Low Molecular Weight Heparin, Inherited Thrombophilia and Pregnancy Complications

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3 Questions/3 Cases

- Do inherited thrombophilias cause placenta mediated pregnancy complications or pregnancy loss?

- Do anticoagulants (specifically Low Molecular Weight Heparin (LMWH)) prevent these complications in…
  - Thrombophilic women?
  - Non-thrombophilic women?

Workshop Style

- Interaction= better learning
- Work through cases together and develop our answers (where we can)

Case 1

30 yo woman with prior pre-eclampsia (PET) and FVL asks:

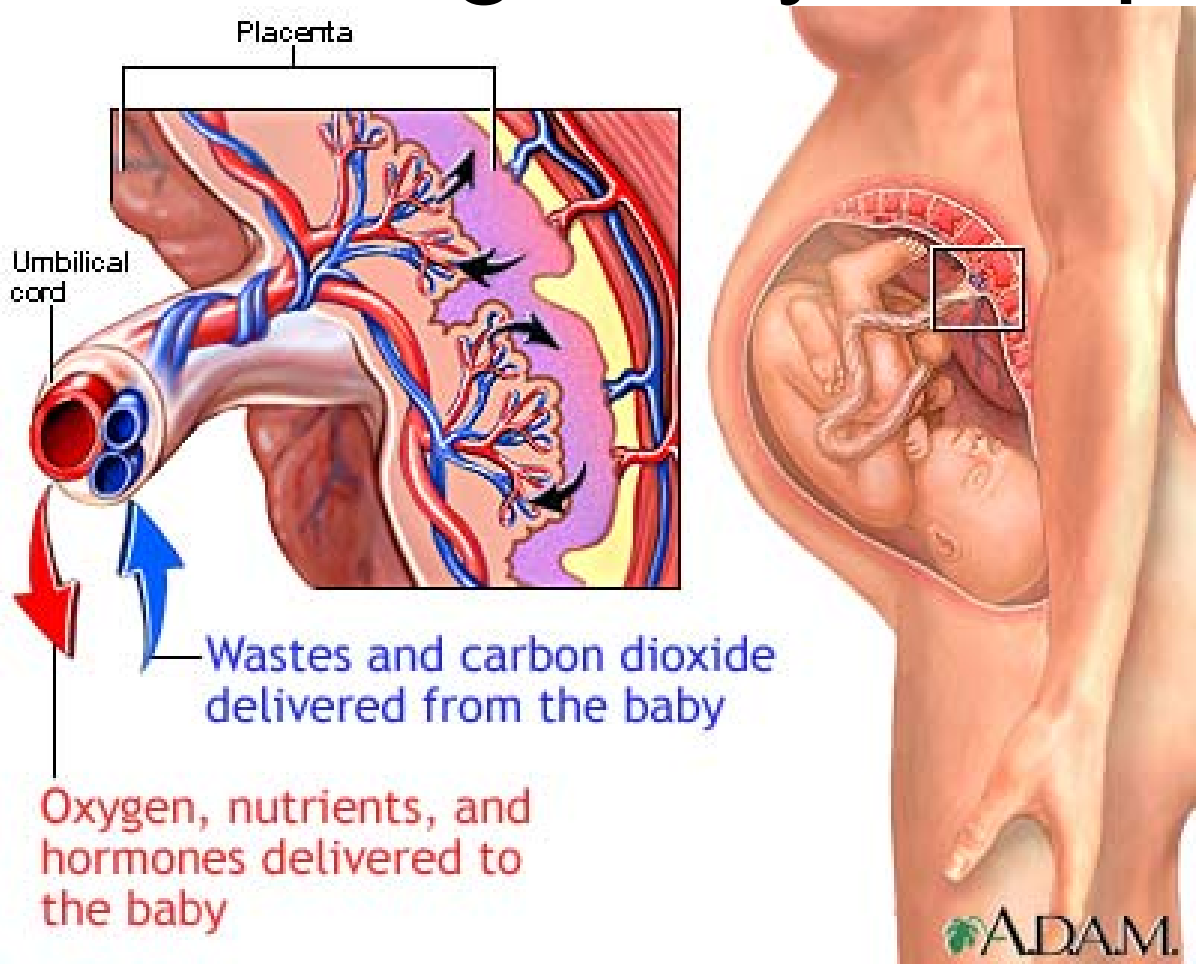
“Did my FVL **cause** my PET?”

Case 1

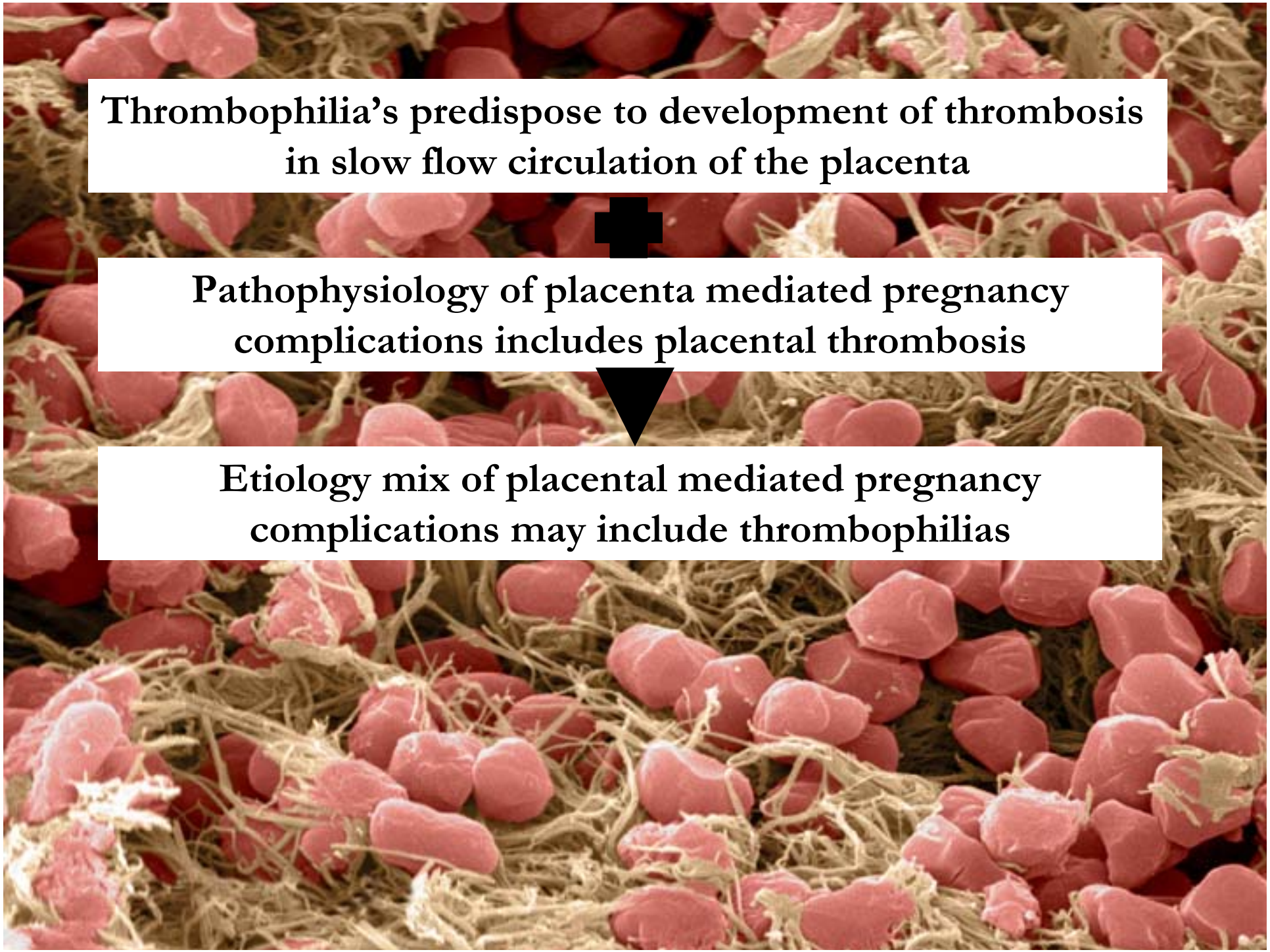
FVL cause PET?

1. Definitely **not** if it was near term and mild disease
2. **Maybe** if it was severe PET
3. Definitely, all PET, mild or severe, **is** caused by thrombophilia
4. Definitely, severe PET **is** caused by thrombophilia
5. 1 and 2

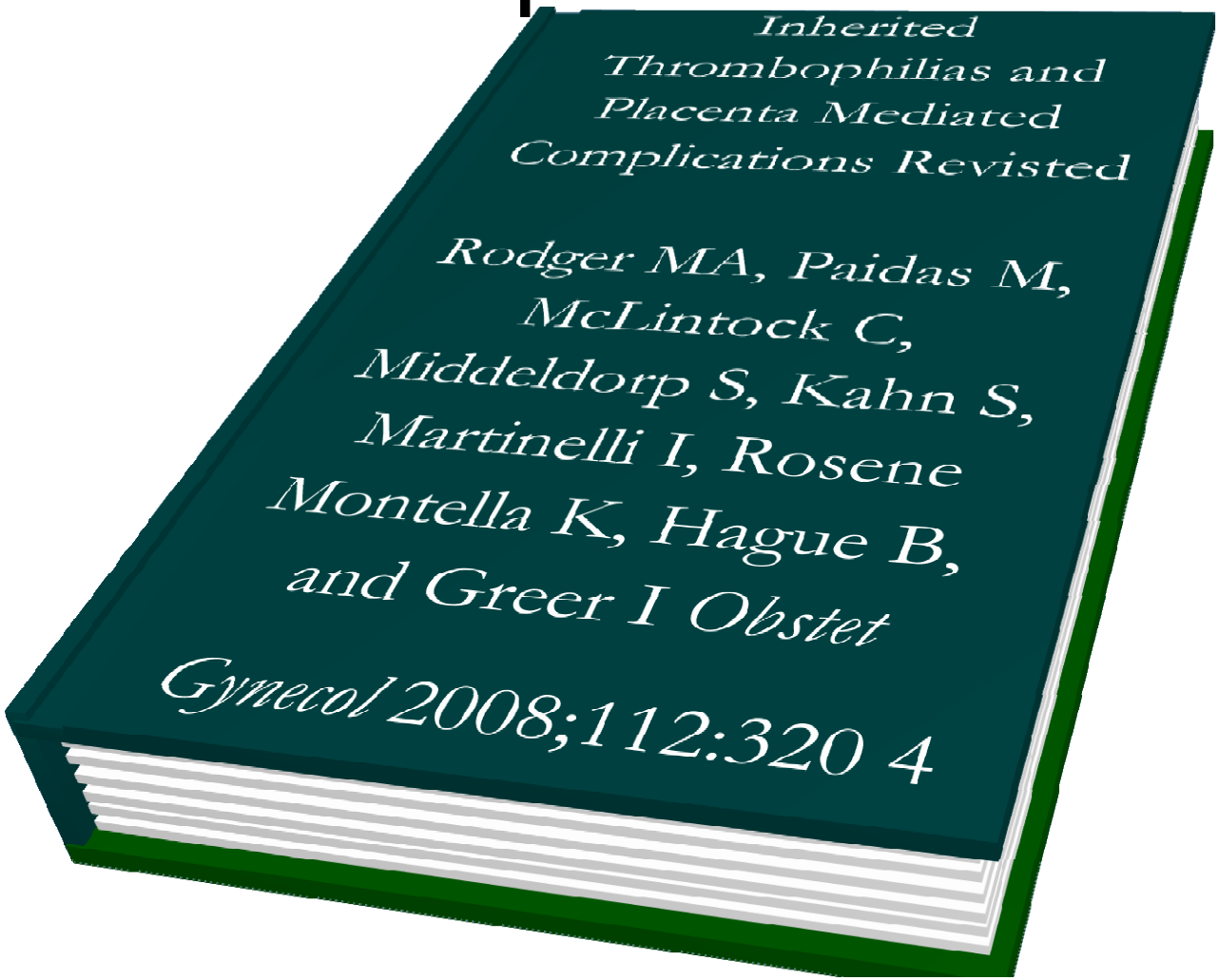
Thrombophilia, Anticoagulants and Placenta Mediated Pregnancy Complications



- Pregnancy loss
- Small for gestational age
- Pre-eclampsia
- Placental Abruption


Thrombophilia's predispose to development of thrombosis in slow flow circulation of the placenta
Pathophysiology of placenta mediated pregnancy complications includes placental thrombosis
Etiology mix of placental mediated pregnancy complications may include thrombophilias

Do inherited thrombophilias cause placenta mediated pregnancy complications?



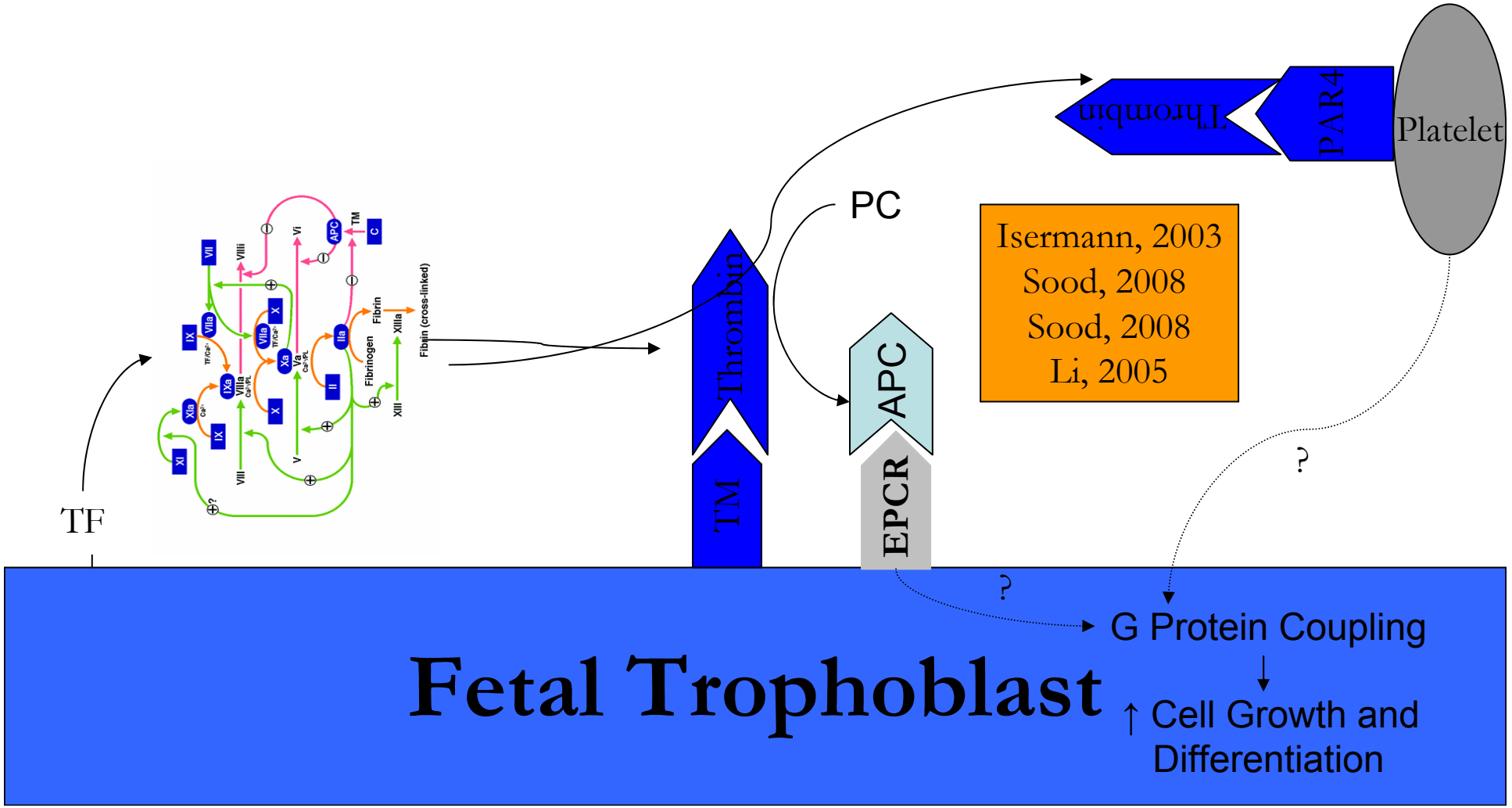
Causation

Sir A. Bradford Hill's Criteria

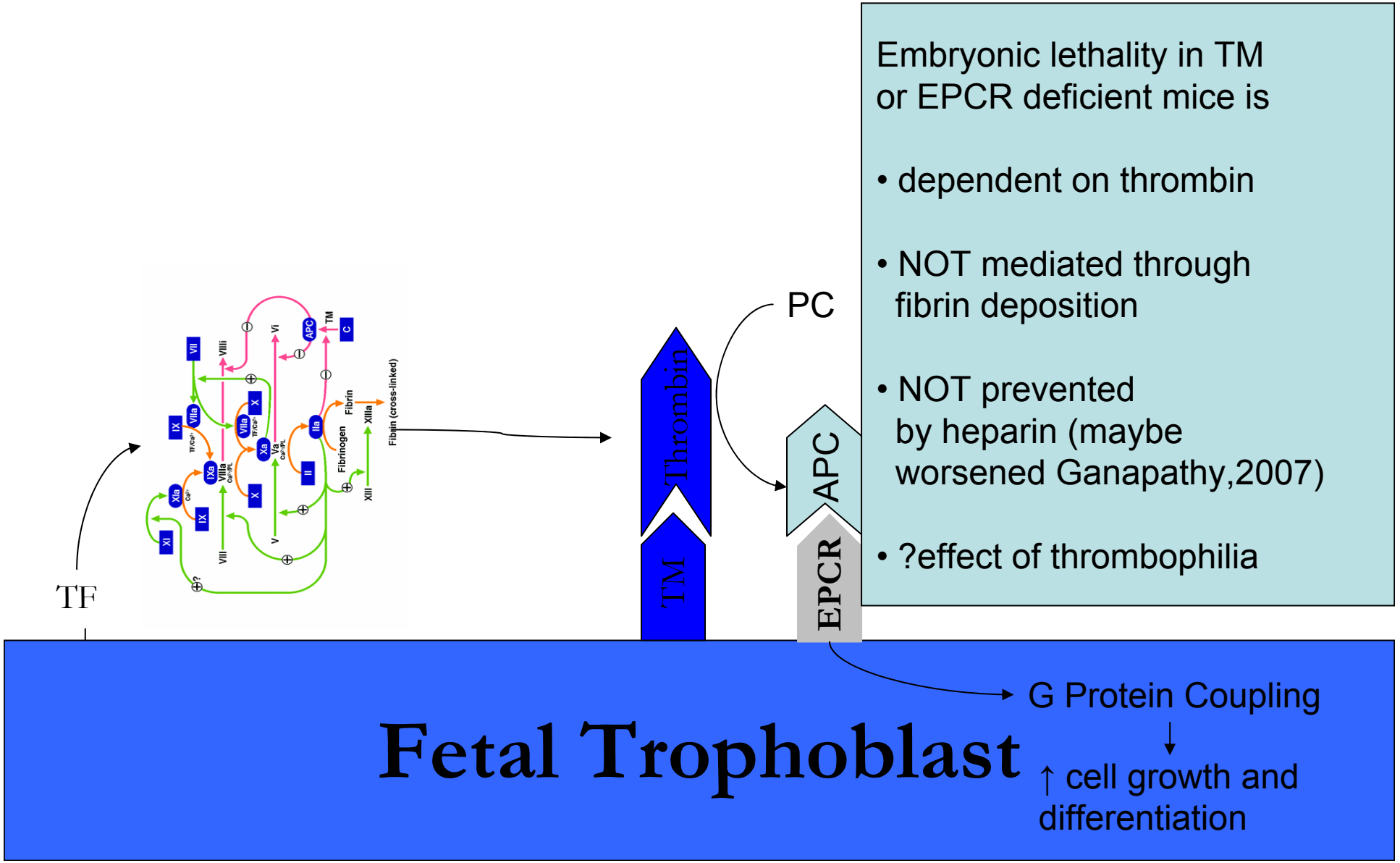
- Strength of association
- Consistency of association
- Specificity
- Temporal relationship
- Biologic gradient
- Biologic plausibility
- Coherence
- Analogy
- Experimentation

Hill, AB, Proc R Soc Med 1965;58:293 300.

Maternal Blood



Maternal Blood



“We are just beginning to understand the biological interactions between placental development and hemostasis”

Inferring causality based on biologic plausibility is risky in this area

Consistency and Strength of Association

Case Control Studies Suggest Association between FVL and…

- –Pregnancy loss
- –SGA
- –Pre-Eclampsia
- –Placental Abruption

But where confidence intervals are narrow, the summary ORs from MAs range 1.5-4.0

Case Control Studies suggest Association with FVL…but summary ORs from MAs range 1.5-4.0

	Severe Pre-eclampsia OR (95% CI)	SGA OR (95% CI)	Abruptio Placenta OR (95% CI)	Recurrent Miscarriage OR (95% CI)	Late Fetal Loss OR (95% CI)
Factor V Leiden	2.24 (1.28-3.94)	2.7 (1.3-5.5)	6.7 (2.0-21.6)	2.0 (1.5-2.7)	3.26 (1.82-5.83)
Prothrombin G20210A	1.98 (0.94-4.17)	2.5 (1.3-5.0)	28.9 (3.5-236.7)	2.0 (1.0-4.0)	2.3 (1.09-4.87)
Protein C deficiency	21.5 (not severe) (1.1-414.4)	–	–	1.57 (0.23-10.54)	1.41 (0.96-2.07)
Protein S deficiency	12.7 (not severe) (4.0-39.7)	10.2 (1.1-91)	–	14.72 (0.99-218.01)	7.39 (1.28-42.83)
Antithrombin deficiency	7.1 (not severe) (0.4-117.4)	–	4.1 (0.3-49.9)	–	–

Danish Birth Cohort: Nested Case Control

- Over 5 years, 50% of Danish pregnant women invited to participate, 1/3rd agreed (n>90,000)
- Cases: Validated severe PET (n=263), SGA <3rd (n=1227), severe PTL <34 wks (n=621) or abruption (n= 308).
- Controls: Random selection (n=1856)

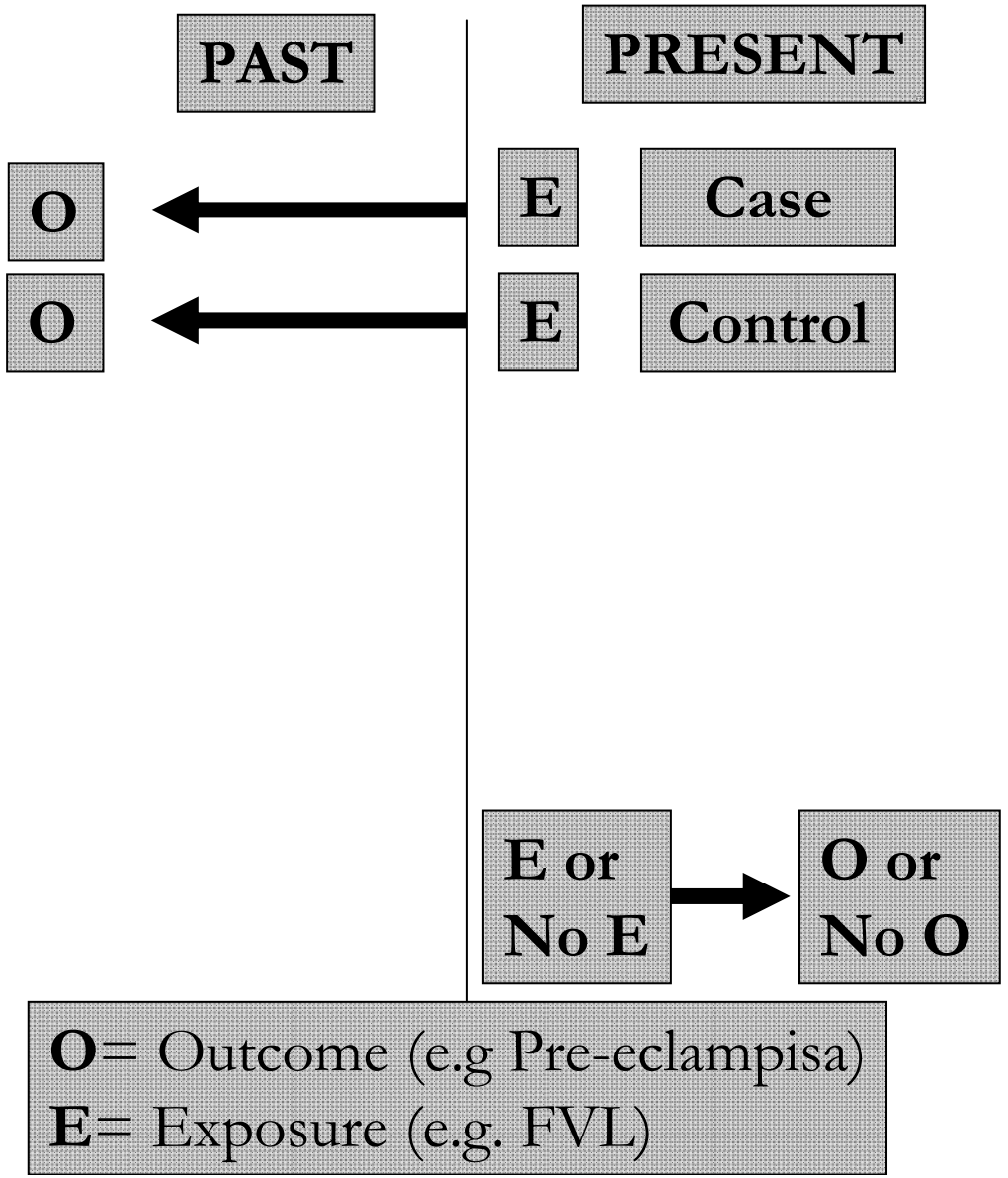
Lykke, JTH, 2012

Danish Birth Cohort: Nested Case Control

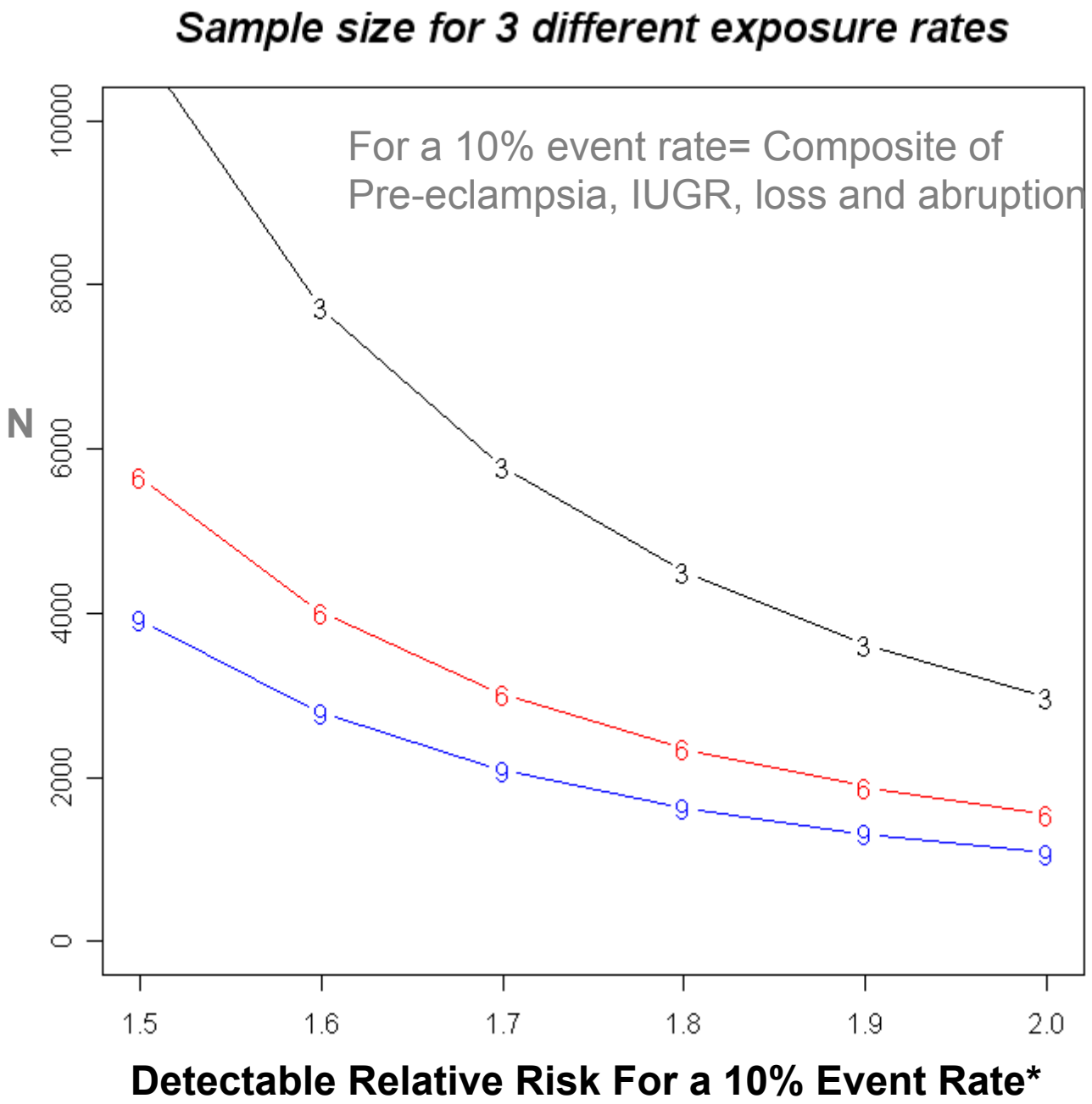
	Composite Outcome	Severe Pre-eclampsia OR (95% CI)	SGA (<3rd) OR (95% CI)	Abruptio Placenta OR (95% CI)
Factor V Leiden	**1.4 (1.1-1.8)**	**1.6 (1.1-2.4)**	**1.4 (1.1-1.8)**	**1.7 (1.2-2.4)**
Prothrombin G20210A	**0.9 (0.6-1.5)**	**1.1 (0.5-2.6)**	**0.9 (0.5-1.5)**	**1.6 (0.8-3.2)**

Lykke, JTH, 2012

Association Study Designs



- Case Control
  - Classification Bias
    - Retrospective outcome
  - Confounder data
    - Differential recall bias
  - Differential participation bias
- Prospective Cohort
  - Limit classification bias
  - Confounder data
  - Absolute event rates


Sample size for 3 different exposure rates
For a 10% event rate= Composite of
Pre-eclampsia, IUGR, loss and abruption
N
10000
8000
6000
4000
2000
0
3
3
3
3
3
6
6
6
6
6
9
9
9
9
9
1.5
1.6
1.7
1.8
1.9
2.0
Detectable Relative Risk For a 10% Event Rate*

Prospective Cohort Studies: Updated Meta- Analysis

Population: Pregnant women enrolled in first or second trimester

Exposure: FV Leiden or Prothrombin Gene Mutation

Outcomes:

- Pre-eclampsia (↑BP140/90 & proteinuria (2+ or 0.3g/24hr))
- Placenta abruption (pathology, imaging or visual)
- Small for Gestational Age (Birth, GA, Gender specific %tile)
- Pregnancy loss (after enrolment)

Rodger, PLoS Medicine, 2010

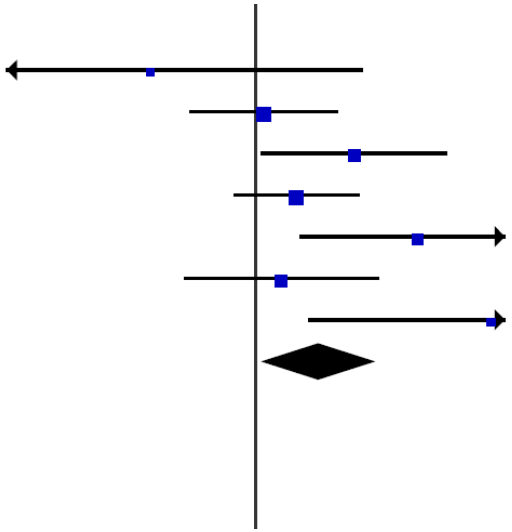
Rodger, Somewhere with good IF, 2013

Factor V Leiden and Pregnancy Loss- Weak association

1.1.3 Pregnancy Loss						
Clark 2008	1	142	71	3802	5.8%	0.38 [0.05, 2.69]
Dizon-Townson 2005	8	134	264	4751	19.7%	1.07 [0.54, 2.13]
Karakantza 2008	4	13	47	379	16.5%	2.48 [1.05, 5.85]
Lindqvist 2006	13	270	73	2210	21.8%	1.46 [0.82, 2.59]
Murphy 2000	3	16	24	572	13.0%	4.47 [1.50, 13.33]
Rodger 2012	5	337	80	6836	15.9%	1.27 [0.52, 3.11]
Said 2006	2	93	4	1633	7.4%	8.78 [1.63, 47.32]
Subtotal (95% CI)		**1005**		**20183**	**100.0%**	**1.79 [1.06, 3.03]**
Total events	36		563			

Heterogeneity: Tau² = 0.25; Chi² = 12.87, df = 6 (P = 0.05); I² = 53%

Test for overall effect: Z = 2.16 (P = 0.03)



Exposure:
4.7% FVL

Outcome Event Rates:
FVL: 3.6% Loss
No FVL: 2.8% Loss

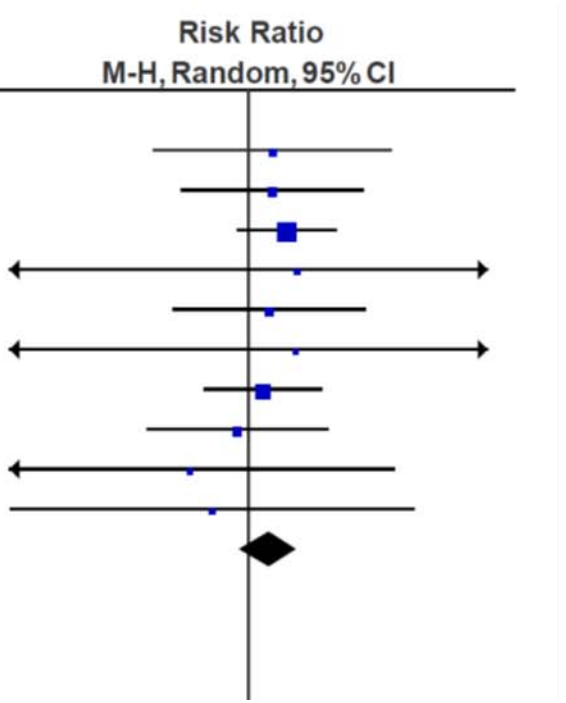
Factor V Leiden and Pre-Eclampsia No Association

Exposure:
5.0% FVL

Study or Subgroup	FVL Positive Events	FVL Positive Total	FVL Neg Events	FVL Neg Total	Weight	Risk Ratio -H, Random, 95% CI
1.1.1 Pre-eclampsia						
Clark 2008	3	141	63	3731	6.0%	1.26 [0.40, 3.96]
Dizon-Townson 2005	5	134	141	4751	10.2%	1.26 [0.52, 3.02]
Dudding 2008	17	243	204	4206	34.4%	1.44 [0.89, 2.33]
Karakantza 2008	0	13	8	379	1.0%	1.60 [0.10, 26.30]
Lindqvist 2006	5	257	34	2137	9.1%	1.22 [0.48, 3.10]
Murphy 2000	0	13	12	548	1.0%	1.57 [0.10, 25.20]
Rodger 2012	12	337	212	6836	24.0%	1.15 [0.65, 2.03]
Said 2006	5	93	98	1633	10.3%	0.90 [0.37, 2.15]
Salomon 2004 (1)	1	38	28	605	2.0%	0.57 [0.08, 4.07]
Sedano-Balbas 2010	1	29	41	837	2.1%	0.70 [0.10, 4.94]
Subtotal (95% CI)		**1298**		**25663**	**100.0%**	**1.21 [0.92, 1.61]**
Total events	49		841			

Heterogeneity: Tau² = 0.00; Chi² = 1.97, df = 9 (P = 0.99); I² = 0%

Test for overall effect: Z = 1.36 (P = 0.17)



>90% power to detect an absolute ↑2%

Outcome Event Rates:
FVL: 3.8% Pre-Eclampsia
No FVL: 3.3% Pre-Eclampsia

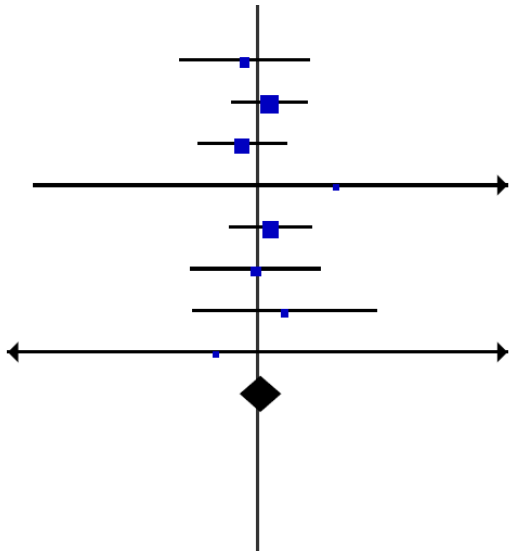
Factor V Leiden and SGA<10th Percentile- No Association

Exposure:
5.7% FVL

1.1.2 SGA						
Dizon-Townson 2005	10	124	403	4428	9.7%	0.89 [0.49, 1.62]
Dudding 2008	33	587	368	7282	29.4%	1.11 [0.79, 1.57]
Lindqvist 2006	23	257	221	2137	21.0%	0.87 [0.57, 1.30]
Murphy 2000	0	13	9	548	0.5%	2.06 [0.13, 33.73]
Rodger 2012	26	337	469	6836	24.4%	1.12 [0.77, 1.64]
Said 2006	10	93	179	1633	9.7%	0.98 [0.54, 1.79]
Salomon 2004	5	38	62	603	4.9%	1.28 [0.55, 2.99]
Sedano-Balbas 2010	0	29	21	878	0.5%	0.68 [0.04, 10.98]
Subtotal (95% CI)		**1478**		**24345**	**100.0%**	**1.03 [0.85, 1.24]**
Total events	107		1732			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.93$, df = 7 (P = 0.96); $I^2 = 0\%$

Test for overall effect: Z = 0.31 (P = 0.76)



>90% power to detect an absolute ↑2.5%

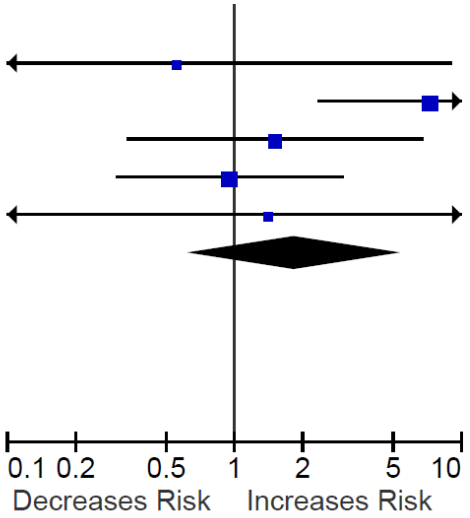
Outcome Event Rates:
FVL: 7.2% SGA(10th%ile)
No FVL: 7.1% SGA(10th%ile)

Factor V Leiden and Abruption

Exposure:
5.0% FVL

1.1.4 Placental Abruption						
Dizon-Townson 2005	0	134	31	4751	11.0%	0.56 [0.03, 9.08]
Karakantza 2008	3	13	12	379	28.0%	7.29 [2.34, 22.74]
Lindqvist 2006	2	257	11	2137	22.8%	1.51 [0.34, 6.78]
Rodger 2012	3	337	64	6836	27.7%	0.95 [0.30, 3.01]
Said 2006	0	93	6	1726	10.5%	1.41 [0.08, 24.90]
Subtotal (95% CI)		**834**		**15829**	**100.0%**	**1.84 [0.62, 5.43]**
Total events	8		124			

Heterogeneity: Tau² = 0.76; Chi² = 8.62, df = 4 (P = 0.07); I² = 54%
Test for overall effect: Z = 1.10 (P = 0.27)

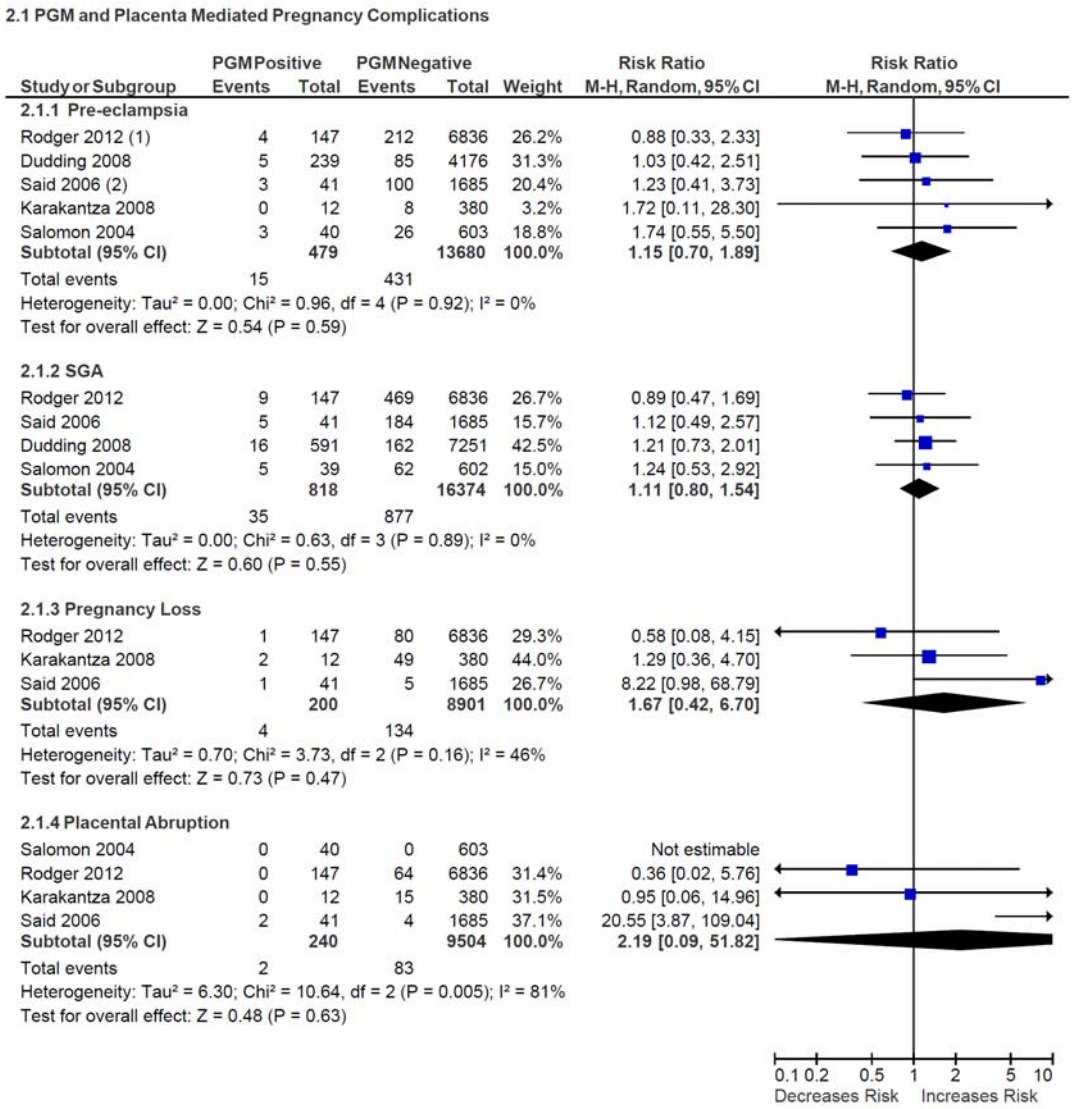


~80% power to detect an absolute ↑1%

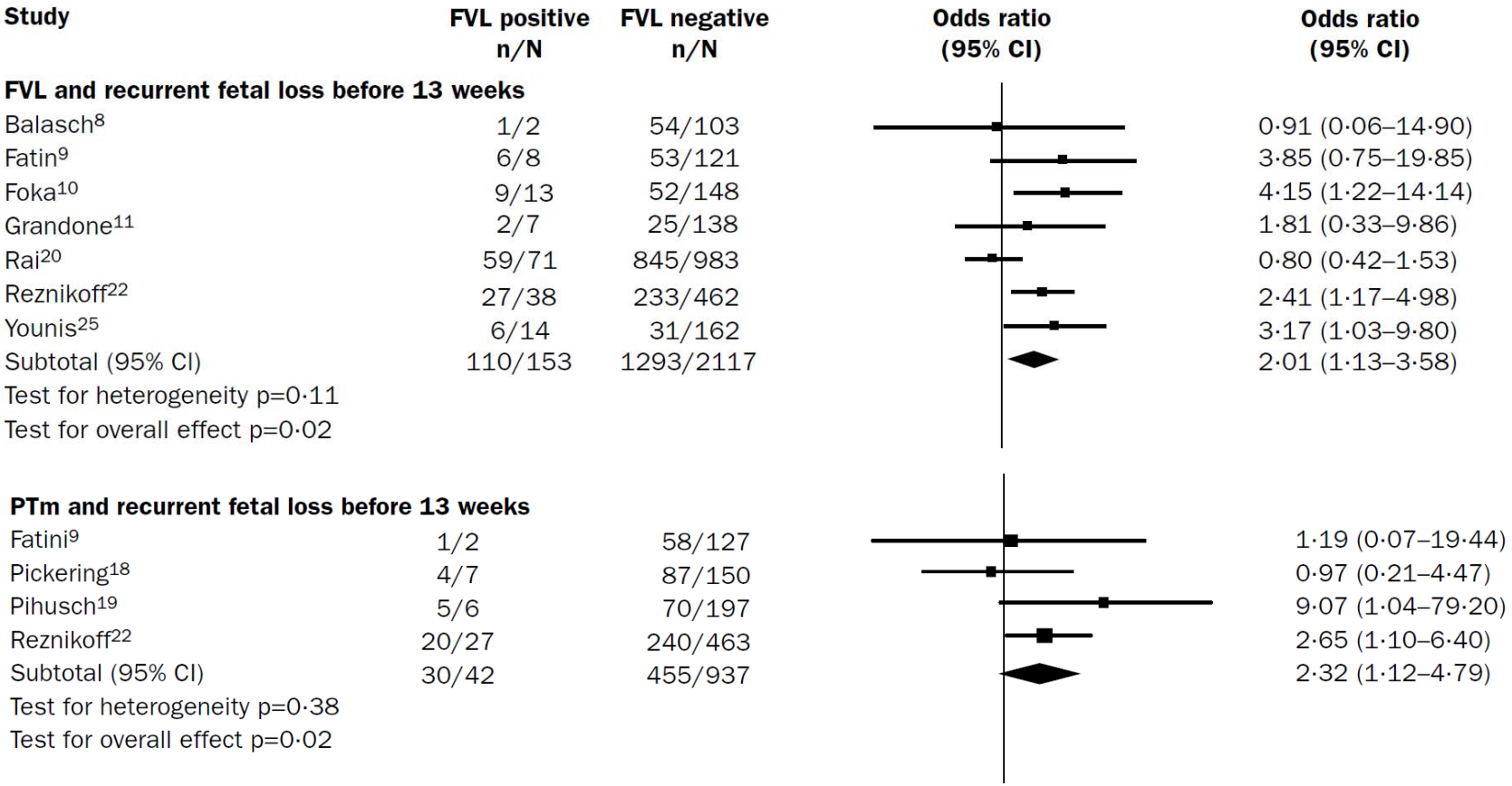
Outcome Event Rates:
FVL: 1.0% Abruption
No FVL: 0.8% Abruption

PGV

- PET:>90% power to detect ↑3%
- SGA:>90% power to detect ↑3%
- Pregnancy loss ~80% to detect ↑3%
- Abruption: Underpow-ered



For early loss need to rely on case control studies



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				
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				

Rey, Lancet, 2003

Time to get more specific…

- Thrombophilia
  - Heterogeneous potency: sparse data for “potent” ones
- Placenta Mediated Pregnancy Complications
  - Early pregnancy loss: Limited to case control studies- likely weakly causal
  - “Later” pregnancy loss: Likely weakly causal
    - Consistent weak signal with RR/OR ~2 ish
  - Pre-eclampsia and Small for Gestational Age
    - Probably no association with FVL and PGV
  - Underpowered cohort data for severe PET, severe SGA(<3rd) or placental abruption but likely weak association (contributor to causal soup)

Case 1

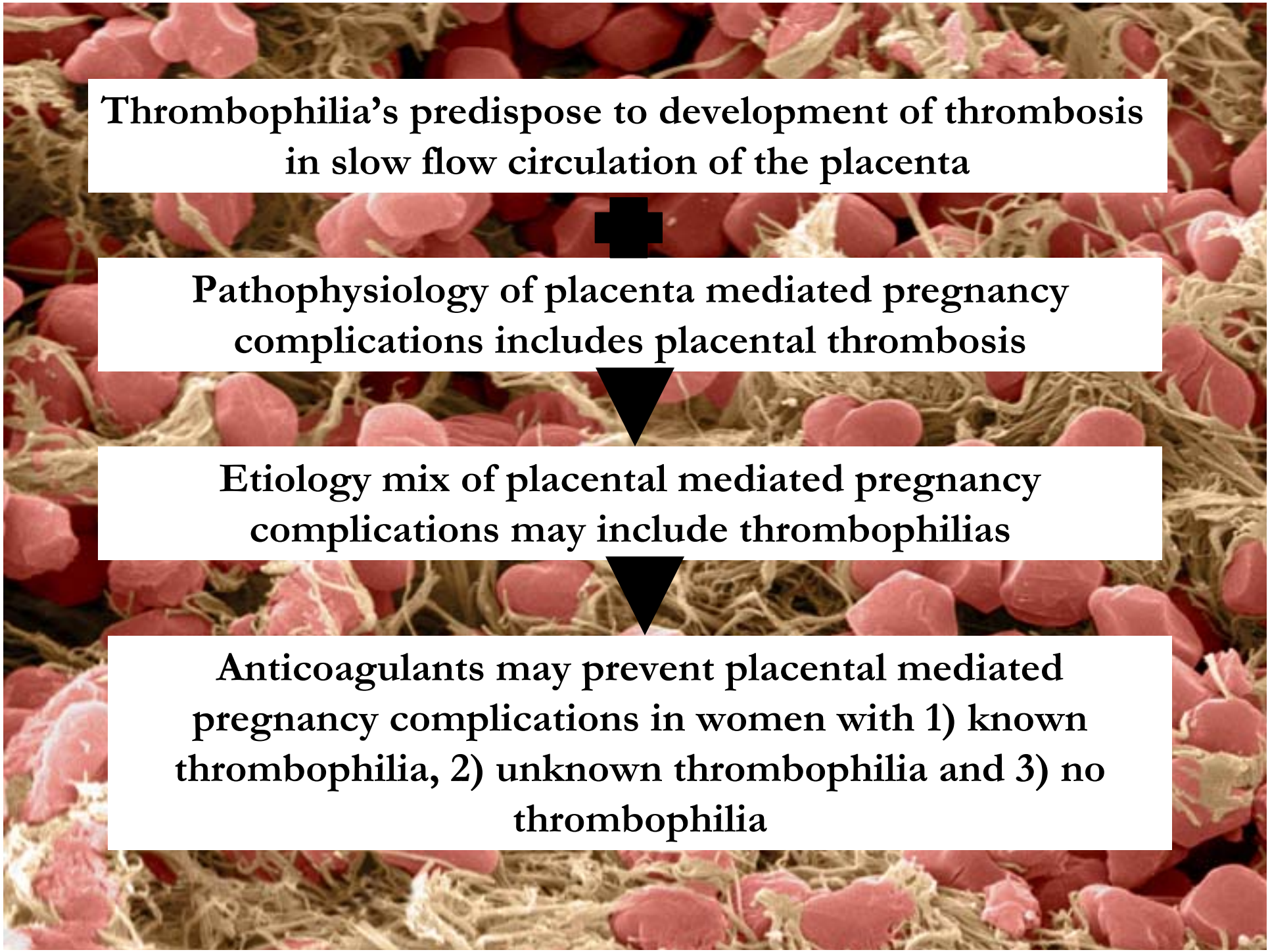
FVL cause PET?

1. Definitely not if it was near term and mild disease
2. Maybe if it was severe PET
3. Definitely, all PET, mild or severe, **is** caused by thrombophilia
4. Definitely, severe PET **is** caused by thrombophilia
5. **1 and 2**

Questions/Comments

3 Questions

- Do inherited thrombophilias cause placenta mediated pregnancy complications?
  - Weakly- Pregnancy loss
  - No- Pre-eclampsia and SGA
  - Maybe- Severe Pre-eclampsia, severe SGA and abruption
- **Do anticoagulants (specifically Low Molecular Weight Heparin (LMWH)) prevent these complications in…**
  - **Thrombophilic women?**
  - **Non-thrombophilic women?**


Thrombophilia's predispose to development of thrombosis in slow flow circulation of the placenta
Pathophysiology of placenta mediated pregnancy complications includes placental thrombosis
Etiology mix of placental mediated pregnancy complications may include thrombophilias
Anticoagulants may prevent placental mediated pregnancy complications in women with 1) known thrombophilia, 2) unknown thrombophilia and 3) no thrombophilia

Case 2

I have had 4 prior early losses; Will LMWH increase chances to have a baby?

1. **Maybe, regardless** of whether you have FVL
2. **Maybe** if you have FVL
3. **No** if you don't have thrombophilia
4. **Definitely**, **regardless** of whether you have FVL
5. **2 and 3**

RCTS of interventions vs control to prevent recurrent loss in “no known” thrombophilia women

- **Recurrent Early Loss**: Kaandorp, NEJM 2010, Clark Blood 2010, others

SPIN

- Population [n=294]
  - History of ≥ 2 consecutive unexplained losses <24 weeks (~40% had >2 losses)
  - Not selected by thrombophilia
  - Exclusions: known Thrombophilia, APLA+RPL (≥3 losses), VTE or Arterial TE
- Intervention
  - Open label **Enoxaparin 40mg and ASA 75mg** until 36 weeks ***vs*** **no intervention**
  - Multi-center (n=11)

Clark, P et al *Blood, 2010*

- Sample size
  - **Primary outcome-** Live birth rate 75% in ASA, 10% MCID, α-0.05, β-0.90= 300 per group
- Stopped at end of funding,
  - no treatment difference
    - Enox+ASA
      - 111 live births/143 (78%)
    - no intervention group
      - 111 live births/140 (80%)

Clark, P et al *Blood* 2010

ALIFE

- Population [n=299 (pregnant)]
  - History of ≥ 2 unexplained losses <20wks (~60%>2)
  - Age 18-42
  - Trying to conceive or <6 wks GA
  - Not selected by thrombophilia
  - Exclusions: APLA+RPL (≥3 losses), VTE or ATE
- Intervention
  - Open label **Nadroparin 2850 IU and ASA 80mg *vs* ASA 80mg *vs* Placebo ASA**
  - Multi-center
  - Stratified by center, age >36, >2 losses

Kaandorp, S et al *NEJM,* 2010

- Sample size
  - **Primary outcome-** Live birth rate 75% in ASA or Placebo ASA, 15% MCID, α-0.05, β-0.80= 309 total
- DSMB stopped trial for futility, no treatment difference
  - Nadroparin/ASA
    - 67 live births/97(69%)
  - ASA group
    - 61 live births/99 (62%)
  - Placebo group
    - 69 live births/103 (67%)

Kaandorp, S et al *NEJM,* 2010

Pooled Results RPL and “no Known” TF

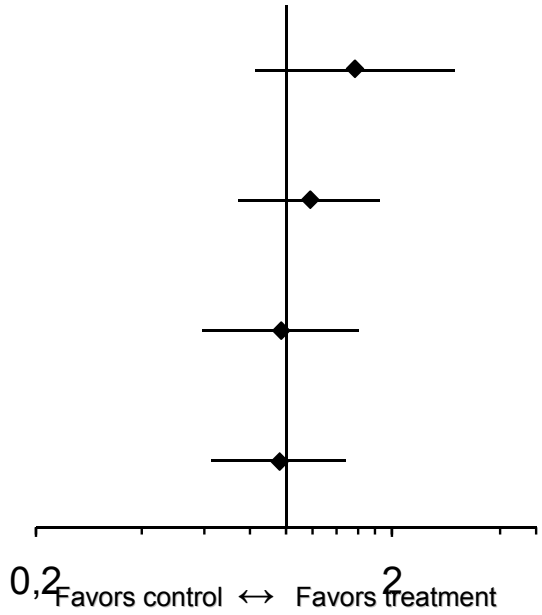
Intervention → ↓Study	LMWH/ ASA	ASA	Control	Quality Impact Factor	Clin. Trial Reg.
ALIFE	55/83	83/88	57/85	50	Yes
SPIN	111/143		111/140	10	Yes
DOLITSKI	44/54	42/50		4	No
VISSER	41/63	46/76		4	Yes
BADAWI	161/170		151/170	0.8	No
FAWZY	46/57	45/53	24/50	0.9	No
Pooled Proportion (95%CI)	458/570 80% (77-84)	216/267 81% (76-85)	343/445 77% 72-80)		

Results - Subgroups

Live births

Aspirin and Nadroparin versus Placebo

Subgroup	Ratio Relative Risk¶ (95% CI)	P-value for interaction
Inherited thrombophilia	1.56 (0.82-2.96)	0.18
Preceding live birth	1.17 (0.74-1.85)	0.49
Age < 36 years	0.97 (0.59-1.49)	0.9
≥ 3 miscarriages	0.96 (0.62-1.49)	0.85



List of completed RCTS of interventions vs control to prevent pregnancy loss in thrombophilic women

- **Later loss**: Gris, Blood, 2004
- **Recurrent Early Loss**: *Subgroups of* 1) Laskin, J Rheumatology, 2009, 2) Kaandorp, NEJM, 2010, 3) Clark, Blood 2010 and 4) Habenox, T and H, 2010

Pooled Results RPL and FVL/PGV

Intervention → ↓Study	LMWH /ASA	LMWH	ASA	Control
ALIFE	9/13		11/17	9/17
SPIN	5/6			2/4
HEPASA	6/9		21/27	
HABENOX	6/9	5/7	2/5	
Totals	26/37	5/7	34/49	11/21
Proportion	70%	71%	69%	52%
(95% Conf	(53-	(29-96%)	(55-	(30-

TIPPS has randomised >160 of these patients

Case 2

I have had 4 prior losses; Will LMWH increase chances to have a baby?

1. **Maybe, regardless** of whether you have FVL
2. **Maybe** if you have FVL
3. **No,** if you don't have thrombophilia
4. **Definitely**, **regardless** of whether she has FVL
5. **2 and 3**

Questions/Comments

Case 1

Prior PET, LMWH prophylaxis in next pregnancy?

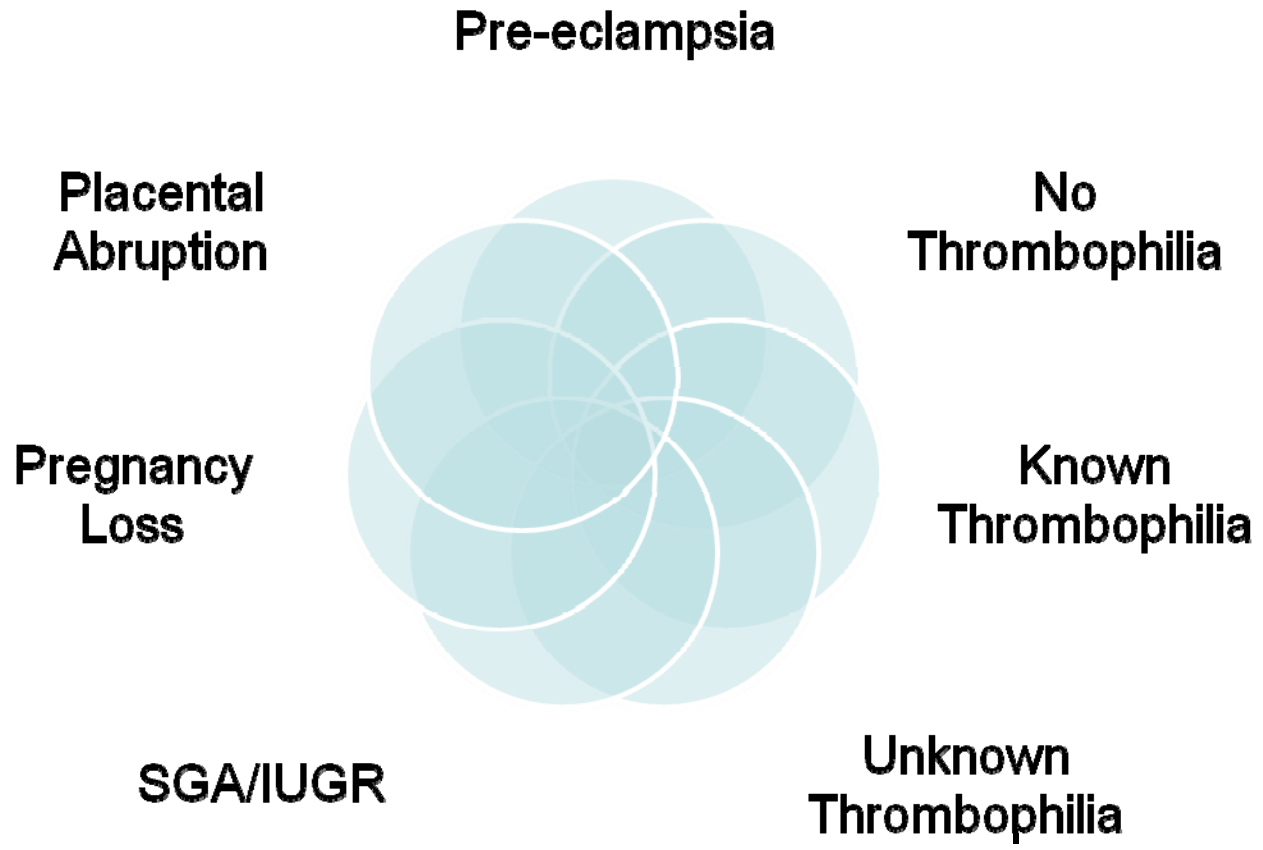
1. **Maybe,** but only if she has FVL
2. **Maybe, regardless** of whether she has FVL
3. **Definitely**, if she has FVL she should receive LMWH
4. **Definitely**, **regardless** of whether she has FVL
5. **2 and 3**

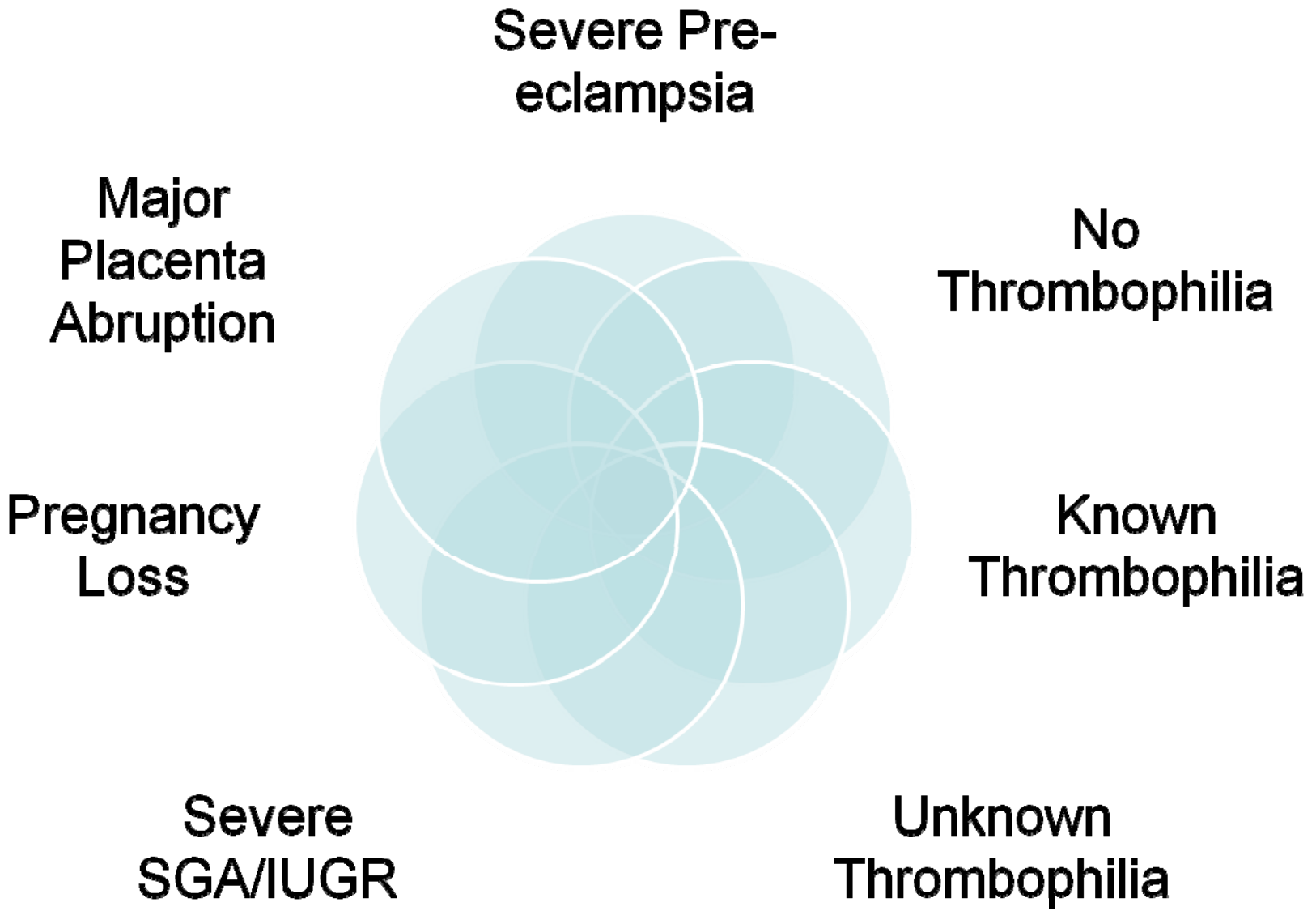
Recurrent Late Complications

- High Risk of Recurrence in Next Pregnancy
  - Not well studied; complicated by ↑ risk for multiple + overlapping late complications
  - Example: Prior Pre-Eclampsia (PET)
    - Prior any PET (~15% recurrent PET, ~8% SGA,, ~3% Abruption, ~2% Late Loss) ^&
    - Prior severe or early PET (~25% PET, ~10% SGA, ~3% Abruption and ~2% Late loss)*
- No Proven Effective Secondary Prevention
  - ASA: weakly effective in prior PET ~10% RRR#

Askie, Lancet, 2007,*Van Rijn, AJOG,2006
^Terje, BMJ, 1998, &Hnat, AJOG, 2002

RCT Data- Patient Groups/Sub-Groups




Severe Pre-eclampsia
Major Placenta Abruption
No Thrombophilia
Pregnancy Loss
Known Thrombophilia
Severe SGA/IUGR
Unknown Thrombophilia

Dalteparin to Prevent Recurrent Placenta Mediated Pregnancy Complications

- **Pilot RCT** of **Antepartum** Dalteparin 5000 units/d vs no prophylaxis
- 116/148 eligible women consented (78% consent rate)
- 110 (6 post-randomisation exclusion) women without thrombophilia but with prior severe placenta mediated pregnancy complications…
    - severe PET necessitating delivery <35 weeks or
    - unexplained SGA <5th%ile or
    - placental abruption necessitating delivery <35 weeks or resulting in fetal death >20 weeks or
    - Unexplained fetal loss >20 weeks or
    - 2 prior unexplained fetal losses between 12 and 20 weeks.

Rey E, et al. *J Thromb Haemost* 2009;7:58-64

Dalteparin to Prevent Recurrent Placenta Mediated Pregnancy Complications

- Composite **primary outcome**: severe pre-e… birth weight <5th %tile **or** major placenta abr… ery <34 weeks or fetal death >20 weeks).
- **Results:** Dalteparin arm (5.5%) … parin arm (23.6%) (OR 0.15, 95% CI 0.03-0.70 … =0.016).
- **Caution**:
  - Did not reach th… ample size of 276 women and interim analy… each the pre-planned level of statistical … (p<0.005).
  - 78.4% … at first author's site
  - … = 3, good allocation concealment
- … **:** Promising but subsequent studies will be required t… borate these findings.

Rey E, et al. *J Thromb Haemost* 2009;7:58-64

Enoxaparin to Prevent Recurrent Placenta Mediated Pregnancy Complications

- **Single Center Pilot RCT** of **Antepartum** Enoxaparin 4000 units/d vs no prophylaxis
- 160/166 (96% gave consent) women **without** thrombophilia with **prior abruption**
- **Primary Composite Outcome**: Pre-eclampsia, SGA birth (<5th %tile), stillbirth (>20 weeks) or abruption
- **Results:** Enoxaparin arm (12.5%; (10/80)) vs no Enoxaparin (31.3%; 25/84) (OR 0.37, 95% CI, 0.18-0.77, NNT 5.4, p<0.004).

Gris JC, et al. *Thromb Haemost* 2010;104:771-779

Enoxaparin to Prevent Recurrent Placenta Mediated Pregnancy Complications

- **Caution**:
  - Single center
  - Mean GA enrolment early ~6 weeks… ester pregnancy loss rate= 0.6% (1/16…
  - Jadad Score= 2, good allo… alment
  - Trial was not register…
- **Bottomline:** Promi… sequent studies will be required to corroborate t… gs.

Gris JC, et al. *Thromb Haemost* 2010;104:771-779

Enoxaparin to Prevent Recurrent Placenta Mediated Pregnancy Complications

- **Single Center Pilot RCT** of **Antepartum** Enoxaparin 4000units/d/ASA/Folate 5mg *vs* ASA/Folate 5mg
- 224/231 (97% gave consent) women **with/without** thrombophilia with **Severe PET**
- **Primary Composite Outcome**: Pre-eclampsia, SGA birth (<5th %tile), stillbirth (>20 weeks) or abruption
- **Results:** Enoxaparin arm (8.9%; (10/112)) vs no Enoxaparin (25.0%; 28/112) (OR 0.32, 95% CI, 0.16-0.66, NNT 6.3, p=0.002).

Gris JC, et al. *Thromb Haemost* 2011; 106: 1053–1061

Enoxaparin to Prevent Recurrent Placenta Mediated Pregnancy Complications

- **Caution**:
  - Single center
  - Jadad Score= 3, good allocation con
  - Trial was not registered
- **Bottomline:** Promising but s tudies will be required to corroborate these findi

Gris JC, et al. *Thromb Haemost* 2011; 106: 1053–1061

Dalteparin to Prevent Recurrent Placenta Mediated Pregnancy Complications

- **Multi-Center Multi-National RCT** of open label **Antepartum** Dalteparin 5000 units/d and ASA vs ASA
- 139/177 (78% gave consent) women <12 wks GA **with thrombophilia** with **prior delivery <34 weeks with PET (incl HELLP/ET)** and/or **SGA (<10th)**
- **2 Primary Outcomes**: Recurrent **PET (incl HELLP/ET) <34 weeks** (Co- primary: any PET but powered for this one)
- **Results:**
  - **Dalteparin/ASA arm** (0%; (0/70)) *vs* **ASA alone** (8.7%; 6/69) (RD 8.7%, 95% CI, +1.9-+15.5%, NNT 12, p<0.012).
  - (co-primary: **Dalteparin/ASA arm** (18.6%; (13/70)) vs **ASA alone** (21.7%; 15/69) (RD 3.1%, 95% CI, -10.5%-+16.7%, p=0.642)

De Vries JIP, et al. *JTH* 2012;10:64-72

Dalteparin to Prevent Recurrent Placenta Mediated Pregnancy Complications

- **Caution**:
  - Sample Size (event any PET rate 35% (actual early onset PET= 4.3%) 80% power to detect 17% ARR) originally 262; Changed to one sided test to get 128pts
- **Strengths**
  - Jadad Score= 3, good allocation concealment
  - Trial registered
- **Bottomline:** Promising but subsequent studies will be required to corroborate these findings.

De Vries JIP, et al. *JTH* 2012;10:64-72

Nadroparin to Prevent Recurrent Placenta Mediated Pregnancy Complications

- **Multi-Center Italian RCT** of open label antepartum **Nadroparin 3800 units/d** *vs* **no intervention control**
- 135/187 (72% gave consent) women <12 wks GA **with/without thrombophilia** with **prior PET (incl HELLP/ET) (30%), PA (3%), PL >15 wks (36%)** and/or **SGA (<10th) (20%)**
- **Primary Composite Outcomes**: adjudicated **PET (incl HELLP/ET), late PL (>15wks), PA or SGA (<10th)**
- **Results: (stopped early for "futility" at pre-planned IA)**
  - **Nadroparin arm** (21%; (13/63)) *vs* **control** (18%; 12/65) (RD 2.2%, 95% CI, -1.6-+16.0%, p=0.76).

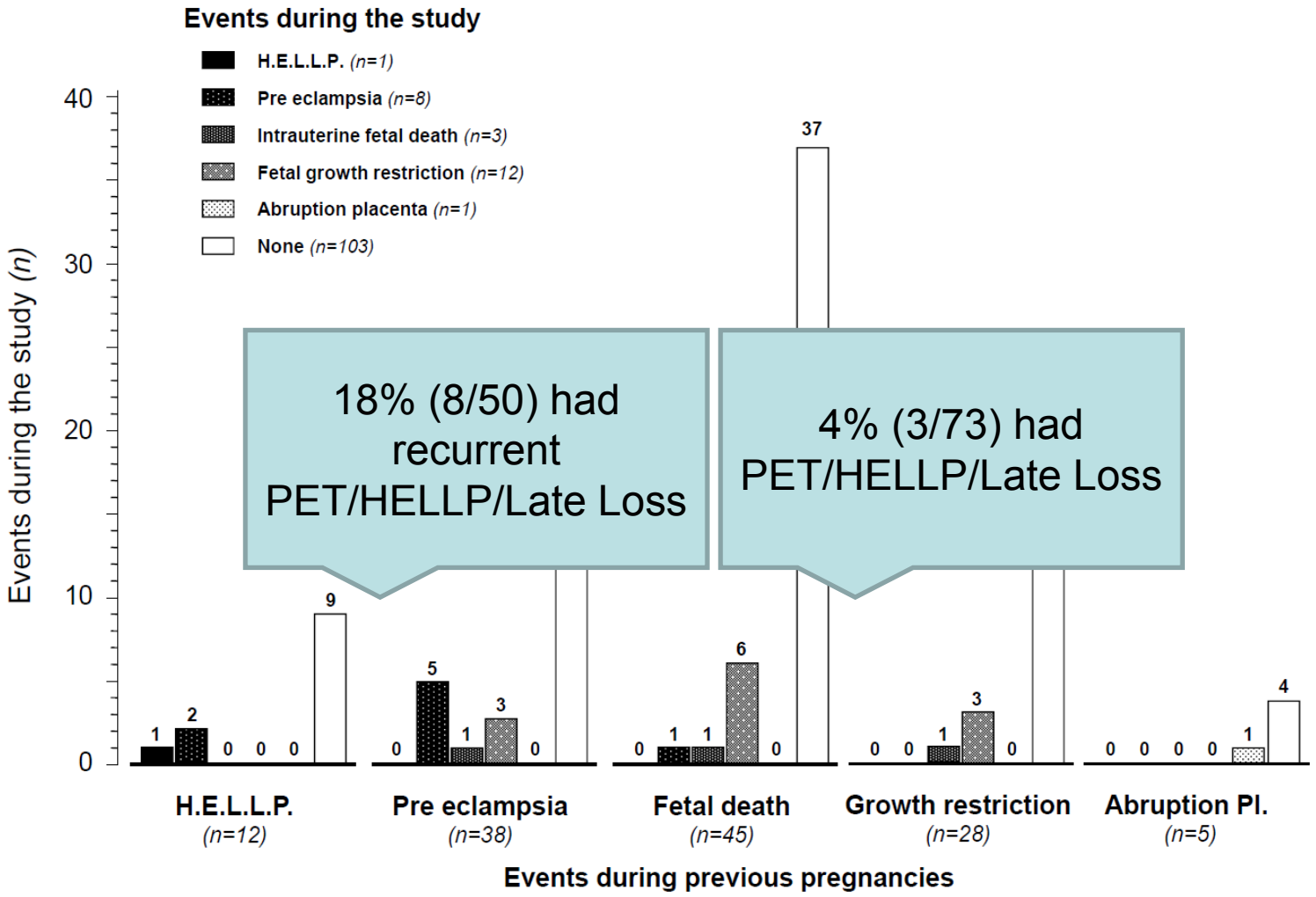
Martinelli I, et al. *Blood* 2012; 119(14):3269-75

Nadroparin to Prevent Recurrent Placenta Mediated Pregnancy Complications

- **Caution**:
  - Sample Size (event rate 40%, 80% power to detect 16% ARR) originally 266.
- **Strengths**
  - Jadad Score= 3, good allocation concealment
  - Trial registered
- **Bottomline:** Stopping early for “futility” problematic- high risk Type II error

Martinelli I, et al. *Blood* 2012; 119(14):3269-75

Maternal Side vs Fetal Side Event Clustering



Meta- Analysis: Objective

- Determine the summary effect of LMWH in preventing placenta mediated pregnancy complications in women with prior late placenta mediated pregnancy complications
  - Examine which outcomes prevented

Methods

- **Population**: Currently pregnant women with prior pregnancies complicated by pre-eclampsia (PET), **or** abruption, **or** small for gestational age (SGA) child (<10th percentile) **or** pregnancy loss >12 weeks
- **Interventions:** Low Molecular Weight Heparin (LMWH) with/without ASA
- **Comparator:** Control with/without ASA

Methods

- **Outcomes**:
  - **Primary**: "mild" Composite of any ≥1: 1) any pre-eclampsia, **or** 2) abruption, **or** 3) small for gestational age child (<10th percentile) **or** 4) pregnancy loss >12 weeks
  - **Secondary**: "severe" Composite of ≥1 of: 1) severe (as defined by authors) **or** early onset (<34 weeks) pre-eclampsia, **or** 2) major abruption, **or** 3) small for gestional age child (<5th percentile) **or** 4) pregnancy loss >12 weeks

Methods

- **Outcomes**:
  - **Secondary (cont'd)**: Any pre-eclampsia (PET), severe or early onset PET, SGA <5th, SGA <10th, pregnancy loss >12 weeks, abruption, delivery prior to 34 weeks and delivery before 37 weeks

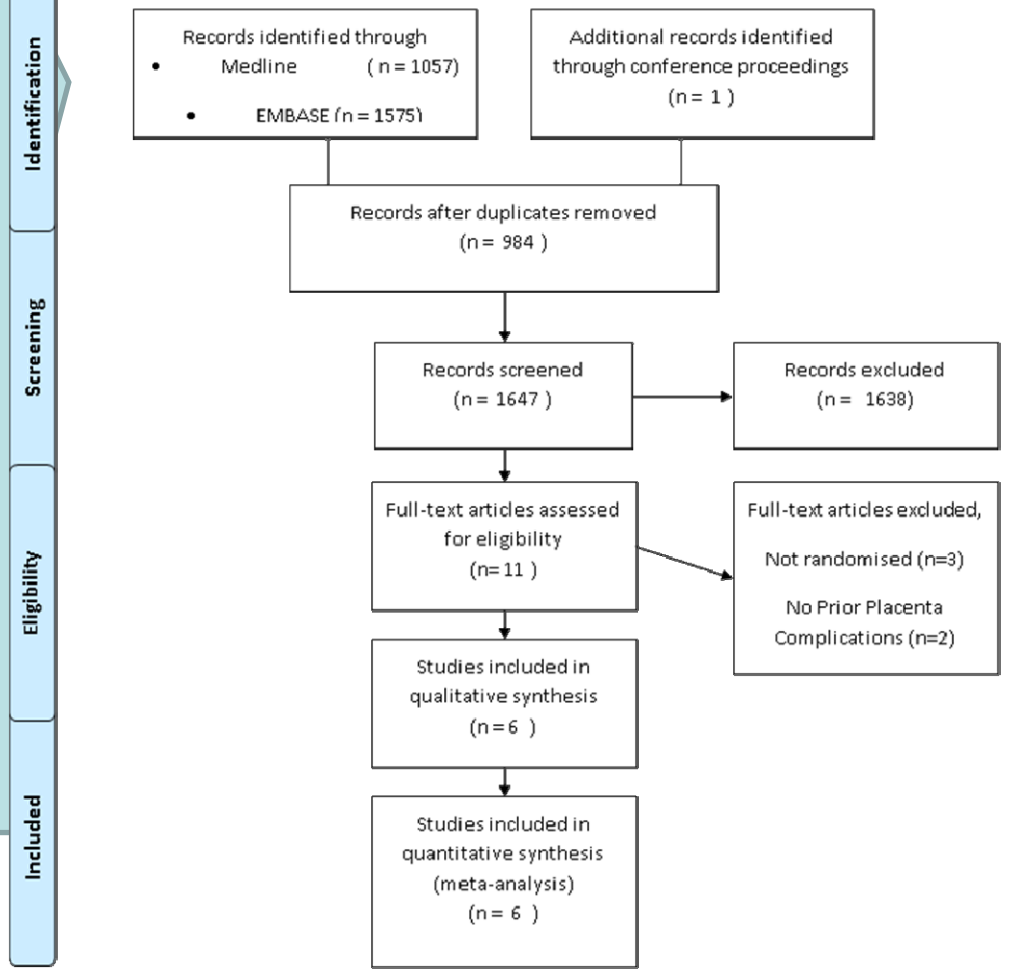
- **Study Designs**: RCTs only

Methods

- **Data Extraction**
  - 2 independent duplicate reviewers: abstract, full publication and data extraction
  - Contacted the authors for data clarifications (response received for 5/6 publications)
- **Data Synthesis**
  - Relative risk (95% CI) random effects model
  - Intention to treat
  - Heterogeneity/Consistency- Higgins I^2
  - Funnel plots examined for publication bias

Figure 1. PRISMA Study Selection Flow Diagram

1. (intrauterine growth and (restriction or retardation)).tw.
2. (preeclampsia or pre eclampsia or pre-eclampsia).tw.
3. (pregnancy loss or fetal loss or miscarriage or abortion or stillbirth).tw.
4. (abruptio placentae or placental abruption).tw.
5. (preterm delivery or preterm labor or prematurity).tw.
6. exp Pregnancy Complications/
7. or/1-6
8. exp Heparin/
9. exp Heparin, low-molecular-weight/
10. LMWH.tw.
11. or/8-10
12. 7 and 11
13. clinical trial.pt.
14. randomized.ab.
15. placebo.ab.
16. randomly.ab.
17. trial.ti.
18. or/13-17
19. animals.sh.
20. Humans/
21. 19 not (19 and 20)
22. 12 not 21



Included Studies: Details

First Author	Year	Country, Centers N= # Participants	Participants	Intervention/ Control	Primary Outcome
De Vries	2012	Multi-National N= 139	Prior early onset PET (n=107) and/or SGA <10th (n=94)	Dalteparin 5000IU+ASA vs ASA	PE prior to 34 weeks GA
Martinelli	2012	Italy, Multi-center N=135	Prior PET (n=52), Prior loss>15weeks (n=49), Prior SGA <10th (n=28) or prior abruption (n=5)	Nadroparin 3800IU vs No Nadroparin	PE, Loss >15 weeks GA, SGA< 10th and/or Abruption
Gris	2011	France, Single Center N=224	Prior Severe PET (n=224)	Enoxaparin 4000IU+ASA vs ASA	PE, SB, Abruption, SGA<5 th
Gris	2010	France, Single Center N=160	Prior Abruption (n=160; 70 with PET)	Enoxaparin 4000IU+/-ASA vs +/- ASA	PET, SB, Abruption, SGA<5 th
Rey	2009	Canada, Multi-center N=116	Prior early PET (n=60) Prior Abruption (n=16) Prior SGA< 5th (n=21) Loss >12 weeks (n=17)	Dalteparin 5000IU+/-ASA vs +/- ASA	PE, SB, Abruption, SGA<5 th
Mello	2005	Italy, Single Center N=80	Prior PET with ACE DD (n=80)	Dalteparin 5000 IU vs No Dalteparin	PE, SGA<10th

Included Studies: characteristics of participants

	LMWH (n=425)	No LMWH (n=423)	Combined (n=848)
Thrombophilia	106/425	107/423	213/848 **(25%)**
Prior PE	296/425	293/423	593/848 **(70%)**
Prior Severe PE	208/304	208/304	416/848 **(49%)**
Prior SGA <10th	76/192	67/192	143/848 (**16%)**
Prior Abruption	91/192	90/203	181/848 **(21%)**
Prior Loss >12 weeks	34/122	32/123	66/848 **(7%)**
Concomitant ASA use	178/495	260/423	438/848 **(52%)**

PE= Pre-eclampsia, SGA (<xth)= Small for gestational age less than xth percentile, ASA= Aspirin

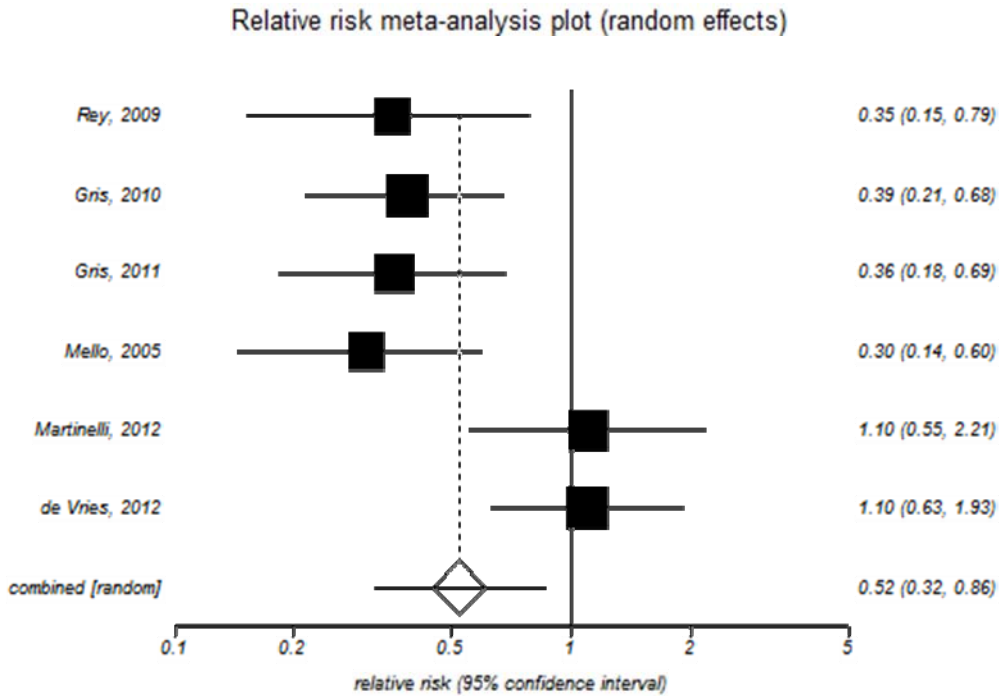
Included Studies:Quality

First Author	Randomn Sequence Generation	Allocation Concealment	Blinding of participant /personnel	Blinding of outcome assessors	Incomplete Outcome data	Selective Reporting	Other bias
DeVries	+	+	-	-	+	+	+
Martinelli	+	+	-	+	+	+	+
Gris	+	+	-	-	+	-	+
Gris	+	+	-	+	+	-	+
Rey	+	+	-	+	+	-	+
Mello	+	-	-	-	-	-	+

+ = Low risk of bias; - = High risk of bias

Primary Outcome: Composite of ≥1 of: 1) any pre-eclampsia, **or** 2) abruption, **or** 3) small for gestional age child (<10th percentile) **or** 4) pregnancy loss >20 weeks

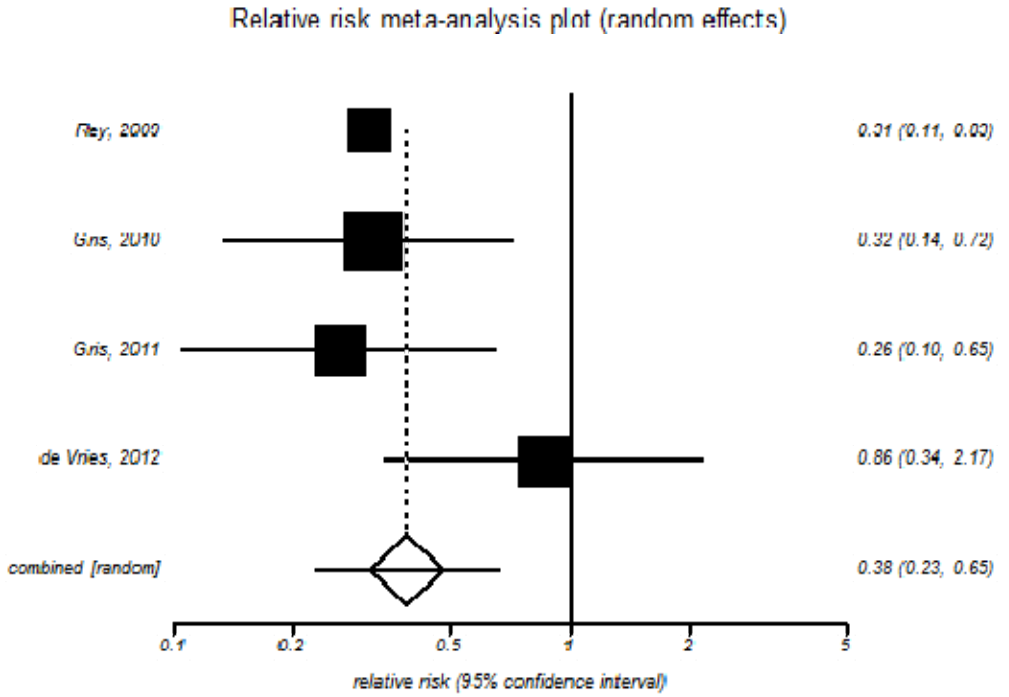
- LMWH n= 425
  Control n= 423
- Absolute Event Rates
  - LMWH= 15.7%
  - Control= 30.0%
- I^2=69%



RR= 0.52 (0.32-0.86)

Secondary Outcome: Composite of ≥1 of: 1) severe (as defined by authors) **or** early onset (<34 weeks) pre-eclampsia, **or** 2) major abruption, **or** 3) small for gestional age child (<5th percentile) **or** 4) pregnancy loss >20 weeks

- LMWH n= 316
- Control n= 317
- Absolute Event Rates
  - LMWH= 7.0%
  - Control= 18.6%
- I^2=0%



RR= 0.38 (0.23-0.65)

Secondary Outcomes (cont'd)

Outcome (LMWH=288/ Control=286)	**Relative Risk 95% CI (p value)**	**I^2**
Severe or early Pre-eclampsia	0.16 (0.07-0.36)(p<0.0001)	0%
Any Pre-eclampsia	0.46 (0.28-0.75)(p=0.0019)	33%
Pregnancy loss >20 weeks	0.41 (0.17-1.02)(p=0.06)	0%
Pregnancy Loss <20 weeks	0.89 (0.50-1.6)(p=0.69)	0%
Abruption	0.42 (0.13-1.4)(p=0.17)	0%

Secondary Outcomes (cont'd)

Outcome (LMWH=288/Control=286)	Relative Risk (p)	I^2
Delivery <34 weeks	0.45 (0.30-0.69) (p=0.0002)	0%
Delivery <37 weeks	0.77 (0.62-0.96)(p=0.02)	0.4%
Small for Gestational Age <5th	0.52 (0.28-0.94)(p=0.03	0%
Small for Gestational Age <10th	0.42 (0.29-0.59) (p<0.0001)	0%
Neonatal Death	0.31 (0.07-1.3)(p=0.10)	0%

Strengths

- PRISMA guidelines in the conduct and reporting of our systematic review
- We were able to obtain data clarifications from 5 out of 6 authors of the component studies in the meta-analysis
- The LMWH dose and timing of initiation of LMWH was relatively homogeneous between studies
- All of the component studies were led by academic centers

Limitations

- Heterogeneity in inclusion criteria
  - ? apply to all a limited sub-set (e.g. severe PET, abruption)
- Heterogeneity in outcomes
  - ? reduces the risk of all or just severe outcomes (severe PE and/or SGA)
- ASA was a co-intervention in over 50%
- Some component studies not high quality
  - 2 highest quality trials demonstrated no effect
- >50% of participants recruited in limited number of centers
  - ?external generalizability

Conclusions

- LMWH appears to be a promising preventative therapy for “severe” recurrent placenta mediated pregnancy complications.

- BUT, IMO high quality multicenter trials should be conducted to confirm this finding

Ongoing Studies….

Trial name/yr	Principle investigator	Description
TIPPS-2000	M. Rodger (Ottawa)	• Thrombophilia and additional risk factors for adverse pregnancy outcomes • Randomized to ante-partum Fragmin 5000U OD/BID vs. no prophylaxis • Multi-center N= 150 per arm
EPPI	C. Mclintock (Auckland)	• Prior PET (<36wks), SGA <10th delivered prior to 36wks or SGA <3rd) • Enox 40mg/d vs control (ASA+/- Ca) • Pilot: n=80 per arm
HEPEPE	B Haddad (Paris)	• Prior severe PET (<34 weeks) • Enox 4000units OD/ASA vs. ASA • Multi-center N=220 per arm

Case 1

Prior PET LMWH prophylaxis in next pregnancy?

1. **Definitely**, if she has FVL she should receive LMWH
2. **Maybe, regardless** of whether she has FVL (especially if prior severe disease)
3. **Maybe,** but only if she has FVL
4. **Definitely**, **regardless** of whether she has FVL
5. **2 and 3**

Final Slide: 3 Questions

- Do inherited thrombophilias cause placenta mediated pregnancy complications?
  - Weakly- Pregnancy loss
  - No- Pre-eclampsia and SGA
  - Don’t know- Severe Pre-eclampsia, severe SGA and abruption

Final Slide: 3 Questions

- Do anticoagulants (specifically Low Molecular Weight Heparin (LMWH)) prevent these complications in…
  - Thrombophilic women?
    - Don't know!
  - Non-thrombophilic women?
    - Recurrent early loss- No
    - Prior severe pre-eclampsia, severe SGA or abruption
      - Promising results require validation

Questions/Comments

Dalteparin to Prevent Recurrent Placenta Mediated Pregnancy Complications

- **Single center RCT** of **Antepartum** Dalteparin 5000 units/d vs no prophylaxis
- 80 women without thrombophilia (had ACE DD) with prior pre-eclampsia
- **Primary outcome**: recurrent pre-eclampsia
- **Results:** Dalteparin arm (7.3%; (3/41)) vs no Dalteparin arm (28.2%; 11/39) (OR 0.26, 95% CI, 0.08-0.86, NNT 5, $p<0.01$).

Mello G, et al. *HTN* 2005;45:86-91

Dalteparin to Prevent Recurrent Placenta Mediated Pregnancy Complications

- **Caution**:
  - Trial was not registered
  - No Figure 1 data, ?Consent rate ?Ex… …ralisability
  - Jadad Score= 2, inadequate all… …cealment
  - Can these results be appli… …n without ACE DD?

- **Bottomline:** Promi… …bsequent studies will be required to corroborate… …gs.

Hypothesis generating only

Mello G, et al. *HTN* 2005;45:86-91