Tekrarlayan Gebelik Kaybı ve Trombofili (sebep mi yoksa birliktelik mi)

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THROMBOPHILIA

Mutations - Hypercoagulable

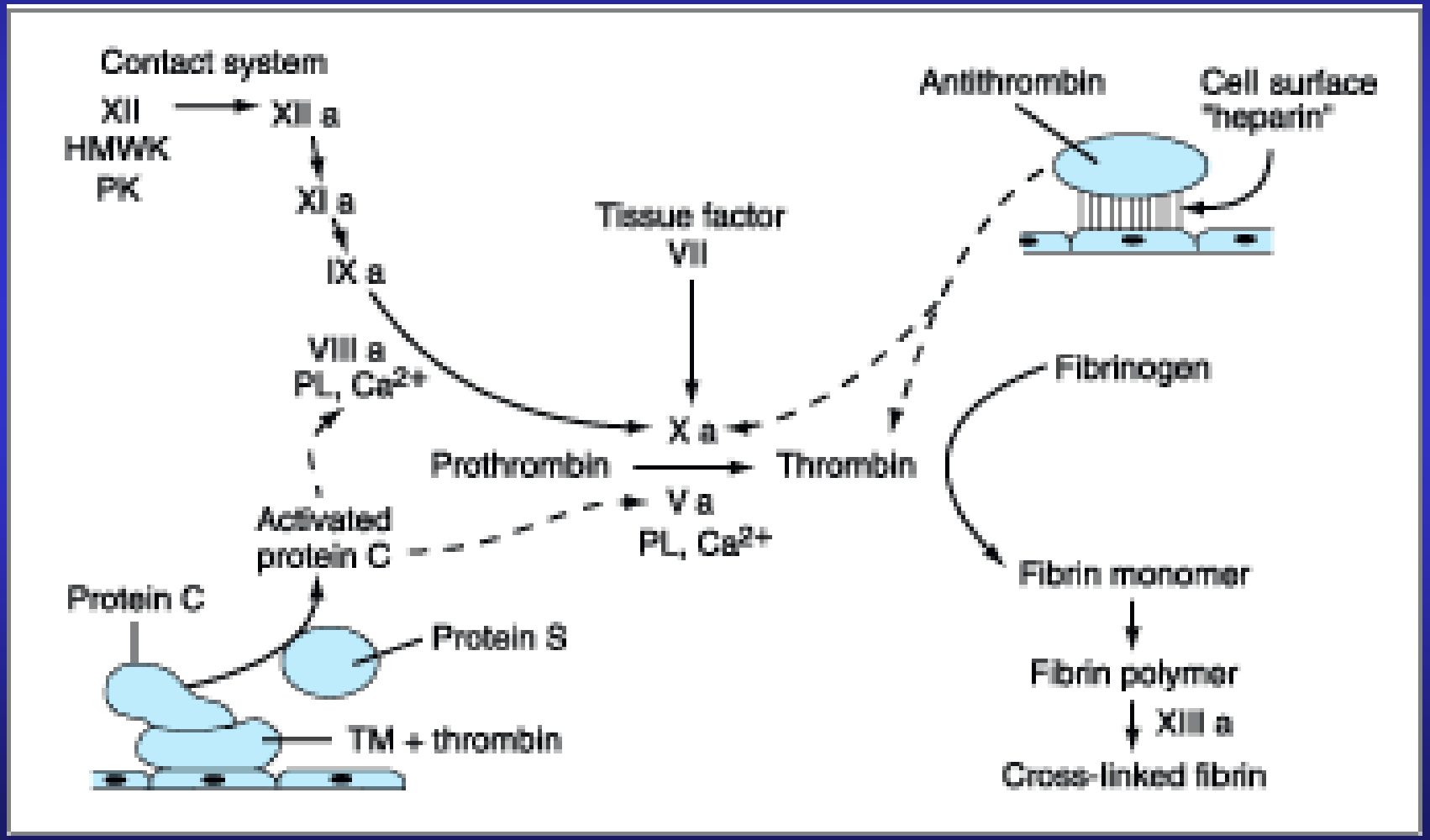
- Factor V Leiden (G1691A)
- Factor II - Prothrombin G20210
- Hyperhomocysteinemia
  (MTHFR C677T, A1298C)

THROMBOPHILIA

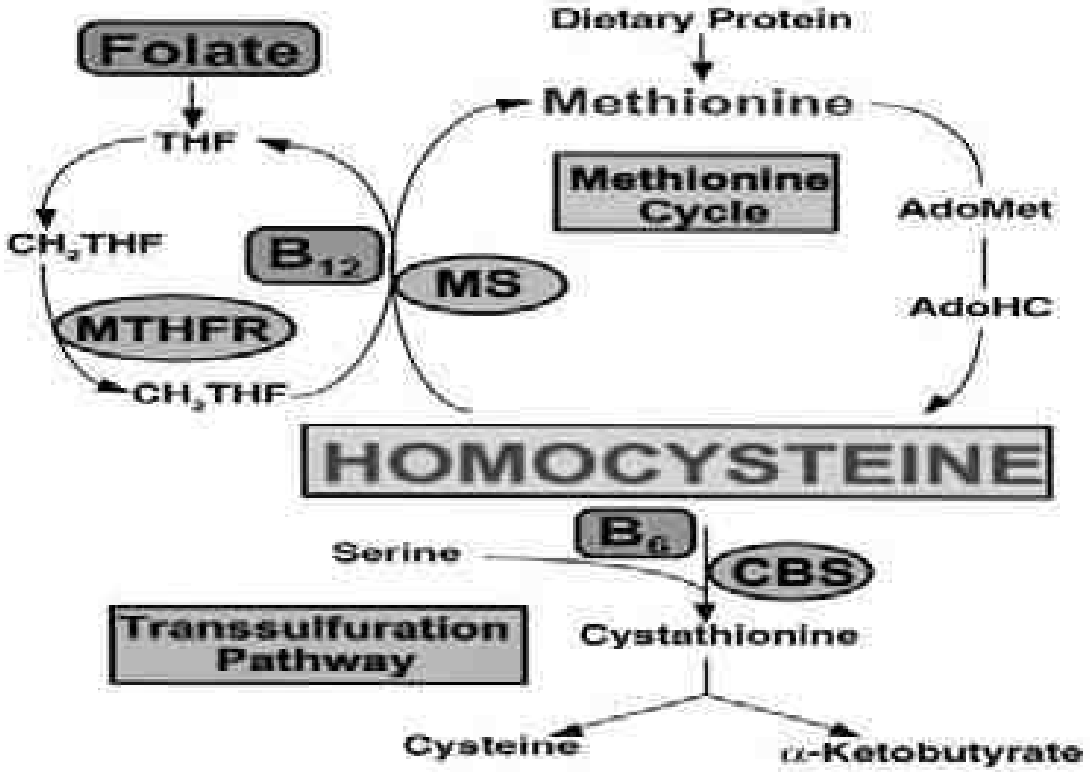
Deficiencies - Hypercoagulable

- Protein C
- Protein S
- Antithrombin III

Thrombotic Pathways



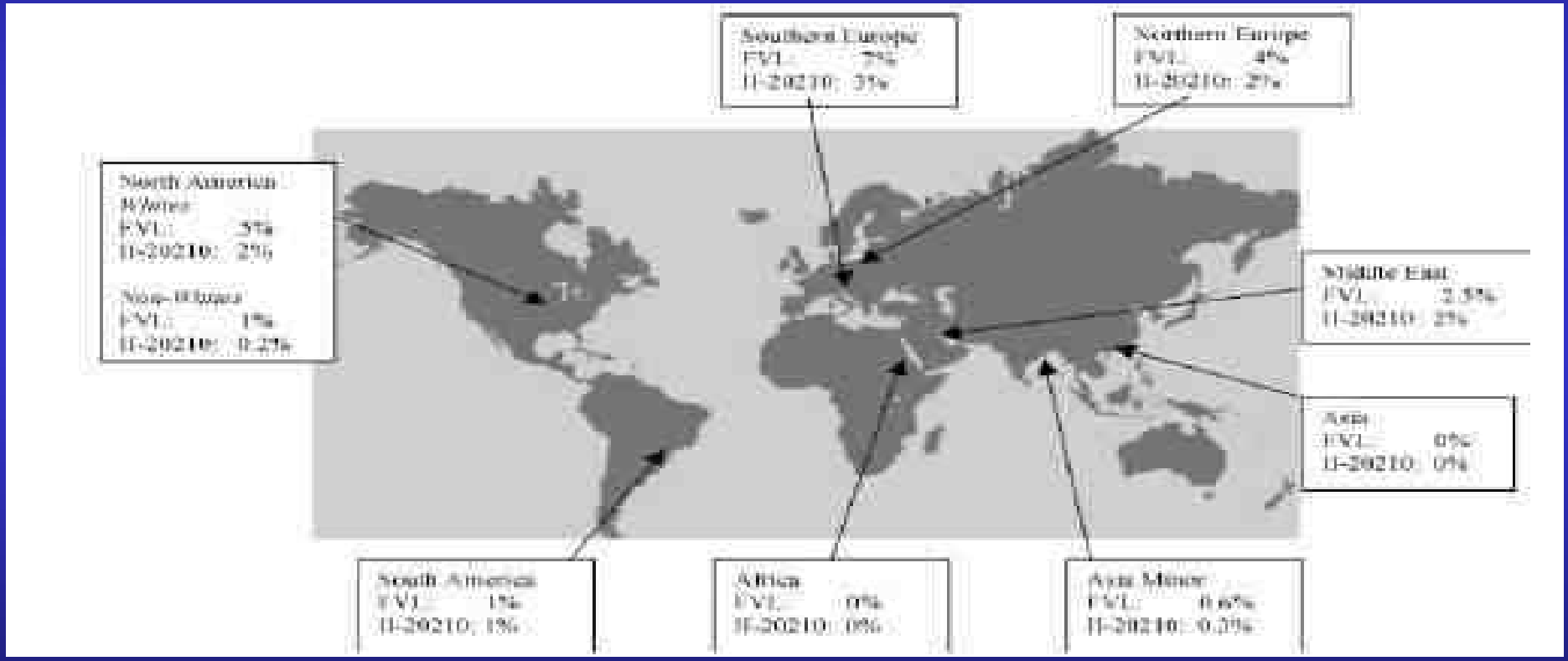
HOMOCYSTEINE METABOLISM



Inherited Thrombophilias (Prevalence)

Thrombophilia	Inheritance	Prevalence
Factor V Leiden Mutation	Autosomal dominant	2-15%
Protrombin II Mutation	Autosomal dominant	2-3%
MTHFR Mutation	Autosomal dominant	11%
Antithrombin III Deficiency	Autosomal dominant	0.02%
Protein C Deficiency	Autosomal dominant	0.2-0.3%
Protein S Deficiency	Autosomal dominant	0.1-0.2%

Geographic distribution of the prevalence of the two most common forms of inherited thrombophilia



Saskia Middeldorp, 2007

Pregnancy-associated changes

- Resistance to activated protein C increases in the second and third trimesters
- Protein S activity decreases due to estrogen-induced decreases in total protein S and increases in the complement 4b binding protein, which binds protein S
- Fibrinogen and factors II, VII, VIII, and X increase
- Levels and activity of the fibrinolytic inhibitors, thrombin activatable fibrinolytic inhibitor (TAFI), PAI-1 and PAI-2 increase

Trombofili ve gebelik patolojileri

- Tekrarlayan gebelik kaybı,
- ölü doğum,
- dekolman,
- IUGG,
- preeklampsia

Konular

- Tekrarlayan gebelik kaybı
- Tekrarlayan ivf başarısızlığı (İmplantasyon)

Tekrarlayan Gebelik Kaybı

- Preston FE, Rosendaal FR, Walker ID, et al. Increased fetal loss in women with heritable thrombophilia.
- *Lancet* 1996;348:913 6.

Link Between Thrombophilias & SAB

Retrospective cohort study of 491 patients with a history of adverse pregnancy outcomes:

- Thrombophilia was protective of recurrent losses at <10 weeks with OR of 0.55 (95% CI: 0.33-0.92).

- Thrombophilia was associated risk of recurrent losses >10 weeks with OR of 1.76 (1.05-2.94).

Roque et al., Thromb Haemost. 2004; 91:290-5.

Genetic thrombophilic mutations among couples with recurrent miscarriage

(i) the prevalence of three thrombophilic mutations [factor V Leiden (FVL), prothrombin G20210A (PTG) and methylenetetrahydrofolate reductase (MTHFR) C677T] amongst 357 Caucasian couples with RM and 68 parous Caucasian couples with no history of miscarriage and (ii) the prospective outcome of untreated pregnancies amongst couples with RM in which either partner carried a thrombophilic mutation.

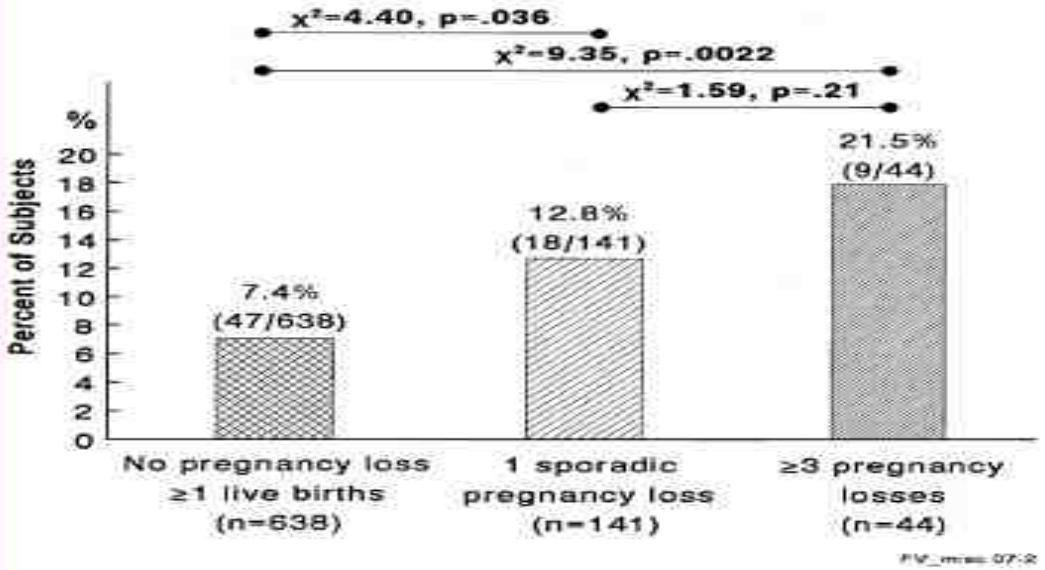
RESULTS: The allele frequencies of FVL (2%), PTG (2%) and MTHFR C677T (31%) were similar between cases and controls. The prevalence of multiple thrombophilic mutations (greater than one mutation) was also similar between cases and controls. Amongst couples in whom either partner carried greater than one thrombophilic allele, the relative risk of miscarriage in a future untreated pregnancy was 1.9 (95% confidence interval, 1.3–2.8) compared with those couples who carried no thrombophilic mutation.

S.Jivraj, 2006

Factor V Leiden mutation: a treatable etiology for sporadic and recurrent pregnancy loss

FIGURE 1

Percentage of women with the factor V Leiden mutation in 141 women with ≥1 pregnancy and 1 pregnancy loss (1 sporadic pregnancy loss), in 638 women with ≥1 pregnancy, ≥1 live birth, and 0 pregnancy loss, and in 44 women with ≥3 pregnancy losses (recurrent pregnancy loss).



Charles J. Glueck, 2008

Etiology of hypercoagulable state in women with recurrent fetal loss without other causes of miscarriage from Southern Italy: new clinical target for antithrombotic therapy

Table 2 Frequency of thrombophilic alterations in women with RPL without other causes of miscarriage and control group

	Study group (115 patients)	Control group (75 patients)	p
MTHFR C677T homozigosity	35/115 (30.0%)	7/75 (9.3%)	<0.001, s
FVL heterozigosity	6/115 (5.2%)	1/75 (1.3%)	0.09, ns
PTHRA20210G heterozigosity	18/115 (15%)	2/75 (2.6%)	0.001, s
PS deficiency	15/115 (13%)	2/75 (2.6%)	0.003, s
PC deficiency	2/115 (1.7%)	0/75 (0%)	0.194, ns
APS	10/115 (8.6%)	0/75 (0%)	0.003, s
Combined defects	6/115 (5.2%)	0/75 (0%)	0.003, s

Abbreviations: RPL, recurrent pregnangy loss; MTHFR C677T, methylene tetrahydro folate reductase gene polymorphism; FVL, factor V Leiden gene polymorphism; PTHR A20210G, prothrombin gene polymorphism; PS, protein S deficiency; PC, protein C deficiency; APS, antiphospholipid syndrome.

Maristella D'Uva, 2008

Inherited thrombophilias and unexplained pregnancy loss: an incident case-control study

Table 3 Comparison of cases and controls with regards to thrombophilic mutations after stratification, according to the gestation time: EPL and LPL groups, at least two losses at or before 12 weeks of amenorrhea or at least one later, according to the number of losses, (three or more in the EPL group)

Subgroups	Factor V Leiden	Prothrombin G20210A	Factor V Leiden or Prothrombin G20210A
EPL			
Female	1.17 [0.59 2.32]	1.35 [0.58 3.12]	1.25 [0.73 2.15]
Male	1.47 [0.62 3.46]	0.87 [0.34 2.2]	1.12 [0.59 2.12]
Couple			1.36 [0.84 2.19]
LPL			
Female	0.82 [0.19 3.55]	0.68 [0.09 5.24]	0.76 [0.23 2.54]
Male	0.6 [0.08 4.79]	1.7 [0.46 6.33]	1.17 [0.38 3.57]
Couple			0.95 [0.38 3.38]
≤12 WA			
Female	1.18 [0.57 2.44]	1.25 [0.5 3.11]	1.25 [0.73 2.15]
Male	1.62 [0.67 3.89]	0.91 [0.35 2.39]	1.26 [0.65 2.43]
Couple			1.4 [0.95 2.3]
> 12 WA			
Female	0.84 [0.25 2.84]	1.42 [0.4 5.01]	1.06 [0.44 2.58]
Male	0.81 [0.17 3.78]	1.51 [0.47 4.89]	1.18 [0.46 3.04]
Couple			1.2 [0.6 2.6]
EPL ≥3			
Female	0.9 [0.38 2.12]	1.3 [0.5 3.4]	1.05 [0.55 2.01]
Male	1.25 [0.47 3.35]	0.8 [0.27 2.34]	1.01 [0.48 2.11]
Couple			1.14 [0.66 1.98]

EPL, Early Pregnancy Loss; LPL, Late Pregnancy Loss; WA, weeks of amenorrhea.

E . PASQUIER, 2008

Paternal Thrombophilic Gene Mutations Are Not Associated with Recurrent Miscarriage

- In this case–control study, German couples with two (n = 49) or three and more RM (n = 102) and 157 German control couples were analyzed for the factor V-Leiden 1691G>A mutation (FVL), the prothrombin (PT) 20210G>A substitution, and the 677C>T replacement in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene.
- Recurrent miscarriage was not associated with paternal thrombophilia. Men of the control group showed an even higher incidence of the PT and MTHFR mutations

Bettina Toth, 2008

Thrombophilic disorders and fetal loss: a meta-analysis

- 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 nonrecurrent fetal loss (3·26, 1·82–5·83).
- 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.

Rey E, 2003

Evaluation of the Association Between Hereditary Thrombophilias and Recurrent Pregnancy Loss

A Meta-analysis

Table 3. Associations Between Factor V Leiden and Prothrombin Mutations With RPL When Examined Within Subgroups

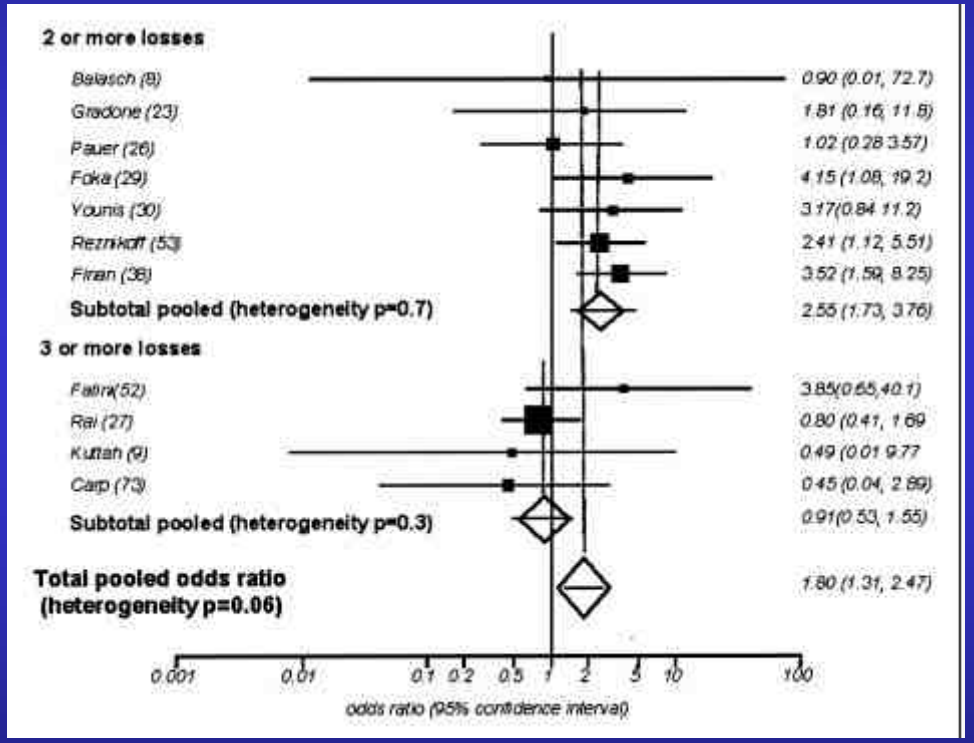
	Factor V Leiden N: 16		Prothrombin Gene (G20210A) N: 7	
	OR	95% CI	OR	95% CI
No. of miscarriages				
≥3	2.1	1.5-3.0	1.6	0.7-3.7
≥2	2.5	1.7-3.6	4.5	1.5-13.3
Time of miscarriages				
First trimester only	1.6	1.2-2.2	3.4	1.5-8.0
First and second trimesters	2.7	2.0-3.7	2.2	1.1-4.4
Race				
White only	1.5	1.1-2.2	3.4	1.3-9.1
Other races included	3.4	2.2-5.1	1.8	0.7-4.4
Other causes				
Unexplained only	2.1	1.5-3.0	1.9	0.7-5.2
Other causes not excluded	2.3	1.5-3.5	3.0	1.3-6.8

Abbreviations: CI, confidence interval; OR, odds ratio; RPL, recurrent pregnancy loss.

George Kovalevsky, 2004

The association between adverse pregnancy outcomes and maternal factor V Leiden genotype: a meta-analysis.

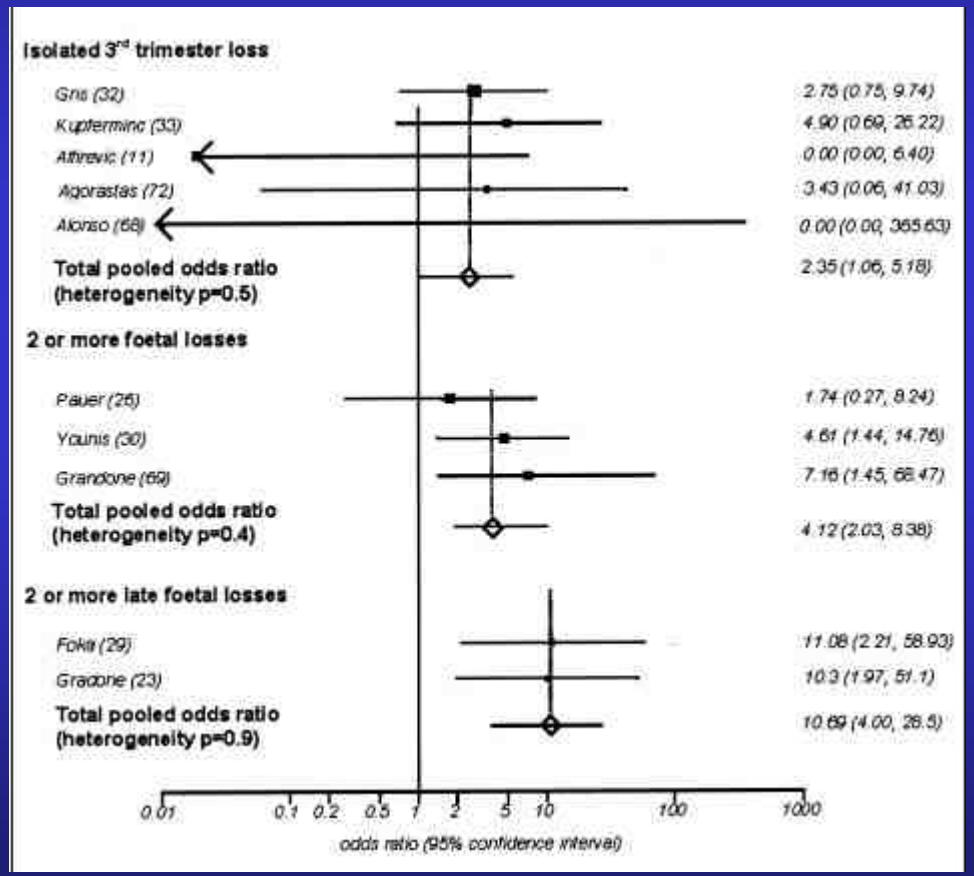
first trimester fetal loss



Tracy E. Dudding, 2004

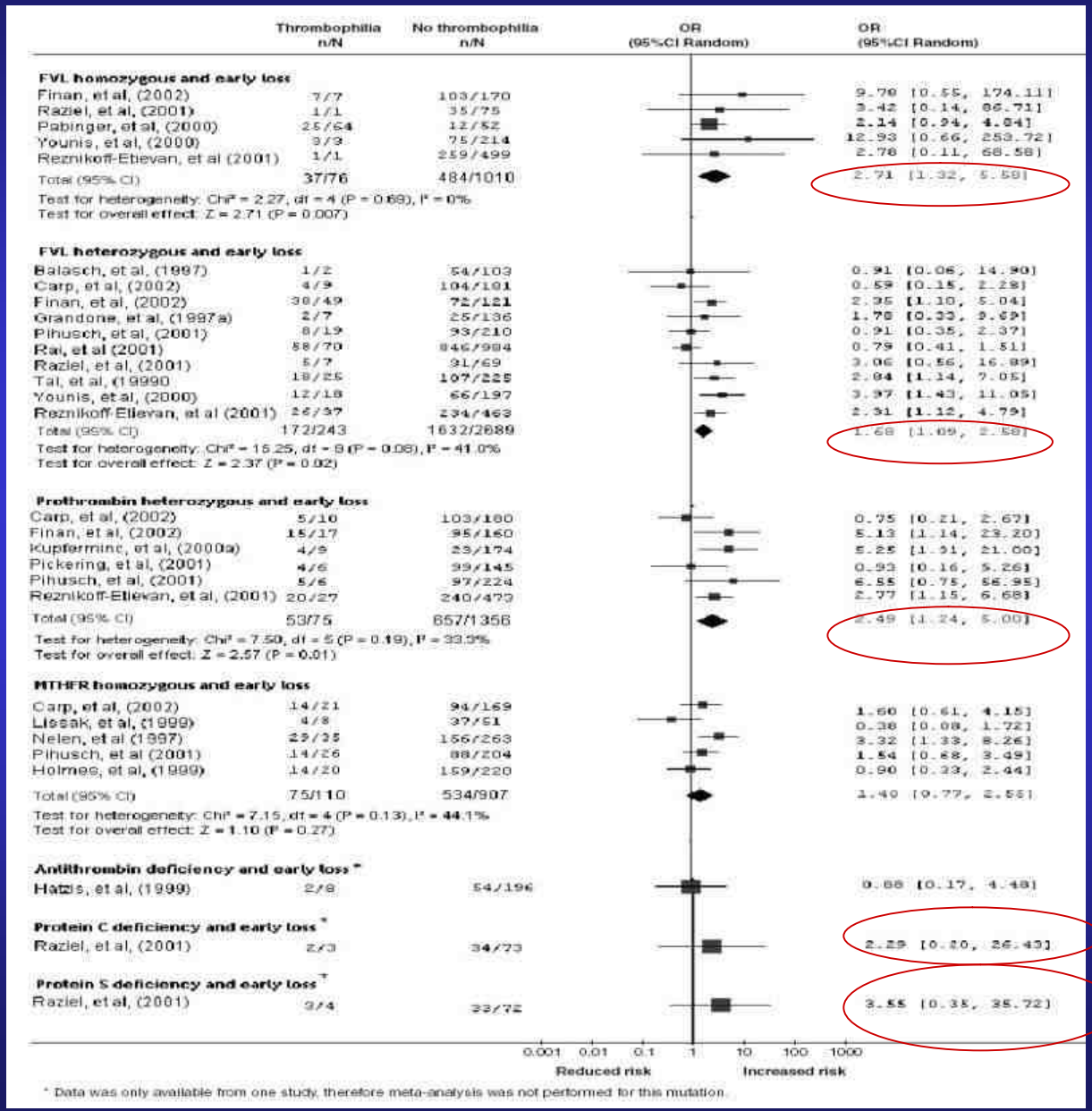
The association between adverse pregnancy outcomes and maternal factor V Leiden genotype: a meta-analysis

second/third trimester fetal loss



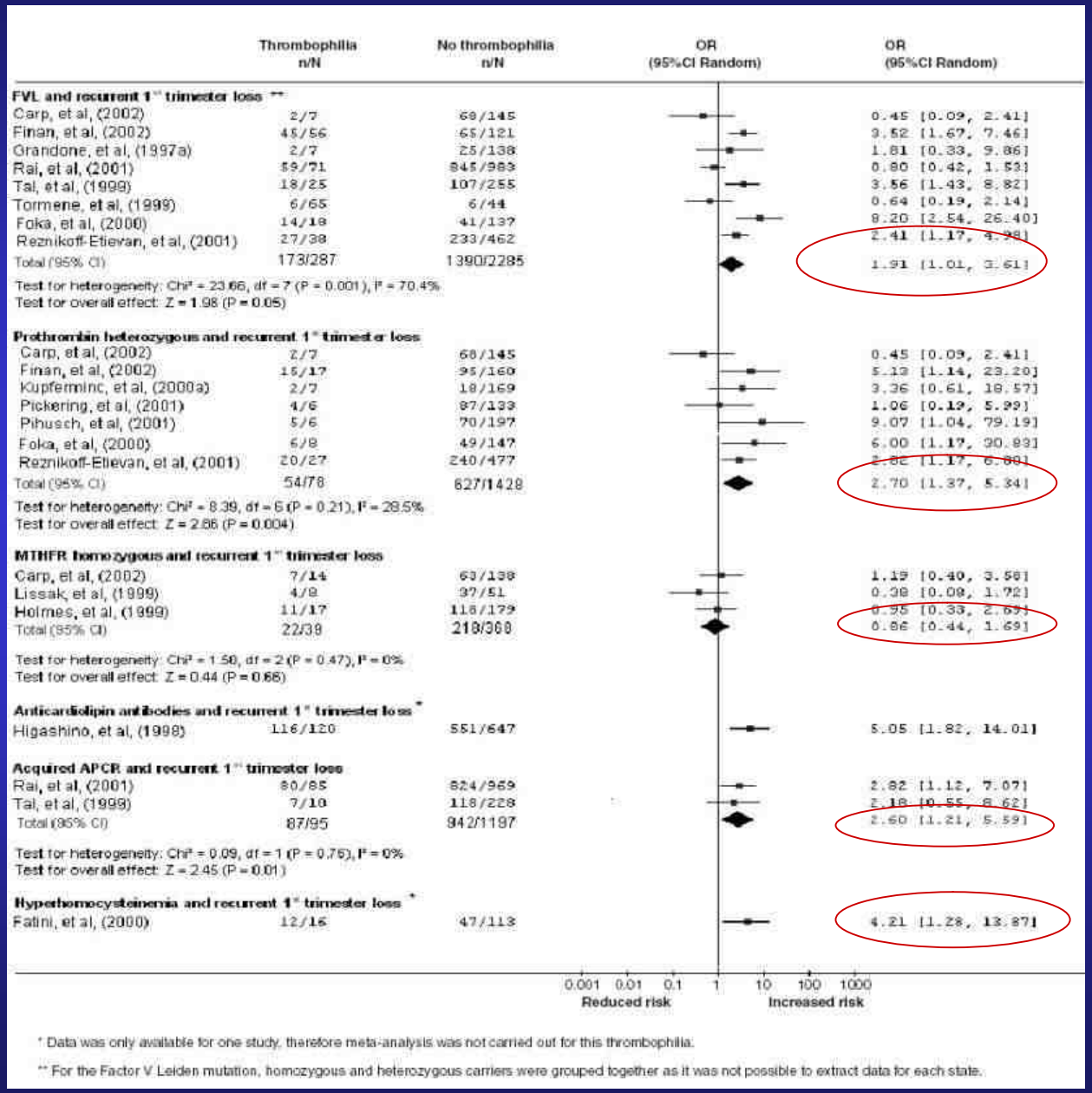
Tracy E. Dudding, 2004

Thrombophilia-Early fetal loss



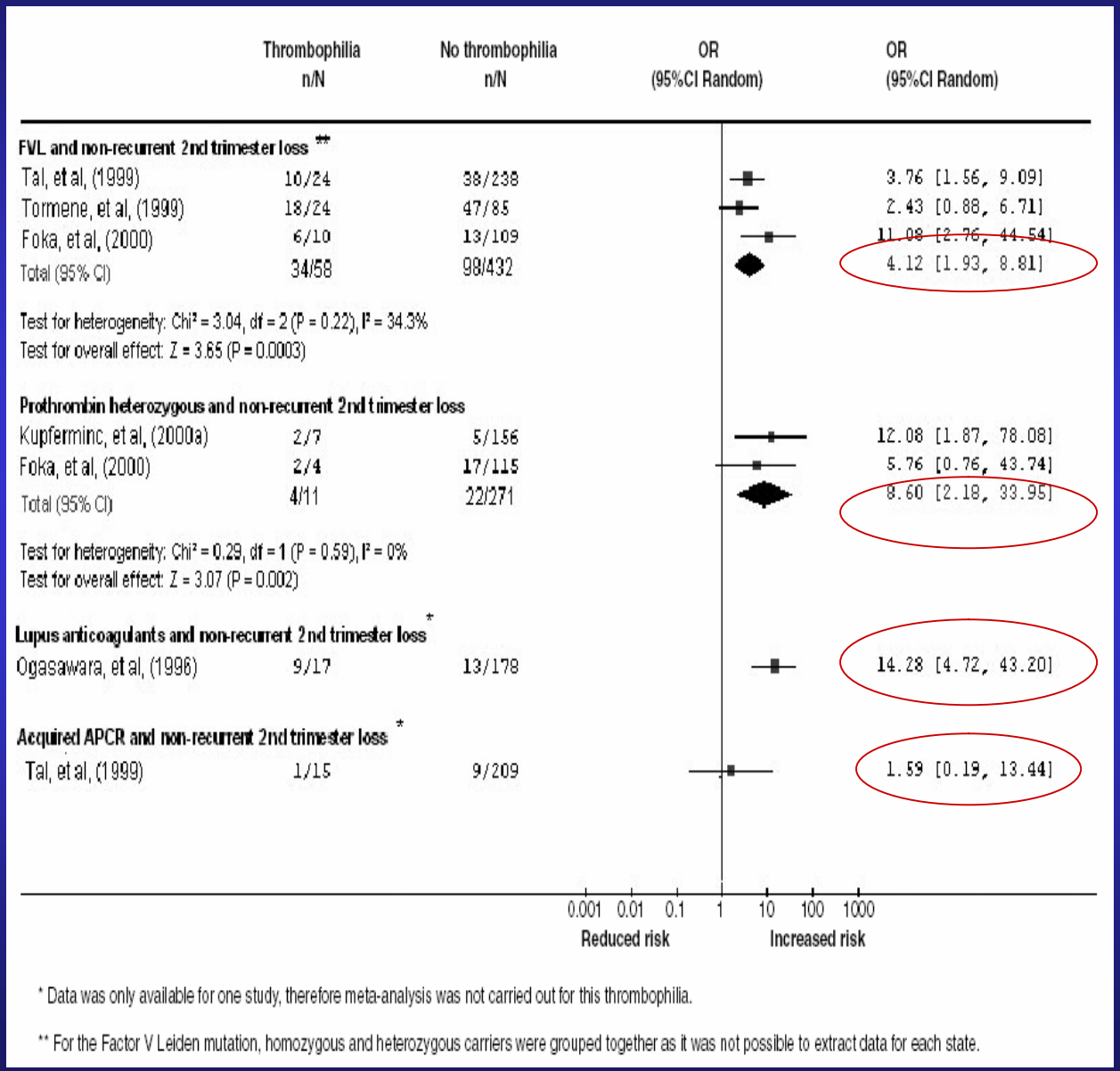
L. Robertson, 2005

Thrombophilia-Recurrent First trimestr loss



L. Robertson, 2005

Thrombophilia- Non-recurrent cecond trimestr loss

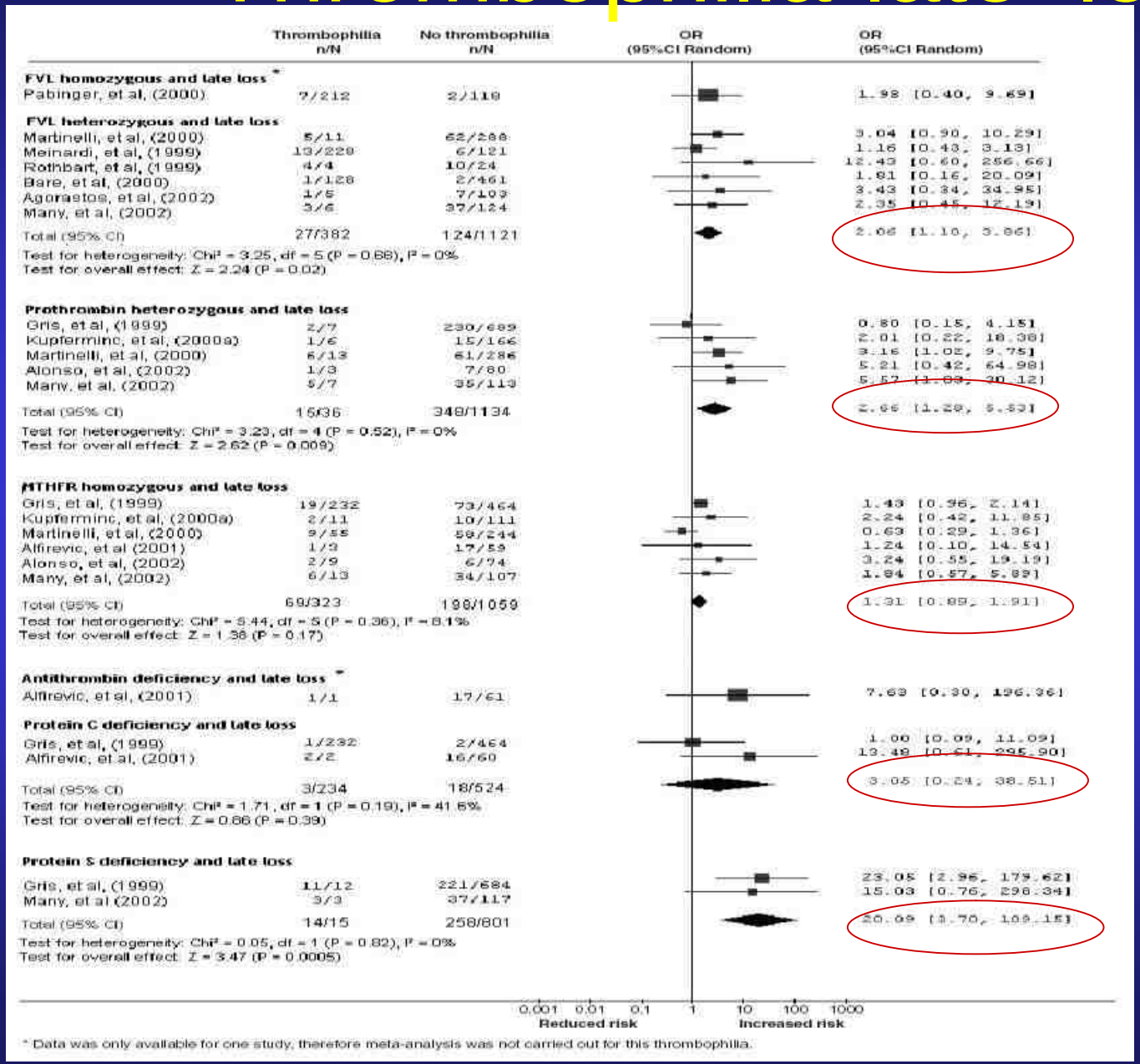


* Data was only available for one study, therefore meta-analysis was not carried out for this thrombophilia.

** For the Factor V Leiden mutation, homozygous and heterozygous carriers were grouped together as it was not possible to extract data for each state.

L. Robertson, 2005

Thrombophilia-late loss



L. Robertson, 2005

Thrombophilias and RPL

- Systematic review of 79 studies
- Publication within last 23 years
- Well-defined study criteria and quality scores
- All women had one or more thrombophilia
- Evaluated associations with early RPL
- No association with antithrombin III, protein C, and protein S deficiency, MTHFR

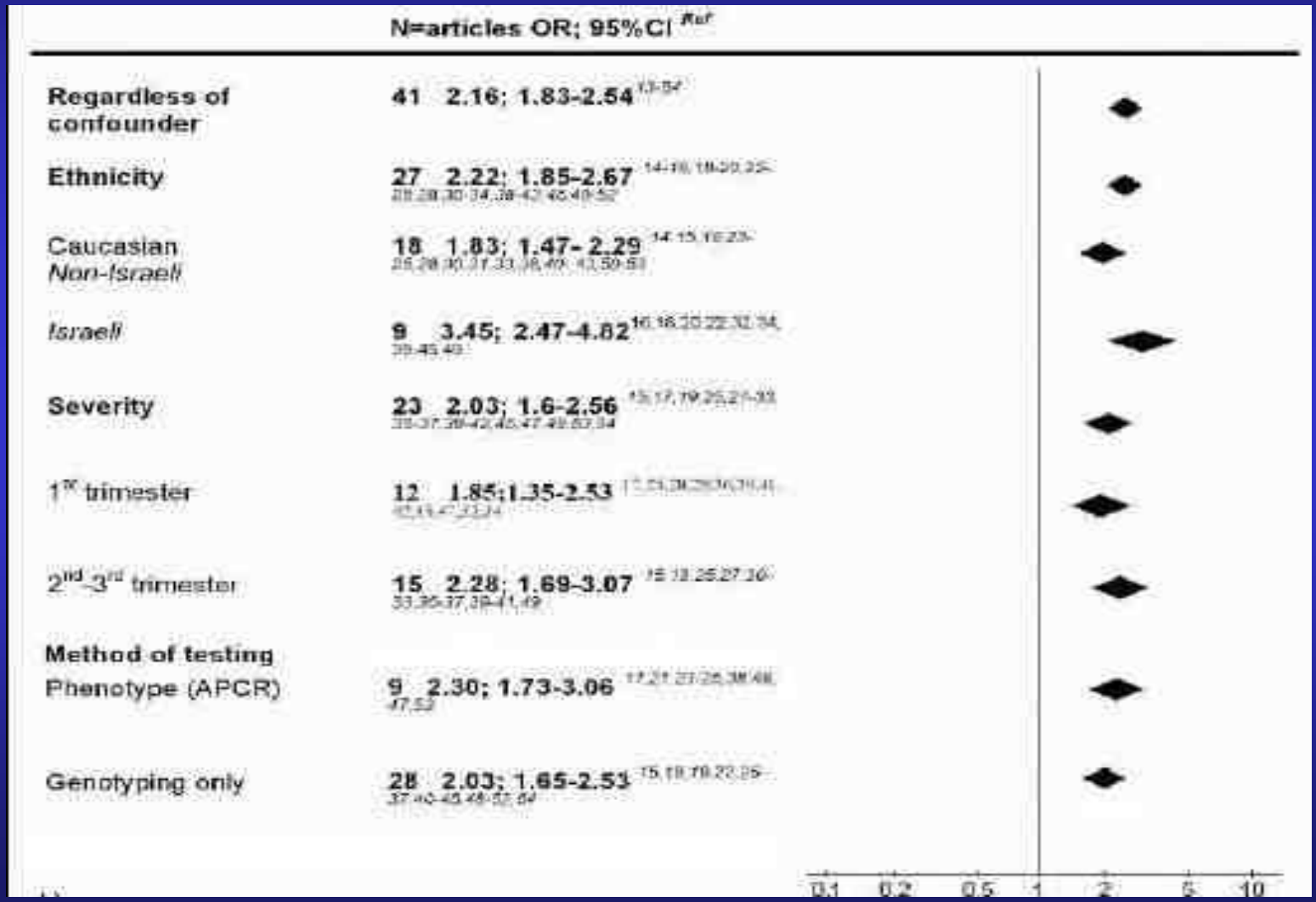
Robertson et al. Br J Haemat 132: 171-196, 2005

Increased Risk of RPL

THROMBOPHILIA	ODDS RATIO (95% CI)
Homocysteine elevation	6.25 (1.37 - 28.42)
Antiphospholipid antibodies	3.40 (1.33 - 8.68)
Lupus Anticoagulant	2.97 (1.03 - 8.56)
Factor V Leiden heterozygous	1.68 (1.09 - 2.58)
Factor V Leiden homozygous	2.71 (2.71 - 5.58)
Activated protein C Resistance	4.04 (1.67 - 9.76)
Prothrombin G20210A mutation	2.49 (1.24 - 5.00)

Robertson et al. Br J Haemat 132: 171-196, 2005

Thrombophilias and adverse pregnancy outcome – A confounded problem



Willem J. Kist, 2008

Screening and treatment for heritable thrombophilia in pregnancy failure: inconsistencies among UK early pregnancy units

Table I. Thrombophilia screening by pregnancy complication.

	Recurrent miscarriage, *n* (%)	Late miscarriage, *n* (%)	Placental abruption, *n* (%)
Do not manage these patients	7	12	67
Assess*	108	103	48
F5 R506Q	78 (72)	82 (80)	39 (81)
F2 G20210A	54 (50)	50 (49)	29 (60)
Protein C deficiency	82 (76)	82 (80)	42 (88)
Protein S deficiency	81 (75)	82 (80)	42 (88)
Antithrombin deficiency	75 (69)	76 (74)	41 (85)
Hyperhomocysteinaemia	15 (14)	14 (14)	7 (15)
Antiphospholipid antibodies	108 (100)	103 (100)	48 (100)

Gillian Norrie, 2008

Tekrarlayan IVF Başarısızlığı (İmplantasyon)

Thrombophilic mutations in Iranian patients with infertility and recurrent spontaneous abortion

Table 1 Frequency of mutations (heterozygous plus homozygous) in control group and patients as well as frequency of abnormal APC-R level

	FVL			MTHFR			FII			decreased APC-R	
	f	%	*P*	*f*	%	*P*	*f*	%	*P*	*f*	%
Inf	11/36	30.6	<0.001	18/36	50.0	0.276	1/36	2.8	1.000	6/24	25.0
RSA	13/65	20.0	<0.001	41/65	63.1	0.006	3/65	4.6	1.000	10/53	18.9
Cont	0/62	0.0	–	24/62	38.7	–	2/62	3.2	–	ND	ND

N:36
N.65
N:63

Inf: infertility, RSA: recurrent spontaneous abortion, Cont: control group, FVL: factor V Leiden, MTHFR: methylenetetrahydrofolate reductase, FII: factor II, *f*: frequency, *P*: P value, ND: not done

Reza Behjati, 2006

The role of thrombophilia in unexplained infertility, implantation failure and recurrent spontaneous abortion

- unexplained infertility (n:31), implantation failure (n:26) and recurrent spontaneous abortion (n:30), control (n:32)
- The prevalence of thrombophilia was high and similar among groups. In the implantation failure group, the prevalence of APCR (15.4%), lupus anticoagulant (11.5%) and combined thrombophilia (19.2%) was higher, but not significantly different, than the other three groups

José´ Bellver, 2008

Enoxaparin-metformin and enoxaparin alone may safely reduce pregnancy loss

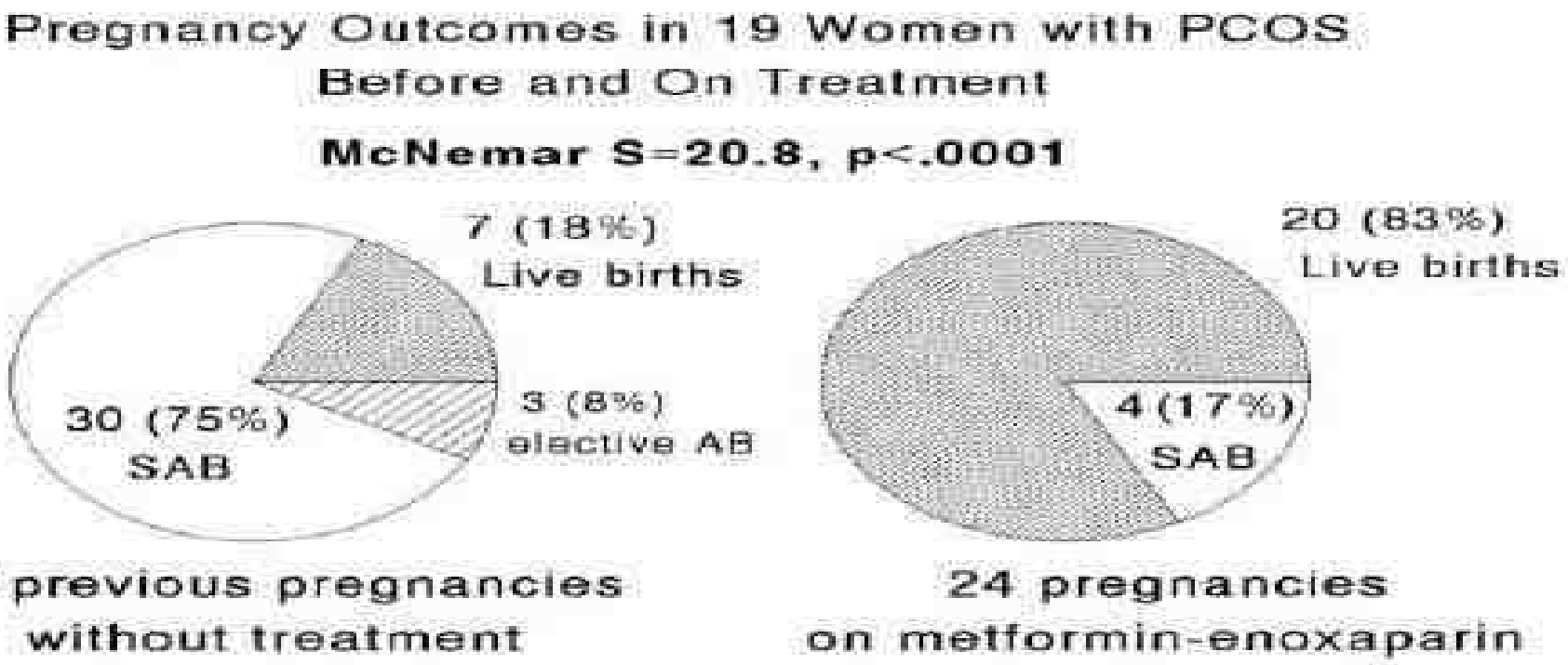


Fig 1. Pregnancy outcomes in 19 women with PCOS that had 40 previous pregnancies without enoxaparin-metformin and 24 pregnancies (24 fetuses) on enoxaparin-metformin.

GANGA RAMIDI, 2009

Selection pressure for the factor-V Leiden mutation and embryo implantation

Variable	First embryo transfer successful* (n=54)	First embryo transfer not successful (n=48)	p
Isolated male infertility	27 (50%)	25 (52%)	0·831
Transfer of one embryo	1 (2%)	2 (4·1%)	0·732
Maternal age <33 years	31 (57%)	19 (40%)	0·535
Previous pregnancies	8 (15%)	11 (23%)	0·393
Mother or infant FVL positive	9 (17%)	1 (2%)	0·038

*One or more infants were born. All values are number (%). p values were calculated with multivariate logistic regression analysis.

Göpel W, 2001

Factor V Leiden: relation to fertility? (n: 9000)

	Number of children	p
All		
Non-carriers (n=8314)	1·55 (0·01)	..
Heterozygotes (n=689)	1·52 (0·05)	0·33
Homozygotes (n=20)	1·65 (0·32)	0·95
Women		
Non-carriers (n=4691)	1·57 (0·02)	..
Heterozygotes (n=395)	1·54 (0·06)	0·63
Homozygotes (n=10)	1·50 (0·31)	0·99
Men		
Non-carriers (n=3623)	1·53 (0·02)	..
Heterozygotes (n=294)	1·50 (0·08)	0·35
Homozygotes (n=10)	1·80 (0·57)	0·94

Klaus Juul, 2002

Embryo implantation and maternal thrombophilia

Table 2. Prevalence of mutations in factor V, prothrombin and methylene-tetrahydrofolate reductase in the women undergoing assisted reproductive procedures and control women.

	Women in whom assisted reproductive procedures failed (n=162)	*Women with spontaneous conception (n=234)*	*Odds ratio* (95% CI)*
	no. (%)		
Factor V gene mutation	8 (5)	5 (2)	2.4 (0.7-8.3)
Prothrombin gene mutation	5 (3)	13 (6)	0.5 (0.2-1.6)
Methylene-tetrahydrofolate reductase gene mutation	31 (19)	46 (20)	1.0 (0.5-1.7)

**adjusted for age, gravidity and smoking status.*

Background and Objectives. Women undergoing assisted reproductive procedures, such as *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), fail to achieve pregnancy in approximately 70% of cases. Postulating that among the possible causes of failure of embryo implantation might be an impairment of the uteroplacental circulation due to hypercoagulability in the mother, we investigated the association between thrombophilia and failure to achieve pregnancy after IVF or ICSI.

Design and Methods. A case-control study was carried out in 234 women undergoing IVF or ICSI and in 234 women who, in the same period, conceived naturally. Thrombophilia due to mutations in genes encoding coagulation factor V (G1691A), prothrombin (G20210A), methylene-tetrahydrofolate reductase (C677T) and the presence of antiphospholipid antibodies was searched for.

Results. The prevalence of factor V, prothrombin and methylene-tetrahydrofolate reductase mutations was similar in the 162 women who failed to achieve pregnancy after IVF or ICSI and in control women (5% and 2% for factor V G1691A, odd ratio 2.4, 95% CI 0.8-7.4; 3% and 6% for prothrombin G20210A, odds ratio 0.5, 95% CI 0.2-1.5; 19% and 20% for homozygous methylene-tetrahydrofolate reductase C677T, odds ratio 1.0, 95% CI 0.6-1.6). Nor was any association found when women who failed to achieve pregnancy were divided according to the total number of assisted reproductive procedures, age, type of procedure and cause of infertility. Antiphospholipid antibodies were not detected in any of the women.

Interpretation and Conclusions. This study provides no evidence for an association between maternal thrombophilia and failure to achieve pregnancy after assisted reproductive procedures. Routine anticoagulant treatment in women undergoing assisted reproductive procedures is not warranted.

Martinelli I, 2003

Increased rates of thrombophilia in women with repeated IVF failures

Table II. Summary of the incidence of inherited thrombophilias in the study population

Thrombophilia	Group A ($n = 45$) [n (%)]	Group B ($n = 44$) [n (%)]	Group C ($n = 15$) [n (%)]
All thrombophilias	20 (44.4)	8 (18.2)[a]	3 (20)
All thrombophilias without MTHFR	12 (26.7)	4 (9.1)[b]	1 (6.7)
MTHFR homozygote	8 (17.8)	4 (9.1)	2 (13.3)
Prothrombin mutation	4 (8.9)	1 (2.3)	1 (6.7)
Protein S deficiency	4 (8.9)	0	0
Protein C deficiency	0	0	0
Factor V Leiden	3 (6.7)	3 (6.8)	0
AT-III	1 (2.2)	0	0

[a] $P = 0.012$; OR 3.6; 95% CI 1.25–10.6.
[b] $P = 0.03$; OR 2.9; 95% CI 1.02–8.4.

Foad Azem, 2004

Acquired and inherited thrombophilia: implication in recurrent IVF and embryo transfer failure

Table II. Frequency of thrombophilic factors in the study groups

Thrombophilic factors	Study group	Control group		*P*-Value	
	Group A ($n = 90$)	Group B ($n = 90$)	Group C ($n = 100$)	A versus B	A versus C
Factor V Leiden					
Heterozygous	9 (10)	1 (1.1)	2 (2)	0.108	0.162
Homozygous	4 (4.4)	0	0	0.049	0.294
Methylenetetrahydrofolate reductase (C677T) mutation					
Heterozygous	7 (7.8)	8 (8.9)	9 (9)	1.00	1.00
Homozygous	13 (14.4)	3 (3.3)	2 (2)	0.046[a]	0.012[a]
Prothrombin G20210A gene					
Heterozygous	5 (5.6)	3 (3.3)	3 (3)	0.720	0.460
Homozygous	1 (1.1)	1 (1.1)	0	1.00	0.474
Protein C deficiency	2 (2.2)	1 (1.1)	0	1.00	0.223
Protein S deficiency	3 (3.3)	2 (2.2)	3 (3)	1.00	1.00
Antithrombin III deficiency	1 (1.1)	0	1 (1)	1.00	1.00
Lupus anticoagulant	8 (8.9)	2 (2.2)	2 (2)	0.294	0.204
Anticardiolipin	9 (10)	2 (2.2)	3 (3)	0.222	0.294
Combined thrombophilia	32 (35.6)	4 (4.4)	3 (3)	<0.0001[a]	<0.0001[a]

3 Ivf basarısız ilk ivfde basarılı

P-Values are adjusted using Bonferroni's correction. Values within parentheses are percentage.
[a]Significant at $\alpha = 0.05$.

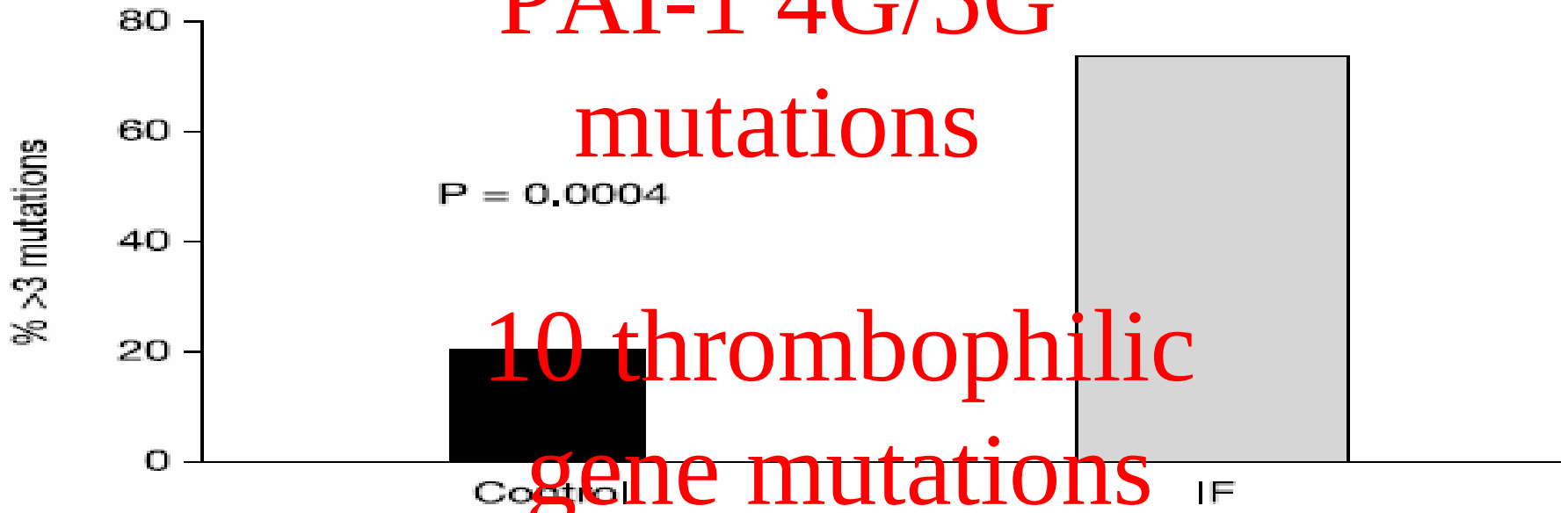
Hussein S.Qublan, 2006

Diagnostic evaluation of women experiencing repeated in vitro fertilization failure

- Fifty-nine patients with at least two unsuccessful IVF attempts and 20 normal fertile control patients
- The prevalence of thyroid abnormalities, aPL and increased NK level was higher in IVF patients whereas no differences were observed in terms of prevalence of inherited thrombophilias .

Elena Vaquero, 2006

Multiple thrombophilic gene mutations are risk factors for implantation failure



PAI-1 4G/5G mutations

10 thrombophilic gene mutations

n:20

n:42

Carolyn B Coulam , 2006

Low-molecular-weight heparin in the treatment of recurrent IVF-ET failure and thrombophilia: A prospective randomized placebo-controlled trial

Table II. Treatment characteristics and reproductive outcome.

	Group A (N = 42)	Group B (N = 41)	p-value
Day 3 FSH (IU/l)	6.1 ± 3.5	6.1 ± 3.3	NS
Days of stimulation	13.4 ± 4.1	13.3 ± 4.2	NS
No. of hMG ampoules	54.5 ± 8.2	54.2 ± 8.1	NS
No of oocytes retrieved	11.3 ± 3.2	11.2 ± 3.1	NS
– Metaphase II oocytes (%)	(83)	(82)	NS
Fertilization rate (%)	(73.1)	(73.3)	NS
No. of day 2 embryos	(6.3)	(6.1)	NS
Grade of embryos			
– Good (%)	(54)	(52)	NS
– Fair (%)	(26)	(25)	NS
– Poor (%)	(20)	(23)	NS
No. of embryos transferred	(3.3)	(3.2)	NS
Implantation rate* (%)	29/139 (19.8)	8/131 (6.1)	<0.001
Pregnancy rate (%)	13/42 (31)	4/41 (9.6)	<0.05
Multiple pregnancy rate (%)	3/13 (23.1)	1/4 (25)	NS
Abortion rate (%)	1/13 (7.7)	2/4 (50)	<0.05
IUFD** rate (%)	2/13 (15.4)	0	NS
Live birth rate (%)	10/42 (23.8)	1/41 (2.4)	<0.01

Values are expressed as mean ± SD and percentages.
*Number of gestational sacs detected by ultrasound/number of transferred embryos.
**IUFD = Intrauterine foetal death.

Rx

PL

H. Qublan, 2008

Repeated in vitro fertilization failure and its relation with thrombophilia.

- The study group included 51 consecutive women with three or more previously failed IVF-embryo transfer cycles (group 1). The control group included 50 women who conceived spontaneously with at least one uneventful pregnancy and no previous history of miscarriage
- 62.7% of women with repeated IVF failure and in 53.9% of women in control group
- These data suggest that factor V Leiden, methylenetetrahydrofolate reductase and prothrombin gene mutation do not have a significant role in IVF-embryo transfer implantation failure.

Simur A, 2009

Anti-phospholipid antibodies do not affect IVF success

The Practice Committee of the American Society for Reproductive Medicine
2008

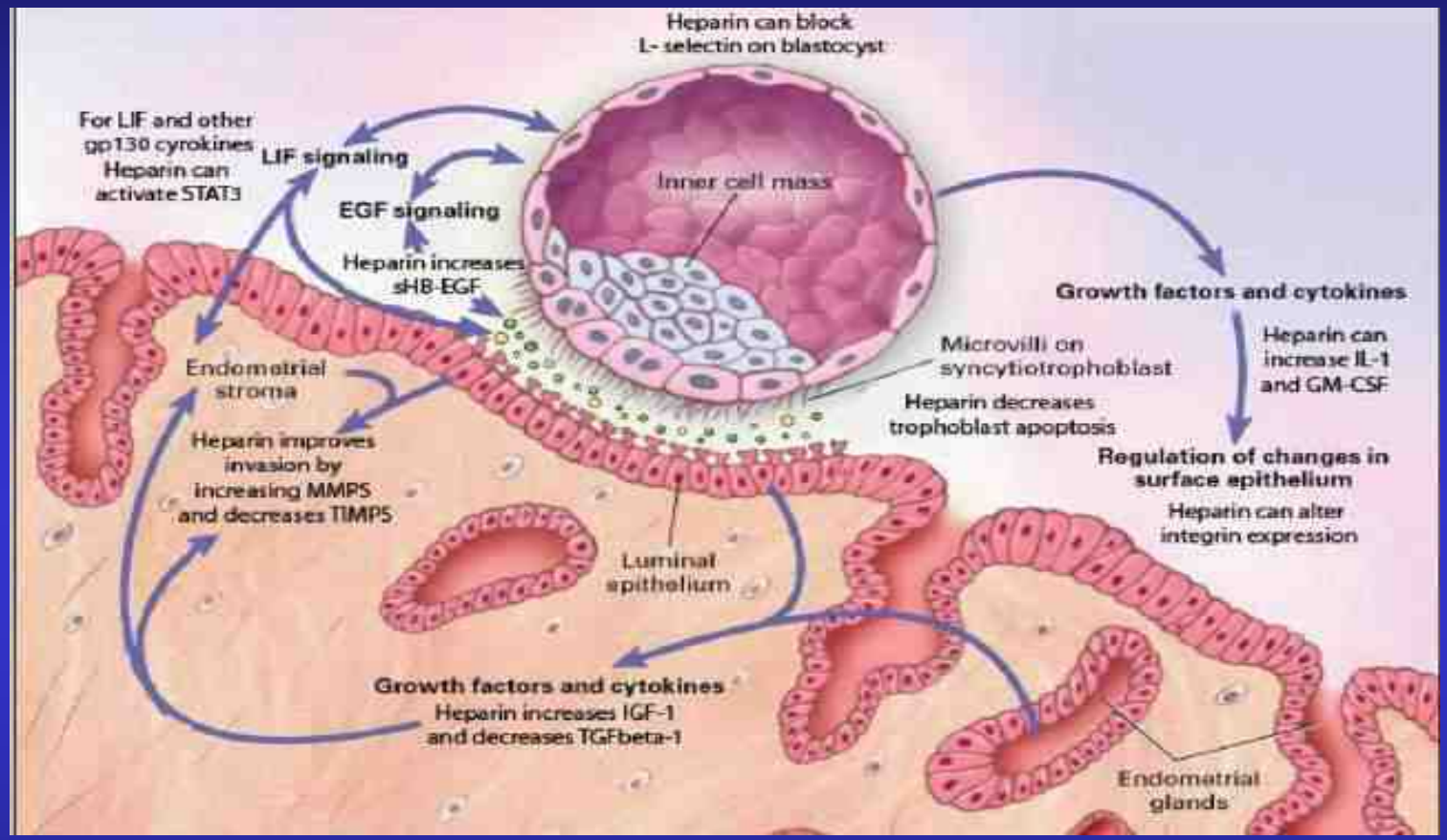
- Although an association between APA abnormalities and IVF failure has been suggested in some retrospective studies, no association is present in the prospective studies summarized here. The assessment of APA is not indicated among couples undergoing IVF. Therapy is not justified on the basis of existing data.

Heparin treatment in pregnancy loss:Potential therapeutic benefits beyond anticoagulation

1. Anticoagulation
2. Reduction of antiphospholipid antibodies binding
3. Antiinflammatory effects
4. Heparin facilitates implantation
5. Heparin as a complement inhibitor

Guillermina Girardi , 2005

The potential role of heparin in implantation



It can also modulate many of the fundamental physiological processes required for blastocyst apposition, adherence and implantation and as well as trophoblast differentiation and invasion due to its similarities with heparan sulphates and has the potential to improve pregnancy rates and outcomes

Scott M. Nelson and Ian A. Greer, 2008

Table 1. Investigations undertaken for recurrent treatment IVF failure.

Investigation	Proportion of centres undertaking investigation (%), $n = 44$
Lupus anticoagulant/anticardiolipin antibodies	75
Karyotype (both partners)	70.4
Hysteroscopy	70.4
Thrombophilia screen	59
TSH	27
HBA1c	20.4
Timed endometrial biopsy	20.4
Untimed endometrial biopsy	2.2
Saline sonography	6.8

Bee K. Tan, 2005

Düsük Moleküler Ağırlıklı Heparin preparatları

- Enoxaparin (Clexane)
- Dalteparin (Fragmin)
- Nadroparin (Fraxiparine)
  - Biyoyararlılığı daha iyi
  - Daha uzun etkili
  - Monitorizasyon gerekmez
  - Yan etkileri daha az
  - Teratojenik ve fetotoksik değil,plasentayı geçmez

Low-molecular-weight heparin versus low-dose aspirin in women with Low-molecular-weight heparin versus low-dose aspirin in women with

Table 3. Effect of the two treatments on pregnancy outcome

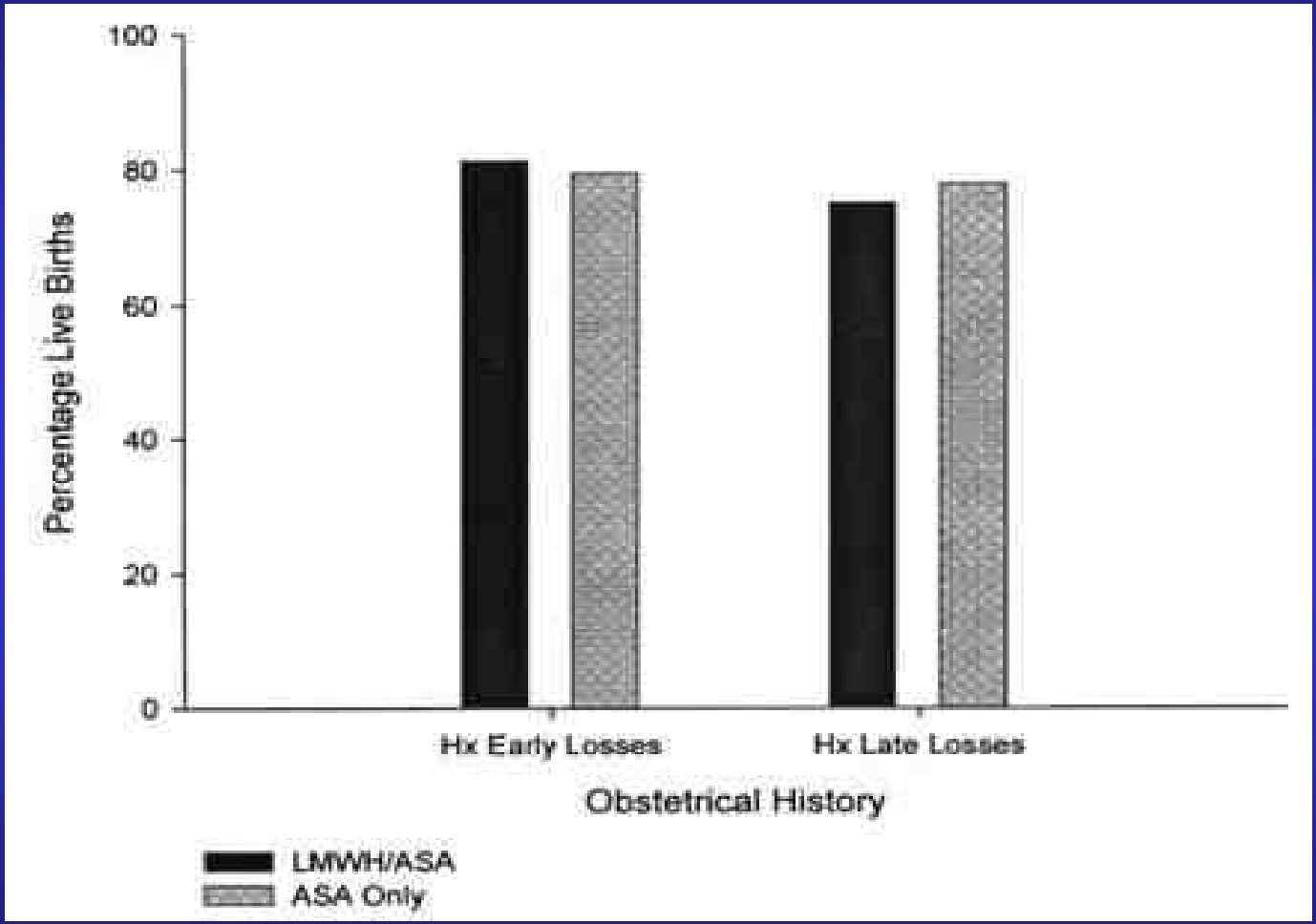
	N	Live births	P*	OR	95% CI	P
All women			< .0001			
Aspirin	80	23 (29%)				
Enoxaparin	80	69 (86%)		15.5	7-34	< .0001
All FVL			< .0001			
Aspirin	36	12 (33%)				
Enoxaparin	36	34 (94%)		34	7-166	< .0001
All FIIL			.0007			
Aspirin	30	10 (33%)				
Enoxaparin	30	24 (80%)		8	2.5-26	.0005
All PS			.0006			
Aspirin	14	01 (07%)				
Enoxaparin	14	11 (79%)		48	4-526	.0016

OR indicates crude odds ratio for giving birth to a live healthy baby after treatment with low-molecular-weight heparin enoxaparin, low-dose aspirin being the treatment of reference; CI, confidence interval; AllFVL, all patients carrying the heterozygous factor V Leiden mutation; AllFIIL, all patients carrying the heterozygous factor II G20210A mutation; AllPS, all patients carrying a protein S deficiency.

Jean-Christophe Gris, 2004

Low Molecular Weight Heparin and Aspirin for Recurrent Pregnancy Loss: Results from the Randomized, Controlled HepASA Trial

N: 88

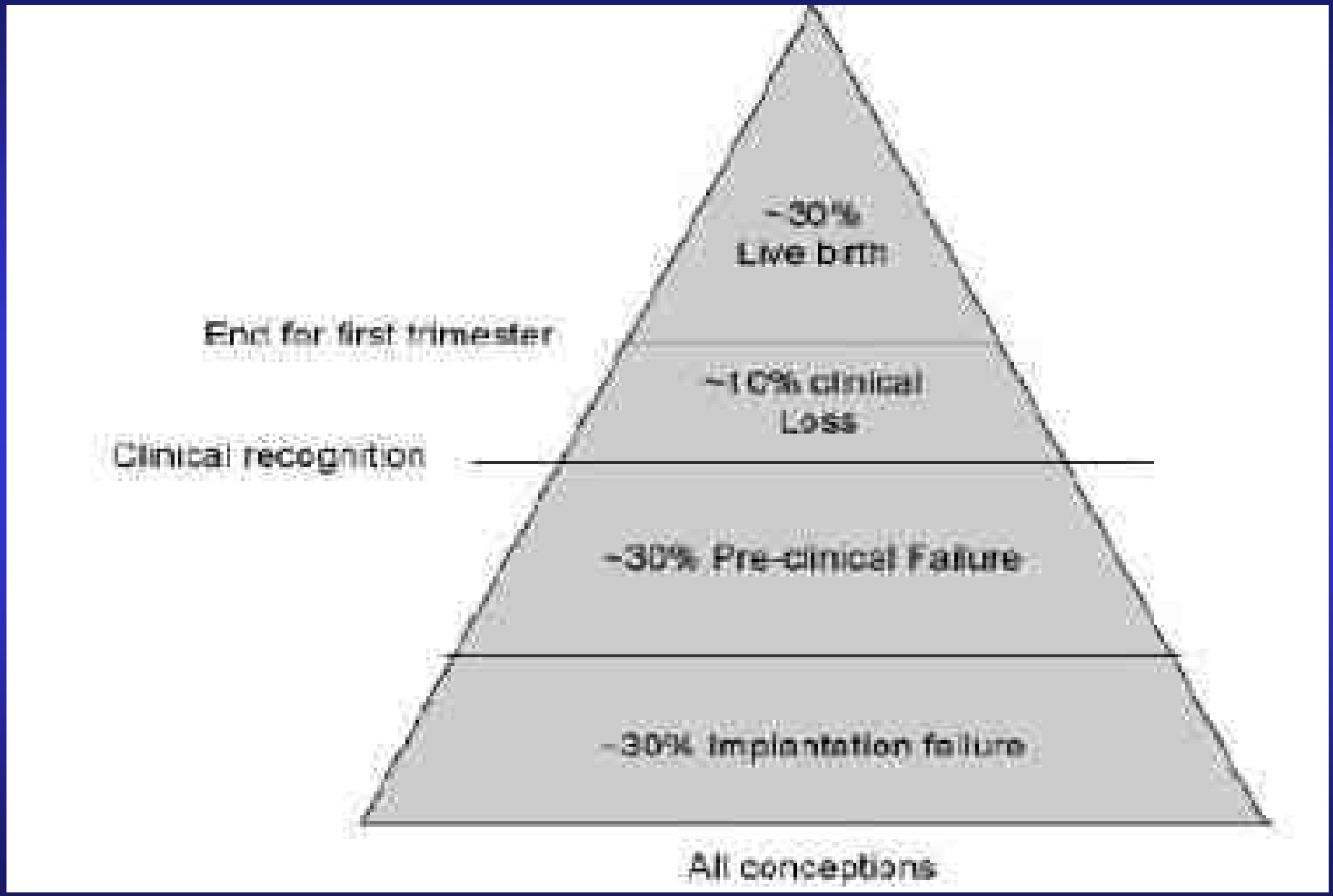


CARL A. LASKIN, 2009

Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome

- **Objectives**
- To evaluate the efficacy and safety of anticoagulant agents, such as aspirin and heparin, in women with a history of at least two miscarriages without apparent causes other than inherited thrombophilia
- **Authors' conclusions**
- There is a paucity in studies on the efficacy and safety of aspirin and heparin in women with a history of at least two miscarriages without apparent causes other than inherited thrombophilia. The two reviewed trials studied different treatments and only one study was placebo-controlled. Neither of the studies showed a benefit of one treatment over the other. Therefore, the use of anticoagulants in this setting is not recommended. However, large randomised placebo-controlled trials are still urgently needed.

Stef Kaandorp, *Cochrane Database of Systematic Reviews, Issue 3, 2009*


~30%
Live birth
End for first trimester
~10% clinical
Loss
Clinical recognition
~30% Pre-clinical Failure
~30% Implantation failure
All conceptions

- *Biochemical loss* *occurs before week 6 (range:* 0-6), and is never associated with the detection of fetal heart activity, pregnancy is not located on ultrasound exams, serum Beta-HCG levels are low then fall.
- *Early pregnancy loss* *typically occurs between* weeks 6 and 8 (range: 4 -10), with no detection of fetal heart activity, ultrasound exams find an empty sac or large sac with minimal structures without foetal heart activity, serum Beta-HCG levels rise then fall.
- *Late pregnancy loss* *develops from week 12* (range: 10-20), fetal heart activity is lost, CRL and fetal heart activity have been previously identified, serum Beta-HCG levels rise then are static or fall.
- *Stillbirth* *is the death of a viable fetus* weighing at least 500 g (or when birth weight is unavailable, after 20 completed weeks post fertilisation or with a crown heel length of 25 cm or more), before the complete expulsion or extraction from its mother

Farquharson RG, ESHRE, 2005