# Effect of Heparin on IVF treatment outcome

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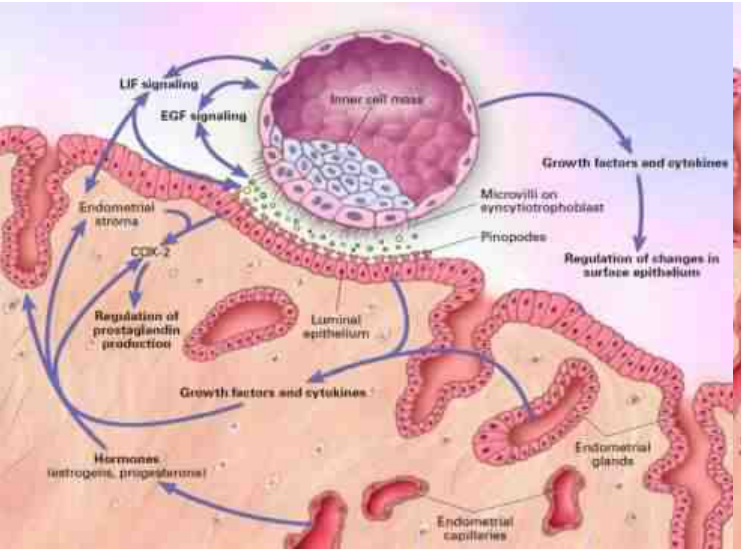
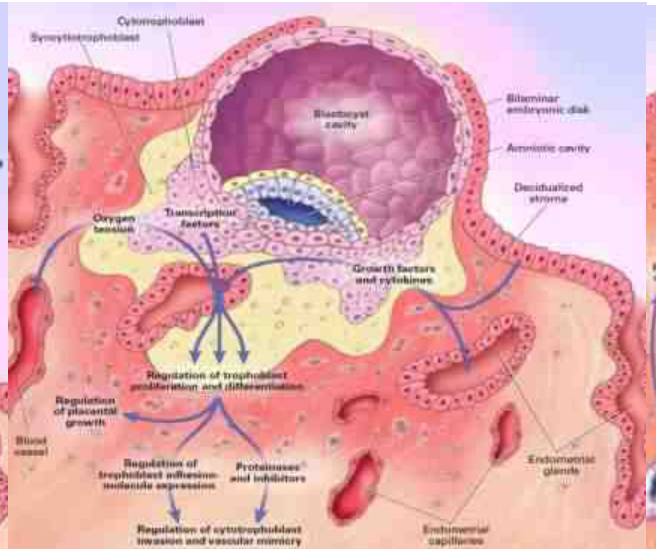
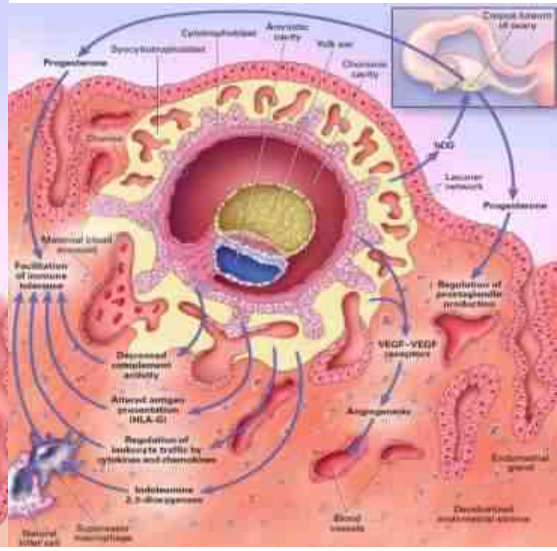
# Embryo implantation

- Implantation is the result of *complex molecular interactions* between the hormonally primed uterus and a mature blastocyst (Norwitz et al., NEJM 2001)

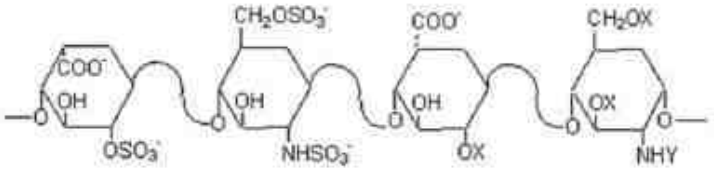
**Blastocyst apposition and adhesion** **Blastocyst implantation** **Early pregnancy maintenance**



# Heparin



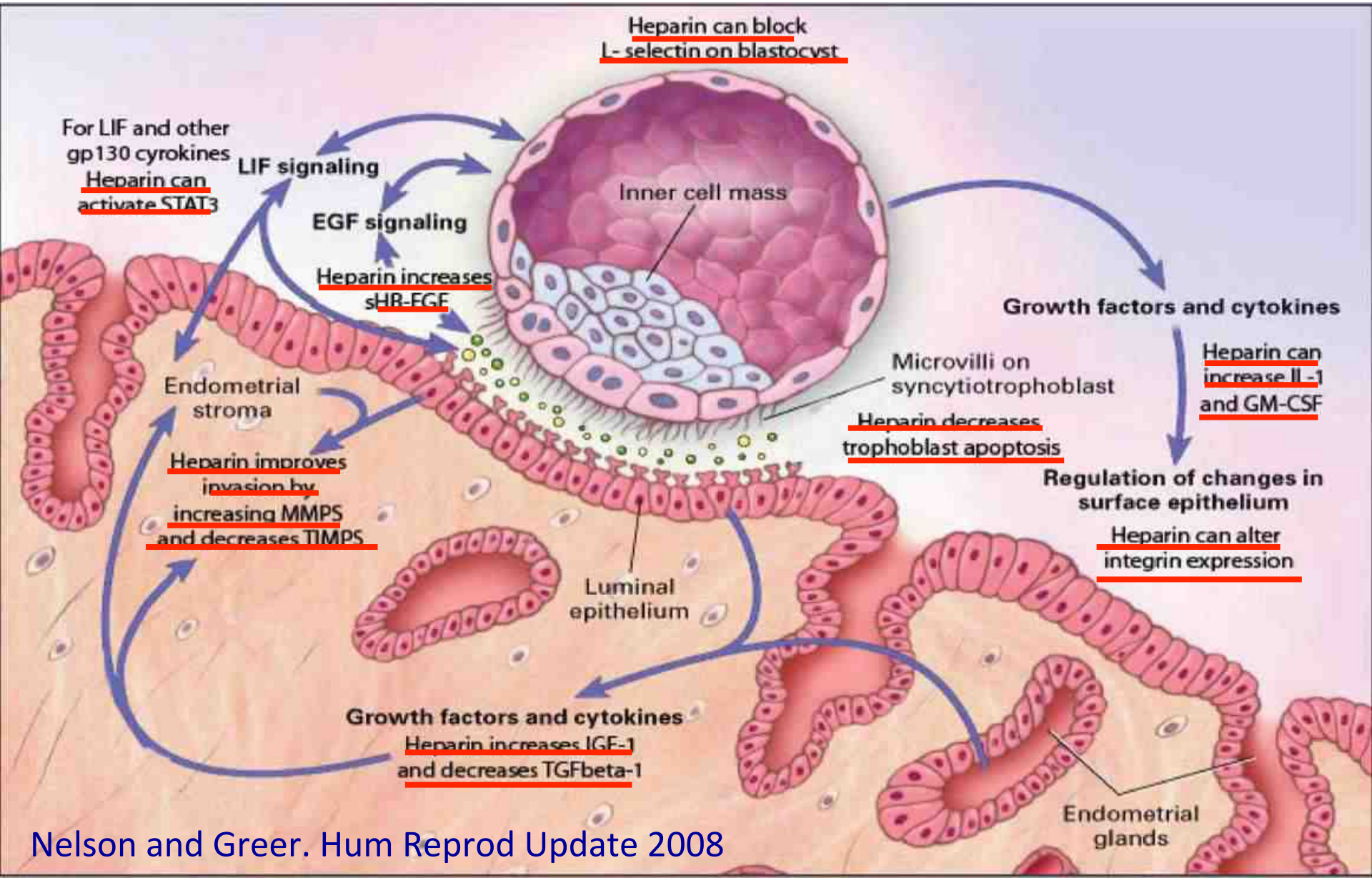

- Heparin is a *sulphated proteoglycan molecule* consisting of several polysaccharide chains linked to a peptide core
- Produced in the mast cells
- Binds to and accelerates antithrombin activity
- Antithrombin inactivates enzymes involved in blood coagulation

# Heparin and embryo implantation

- Prevents thrombosis facilitating trophoblast invasion and placentation
- Modulates physiological processes of blastocyst activation, adhesion, invasion
- Regulates endometrial stromal decidualization
- Interacts with adhesion molecules, cytokines, enzymes involved in implantation

Nelson and Greer. Hum Reprod Update 2008

# Heparin and embryo implantation



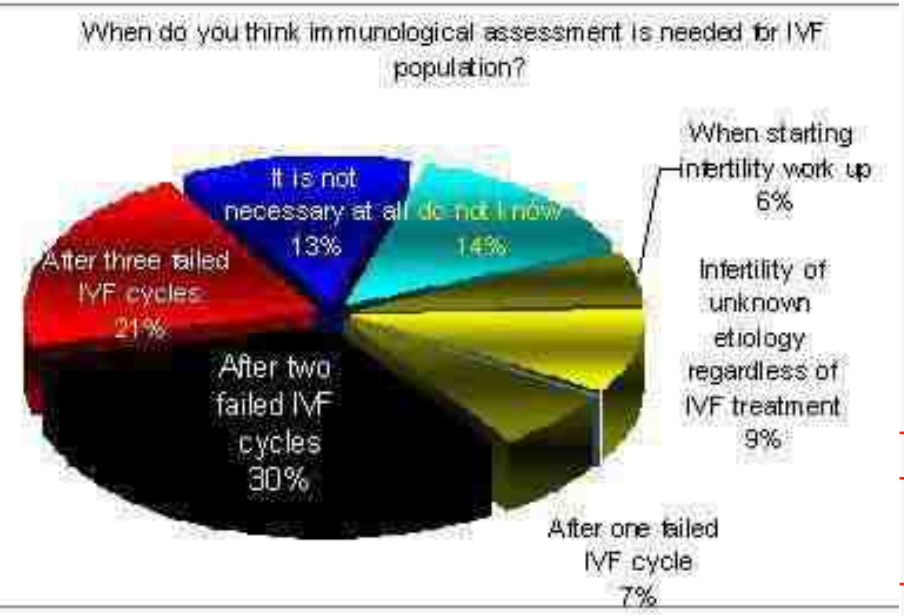

Nelson and Greer. Hum Reprod Update 2008

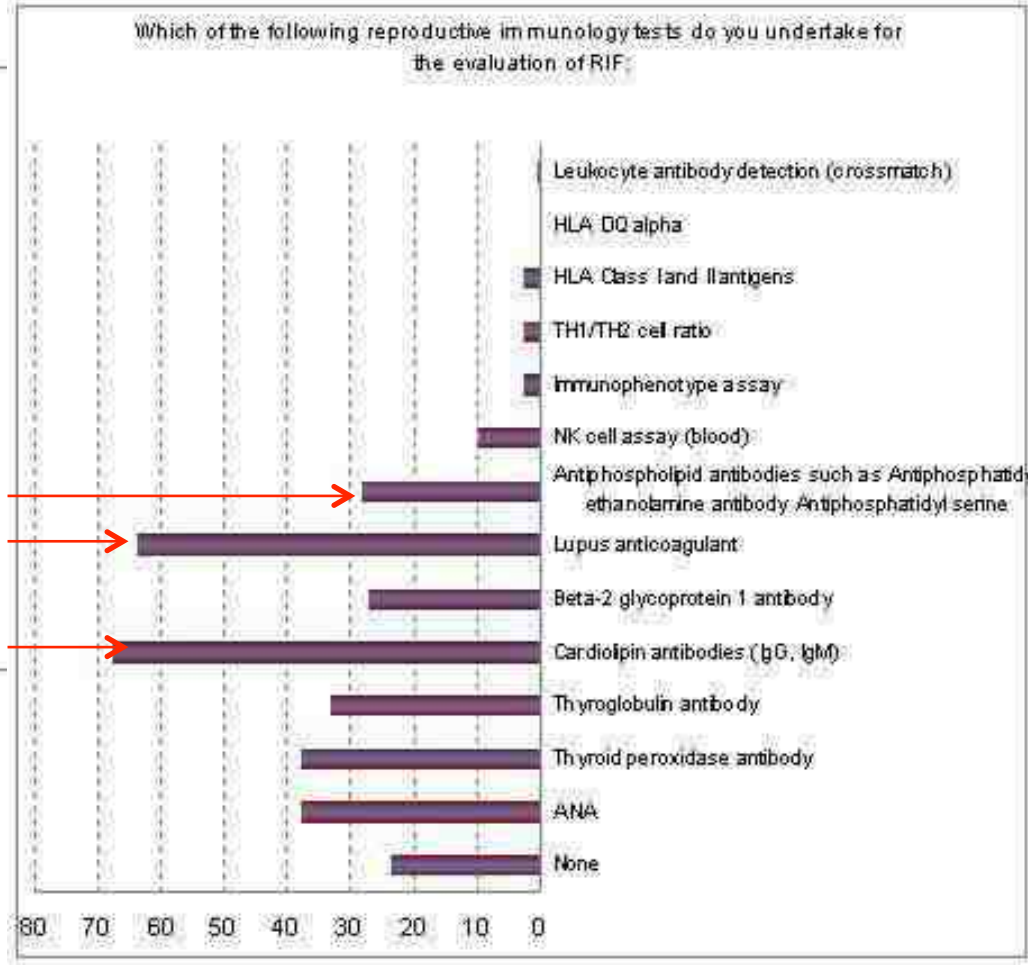
# Heparin in IVF

- Inherited or acquired thrombophilia without previous IVF failure
- Recurrent implantation failure (RIF)
- RIF and thrombophilia
- Empirical use

# Current practice

- Survey of 217 IVF Centres (www.ivfworldwide.com)



# Thrombophilia and IVF outcome

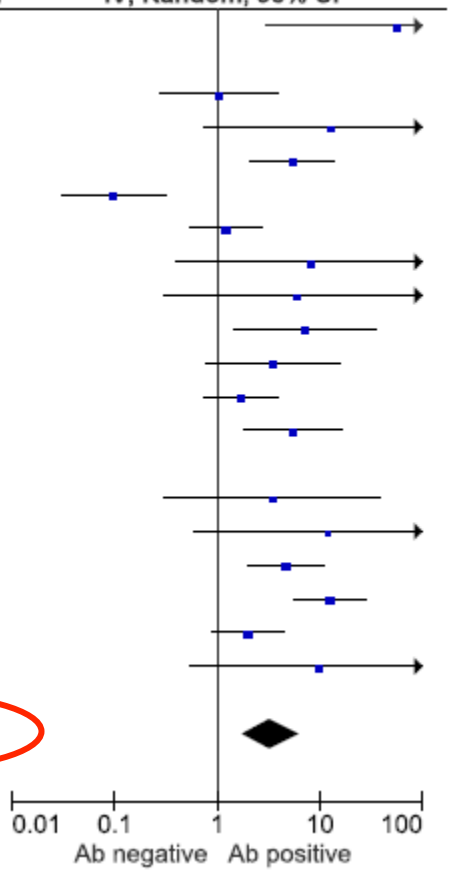
- Is thrombophilia more prevalent among women having unsuccessful IVF?
- Are women with thrombophilia at higher risk of unsuccessful IVF?
- Association between thrombophilia and pregnancy outcomes?

# Antiphospholipid antibodies: prevalence in IVF failures

| Study or Subgroup | Cases Events | Cases Total | Controls Events | Controls Total | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Balasch1996 | 4 | 40 | 0 | 226 | 3.0% | 55.85 [2.94, 1059.17] |
| Balasch1999 | 0 | 75 | 0 | 100 | | Not estimable |
| Bellver2008 | 5 | 26 | 6 | 32 | 6.4% | 1.03 [0.28, 3.86] |
| Birkenfeld1994 | 17 | 56 | 0 | 14 | 3.1% | 12.85 [0.72, 227.70] |
| Coulam1997 | 69 | 312 | 5 | 100 | 7.4% | 5.40 [2.11, 13.79] |
| Coulam2002 | 34 | 122 | 16 | 20 | 6.8% | 0.10 [0.03, 0.31] |
| Eldar-Geva1999 | 36 | 78 | 15 | 36 | 7.8% | 1.20 [0.54, 2.67] |
| Geva1994 | 3 | 21 | 0 | 21 | 2.9% | 8.14 [0.39, 167.98] |
| Geva1995 | 3 | 50 | 0 | 40 | 3.0% | 5.97 [0.30, 119.01] |
| Kaider1996 | 11 | 42 | 2 | 42 | 5.7% | 7.10 [1.46, 34.38] |
| Kaider1999 | 34 | 122 | 2 | 20 | 5.9% | 3.48 [0.77, 15.80] |
| Kutteh1997 | 9 | 84 | 19 | 284 | 7.7% | 1.67 [0.73, 3.85] |
| Lucena 1999 | 67 | 162 | 4 | 35 | 7.0% | 5.47 [1.84, 16.21] |
| Martinelli2003 | 0 | 162 | 0 | 234 | | Not estimable |
| Martinuzzo2005 | 2 | 48 | 1 | 80 | 3.8% | 3.43 [0.30, 38.93] |
| Putowski2004 | 6 | 17 | 0 | 10 | 3.0% | 11.87 [0.59, 237.37] |
| Qublan2006 | 17 | 90 | 9 | 190 | 7.7% | 4.68 [2.00, 10.98] |
| SanMarco2007 | 40 | 101 | 8 | 160 | 7.8% | 12.46 [5.51, 28.15] |
| Stern1998 | 18 | 105 | 10 | 106 | 7.7% | 1.99 [0.87, 4.54] |
| Vaquero2006 | 11 | 59 | 0 | 20 | 3.1% | 9.72 [0.55, 172.86] |
| **Total (95% CI)** | | **1772** | | **1770** | **100.0%** | **3.33 [1.77, 6.26]** |
| Total events | 386 | | 97 | | | |

Heterogeneity: Tau² = 1.17; $\chi^2$ = 67.18, df = 17 (P < 0.00001); I² = 75%

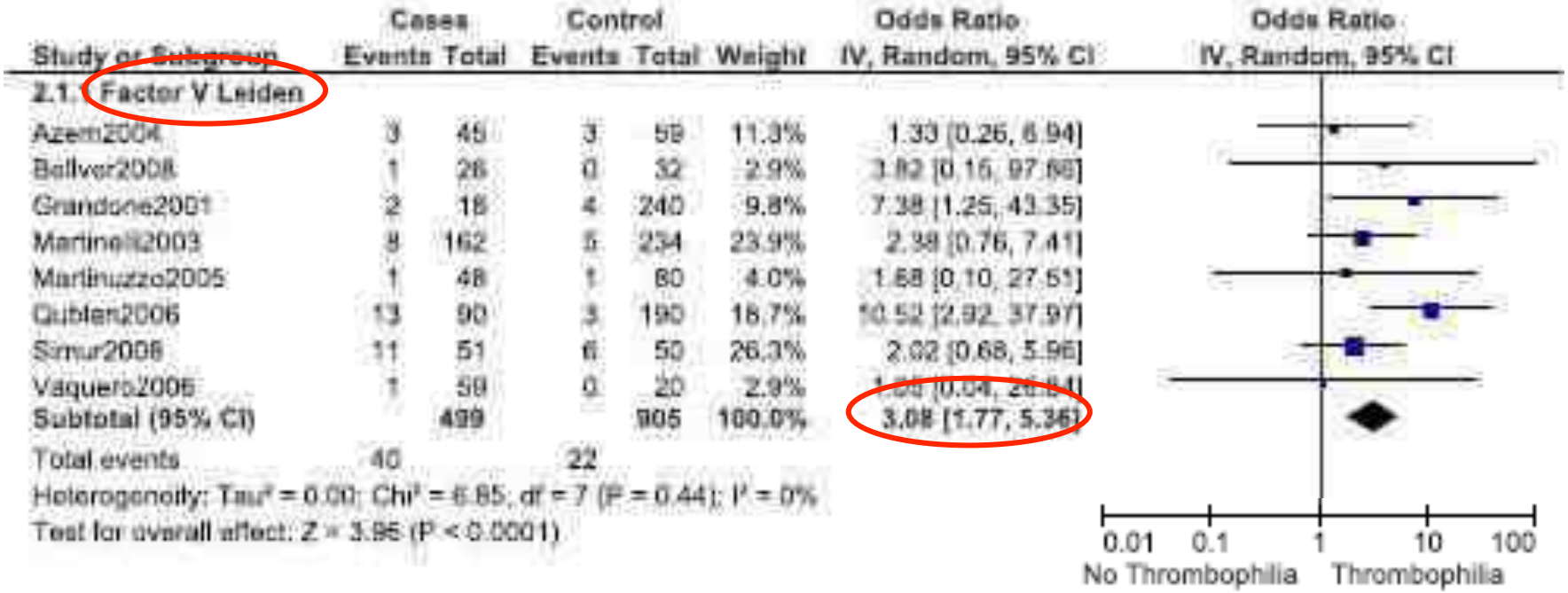
Test for overall effect: Z = 3.73 (P = 0.0002)




- Higher prevalence of antiphospholipid antibodies in women with ART failures

Di Nisio et al., Blood 2011

# Inherited thrombophilia: prevalence in IVF failures

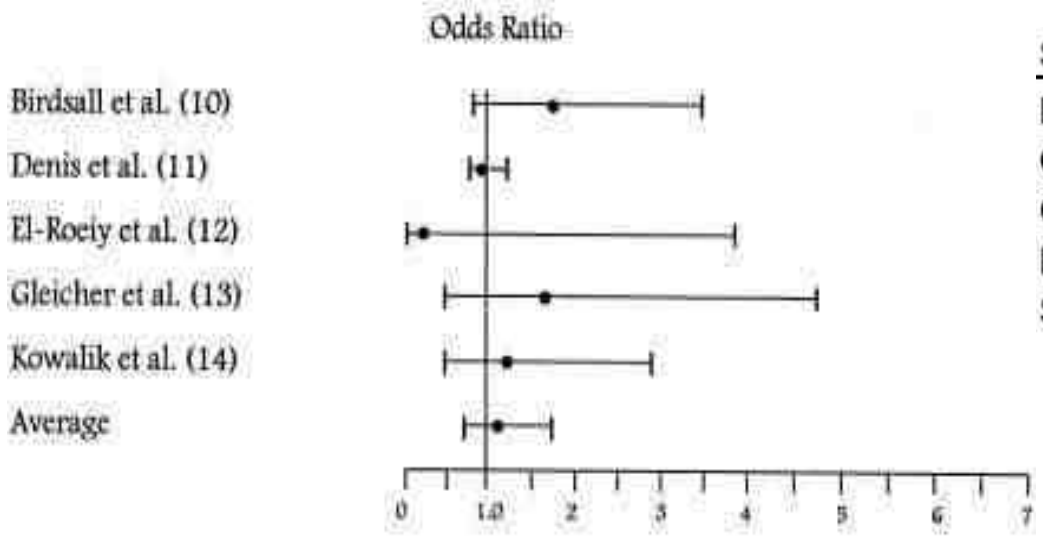



- Prothrombin mutation, MTHR mutation, protein C, S, antithrombin deficiency not associated with ART failures

Di Nisio et al., Blood 2011

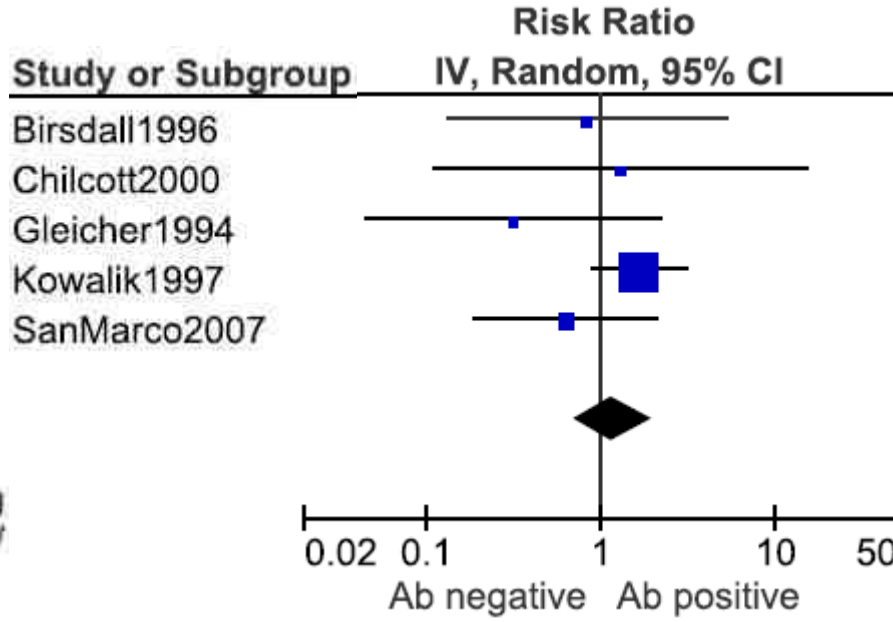
# Antiphospholipid antibodies: IVF outcome

Hornstein al., Fertil Steril 2001




***OR 1.07; 95% CI 0.66 – 1.75***

Di Nisio et al., Blood 2011




***RR 1.17; 95% CI 0.70 – 1.95***

- No significant difference in LBR between APA +ve and APA –ve women

# Inherited thrombophilia: IVF outcome

- Impact of Factor V Leiden, prothrombin and MTHR mutation on IVF (Martinelli at al., Heamatologica 2003; Tormene et al., Thromb Res 2011)

- No significant difference in viable pregnancy rates in thrombophilia +ve vs thrombophilia –ve women

- *Inconclusive evidence of association between thrombophilia and IVF?*

- *No justification for thrombophilia testing in the context of failed IVF*

# Heparin in RIF

Human Reproduction, Vol.24, No.7 pp. 1640–1647, 2009

## Luteal phase empirical low molecular weight heparin administration in patients with failed ICSI embryo transfer cycles: a randomized open-labeled pilot trial

B. Urman[1], B. Ata, K. Yakin, C. Alatas, S. Aksoy, R. Mercan, and B. Balaban

Fertility and Sterility® Vol. 95, No. 8, June 30, 2011

## The role of low-molecular-weight heparin in recurrent implantation failure: a prospective, quasi-randomized, controlled study

Bülent Berker, M.D.
Salih Taşkın, M.D.
Korhan Kahraman, M.D.
Elif Aylin Taşkın, M.D.
Cem Atabekoğlu, M.D.
Murat Sönmezer, M.D.

# Heparin in RIF

**Human Reproduction, Vol.24, No.7 pp. 1640–1647, 2009**

***RIF: ≥ 2 consecutive failed IVF cycles***

| | LMWH 75 | Control 75 | Absolute difference, 95% CI |
|---|---|---|---|
| Clinical pregnancy (%) | 34/75 (45.3) | 29/75 (38.7) | 6.6%, −9.0% to +21.8% |
| Multiple pregnancy (%) (twins, triplets, quadruplets) | 12/34 (35.3) (9,1,2) | 10/29 (34.5) (8,2,0) | 0.8%, −22.8% to +24.4% |
| Implantation | 24.5% | 19.8% | 4.7%, −4.7% to +14.1% |
| Ongoing pregnancy[a] (%) (>20 weeks) | 28/75 (37.3) | 20/75 (26.7) | 10.6%, −4.2% to +24.9% |
| Live birth[b] (%) | 26/75 (34.7) | 20/75 (26.7) | 8.0%, −6.7% to +22.7% |

Fertility and Sterility® Vol. 95, No. 8, June 30, 2011

| Characteristic | LMWH group (n = 104) | Control group (n = 103) |
|---|---|---|
| CPR | 34.6%, | 33.9% |
| LBR | 30.7%, | 29.1%, |
| implantation rate | 22.6% | 21.1%, |

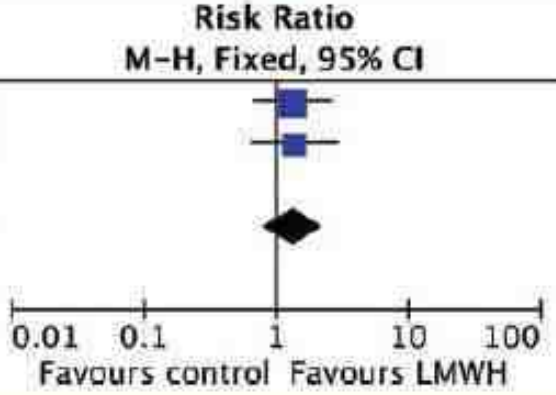
# Heparin in RIF

- *RIF: ≥3 consecutive IVF failures*

Potdar et al., Hum Reprod Update 2013

| Study or Subgroup | LMWH Events | LMWH Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Berker et al., 2011 | 15 | 48 | 10 | 43 | 55.9% | 1.34 [0.68, 2.67] |
| Urman et al., 2009 | 12 | 37 | 8 | 34 | 44.1% | 1.38 [0.64, 2.96] |
| **Total (95% CI)** | | **85** | | **77** | **100.0%** | **1.36 [0.82, 2.26]** |
| Total events | 27 | | 18 | | | |

Heterogeneity: $Chi^2 = 0.00$, $df = 1$ ($P = 0.96$); $I^2 = 0\%$
Test for overall effect: $Z = 1.18$ ($P = 0.24$)




Live birth rate(LBR) in women with ≥3 unexplained recurrent implantation failure and LMWH as treatment adjunct.

With 80% power and an $\alpha$-value of 0.05 for an approximately 8% difference in overall LBR per cycle and 9% difference in ≥3 RIF, the patient number for each study arm should be 520 and 400, respectively, for the confirmation of statistical significance. Thus,

# Heparin in RIF and thrombophilia

Table II. Treatment characteristics and reproductive outcome.

| | Group A (N = 42) | Group B (N = 41) | p-value |
|---|---|---|---|
| Day 3 FSH (IU/l) | 6.1 ± 3.1 | 6.1 ± 3.3 | NS |
| Days of stimulation | 13.4 ± 4.1 | 13.3 ± 4.2 | NS |
| No. of hMG ampoules | 54.5 ± 8.3 | 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 |

Qublan et al., Human Fertility 2008

# Heparin in RIF and thrombophilia

FERTILITY AND STERILITY 2003

## A randomized, double-blind, placebo-controlled trial of heparin and aspirin for women with in vitro fertilization implantation failure and antiphospholipid or antinuclear antibodies

*Catharyn Stern, M.D.,[a] Lawrence Chamley, Ph.D.,[b] Helen Norris, R.M., Lyndon Hale, M.D.,[a] and H. W. Gordon Baker, Ph.D.[c]*

| Treatment | Total embryos transferred | Fetal hearts | Fetal heart implantation rate (95% CI), % | No. of babies born | Live-birth rate (95% CI), % |
|---|---|---|---|---|---|
| Heparin and aspirin | 296 | 20 | 7 (4–10) | 18 | 6 (3–10) |
| Placebo | 259 | 22 | 8 (5–12) | 17 | 7 (4–10) |

Reproductive BioMedicine Online (2011)

# Effect of dalteparin sodium administration on IVF outcome in non-thrombophilic young women: a pilot study

Ivo Noci [a,*], Maria Novella Milanini [a], Maria Ruggiero [b], Francesca Papini Beatrice Fuzzi [a], Paolo Giovanni Artini [b]

- RCT, ***1st IVF cycle***, no thrombophilia

| | *Treatment (n = 73)* | *Control (n = 80)* |
|---|---|---|
| Clinical pregnancy (*n*) | 19 | 16 |
| Clinical pregnancy rate per transfer (%) | 26 | 20 |
| Implantation rate (%) | 15 | 12 |
| Spontaneous miscarriages (%) | 21 | 19 |
| Delivery (*n*) | 15 | 13 |
| Newborns (*n*) | 21 | 15 |
| Live birth rate/embryo transfer (%) | 21 | 16 |

There were no statistically significant differences between the two groups.

Reproductive BioMedicine Online (2012)

# Effect of heparin on the outcome of IVF treatment: a systematic review and meta-analysis

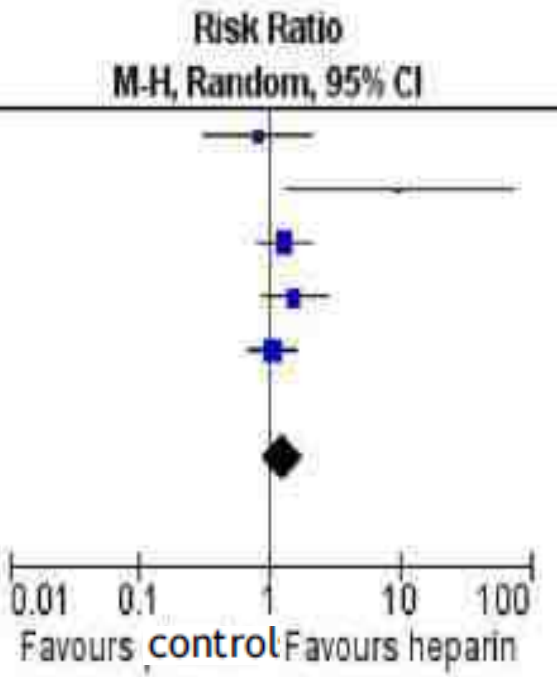
S Seshadri *, SK Sunkara, Y Khalaf, T El-Toukhy, H Hamoda

The effect of heparin versus control on the live birth rate (randomized controlled trials)

| | Heparin | | control | | | Risk Ratio | |
|---|---|---|---|---|---|---|---|
| Study or Subgroup | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | Year |
| Stern et al., 2003 | 7 | 66 | 8 | 61 | 11.4% | 0.81 [0.31, 2.10] | 2003 |
| Qublan et al., 2008 | 10 | 42 | 1 | 41 | 3.0% | 9.76 [1.31, 72.86] | 2008 |
| Urman et al., 2009 | 26 | 75 | 20 | 75 | 28.4% | 1.30 [0.80, 2.12] | 2009 |
| Noci et al., 2011 | 21 | 73 | 15 | 80 | 23.2% | 1.53 [0.86, 2.74] | 2011 |
| Berker et al., 2011 | 34 | 110 | 32 | 109 | 34.0% | 1.05 [0.70, 1.58] | 2011 |
| **Total (95% CI)** | | **366** | | **366** | **100.0%** | **1.27 [0.89, 1.81]** | |
| Total events | 98 | | 76 | | | | |

Heterogeneity: Tau² = 0.06; Chi² = 6.17, df = 4 (P = 0.19); I² = 35%

Test for overall effect: Z = 1.29 (P = 0.20)



# Does heparin improve pregnancy outcomes?

- Heparin in unexplained recurrent miscarriage

Kaandorp, S. P. N ENGL J MED 2010

**Table 2. Live-Birth Rate (Primary Outcome).***

| Variable | Aspirin plus Nadroparin | Aspirin Only | Placebo | P Value |
|---|---|---|---|---|
| Intention-to-treat population | | | | |
| No. of patients | 123 | 120 | 121 | |
| Live birth — no. (%) | 67 (54.5) | 61 (50.8) | 69 (57.0) | 0.63 |
| Relative risk (95% CI) | 0.96 (0.76 to 1.19) | 0.89 (0.71 to 1.13) | 1.00 | |
| Absolute difference in live-birth rate (95% CI) — % | −2.6 (−15.0 to 9.9) | −6.2 (−18.8 to 6.4) | — | |
| Women who became pregnant | | | | |
| No. of patients | 97 | 99 | 103 | |
| Live birth — no. (%) | 67 (69.1) | 61 (61.6) | 69 (67.0) | 0.52 |
| Relative risk (95% CI) | 1.03 (0.85 to 1.25) | 0.92 (0.75 to 1.13) | 1.00 | |
| Absolute difference in live-birth rate (95% CI) — % | 2.1 (−10.8 to 15.0) | −5.4 (−18.6 to 7.8) | — | |

BLOOD, 2010

# SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage

Peter Clark,[1] Isobel D. Walker,[2] Peter Langhorne,[3] Lena Crichton,[4] Andrew Thomson,[5] Mike Greaves,[6] Sonia Whyte,[7] and Ian A. Greer,[8] on behalf of the Scottish Pregnancy Intervention Study (SPIN) collaborators

- RM: ≥2 consecutive unexplained miscarriages

| | Aspirin and enoxaparin 143 | Control 140 |
|---|---|---|
| **Pregnancy losses** | **32 (22%)** | **29 (20%)** |
| **Antepartum haemorrhage** | **10** | **10** |

**Successful pregnancy: OR 0.91; 95% CI 0.52 – 1.59**

# Heparin for RM

Paulien G de Jong[1], Stef Kaandorp[2], Marcello Di Nisio[1,3], Mariëtte Goddijn[4], Saskia Middeldorp

*Cochrane Database of Systematic Reviews* 2014

| Outcome: 1 Live birth | | | | Risk Ratio |
|---|---|---|---|---|
| Badawy 2008 | 159/170 | 148/170 | 43.8 % | 1.07 [ 1.00, 1.15 ] |
| Fawzy 2008 | 46/57 | 24/50 | 34.2 % | 1.68 [ 1.23, 2.30 ] |
| Martinelli 2012 | 4/4 | 2/2 | 22.0 % | 1.00 [ 0.56, 1.79 ] |
| **Total (95% CI)** | **231** | **222** | **100.0 %** | **1.23 [ 0.84, 1.81 ]** |

**Authors' conclusions**

There is a limited number of studies on the efficacy and safety of aspirin and heparin in women with a history of at least two unexplained miscarriages with or without inherited thrombophilia. Of the nine reviewed studies quality varied, different treatments were studied and of the studies at low risk of bias only one was placebo-controlled. No beneficial effect of anticoagulants in studies at low risk of bias was found. Therefore, this review does not support the use of anticoagulants in women with unexplained recurrent miscarriage. The effect of anticoagulants in women with unexplained recurrent miscarriage and inherited thrombophilia needs to be assessed in further randomised controlled trials; at present there is no evidence of a beneficial effect.

STUDY PROTOCOL Open Access

# ALIFE2 study: low-molecular-weight heparin for women with recurrent miscarriage and inherited thrombophilia - study protocol for a randomized controlled trial

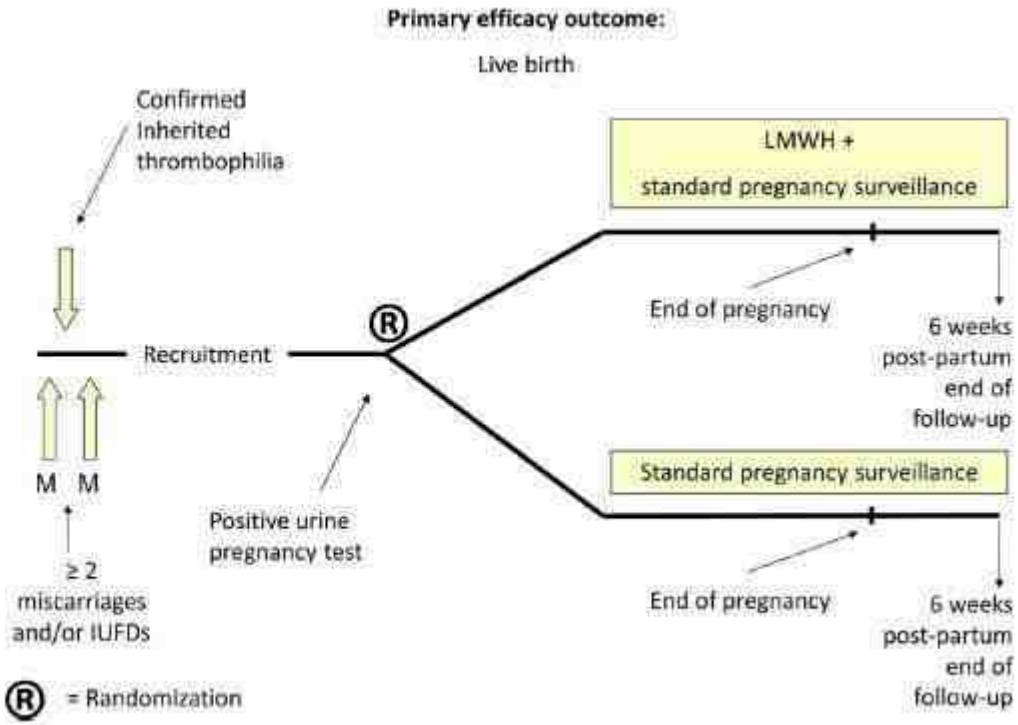
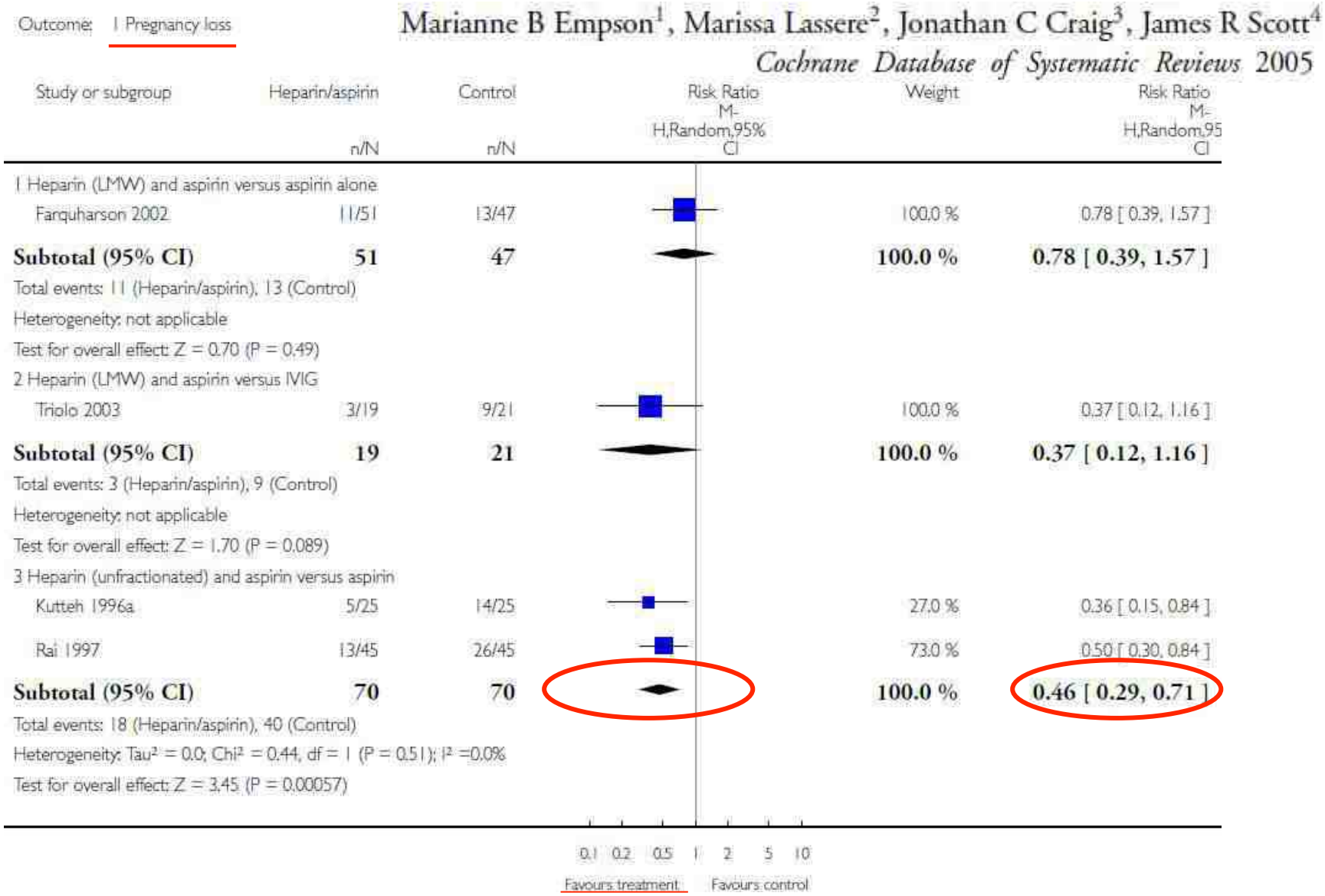



**Figure 1** Flowchart of the ALIFE2 study.

# Heparin for RM with APS



www.thelancet.com Vol 384 November 8, 2014

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

| | Antepartum dalteparin (n=146) | No antepartum dalteparin (n=143) | Difference (95% CI) | p value |
|---|---|---|---|---|
| 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 |

Choosing Wisely®

*An initiative of the ABIM Foundation*

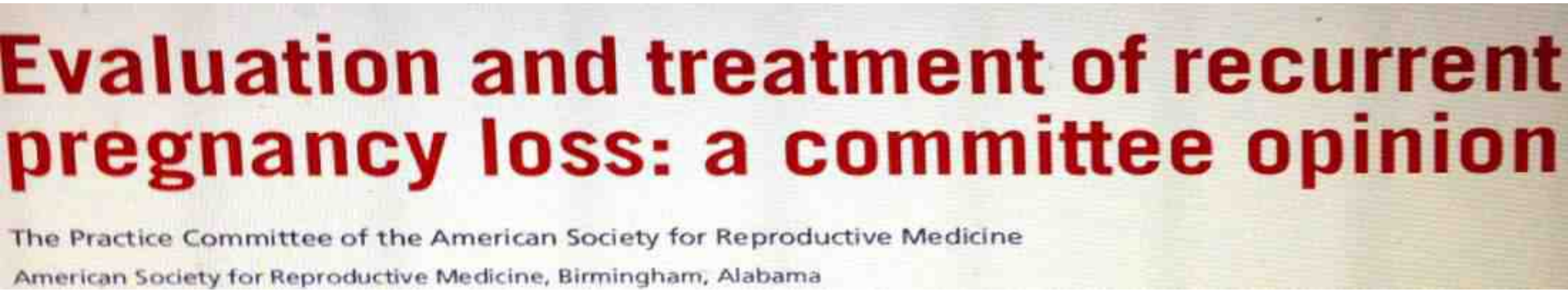
American Society for Reproductive Medicine

# Ten Things Physicians and Patients Should Question

4

## Don't routinely order thrombophilia testing on patients undergoing a routine infertility evaluation.

There is no indication to order these tests, and there is no benefit to be derived in obtaining them in someone that does not have any history of bleeding or abnormal clotting and in the absence of any family history. This testing is not a part of the infertility workup. Furthermore, the testing is costly, and there are risks associated with the proposed treatments, which would also not be indicated in this routine population.




**Women with recurrent pregnancy loss should be offered testing for antiphospholipid antibodies.**

**Standard treatment for documented antiphospholipid syndrome consists of low-dose aspirin and heparin.**

# The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage

Royal College of Obstetricians & Gynaecologists

**All women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriage should be screened before pregnancy for antiphospholipid antibodies.**

**Pregnant women with antiphospholipid syndrome should be considered for treatment with low-dose aspirin plus heparin to prevent further miscarriage.**

**Adjuvants in IVF: evidence for good clinical practice. On behalf of the British Fertility Society P&P Committee**

**Recommendation(s):** Available weak evidence does not warrant routine use of LMWH in the wide population of women undergoing IVF treatment, but it should be carefully considered in women with thrombophilia.

# Conclusion

- No justification for routine thrombophilia testing in IVF
- *Available evidence does not support routine use of Heparin in IVF*
- Current guidance to screen women with RM for antiphospholipid antibodies

# Conclusion

- *Heparin and aspirin for women with antiphospholipid syndrome*
- *Robust multi-centred RCT to test the efficacy of heparin in IVF*
- Consensus on who is most likely to benefit
  - All, RIF (≥2 vs ≥3), RIF and thrombophilia