Outcome of the subsequent pregnancy after a first loss in women with common thrombophilia

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Thrombophilia and Pregnancy Loss

- Association first established in 1996 [1]
- Mechanism unclear. Thrombosis in the placental (micro) vessels?
- Factor V Leiden (FVL) and Prothrombin mutation (PTm): meta-analysis of case control studies[2]
  - 2-3 Fold increased risk for
    - Recurrent early pregnancy loss (≤ 12 weeks of gestation)
    - Single late pregnancy loss (> 12 weeks)

[1] Sanson, Thromb Haemost 1996 / [2] Rey, Lancet 2003

Thrombophilia and Pregnancy Loss

Current patient management

- No treatment, wait and see
- Treatment with anticoagulants (aspirin, LMW heparins)
  - Pathophysiologically attractive
  - Efficacy not proven
  - Potentially harmful

Prognosis after 1st loss

Contradicting reports in women with thrombophilia

- Poor: live birth rate 11-23% after a single late pregnancy loss [1,2]
- Good: live birth rate after late pregnancy loss [3]
  - single loss: 98%
  - two or more losses: 80%

[1] Rai, Hum Reprod 2002 / [2] Lissalde-Lavigne, J Thromb Haemost 2006
[3] Lindqvist, J Thromb Haemost 2006

Management dilemmas

- What is the prognosis after a first pregnancy loss?
- Different for early vs late loss?
- Different for carriers vs non-carriers?
  - Factor V Leiden
  - Prothrombin mutation

Methods

- Two retrospective multicenter cohort studies with [1,2]:
  - Patients with FVL or PTm and VTE or premature atherosclerosis
  - And their first degree relatives
    - mainly asymptomatic, 50% carrier (by definition)
  - Full obstetric histories present
- Exclusion criteria for pregnancies
  - Ectopic and terminated pregnancies
  - Known chromosomal abnormalities
  - Toxicosis or HELLP syndrome
  - Anticoagulant use during pregnancy (aspirin, LMW heparins, VKA)

[1] Middeldorp, Ann Intern Med 1998 / [2] Bank, Arch Intern Med 2004

Results: Patients

	Carriers	Non-carriers
Women (n)	797	715
Women with ≥ 2 pregnancies	479	437
Excluded for heparin use after prior VTE	20	6
Other exclusions	12	11

1st pregnancy

	Carriers	Non-carriers	RR
N	498	495	
Pregnancy loss	13%	9%	1.5 (1.1-2.2)
• Early loss	9%	7%	1.4 (0.9-2.1)
• Late loss	4%	2%	2.1 (1.0-4.4)
Live birth rate	87% (83-89)	91% (89-94)	0.9 (0.9-1.0)

2nd pregnancy

	Carriers	Non-carriers	RR (95%CI)
Live birth in 1st pregnancy			
N	421	404	
Live birth rate	86% (82-89)	90% (86-92)	1.0 (0.9-1.0)
Early loss in 1st pregnancy			
N	39	25	
Live birth rate	77% (62-87)	76% (57-89)	1.0 (0.8-1.3)
Late loss in 1st pregnancy			
N	19	10	
Live birth rate	68% (46-85)	80% (49-94)	0.9 (0.5-1.3)

Potential limitations

- Thrombosis cohort
  - No referral bias for women with obstetric complications
  - Effect of a thrombotic tendency?
    - No difference between outcome in women with and without VTE
- Lack of statistical power to detect small differences
  - especially in subcategories

Anticoagulant treatment

- Suggestion of efficacy of heparins [1]

→ Retrospective studies
→ No randomisation of treatment
→ Not blinded

[1] Folkeringa, *Br J Haem* 2007

Necessity of high-quality trials

- Stray-Pedersen *et al*, Am J Obstet Gynecol 1984
- 195 couples with recurrent pregnancy loss
- Etiologic screening program and targeted therapy
- 85 couples with unknown aetiology
  - Tender-loving care
    - Weekly medical examinations / psychological support
- Live birth rate
  - With TLC → 86%
  - Without TLC → 33%

Conclusions

1. First pregnancy

- Increased relative risk
  - Late pregnancy loss
- Small absolute differences

Conclusions

2. Second pregnancy

- Lower live birth rate after 1st loss
- Fairly similar for carriers and non-carriers
  - 12% lower for women with late loss
- Favourable prognosis for women with thrombophilia and a first loss without any treatment (live birth rate 74%)

Conclusions

3. High demands on potential treatment
   - Small margins for side-effects (bleeding)

4. Insufficient evidence of efficacy of anticoagulants
   - Trials ongoing

5. No treatment may be the best option

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