charm

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The Role of the Thromboelastogram in Unexplained Recurrent Pregnancy Loss

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Declaration of Interests

- No interests to declare

Background

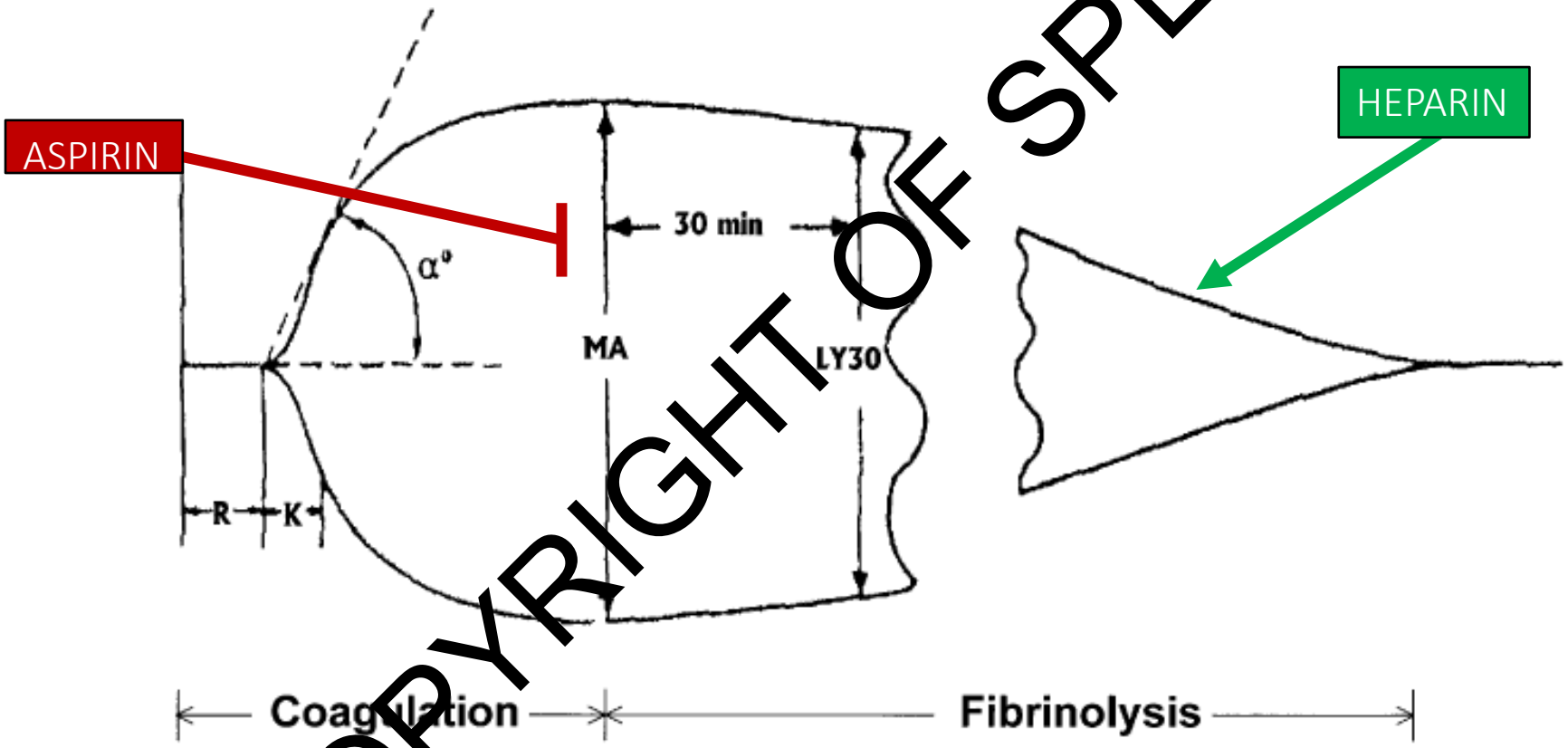
- Recurrent pregnancy loss (RPL): loss of three or more consecutive pregnancies, before 24 weeks' gestation
- Heterogeneous aetiologies: majority of cases *unexplained*
- Normal pregnancy causes a physiological shift towards 'prothrombotic' state
- Some cases of RPL have a known thrombotic basis → 'Theory of hypercoagulability' in unexplained RPL

  Empirical prescription of anticoagulation
- Indiscriminate use of anticoagulation in unexplained RPL not justified

  However RPL is heterogeneous → subgroup may benefit from targeted intervention

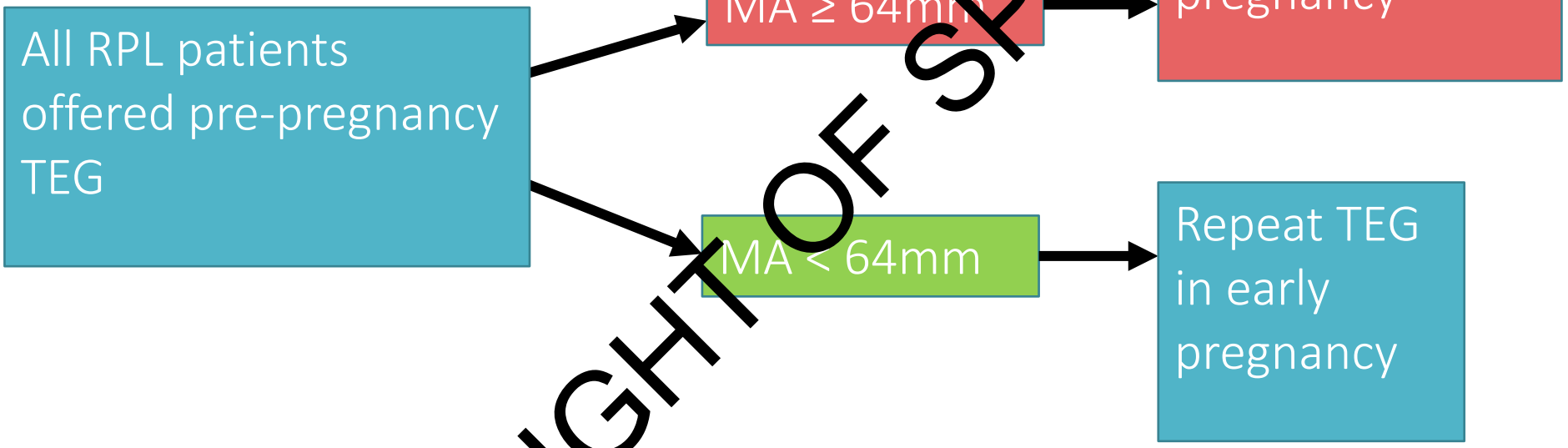
Clifford et al. *Hum Reprod* 1997; 12(2):387-9
Clark et al. *Blood* 2010;115:4162–7
Kaandorp et al. *N Engl J Med* 2010;362:1586–96

The Thromboelastogram (TEG): A Tool for Stratification of Thromboprophylaxis?



MA= Maximum amplitude. LY30/ LY60= Percentage lysis at 30 and 60 minutes respectively.
Figure adapted from Rai R et al. *Hum Reprod* 2003; 18(12):2540-3.

Current Practice at St Mary's



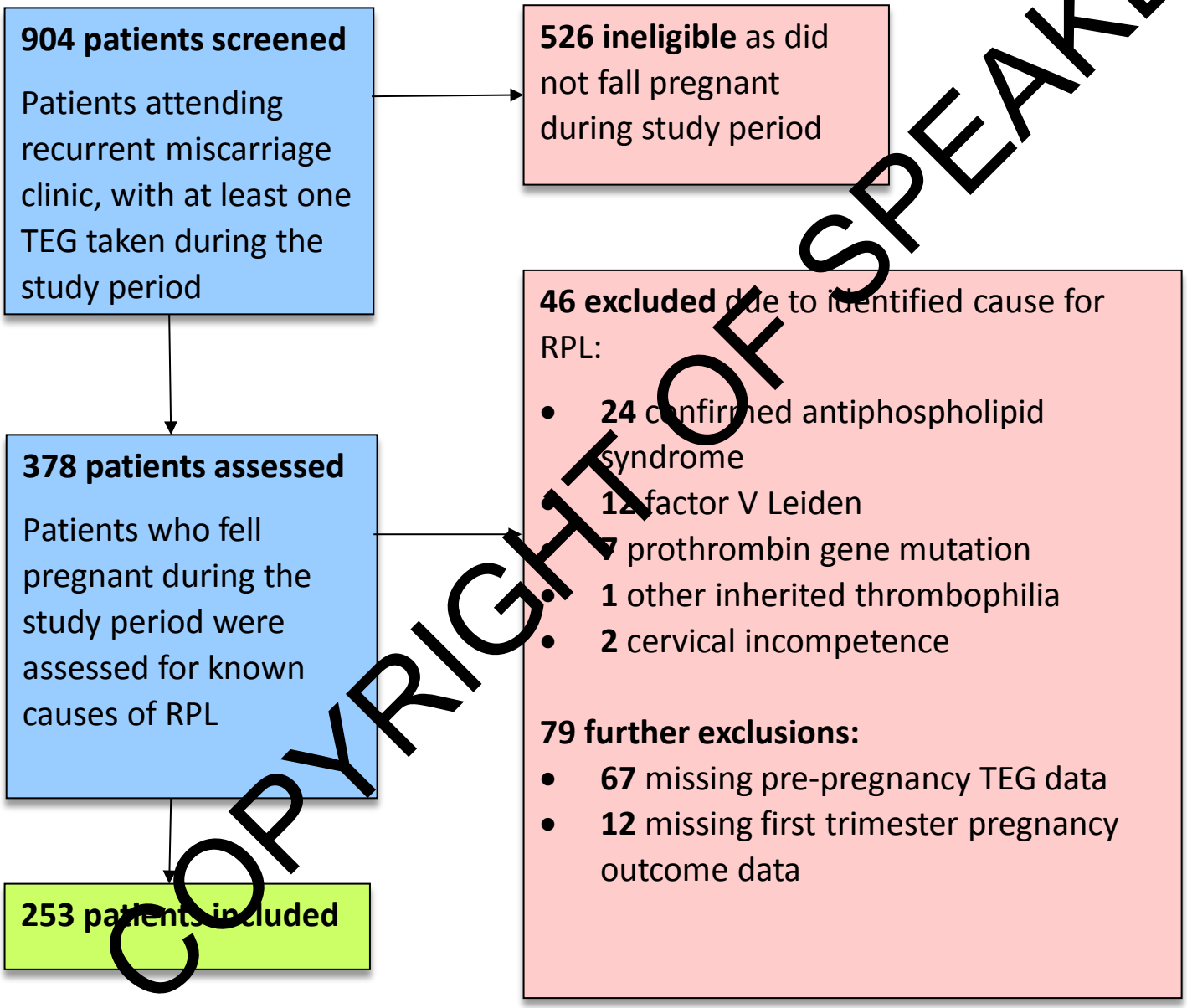
- Current guidance for aspirin prescription based largely on study by Rai et al
- Heparin prescription guidance much less well-defined

Rai R et al. *Hum Reprod* 2003; 18(12):2540-3.

Study aims

1) To examine the relationship between pre-pregnancy TEG parameters MA, LY30 and LY60 and first-trimester pregnancy outcome;
2) To assess the changes in MA, LY30 and LY60 from pre-pregnancy to early pregnancy;
3) To assess the relationship between the magnitude of change of MA, LY30 and LY60 from pre-pregnancy to early pregnancy, and first-trimester pregnancy outcome.

Study flowchart



Demographic data

	Total participants (n=253)
Age (years) §	34.7 (±4.4)
Ethnicity, n (%)†	
White	178 (72.1)
Black/Black British	14 (5.7)
Asian/ Asian British	35 (14.2)
Other	20 (8.1)
BMI (kgm^{-2}) §	24.3 (±4.2)
Current smoking status, n (%)	
Non-smoker	220 (94.4)
Smoker	13 (5.6)
Number with a previous live birth, n (%)†	
No previous live birth	58 (64.5)
Previous live birth	87 (35.5)
Number of previous miscarriages §	3.6 (±1.0)
Uterine anomaly, n (%)†	
No known anomaly	226 (89.3)
Corrected anomaly	23 (9.1)
Untreated anomaly	4 (1.6)

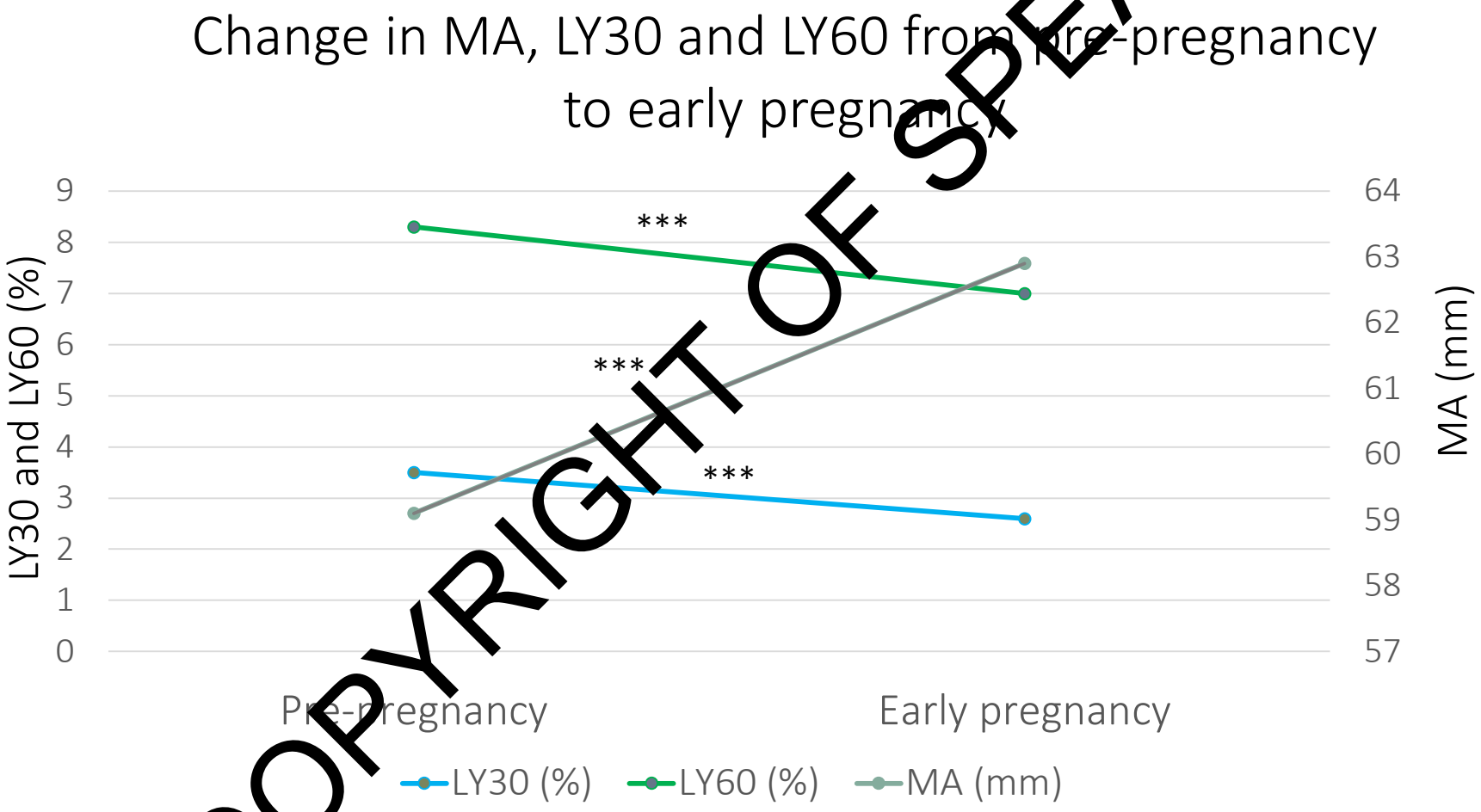
§= mean (± standard deviation)
† = number of women (% of total)

Results 1: Pre-pregnancy TEG parameters and first trimester pregnancy outcome

	First trimester pregnancy outcome		P value
	Miscarriage (n=67)	Continued (n=186)	
MA (mm)	62.7 (59.7-65.4)	60.75 (56.9-64.9)	0.017*
LY30 (%)	2.4 (1.4-4.2)	3.3 (1.3-7.8)	0.061
LY60 (%)	6.4 (4.6-8.3)	8.0 (4.9-13.4)	0.019*

Data are presented as median (interquartile range) with differences between groups calculated using the independent Mann-Whitney rank-sum test. *= $p<0.05$.

Results 2: Changes in TEG parameters from non-pregnant to early pregnancy



Significance of difference calculated by Wilcoxon matched-pairs signed-rank test. ***= $p<0.001$.

Results 3: Level of change in TEG parameters (Δ) and first trimester pregnancy outcome

	First-trimester pregnancy outcome		P value
	Miscarriage (n=33)	Continued (n=119)	
ΔMA (mm)	+2.0 (-3.6-4.9)	+4.2 (1.2-8.6)	0.021*
ΔLY30 (%)	-0.6 (-2.1-1.2)	-1.2 (-4.9-0.7)	0.182
ΔLY60 (%)	-0.2 (-2.7-1.3)	-1.4 (-5.6-1.1)	0.200

Data are presented as median (interquartile range) absolute changes in TEG parameters, with differences between groups calculated using the independent Mann-Whitney rank-sum test

*= P<0.05.

Key findings and implications

1) Increased clot strength and reduced fibrinolysis in the non-pregnant state, in those with first trimester miscarriage

- Role in pathogenesis of unexplained RPL?
- Median pre-pregnancy MA in first-trimester miscarriage group did not cross current treatment thresholds

2) Increased clot strength and reduced fibrinolysis in early pregnancy, compared to non-pregnant state

- Impaired fibrinolysis observed earlier in this cohort than in past longitudinal TEG study during normal pregnancies: reflection of underlying pathological phenomenon in unexplained RPL?

3) Those with first-trimester miscarriage had significantly lower median increase in clot strength from non-pregnant to early pregnancy

- Appears to contradict the theory that an exaggeration of the haemostatic response in early pregnancy is directly responsible for pregnancy loss in unexplained RPL
  - *Several possible explanations*

Karlsson et al. *Anesth Analg* 2012;115(4):890-8.

Future work

- **Prospective comparison of serial TEG readings throughout pregnancy, from implantation to late pregnancy**
  - Unexplained RPL patients vs. control group, in women with both normal and abnormal MA
  - Identification of appropriate risk thresholds
  - Insight into pathophysiology in pregnancy

- **Randomised controlled trials to assess potential benefit of heparin and aspirin in unexplained RPL**
  - Stratify based on pathophysiological markers, not outcome
  - Requires further investigation of complex pathophysiological mechanisms of coagulation and benefits of heparin in unexplained RPL