HEREDITARY THROMBOPHILIAS AND LOW MOLECULAR WEIGHT HEPARIN *(HEREDİTER TROMBOFİLİLERDE DÜŞÜK MOLEKÜLER AĞIRLIKLI HEPARİN KULLANIMI)*

Prof Dr Rıza Madazlı
Cerrahpaşa Tıp Fakültesi Kadın Hastalıkları ve Doğum Anabilim Dalı Perinatoloji Bilim Dalı

Kalıtsal Trombofili – Sıklığı

	Sıklık (%)
AT III	0.02-0.17
Protein C	0.14-0.50
Protein S	0.10-1
FVL (F5) Heterozigot Homozigot	3-8 0.004-0.065
PGM (F2) Heterozigot Homozigot	1-4 0.001-0.012
FVL + PGM Heterozigot	0.02-0.1

Kalıtsal Trombofili – Sorun

- **DVT- Emboli**

- **Plasenta Kaynaklı Kötü Obstetrik Sonuçlar (KOS)**
  - **TGK**
  - **Preeklampsi**
  - **FGK**
  - **Geç gebelik kayıpları**
  - **Dekolman(PA)**

%5 gebelik

Tekrarlama riski

TABLE 4

Prevalence and risk of recurrence of APO *without* thrombophilia

Previous pregnancy complication	Prevalence of pregnancy complication (%)	Pregnancy complication in subsequent pregnancy (%)
Fetal loss after or at 20 wks	0.5	8.5
Severe preeclampsia	2	26
HELLP	1	4
Eclampsia	0.5	3
Abruption	0.8	5
IUGR $\leq$ 5th percentile	5.3	16
One or more	8	61-85

Am J Obstet Gynecol 2007;197:457.e1-457.e21.

Kalıtsal Trombofili – DVT

	Sıklık (%)	Risk
FVL		
Het	3.6 - 8	3-9
Hom	0.1 - 0.02	40-80
PGM Het	1 – 4	2-9
MTHFR (Hom)	10 – 20	
AT III	0.17 - 0.02	25-50
Protein C	0.14 - 0.5	3-15
Protein S	0.2	2

- **Gebeliğe bağlı venöz tromboembolilerin yaklaşık %30-50'sinde de kalıtsal trombofili mevcuttur**
  (***Lim ve ark.,2007***)

Estimated relative and absolute risks of first pregnancy-associated VTE with inherithed thrombophilia.

Thrombophilia	Risk of VTE		
	Estimated relative risk	Observed or estimated absolute risk	
		Non-family studies †	Family studies
	OR (95% CI)	%/pregnancy (95% CI)	%/pregnancy (95% CI)
Factor V Leiden (homozygous)	34.4 (9.9-120.1) [43]	4.8 (1.4-16.8)	14.0 (6.3-25.8) [36,38]
Prothrombin G20210A mutation (homozygous)	26.4 (1.2-559.3) [43]	3.7 (0.2-78.3)	n/a
FV Leiden (heterozygous)	8.3 (5.4-12.7) [43]	1.2 (0.8-1.8)	3.1 (2.1-4.6) [68,69]
Prothrombin G20210A mutation (heterozygous)	6.8 (2.5-18.8) [43]	1.0 (0.3-2.6)	2.6 (0.9-5.6) [67,70]
Antithrombin deficiency	4.7 (1.3-17.0) [43]	0.7 (0.2-2.4)	3.0 (0.08-15.8) [40]
Protein C deficiency	4.8 (2.2-10.7) [43]	0.7 (0.3-1.5)	1.7 (0.4-8.9) [40]
Protein S deficiency	3.2 (1.5-6.0) [43]	0.5 (0.2-1.0)	6.6 (2.2-14.7) [40]
Compound heterozygosity FV Leiden and prothrombin G20210A mutation	n/a	n/a	1.8 (95% CI: 0.5-6.3) [44]

Kalıtsal Trombofili – DVT- Tarama

- **Rutin**
  - **ÖNERİLMEMEKTE**
    - **Fayda / maliyet**
    - **Gereksiz endişe**

- **Ailede Tromboemboli Öyküsü**
  - **Bilinen ATIII mutasyonu yoksa ÖNERİLMEMEKTE?**

- **Tromboemboli öyküsü**
  - **ÖNERİLMEKTE**
  - **Tartışma**
    - **İlave risk faktörü yoksa tekrarlama riski %3 - 5**
    - **Yüksek riskli trombofili insidansı çok düşük**

Kalıtsal Trombofili – DVT- Yönetim

- DVT Öykü Yok

	ACCP 2012
FVL / PGM Homozigot	Proflaktik veya Intermediate
FVL/ PGM Heterozigot	Aile +/Proflaktik Aile - / Takip
FVL+PGM Heterozigot	Aile + / Proflaktik Aile - / Takip
AT III	Aile + / Post Prof Aile - / Takip
Protein S / C	Aile+ / Post Prof Aile- / Takip

- DVT Öykü Var

	ACCP 2012
>1 DVT öykü	Proflaktik veya Intermediate
1/ Gebeliğe bağlı	Proflaktik veya Intermediate
1 / Trombofili +	Proflaktik veya Intermediate
1/ Risk faktör +	Antepartum- Takip Postpartum- Proflaksi
1/ Risk faktör -	Proflaktik veya Intermediate

Kalıtsal Trombofili – DVT- Yönetim

	Proflaksi	Ara	Tedavi
Enoxaparin Sodyum (Clexane)	40 mg IU TD	80 mg TD	1mg(100IU)/kg BID
Dalteparin Sodyum (Fragmin)	5000 IU TD	100-120 IU /kg TD	120 IU/kg BID
Nadroparin Kalsiyum (Fraksiparine)	3800 IU TD	90IU/kg TD	180 IU/kg TD
Tinzaparin Sodyum (Innohep)	3500 IU TD	75 IU TD	175 IU/kg TD

Kalıtsal Trombofili – KOS ilişkisi

- Robertson et al (2006) – Meta Analiz / Case-kontrol
- Rodger ve al (2010)- Meta Analiz / Prospektif cohort çalışmalar
- Lykke et al (2012)- Danimarka national cohort
- Rodger et al (2014)- Prospektif cohort

- Robertson et al(2006) Thrombophilia in pregnancy: a systematic review. British Journal of Haematology, 132, 171–196
  - 79 çalışma – çoğunluğu case-control
  - Diğer faktörler dikkate alınmamış

Table I. Association between inherited thrombophilia and placenta-mediated pregnancy complications (Robertson *et al*, 2006).

Thrombophilia	VTE, OR (95% CI)	Early pregnancy loss prior to 24 weeks gestation, OR (95% CI)	Late pregnancy loss after 24 weeks gestation, OR (95% CI)	Preeclampsia, OR (95% CI)	Placental abruption, OR (95% CI)	Intrauterine growth restriction, OR (95% CI)
Homozygous *F5* G1691A	**34·40 (9·86–120·05)**	**2·71 (1·32–5·58)**	1·98 (0·40–9·69)	1·87 (0·44–7·88)	8·43 (0·41–171·20)	4·64 (0·19–115·68)
Heterozygous *F5* G1691A	**8·32 (5·44–12·70)**	**1·68 (1·09–2·58)**	**2·06 (1·10–3·86)**	**2·19 (1·46–3·27)**	**4·70 (1·13–19·59)**	2·68 (0·59–12·13)
Homozygous *F2* G20210A	**26·36 (1·24–559·29)**	–	–	–	–	–
Heterozygous *F2* G20210A	**6·80 (2·46–18·77)**	**2·49 (1·24–5·00)**	**2·66 (1·28–5·53)**	**2·54 (1·52–4·23)**	**7·71 (3·01–19·76)**	2·92 (0·62–13·70)
AT deficiency	**4·69 (1·30–16·96)**	0·88 (0·17–4·48)	7·63 (0·30–196·36)	3·89 (0·16–97·19)	1·08 (0·06–18·12)	–
PC deficiency	**4·76 (2·15–10·57)**	2·29 (0·20–26·43)	3·05 (0·24–38·51)	5·15 (0·26–102·22)	5·93 (0·23–151·58)	–
PS deficiency	**3·19 (1·48–6·88)**	3·55 (0·35–35·72)	**20·09 (3·70–109·15)**	2·83 (0·76–10·57)	2·11 (0·47–9·34)	–

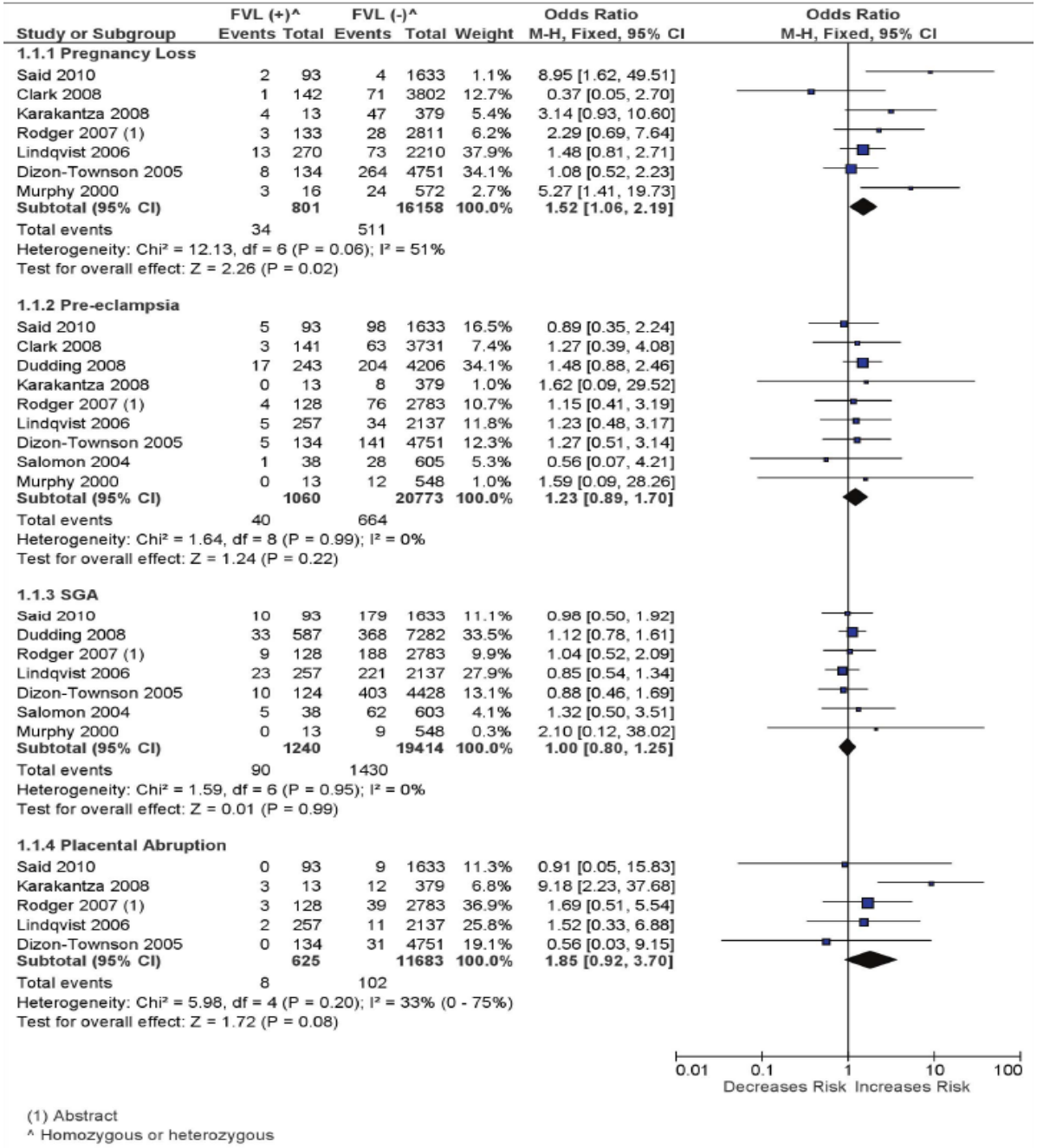
The Association of Factor V Leiden and Prothrombin Gene Mutation and Placenta-Mediated Pregnancy Complications: A Systematic Review and Meta-analysis of Prospective Cohort Studies

Marc A. Rodger[1,2]*, Marisol T. Betancourt[1,2], Peter Clark[3], Pelle G. Lindqvist[4], Donna Dizon-Townson[5], Joanne Said[6,7], Uri Seligsohn[8], Marc Carrier[1,2], Ophira Salomon[8], Ian A. Greer[9]

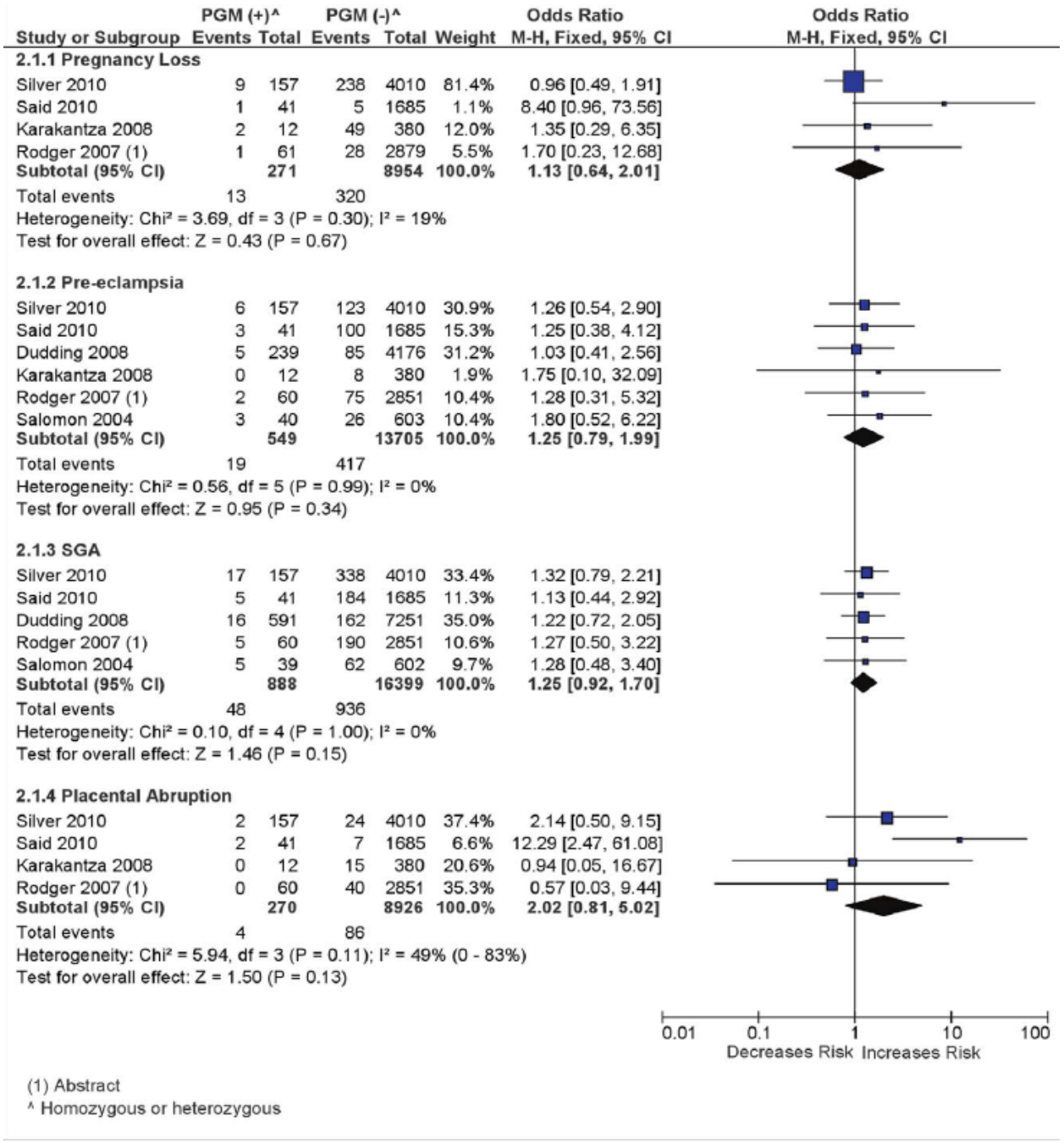
PLoS Medicine, 7, e1000292. (2010)

Prospektif cohort çalışma (10 çalışma - 20 000 olgu)

- F5
  - Geç gebelik kaybı az oranda ilişkili OR 1.52 (95% CI 1.06–2.19)
- F2
  - ilişkili değil



- **F5**
  - **Geç gebelik kaybı / Az oranda ilişkili**
  - **SGA, Preeklampsi / ilişkili değil**
  - **Dekolman / Yetersiz kanıt**
- **Araştırılması akademik**



- **F2**
  - **Preeklampsi ve SGA / ilişkili değil**
  - **Gebelik kaybı ve dekolman / Yetersiz kanıt**
- **Araştırılması akademik**

Lykke et al (2012) / Thrombophilias and adverse pregnancy outcomes: results from the Danish National Birth Cohort.
Journal of Thrombosis and Haemostasis, 10, 1320–1325

Danimarka cohort / 100 000 gebelik 5 yıl / F2, F5 – Ağır PE, FGK, <34 gh doğum, PA / İlişki ve tekrarlama

- F5
  - Birleşik komplikasyonlar — OR 1.47, (95% CI 1.16–1.88)
  - PE — OR 1.94, (95% CI 1.27–2.96)
  - FGK — OR 1.51, (95% CI 1.15–1.98)
  - PA — OR 1.87, (95% CI 1.25–2.81)
- F2
  - ilişkili değil

Is thrombophilia associated with placenta-mediated pregnancy complications? A prospective cohort study

M. A. RODGER,*†‡ M. C. WALKER,*§¶ G. N. SMITH,**†† P. S. WELLS,*†‡ T. RAMSAY,*‡‡ N. J. LANGLOIS,* N. CARSON,§§¶¶ M. CARRIER,*†‡ R. RENNICKS WHITE,* S. SHACHKINA*** and S. W. WEN*§¶

Journal of Thrombosis and Haemostasis, **12**: 469–478 2014;

Table 3 Association between placenta-mediated complications and thrombophilia exposure

Outcome N (%)	Without thrombophilia (n = 6836)	With FVL and/or PGM (n = 507)	RR (95% CI)	aRR (95% CI)
Any placenta-mediated complication (primary outcome)	768 (11.23)	59 (11.64)	1.04 (0.81, 1.33)	1.07 (0.83, 1.37)*
Small for gestational age (SGA)	469 (6.93)	36 (7.20)	1.04 (0.75, 1.44)	1.03 (0.75, 1.43)*
Preeclampsia	212 (3.10)	17 (3.35)	1.08 (0.66, 1.76)	1.14 (0.70, 1.85)†
Placental abruption	64 (0.94)	3 (0.59)	0.63 (0.20, 2.00)	0.60 (0.19, 1.91)‡
Pregnancy loss	80 (1.17)	6 (1.18)	1.01 (0.44, 2.31)	1.02 (0.45, 2.34)§

- F5 ve /veya F2 ile
  - PE, FGK PA ile anlamlı ilşki yok (yeterli güçte ve ilave çalışmaya gerek yok)

- Diğer potatent trombofililer (AtIII, PrC, PrS, homozigot ve double heterozigot)
  - İlişki olabilir ancak ortaya koymak zor

- Trombofililer ile ağır plasenta kaynaklı komplikas. (ağır erken PE, ağır FGK, major PA)
  - ilişki olabilir ancak kanıtlanmış değil

Kalıtsal Trombofili – PK-KOS/ Tarama

- **<u>RUTİN TARAMA ÖNERİLMEMEKTE</u>**

LMWH- Kullanımı

- Tekrarlayan Gebelik Kayıpları
  - ≥3 %1; ≥ 2 %3-5
  - % 50-60 neden belirlenemez
  - % 70-75 canlı doğum

- Kalıtsal Trombofililer ile İlişkili değil

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

2014, Issue 7

de Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S

THE COCHRANE COLLABORATION®

≥ 2 kayıp <24 GH

- LMWH vs placebo — RR 1.16, 95% CI 0.93–1.45
- LMWH vs aspirin — RR 1.23, 95% CI 08.4–1.81
- LMWH + aspirin vs placebo — RR 1.01, 95% CI 0.87–1.16
- LMWH + aspirin vs aspirin — RR 1.11, 95% CI 094–130

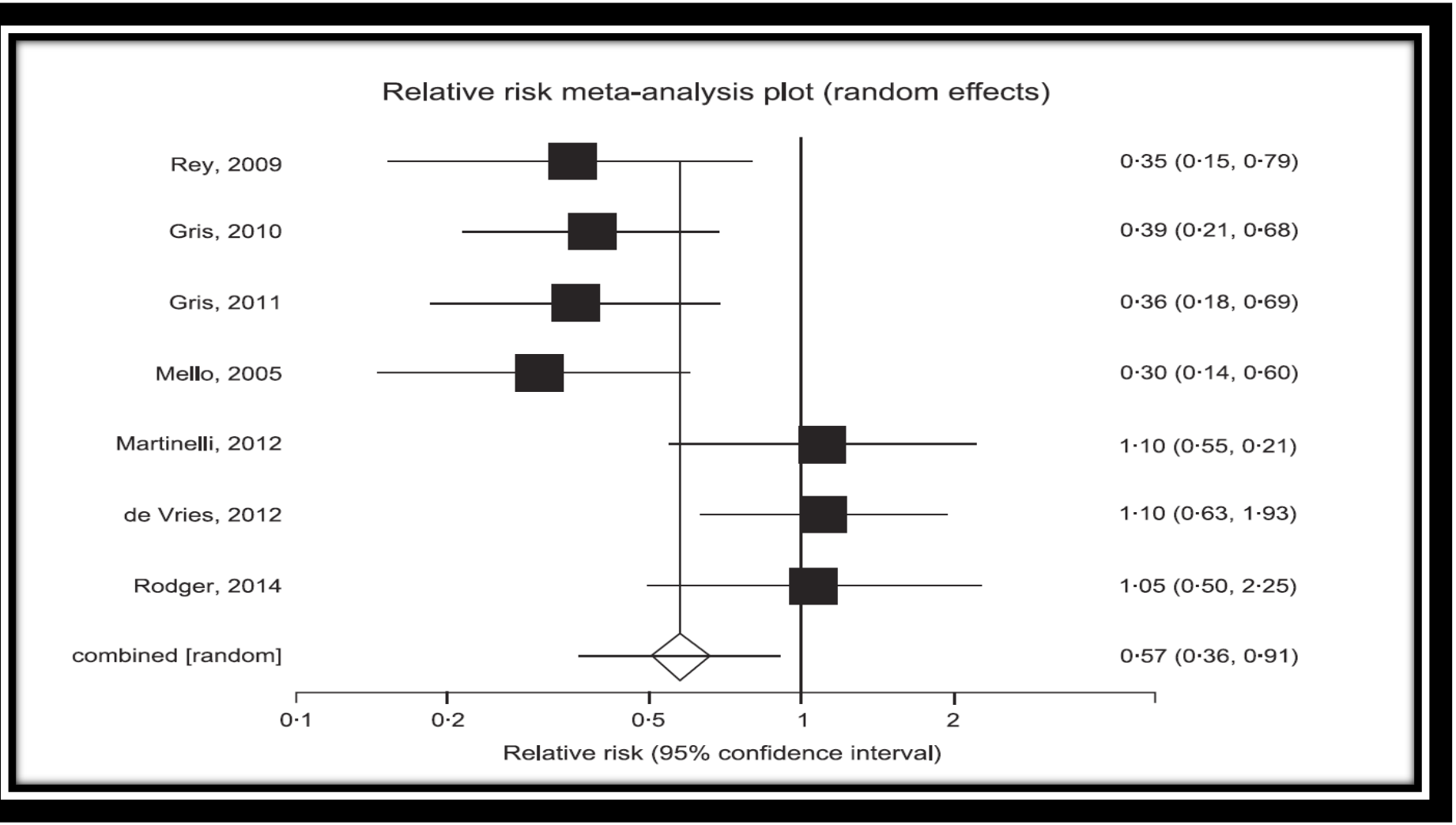
- LMWH TGK Kullanımının Yararı Yok

Tekrarlayan PK-KOS Önlenmesinde LMWH

LMWH to prevent placenta-mediated pregnancy complications: an update

Lisa Duffett[1] and Marc Rodger[1,2]

British Journal of Haematology, 2015, **168,** 619–638



Çalışma	Ulke	N	Olgular	Tedavi	Sonuç
Mello 2005	Italya TM	80	PE+ACE	Dalteparin 5000 IU vs no	PE, SGA 10th
Rey 2009	Kanada ÇM	116	PE, PA, FGK GK	Dalteparin 5000 IU +- ASA vs +-ASA	PE, FK,FGK,PA
Gris 2010	Fransa TM	160	PA+-PE	Enoxaparin 4000 IU +- ASA vs +- ASA	PE, FK,FGK,PA
Gris 2011	Fransa TM	224	Ağır PE	Enoxaparin 4000 IU +-ASA vs ASA	PE, FK,FGK,PA
Martinelli 2012	Itaya ÇM	135	PE, PA, FGK GK	Nadroparin 3800 IU vs no	PE, FK,FGK,PA
De Vires 2012	ÇU ÇM	139	Erken PE	Dalteparin 5000 IU + ASA vsASA	Erken PE
Rodger 2014	ÇU ÇM	292	PE, PA, FGK GK + Tombofili	Dalteparin 5000 IU vs no	PE, FK,FGK,PA

Table 2. Summary characteristics of participants in the studies included in the meta-analysis

	LMWH (n = 425)	No LMWH (n = 423)	Combined (n = 848)	
	n/N	n/N	n/N	%
Thrombophilia	106/425	107/423	213/848	25
Prior PE	296/425	293/423	593/848	70
Prior severe PE	208/304	208/304	416/608	68
Prior SGA <10th percentile	76/192	67/192	143/384	37
Prior abruption	91/192	90/203	181/405	45
Prior loss >12 wk	34/122	32/123	66/245	27
Concomitant ASA use	178/495	260/423	438/848	52

Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial

Lancet 2014; 384: 1673–83

- 36 merkez, 5 ulke, 2000-2012

	Antepartum dalteparin group (n=146)	No antepartum dalteparin group (n=143)
Thrombophilia inclusion criteria		
Factor V Leiden*	94 (64%)	82 (57%)
Prothrombin gene mutation	30 (21%)	33 (23%)
Protein S deficiency	11 (8%)	13 (9%)
Protein C deficiency	6 (4%)	11 (8%)
Antithrombin deficiency	2 (1%)	1 (1%)
Antiphospholipid antibody	12 (8%)	10 (7%)

High-risk inclusion criteria		
Previous pregnancy complications (any of those listed below)	92 (63%)	84 (59%)
Pre-eclampsia	20 (14%)	25 (18%)
Eclampsia	3 (2%)	3 (2%)
SGA infant (<10th percentile)	26 (18%)	19 (13%)
Major placental abruption	16 (11%)	10 (7%)
Three or more miscarriages at <10 weeks' gestation	24 (16%)	20 (14%)
Two or more fetal losses at 10–16 weeks' gestation	11 (8%)	14 (10%)
One or more fetal losses at ≥16 weeks' gestation	27 (19%)	33 (23%)
VTE risk factors/events (any of the following)	67 (46%)	61 (43%)
Family history of VTE in first-degree relatives	45 (31%)	46 (32%)
Mean number of first-degree relatives with VTE, per participant	1·1	1·1
Previous secondary VTE	11 (8%)	9 (6%)
Previous calf deep vein thrombosis	10 (7%)	6 (4%)
Previous superficial phlebitis	7 (5%)	5 (4%)

	Antepartum dalteparin (n=146)	No antepartum dalteparin (n=143)	Difference (95% CI)	p value
Primary analysis				
Patients with one or more of major VTE, severe or early onset pre-eclampsia, SGA (<10%), or pregnancy loss	25 (17·1%)	27 (18·9%)	−1·8% (−10·6 to 7·1)	0·70
Secondary analysis: efficacy outcomes				
Symptomatic major VTE	1 (0·7%)	2 (1·4%)	−0·7 (−3·1 to 1·6)	0·62
Pre-eclampsia	8 (5·5%)	5 (3·5%)	2·0 (−2·8 to 6·8)	0·42
Severe or early onset pre-eclampsia	7 (4·8%)	4 (2·8%)	2·0 (−2·4 to 6·4)	0·38
Small-for-gestational-age infant (<10%)	9 (6·2%)	12 (8·4%)	−2·2 (−8·2 to 3·8)	0·47
SGA (<5%)	2 (1·4%)	3 (2·1%)	−0·7 (−3·7 to 2·3)	0·68
SGA (<3%)	3 (2·0%)	0	2·0 (−0·2 to 4·4)	0·25
Pregnancy loss (any)	12 (8·2%)	10 (7·0%)	1·2 (−4·9 to 7·3)	0·69
Early (≥3 at <10 weeks)	4 (2·7%)	5 (3·5%)	0·8 (−4·8 to 3·2)	0·75
Late (≥2 at >10 weeks or ≥1 at >16 weeks)	6 (4·1%)	2 (1·4%)	2·7 (−1·0 to 6·5)	0·28
Any pre-eclampsia, SGA, or loss or abruption	27 (18·5%)	28 (19·6%)	−1·1 (−10·1 to 8·0)	0·81
Placental abruption	4 (2·7%)	3 (2·1%)	0·6 (−2·9 to 4·2)	0·72
Preterm delivery (<37 weeks)	23 (15·8%)	17 (11·9%)	3·9 (−4·1 to 11·8)	0·34
Birthweight of livebirths (g)	3186·2 (758)	3241·4 (764)	−55·2 (−238·6 to 128·1)	0·55
Gestational age at delivery (weeks)				
Of livebirths	38·1 (2·84)	38·2 (3·1)	−0·13 (−0·86 to 0·59)	0·72
Of pregnancy loss	16·8 (8·2)	10·8 (5·3)	6·0 (−0·09 to 12·11)	0·06

Comment *Lancet* 2014; 384

TIPPing practice away from anticoagulation in pregnancy

*Paul S Gibson, Kara A Nerenberg

- PK-KOS önlenmesinde LMWH kullanımı için yeterli kanıt yok

- Ağır PK-KOS olgularda- Olası yarar olabilir ancak KANITLANMIŞ değil ve çalışmalara gereksinim var

LMWH – Yan Etkiler

- Teratojenik değil
- Laktasyon kullanılabilir
- Kanama %1.98
  - Antepartum % 0.43
  - Postpartum %0.94
  - Hematom %0.61
- Osteoporoz
  - 1/2777 (%0.04) / Kırık
- Trombositopeni <%1
- Alerjik reaksiyon %2
- Ağrı,yanma %30
- Maliyet- 200-400 enj

LMWH – Kullanım

- **Nedeni bilinmeyen TKG ampirik kullanım ÖNERİLMEMEKTE**
- **IVF başarı şansını artırmak için ampirik kullanım ÖNERİLMEMEKTE**
- **Kalıtsal trombofili kötü obstetrik sonuçları önlemek için YARARI KANITLANMIŞ DEĞİL**

Journal of Reproductive Immunology 90 (2011) 82–90

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Effects and effectiveness of heparin in assisted reproduction

Michael K. Bohlmann*

University Hospital of Schleswig-Holstein, Campus Luebeck, Department of Obstetrics and Gynaecology, Ratzeburger Allee 160, 23538 Luebeck, Germany

5. A word of caution

A 38-year-old nulliparous woman with positive APAs died from complications of a cerebral haemorrhage after she had been given a combination of heparin and aspirin to improve her ART outcome. She had no history of thromboembolic events (CDC, 1998). However, other side effects

Although frequently seen in clinical practice, potent medication for anticoagulation, such as aspirin and heparin, should not be given to patients in the absence of proven effects when the only indication is to improve their ART outcome.

Teşekkürler