Anticoagulants to prevent recurrent placenta mediated pregnancy complications: Is it time to put the needles away?

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Senior Scientist, Ottawa Hospital Research Institute
Professor, University of Ottawa
In the past: Cures for obesity...
In the past: Cures for male infertility/impotence...
Nuremberg salt RCT of 1835

Study Design: Double blind 1:1 RCT

Intervention: C30 dilution of NaCl in snow water vs snow water

Sample Size: Powered to detect a “improvement by 10 to 1 odds to experience some “extraordinary sensations” (primary outcome)"

Transparent: The design, hypothesis, methods and outcomes were agreed upon beforehand and explained in detail to all participants results were published quickly, and any deviation from protocol was acknowledged (but NOT registered on clinicaltrials.gov)

Sponsor: Allgemeine Zeitung von und für Bayern (local newspaper)

Results: 54 participants enrolled, 50 completed the study (4 lost to follow-up) 5/25 “extraordinary sensations” in the homeopathic group, 3/25 “extraordinary sensations” in the control group (p=0.44)

Stollberg, Journal of the Royal Society of Medicine, 2006
2018: Practice continues…

“Like salt to the palate, Nat mur given to a salt patient restores their appetite and taste for life, and aids the digestion of life’s tribulations.” David Lilley, Fellow of the Faculty of Homeopathy, Royal London Homeopathic Hospital
Law in Argentina
Placenta Mediated Pregnancy Complications

- Late pregnancy loss
- Intra-uterine growth restriction/ Small for gestational age (SGA)
- Pre-eclampsia (PET)
- Placental Abruption

- THE leading causes of maternal, fetal, and neonatal morbidity/mortality in developed nations
- Poverty of effective therapies to prevent recurrence
Pathophysiology of placenta mediated pregnancy complications includes placental thrombosis.

Thrombophilia’s predispose to development of thrombosis in slow flow circulation of the placenta.

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.
Thrombophilia- Associated with Placenta Mediated Pregnancy Complications (PMPC)

- Kupferminc, NEJM Jan 99
  - Case Control
  - Case- 65% ♀ with PMPC had thrombophilia
  - Control- 17% ♀ with normal pregnancies had thrombophilia
  - OR 8.2 (4.4-15.3)
Subsequent association work...

• Thrombophilia weakly associated with...
  – Recurrent early loss (OR ~1.5-2)
  – Late pregnancy loss (OR ~1.5-2)
  – Severe pre-eclampsia, abruption (OR ~1.5-2)

• Thrombophilia not associated with...
  – Non-severe pre-eclampsia
  – SGA
Pharmacoprophylaxis the options...

• Low Molecular Weight Heparin (LMWH) is the preferred choice in pregnancy (ACCP 2012)
  – Unfractionated heparin
    • BID or TID, 10x ↑ risk of HIT and >10x ↑ risk of osteoporotic fracture
  – Warfarin
    • Teratogenic ante-partum and inconvenient post-partum
  – Direct Oral AntiCoagulants
    • Cross placenta and enter breast milk
LMWH the downsides...

Burdens
- Self injections (up to 400 ante-partum, 42 post-partum)
- Cost (up to > 10,000 USD per ante-partum period)

Side effects
- Common (>5%)- Minor bleeding, ↑ LFTs, complicates regional anesthetic options
- Uncommon (0.1-5%)- Major bleed*, skin reactions, post-partum wound complications
- Rare (<0.1%)- HIT, osteoporotic fractures

*Major bleed= Death +/- critical organ (e.g. brain, spine, eye, retro-peritoneum) +/- 2g Hgb drop or 2 units RBCs
Case 1

30 yo woman with prior severe pre-eclampsia (PET) who delivered at 32 weeks asks:

“Should I be treated with LMWH in my next pregnancy?”
Case 1

Prior severe PET LMWH prophylaxis in next pregnancy?

1. Definitely for all
2. Definitely if she has FVL
3. Maybe
4. Definitely NOT
Study Level Meta-Analysis

Objective

• Determine the effect of LMWH in preventing placenta mediated pregnancy complications in women with prior late placenta mediated pregnancy complications

• Women with or without thrombophilia

• Compare LMWH with with no LMWH

Rodger MA, Carrier M, Le Gal G, Martinelli I, Perna A, Rey E, de Vries JI, Gris JC; Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications Study Group
Blood, 2014
Study Level Meta-Analysis

50 participants treated with X

Outcomes:

2% (1/50)

50 participants NOT treated with X

Outcomes:

4% (2/50)
## Study Level Meta-Analysis

### Study 1
- Treated with X: 1/50
- Not treated with X: 2/50

### Study 2
- Treated with X: 2/50
- Not treated with X: 4/50

### Study 3
- Treated with X: 1/50
- Not treated with X: 3/50

### Summary
- Treated with X: 4/150 (2.6%)
- Not treated with X: 9/150 (6.0%)
Study Level Meta-Analysis

**Primary Outcome:** Composite of ≥1 of: 1) any pre-eclampsia, or 2) abruption, or 3) small for gestational age child (<10th percentile) or 4) pregnancy loss >12 weeks

- LMWH n= 499
- Control n= 488

- **Absolute Event Rates**
  - LMWH= 15.8%
  - Control= 28.0%

- $I^2$=68%

RR= 0.57 (0.30-0.91)
Single Center Trials

- LMWH n= 233
  Control n= 231
- Absolute Event Rates
  - LMWH= 12.5%
  - Control= 35.1%
- $I^2=0\%$

$$RR = 0.35\ (0.24-0.52)$$
Multi-Center Trials

- LMWH n= 50/266  
  Control n= 56/257
- Absolute Event Rates
  - LMWH= 18.8%
  - Control= 21.8%
- $I^2=47\%$

Relative risk meta-analysis plot (random effects)

$RR= 0.86 \ (0.53-1.41)$
Severe PMPC only at study level

- LMWH n= 28/247
- Control n= 76/247
- Absolute Event Rates
  - LMWH= 11.3%
  - Control= 30.8%
- $I^2=0\%$

RR= 0.37 (0.25-0.55)
Non-Severe PMPC allowed at study level

- LMWH n= 51/252
  Control n= 61/241
- Absolute Event Rates
  - LMWH= 20.2%
  - Control= 25.3%
- $I^2=68\%$

$RR= 0.80 \ (0.44-1.40)$
Individual Data Meta-Analysis
Patient Groups/Sub-Groups/Outcomes

Pre-eclampsia/Severe Pre-clampsia

Placental Abruption

Pregnancy Loss (Early/Late)

SGA/IUGR (<10th, <5th, <3rd)

No Thrombophilia

Known Thrombophilia

Unknown Thrombophilia
Individual Patient Data Meta-Analysis

50 participants treated with X
Outcomes: 8% (4/50)

50 participants NOT treated with X
Outcomes: 12% (6/50)

50 participants treated with X
Outcomes: 8% (4/50)

50 participants NOT treated with X
Outcomes: 12% (6/50)

50 participants treated with X
Outcomes: 8% (4/50)

50 participants NOT treated with X
Outcomes: 12% (6/50)

Treated with X
Not treated with X
Individual Patient Data Meta-Analysis

Treated with X

Not treated with X

😊 = mild disease
😊 = severe disease

Treated with X

Not treated with X

OUTCOMES
Individual Patient Data Meta-Analysis (IPDMA)

- **Question:** Does LMWH prevent specific placenta mediated pregnancy complications (PMPCs) in women with specific prior late PMPCs?

- **Patients:** Pregnant women with prior late PMPCs (PET, abruption, SGA newborn (<10th percentile), 1 loss >16 wks or ≥ 2 losses > 12 wks).

- **Intervention:** LMWH vs no LMWH

Rodger, Lancet, 2016
AFFIRM: An individual patient data meta-analysis of low-molecular-weight heparin for prevention of placenta-mediated pregnancy complications

- Johanna IP de Vries
- Evelyne Rey
- Jean-Christophe Gris
- Ida Martinelli
- Ekkehard Schleussner
- Saskia Middeldorp
- Shannon M Bates
- Paulien de Jong
- Nicole Langlois
- Ranjeeta Mallick
- Timothy Ramsay
- David Petroff
- Dick Bezemer
- Marion van Hoorn
- Carolien Abheiden
- Risto Kaaja
- Annalisa Perna
- Alain Mayhew
Methods

Systematic Review:

Records Screened (n= 472)

Potentially Eligible Study (n= 14)

Participated in Individual Patient Data Meta Analysis (n= 9) 1049 patients

Not Included:
- Unable to contact PI (n=2)
- Trial Ongoing (n=3)

Rodger, Systematic Reviews, 2014
Methods

• Data pooling:
  – After REB approval
  – Individual patient data re-coded at each site
  – De-identified data → Ottawa and combined

• Study Quality:
  – Cochrane Risk of Bias tool
  – Single center vs multi-center
Methods

• Composite Primary outcome (1 or more):
  – 1) early-onset (<34 wks) or severe PET, 2) SGA newborn < 5th percentile, 3) late pregnancy loss (> 20 weeks), or 4) placental abruption.

• Data analysis:
  – **Validation:** Primary analyses of original trials replicated in combined dataset
  – **Analysis:** Risk difference calculated using Generalized Estimating Equation to adjust for study level clustering
## Results: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LMWH (n=525)</th>
<th>No LMWH (n=524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (mean, SD)</td>
<td>31.0 (4.9)</td>
<td>30.9 (5.1)</td>
</tr>
<tr>
<td>Race (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>454 (90.4%)</td>
<td>424 (86.7%)</td>
</tr>
<tr>
<td>Thrombophilia (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVL mutation</td>
<td>93 (19.8%)</td>
<td>95 (20.2%)</td>
</tr>
<tr>
<td>PTG mutation</td>
<td>43 (8.4%)</td>
<td>38 (7%)</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>3 (0.6%)</td>
<td>4 (0.8%)</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>9 (1.7%)</td>
<td>10 (2.0%)</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>54 (10.7%)</td>
<td>57 (11.6%)</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>20 (4.2%)</td>
<td>11 (2.3%)</td>
</tr>
<tr>
<td>Smoker (n, %)</td>
<td>36 (8.0%)</td>
<td>38 (8.3%)</td>
</tr>
<tr>
<td>Chronic hypertension (n, %)</td>
<td>82 (19.4%)</td>
<td>75 (17.9%)</td>
</tr>
</tbody>
</table>
## Results: Prior Pregnancies

<table>
<thead>
<tr>
<th>Pregnancy History</th>
<th>LMWH (n= 525)</th>
<th>No LMWH (n=524 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravida</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>325 (61.9%)</td>
<td>317 (60.5%)</td>
</tr>
<tr>
<td>≥3</td>
<td>200 (38.1%)</td>
<td>207 (39.5%)</td>
</tr>
<tr>
<td>Previous late pregnancy losses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 x &gt;12</td>
<td>159/506 (31.4%)</td>
<td>160/499 (32.1%)</td>
</tr>
<tr>
<td>1 x &gt;16</td>
<td>173/511 (33.9%)</td>
<td>170/505 (33.7%)</td>
</tr>
<tr>
<td>Previous small for gestational age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA &lt; 10&lt;sup&gt;th&lt;/sup&gt;</td>
<td>161/453 (35.5%)</td>
<td>156/454 (34.4%)</td>
</tr>
<tr>
<td>SGA &lt; 5&lt;sup&gt;th&lt;/sup&gt;</td>
<td>82/403 (20.4%)</td>
<td>84/390 (21.6%)</td>
</tr>
<tr>
<td>SGA &lt; 3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>31/346 (9.0%)</td>
<td>39/334 (11.7%)</td>
</tr>
<tr>
<td>Previous placental abruption</td>
<td>143/441 (32.4%)</td>
<td>143/446 (32.1%)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>293/480 (61.0%)</td>
<td>303/484 (62.6%)</td>
</tr>
<tr>
<td>Severe preeclampsia</td>
<td>225/434 (51.8%)</td>
<td>216/418 (51.7%)</td>
</tr>
<tr>
<td>Early-onset preeclampsia</td>
<td>160/407 (39.3%)</td>
<td>147/394 (37.3%)</td>
</tr>
</tbody>
</table>
Primary Composite Outcome: Abruption, Severe/Early PET, SGA (<5th) or Late Loss

<table>
<thead>
<tr>
<th></th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH (n=459)</td>
<td>13.1%</td>
</tr>
<tr>
<td>No LMWH (n=449)</td>
<td>20.5%</td>
</tr>
</tbody>
</table>

Difference = -7.4%
(95% CI, -16.1% to +1.3%)

\( p = 0.10 \)
Primary Composite Outcome: Abruption, Severe/Early PET, SGA (<5\textsuperscript{th}) or Late Loss

Multi-Center Trials (n=6)

Difference = -0.7%
(95% CI, -10.7\% to +9.3\%)

\[ p = 0.89 \]

LMWH (n=267) No LMWH (n=257)
Primary Composite Outcome: Abruption, Severe/Early PET, SGA (<5<sup>th</sup>) or Late Loss

Single-Center Trials (n=2)

Difference = -16.7%
(95% CI, -20.5% to -12.8%)

\[ p = 0.001 \]

<table>
<thead>
<tr>
<th>6.7%</th>
<th>23.4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH (n=192)</td>
<td>No LMWH (n=192)</td>
</tr>
</tbody>
</table>
## Secondary Outcomes

<table>
<thead>
<tr>
<th>Individual outcomes</th>
<th>All Studies (n=8)</th>
<th>Multi-Center Studies (n=6)</th>
<th>Single Center Studies (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preeclampsia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk difference</td>
<td>-5% (-12, +1)</td>
<td>-1% (-1, +7)</td>
<td>-12% (-15, -8)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td><em>p = 0.10</em></td>
<td><em>p = 0.82</em></td>
<td><em>p &lt; 0.0001</em></td>
</tr>
<tr>
<td><strong>Severe or Early Preeclampsia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk difference</td>
<td>-4% (-10, +2)</td>
<td>+1% (-6, +7)</td>
<td>-11% (-16, -7)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td><em>p = 0.20</em></td>
<td><em>p = 0.81</em></td>
<td><em>p &lt; .0001</em></td>
</tr>
<tr>
<td><strong>SGA &lt;10</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk difference</td>
<td>-8% (-14, -2)</td>
<td>-3% (-10, +3)</td>
<td>-14% (-18, -10)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td><em>p = 0.01</em></td>
<td><em>p = 0.32</em></td>
<td><em>p &lt; 0.0001</em></td>
</tr>
<tr>
<td><strong>SGA &lt;5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk difference</td>
<td>-3% (-5, -0.1)</td>
<td>-1% (-4, +0.02)</td>
<td>-5% (-5, -5)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td><em>p = 0.04</em></td>
<td><em>p = 0.60</em></td>
<td><em>p &lt; .0001</em></td>
</tr>
</tbody>
</table>
## Multi-Center Trials: 2° Outcomes

<table>
<thead>
<tr>
<th>Individual outcomes</th>
<th>LMWH</th>
<th>No LMWH</th>
<th>Absolute Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>29/279 (10.3%)</td>
<td>32/283 (11.3%)</td>
<td>-1.0% (p=0.82)</td>
</tr>
<tr>
<td>Severe preeclampsia</td>
<td>19/277 (6.9%)</td>
<td>19/283 (6.7%)</td>
<td>0.2% (p=0.96)</td>
</tr>
<tr>
<td>Early-onset preeclampsia</td>
<td>11/279 (3.9%)</td>
<td>14/283 (4.9%)</td>
<td>-1.0% (p=0.73)</td>
</tr>
</tbody>
</table>
## Multi-Center Trials: 2º Outcomes

<table>
<thead>
<tr>
<th>Individual outcomes</th>
<th>LMWH</th>
<th>No LMWH</th>
<th>Absolute Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA &lt; 10&lt;sup&gt;th&lt;/sup&gt;</td>
<td>47/272 (17.3%)</td>
<td>53/257 (20.1%)</td>
<td>-2.8% (p=0.32)</td>
</tr>
<tr>
<td>SGA &lt; 5&lt;sup&gt;th&lt;/sup&gt;</td>
<td>22/266 (8.3%)</td>
<td>23/253 (9.1%)</td>
<td>-0.8% (p=0.60)</td>
</tr>
<tr>
<td>SGA &lt; 3&lt;sup&gt;rd&lt;/sup&gt; percentile</td>
<td>13/266 (4.9%)</td>
<td>9/253 (3.6%)</td>
<td>1.3% (p=0.33)</td>
</tr>
</tbody>
</table>
## Multi-Center Trials: 2º Outcomes

<table>
<thead>
<tr>
<th>Individual outcomes</th>
<th>LMWH</th>
<th>No LMWH</th>
<th>Absolute Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any pregnancy loss</td>
<td>30/285 (10.5%)</td>
<td>37/287 (12.9%)</td>
<td>-2.4% (p=0.59)</td>
</tr>
<tr>
<td>Pregnancy loss ≥ 20 weeks gestation</td>
<td>8/288 (2.8%)</td>
<td>5/292 (1.7%)</td>
<td>1.1% (p=0.46)</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>3/278 (1.1%)</td>
<td>5/283 (1.8%)</td>
<td>-0.7% (p=0.53)</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>1/213 (0.5%)</td>
<td>3/216 (1.4%)</td>
<td>-0.9% (p=0.03)</td>
</tr>
</tbody>
</table>
## Subgroups that benefit?

<table>
<thead>
<tr>
<th>Subgroup Analyses</th>
<th>All Studies (n=8)</th>
<th>Multi-Center Studies (n=6)</th>
<th>Single Center Studies (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior preeclampsia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk difference</td>
<td>-12%</td>
<td>-6%</td>
<td>-17%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-19, -4)</td>
<td>(-19, +6)</td>
<td>(-24, -11)</td>
</tr>
<tr>
<td><em>p</em></td>
<td>0.002</td>
<td>0.34</td>
<td><em>p &lt; .0001</em></td>
</tr>
<tr>
<td><strong>Prior severe or early onset Preeclampsia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk difference</td>
<td>-10%</td>
<td>-4%</td>
<td>-17%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-19, -2)</td>
<td>(-19, +12)</td>
<td>(-23, -11)</td>
</tr>
<tr>
<td><em>p</em></td>
<td>0.02</td>
<td>0.65</td>
<td><em>p &lt; .0001</em></td>
</tr>
<tr>
<td><strong>Prior SGA &lt; 5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk difference</td>
<td>-14%</td>
<td>-10%</td>
<td>-27%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-28, -1)</td>
<td>(-27, +7)</td>
<td>(-46, -9)</td>
</tr>
<tr>
<td><em>p</em></td>
<td>0.03</td>
<td>0.25</td>
<td><em>p = 0.01</em></td>
</tr>
</tbody>
</table>
## Multi-Center Trials: Subgroups

<table>
<thead>
<tr>
<th>Subgroup Analyses</th>
<th>LMWH</th>
<th>No LMWH</th>
<th>Absolute Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Any preeclampsia</td>
<td>26/141 (18.4%)</td>
<td>36/147 (24.5%)</td>
<td>-6.1% (p=0.34)</td>
</tr>
<tr>
<td>Prior Severe preeclampsia</td>
<td>18/95 (19.0%)</td>
<td>20/88 (22.7%)</td>
<td>-3.7% (p=0.69)</td>
</tr>
<tr>
<td>Prior Early-onset preeclampsia</td>
<td>22/105 (20.1%)</td>
<td>25/95 (26.3%)</td>
<td>-6.2% (p=0.51)</td>
</tr>
</tbody>
</table>
## Multi-Center Trials: Subgroups

<table>
<thead>
<tr>
<th>Subgroup Analyses</th>
<th>LMWH</th>
<th>No LMWH</th>
<th>Absolute Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prior loss &gt;12 weeks</td>
<td>22/131 (16.8%)</td>
<td>19/114 (16.7%)</td>
<td>0.1% (p=0.98)</td>
</tr>
<tr>
<td>1 or more late loss &gt; 16 weeks</td>
<td>21/123 (17.1%)</td>
<td>19/109 (17.4%)</td>
<td>-0.3% (p=0.95)</td>
</tr>
<tr>
<td>2 or more late loss &gt;12 weeks</td>
<td>4/22 (18.2%)</td>
<td>2/14 (14.3%)</td>
<td>3.9% (p=0.72)</td>
</tr>
</tbody>
</table>
## Multi-Center Trials: Subgroups

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<tr>
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<th>LMWH</th>
<th>No LMWH</th>
<th>Absolute Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior SGA &lt; 10th percentile</td>
<td>21/107 (19.6%)</td>
<td>22/96 (23.0%)</td>
<td>-3.4% (p=0.64)</td>
</tr>
<tr>
<td>Prior SGA &lt; 5th percentile</td>
<td>8/60 (13.3%)</td>
<td>13/56 (23.2%)</td>
<td>-9.9% (p=0.25)</td>
</tr>
<tr>
<td>Prior SGA &lt; 3rd percentile</td>
<td>6/21 (28.6%)</td>
<td>6/25 (24.0%)</td>
<td>4.6% (p=0.41)</td>
</tr>
</tbody>
</table>
# Multi-Center Trials: Subgroups

<table>
<thead>
<tr>
<th>Subgroup Analyses</th>
<th>LMWH</th>
<th>No LMWH</th>
<th>Absolute Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Placental abruption</td>
<td>3/48 (6.3%)</td>
<td>9/47 (19.1%)</td>
<td>-12.8% (p=0.01)</td>
</tr>
</tbody>
</table>
## Multi-Center Trials: Subgroups

<table>
<thead>
<tr>
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<th>LMWH</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Start LMWH &lt;10 weeks</td>
<td>23/122 (19.0%)</td>
<td>47/255 (18.0%)</td>
<td>0.4% (p=0.95)</td>
</tr>
<tr>
<td>Start LMWH &lt;16 weeks</td>
<td>43/235 (18.0%)</td>
<td>47/255 (23.2%)</td>
<td>-0.1% (p=0.98)</td>
</tr>
<tr>
<td>Start LMWH &lt;20 weeks</td>
<td>47/260 (18.0%)</td>
<td>6/25 (24.0%)</td>
<td>-0.4% (p=0.94)</td>
</tr>
</tbody>
</table>
## Multi-Center Trials: Subgroups

<table>
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<th>No LMWH</th>
<th>Absolute Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>26/146 (18%)</td>
<td>32/140 (23.0%)</td>
<td>-5.1% (p=0.35)</td>
</tr>
<tr>
<td>No ASA</td>
<td>21/114 (18%)</td>
<td>14/100 (14.0%)</td>
<td>4.4% (p=0.26)</td>
</tr>
</tbody>
</table>
Prior Pre-eclampsia (PET) and Preventing pre-eclampsia (PET)

<table>
<thead>
<tr>
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<th>LMWH</th>
<th>No LMWH</th>
<th>Absolute Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior any PET Prevent any PET</td>
<td>21/144 (14.6%)</td>
<td>26/153 (17.0%)</td>
<td>-2.4% (p=0.64)</td>
</tr>
<tr>
<td>Prior Severe/Early onset PET Prevent</td>
<td>16/124 (12.9%)</td>
<td>16/116 (13.8%)</td>
<td>-0.1% (p=0.88)</td>
</tr>
<tr>
<td>Prevent Severe/Early Onset PET</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Discussion

• Strengths
  – Pooled RCT data at patient level from all the large trials in this area

• Limitations
  – Power: limited numbers of patients (e.g. sub-groups)
  – Large differences between single center and multi-center trials
    • No clear explanation
Another recent negative RCT...

**Study design:** Open label RCT

**Intervention:** Enoxaparin/ASA vs ASA alone

**Participants:** Prior severe pre-eclampsia with onset <34 weeks; Pregnant with GA 7-13 weeks

**Primary Outcome:** Death (mom or baby), pre-eclampsia, SGA <10th, or abruption

**Results:**
- Enox/ASA- 42/122 (34.4%) **vs**
- ASA- 50/122 (41%)  

P=0.29

Haddad, Obs Gyn, 2016
Yet another recent negative RCT...

**Study design:** Open label RCT

**Intervention:** Enoxaparin/ASA vs ASA alone

**Participants:** Prior 1) “any pre-eclampsia” or SGA <10th with delivery <36 weeks or 2) SGA < 3rd; Pregnant with GA 6-16 weeks

**Primary Outcome:** Pre-eclampsia or SGA <5th

**Results:**

- Enox/ASA- 18/72 (25.0%) vs
- ASA- 17/77 (22.1%)

Groom, AJOG, 2017
Case 1

Prior severe PET LMWH prophylaxis in next pregnancy?

1. Definitely for all
2. Definitely if she has FVL
3. Maybe
4. Definitely NOT
• LMWH does not appear to reduce the risk of recurrent placenta mediated pregnancy complications (PMPC) in women with prior PMPC

• Put the needles away...

• If you insist on intervening suggest home made C30 dilutions instead i.e. water
Questions?