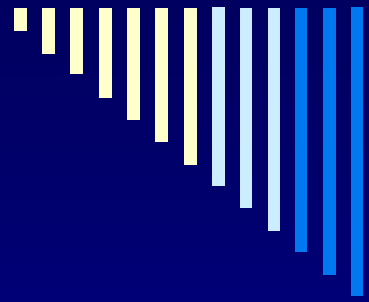


OR 1.07; 95% CI 0.66 – 1.75



RR 1.17; 95% CI 0.70 – 1.95

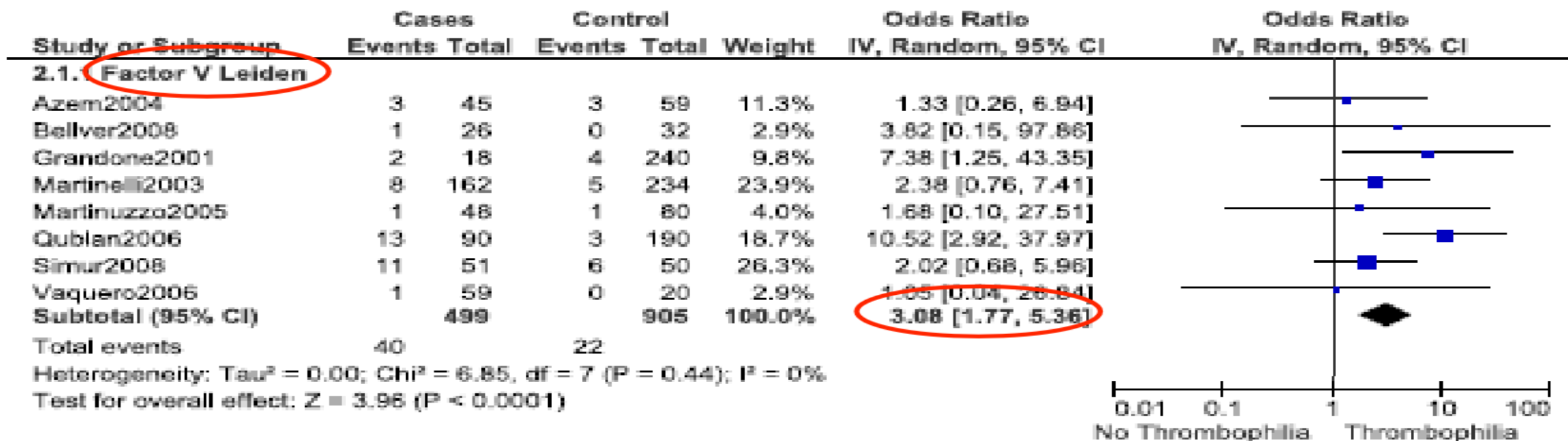
- No significant difference in LBR between APA +ve and APA -ve women



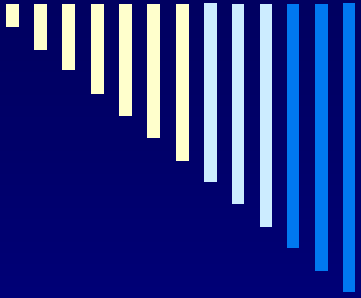
→ Heparin ve aspirin ile tedavi antifosfolipid antikor (+)
IVF hastalarında gebelik ve implantasyon oranlarını
etkilemiyor

ASRM, 2008

Inherited thrombophilia: prevalence in IVF failures



- Prothrombin mutation, MTHR mutation, protein C, S, antithrombin deficiency not associated with ART failures



- Trombofili olan ve olmayan IVF hastalarında canlı gebelik oranları arasında fark saptanmamış.
- IVF başarısızlığı olan hastalarda trombofili taraması önerilmez.



Tekrarlayan implantasyon başarısızlığı

- Bu hastalarda trombofilinin daha sık olup olmadığı tartışmalı
- Trombofili tedavisi veya proflaktik heparin kullanımının faydası tartışmalı.



Tekrarlayan gebelik kaybı

- Ardışık 2 veya 3 gebelik kaybı.
- Primer, sekonder
- AFS'de heparin+aspirin canlı doğum oranını artırıyor.

(Empson M,2005 Cochrane)

Etiyoloji

Sebeup	Sıklık
Anatomik	10-15%
Genetik	2-5%
Endokrinolojik	17-20%
İmmunolojik	20%
Mikrobiolojik	0.5-5%
İdiopatik	40-50%

Trombofili

- Trombofili (tromboz eğilimi) çeşitli mekanizmalar ile TGK'a sebep olur:
 - trombolitik sistem inhibisyonu
 - plasental tromboz
 - plasental dolaşım bozukluğu
 - anormal prostasiklin metabolizması
 - direk sitotoksik etki

	Erken kayıp	Geç Kayıp	RPL	Hafif PIH	Ağır PIH	FGR	Abruptio
APS	+?	++	+	-?	++	+	+
FVL het		++	+?	-?	++	+?	++
FVL hom	+	+	+	-?		+?	
PGM het	+	++	+?	-?	+	+?	++
PGM hom			+	-?			
ATIII		++		-?	++		
Protein S		+	?	-?	+?		+?
Protein C		++		-?	++		+?
MTHFR	-	+?		-?	+	+?	+?

Trombofili

- 31 alıřmanın deęerlendirildięi bir metaanalizde fetal kayıp ile herediter trombofili tařıyıcılıęı arasında deęiřken bir iliřki bulunduęu bildirilmiř.

Rey E 2003

- FVL veya protrombin gen mutasyon tařıyıcılıęı TGK riskini 2 katına ıkarır.

Arch Intern Med 2004

Table 19.2 Comparison of three protocols for the investigation and treatment of recurrent pregnancy loss

Investigation or treatment	RCOG protocol	ACOG protocol	ESHRE protocol
Parental karyotyping	Recommended	Recommended	Recommended
APS assessment (aCL and LA)	Recommended	Recommended	Recommended
Fetal karyotyping	Recommended	Insufficient evidence	Trial required
Uterine cavity assessment	Recommended by ultrasound or hydrosalpingography	Insufficient evidence	Recommended by ultrasound or hysterosalpingography
Resection of uterine septum	Insufficient evidence	Recommended despite lack of evidence	—
APS assessment (aCL and LA)	Recommended	Recommended	Recommended
Treatment of APS with heparin and aspirin	Recommended	Recommended	Insufficient evidence
Luteal phase investigation	—	Insufficient evidence	Insufficient evidence: trials required
Progesterone or hCG supplementation	Insufficient evidence	Insufficient evidence	Insufficient evidence: more RCTs required
Bacterial vaginosis	Insufficient evidence	Not recommended	—
Hereditary thrombophilias	Insufficient evidence	Insufficient evidence	Recommended as advanced investigation
Anticoagulants for hereditary thrombophilia	Insufficient evidence	Insufficient evidence	Insufficient evidence
Thyroid function	Not recommended	Not recommended	Recommended
Glucose challenge test	Not recommended	Not recommended	Recommended
TORCH testing	Not recommended	Not recommended	Not recommended
Alloimmune testing	Not recommended	Not recommended	Insufficient evidence
Immunotherapy	Not recommended	Not recommended	Insufficient evidence: RCT required for IVIG and third-party leukocytes; PLI no proven effect
‘Tender loving care’	Insufficient evidence	—	Recommended
Diet, smoking, alcohol reduction	—	—	Recommended
Folic acid for hyperhomocysteinemia	—	—	Insufficient evidence
Vitamin supplementation	—	—	Not recommended
Steroids	Not recommended	—	Not recommended

APS, antiphospholipid syndrome; aCL, anticardiolipin antibodies; LA, lupus anticoagulant; hCG, human chorionic gonadotrophin; RCT, randomized controlled trial; IVIG, intravenous immunoglobulin; PLI, paternal antibody-positive leukocytes.

Ülkemizde durum ne?

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healthcare

OBSTETRICS

A critical analysis of low molecular weight heparin use during pregnancy in a tertiary referral centre

M. S. Kutuk¹, A. Terzioglu², M. T. Ozgun¹, S. Uludag¹, M. Dolanbay¹ & M. Tas¹

¹Department of Obstetrics and Gynaecology, Faculty of Medicine, Erciyes University, Kayseri and ²School of Nursing and Health Sciences, Koc University, Istanbul, Turkey

Table I. Indication of low molecular weight heparin use during pregnancy.

Indication	Patients (n)	(%)
Thrombophilia	55	37.4
Isolated	38	25.8
Associated with previous single pregnancy loss	17	11.6
RPL	47	32.0
Previous thromboembolic disease	12	8.2
Isolated	5	3.4
Associated with thrombophilia or RPL	7	4.7
Previous single pregnancy loss	18	12.2
Acute deep vein thrombosis	5	3.4
History of adverse pregnancy outcome (pre-eclampsia, IUFD)	4	2.7
Pulmonary embolism	3	2.0
Lower extremity varicose veins	3	2.0

RPL, recurrent pregnancy loss; MTHFR, methylene tetrahydrofolate reductase gene mutation; IUGR, intrauterine growth retardation; IUFD *in-utero* fetal demise.

47 TGK

Karyotip, anti fosfolipid antikor, uterin kavite değerlendirilmesi

%53.1 hiç yapılmamış

%31.9 eksik

%15 tam yapılmış.

Testler+ilaç hasta başına 2000 USD'den fazla maliyet.

TGK& Trombofili tarama ve tedavisi

Kimleri tarayalım?

- Kişisel öyküsünde venöz tromboemboli
- 1° akrabalarında bilinen/şüphelenilen yüksek riskli trombofili
- Plasental patoloji ile konfirme edilen geç obstetrik komplikasyon

Hangilerini tarayalım?

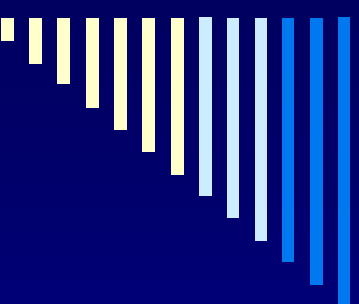
- FVL ve PGM
- Protein C
- Protein S
- Antitrombin eksikliği
- APCR(ikinci jenerasyon tarama)

Tedavi verelim mi?

- Trombofili ile ilişkili gebelik kayıplarında gebelik prognozunu iyileştirmek için Aspirin veya Heparin tedavisini destekleyen RCT Ø ► Kanıt yetersiz

• *Dizon-Townson D ,2005*

• *Silver RM ,2010*



KİLO	ENOKSAPARIN (Clexan)	DALTEPARIN (Fragmin)	TINZAPARIN (İnnohep)
<50	20 mg	2.500 Ü	3.500 Ü
50-90	40 mg	5.000 Ü	4.500 Ü
90-130	60 mg	7.500 Ü	7.000 Ü
131-170	80 mg	10.000 Ü	9.000 Ü
YÜKSEK PROFLAKSİ	40 mg 12 h ara	5.000 Ü 12 h	4.500 Ü/12h
TEDAVİ	1 mg/kg 12h ante. 1.5 mg/kg/d post.	100 Ü/kg/12h ante. 200 Ü/kg/d post.	175 Ü/kg/d ante. Ve post.