Title

Meta-analysis of low molecular weight heparin to prevent recurrent placenta-mediated pregnancy complications

Author Names & Degrees

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A 35 year old woman with recurrent severe placenta mediated pregnancy complications in her 2 pregnancies asks: Will low molecular weight heparin help prevent recurrent placenta mediated pregnancy complications in my next pregnancy? We performed a meta-analysis of randomised controlled trials (RCTs) comparing low molecular weight heparin (LMWH) versus no LMWH for the prevention of recurrent placenta-mediated pregnancy complications. We identified six RCTs, including a total of 848 pregnant women with prior placenta-mediated pregnancy complications. The primary outcome was a composite of PE, birth of a SGA newborn (<10th percentile), placental abruption, or pregnancy loss >20 weeks. Overall, 67/358 (18.7%) of women on prophylactic LMWH had recurrent severe placenta-mediated pregnancy complications, as compared with 127/296 (42.9%) women with no LMWH [relative risk reduction 0.52 (95% CI 0.32-0.86) (p=0.01) (I² 69% indicating moderate heterogeneity)]. We identified similar relative risk reductions with LMWH for individual outcomes including any PE, severe PE, SGA <10th, SGA <5th, preterm delivery <37 weeks and preterm delivery <34 weeks with minimal heterogeneity. Low molecular weight heparin may be a promising therapy for recurrent, especially severe, placenta mediated pregnancy complications but further research is required.
Introduction

A successful pregnancy requires the development of adequate placental circulation. The placenta-mediated pregnancy complications, which include pre-eclampsia (PE), late pregnancy loss, placental abruption and small for gestational age (SGA) newborn, are distressing and often devastating pregnancy outcomes for women, their families and society. Hypothesised to be a result of placental insufficiency, these complications are common, affecting more than one in six pregnancies. It has been postulated that placental vascular thrombosis and abnormal placentation are at least partly responsible for the placenta-mediated pregnancy complications. It has been postulated that anticoagulants might prevent placental thrombosis and in turn might prevent placenta-mediated pregnancy complications.

The risk of recurrent placenta-mediated pregnancy complications in subsequent pregnancies is substantial. For example, women with prior severe PE will have a 25-65% risk of recurrent PE and 3% risk of placental abruption and 10% risk of SGA (<10th percentile). These complications may be multiple (e.g. both PE and SGA) and are not isolated to the placenta-mediated complication experienced in a prior pregnancy. There are no highly effective preventative strategies in subsequent pregnancies, with only aspirin offering very small relative risk reductions in patients with prior PE. Recent randomised controlled trials conducted to determine if low molecular weight heparin (LMWH) can prevent recurrent placenta-mediated pregnancy complications suggest an important treatment effect but this finding has not been universal.

Given the importance of preventing recurrent placenta-mediated pregnancy complications, limited current preventative options and these early promising trials, we sought to determine a
summary effect from randomised trials comparing prophylactic LMWH to no LMWH in pregnant women with prior placenta-mediated pregnancy complications.

Methods

We conducted a systematic review and meta-analysis following a systematic review protocol developed \textit{a priori} in February 2011 and available on request. A systematic literature search strategy was conducted to identify potential studies using Medline (1950 to September week 4 2012), Embase (1980 to 2012 week 12), the Cochrane Register of Controlled Trials (2nd quarter 2012) and OVID Health Star (1999-February 2012) using the OVID interface. Publications were also sought through a hand-search of potentially relevant journals. The systematic search strategy is documented in Appendix 1. The search was restricted to humans. There were no restrictions on language, publication year or type of publication. References of included studies and narrative reviews were searched for potential studies. Publications were also sought through a hand-search of conference proceedings (American Society of Hematology annual meeting (1999 to 2011), International Society of Thrombosis and Hemostasis (1999 to 2011) and Women’s Health Issues in Thrombosis and Hemostasis (2009, 2011). We also contacted all study authors of relevant abstracts and experts in the field to identify additional studies. The search was updated in May 2013, and did not identify any additional relevant articles. Abstracts were reviewed by two reviewers (MC and MR) who independently and in duplicate determined if the publication satisfied the following eligibility criteria: 1) The study population included currently pregnant women with prior pregnancies complicated by one or more of the following: PE, placental abruption, SGA newborn (\textless10^{th}\text{ percentile}) or pregnancy loss \textgreater12 weeks (one or more); 2) RCTs comparing participants who received LMWH with/without aspirin (ASA) compared to no LMWH control with/without ASA; 3) the primary outcome of interest for this meta-analysis was
a composite of 1) any PE, 2) placental abruption, 3) SGA newborn (<10\textsuperscript{th} percentile) or 4) pregnancy loss >20 weeks in the study pregnancy. Patients with more than one composite outcome were counted once. A composite outcome was selected because of the frequent overlap of these complications (e.g. pregnancies complicated by PE are more likely have placental abruption and/or birth of an SGA child or late pregnancy loss). Secondary outcomes we examined included 1) a composite of severe (as defined by the authors) or early onset (<34 weeks) PE, major abruption (as defined by the authors), small for gestational age child (<5\textsuperscript{th} percentile) or pregnancy loss >20 weeks, and the following individual outcomes: 1) any PE (as defined by the authors), 2) severe (as defined by the authors) or early onset PE (<34 weeks), 3) SGA <5\textsuperscript{th} percentile, 4) SGA <10\textsuperscript{th} percentile, 5) pregnancy loss >20 weeks, 6) placental abruption, 7) delivery < 34 weeks and 8) delivery < 37 weeks.

Data extraction was conducted independently and in duplicate using piloted forms (MR and MC). Disagreements were resolved by consensus. We contacted the authors for data clarifications (five authors provided responses to queries and one did not). Data extraction included the number of participants, study level inclusion criteria and exclusion criteria, intervention and control details (drug, dose), ASA co-intervention, subject characteristics including prior history of each of the placenta-mediated pregnancy complications and outcome data (primary composite, secondary composite and individual secondary outcomes listed above). We assumed that patients reported to have SGA<5\textsuperscript{th} percentile had SGA <10\textsuperscript{th} percentile.

Quality assessment was conducted for all eligible publications using the risk of assessment bias tool from the Cochrane Handbook for randomised trials.\textsuperscript{15}
Data synthesis was conducted with StatsDirect Statistical Software Version 2.7.8 (Cheshire, United Kingdom). We examined relative risk and 95% CIs around relative risks using random effects models. Analyses were done with intention to treat. We explored heterogeneity and consistency of effects across studies with Higgins $I^2$. Higgins suggests categorisation of $I^2$ into low (<25%), moderate (25-75%), and high (>75%) heterogeneity.15

Results

Our search strategy (see Appendix 1) identified 1647 potential publications for review of which we identified six RCTs that met our eligibility criteria (See Figure 1).

The details of the included studies are provided in Table I and summary characteristics of included participants are provided in Table II. The majority of randomised participants were recruited in single centre studies, with over 40% recruited from one centre (Nimes, France). Most of the participants had prior PE (70%) with the majority (70%) of these having had severe or early onset PE. A quarter of participants had an identified thrombophilia. Some studies only included thrombophilic participants,12 others permitted inclusion of thrombophilic participants9;11;13 and others excluded participants with known thrombophilia.10;14 In all studies, the intervention was a standard prophylactic dose of a marketed LMWH. While the primary outcome variable was available for all study participants, some secondary outcomes could not be extracted from the publication nor were they provided by the authors (unavailable after requested). The quality of each of the included studies is reviewed in Table III. There were no double blind studies. All of the studies had adequate random sequence generation; most studies had adequate allocation concealment (5/6), half of the studies reported blind independent adjudicated
outcomes (3/6) and two of the studies reported *a priori* clinical trial registration\textsuperscript{12,13} to limit selective reporting.

In our primary outcome analysis, the composite measure of any PE, abruption, SGA newborn (<10\textsuperscript{th} percentile) or pregnancy loss >20 weeks, was significantly reduced by LMWH, with a relative risk reduction of 0.52 (95% CI 0.32-0.86) (p=0.01) (see Table IV and Figure 2). Heterogeneity was high (I\textsuperscript{2}= 69%) for our primary analysis. In a secondary analysis of a composite measure of more severe placenta-mediated pregnancy complications (severe PE (as defined by authors) or early onset (<34 weeks) PE, placental abruption, SGA newborn (<5\textsuperscript{th} percentile) or pregnancy loss >20 weeks), LMWH similarly significantly reduced this more severe composite outcome with a relative risk reduction of 0.39 (p=0.0004) with little heterogeneity noted in this analysis (I\textsuperscript{2} = 20%). We note that higher quality trials (see Table III) suggested no treatment effect (see Figure 2).

In secondary analyses of individual outcomes (see Table IV), any PE, severe PE, SGA <10\textsuperscript{th}, SGA <5\textsuperscript{th}, preterm delivery <37 weeks and preterm delivery <34 weeks were all importantly and statistically significantly reduced with LMWH with no or little heterogeneity in any of these analyses. Pregnancy loss >20 weeks and neonatal death were importantly but not statistically significantly reduced with LMWH. There were no differences in risk of early pregnancy loss (<20 weeks) with LMWH use.
Discussion

In this systematic review and meta-analysis we found that LMWH appears to significantly and importantly reduce the risk of recurrent placenta-mediated pregnancy complications in women with prior placenta-mediated pregnancy complications. LMWH appears to be a very promising preventative therapy for these common and serious pregnancy complications for which no effective or modestly effective (e.g. ASA for PE) currently available secondary prevention strategies exist. However, we consider that further multi-centre corroborative trials are required prior to this intervention being adopted as standard of care due to several limitations in the quality of the evidence (outlined below) and uncertainty regarding which patient sub-groups benefit from this costly and inconvenient therapy.

The placenta-mediated pregnancy complications are common and are serious complications. Pre-eclampsia is the most important cause of premature delivery with a resultant impact on fetal and neonatal morbidity and mortality. Pregnancy loss, especially recurrent or late pregnancy loss is a painful event for pregnant women and their families. SGA birth often results in long-term effects in the developing child, including developmental delay and poor school performance and, as adults, children that were SGA are significantly less likely to attain higher academic and professional achievement. Effective interventions to reduce the risk of the placenta-mediated pregnancy complications are desperately needed.

Recently randomised controlled trials have been conducted to determine if LMWH can prevent recurrent early pregnancy loss. While the findings of these studies are not uniform, they suggest no important treatment effect of anticoagulant prophylaxis. Interestingly our meta-analysis similarly demonstrated no effect on reduction of earlier pregnancy loss (<20 weeks) in patients
with prior placenta-mediated pregnancy complications whereas a non-statistically significant reduction in late pregnancy loss (>20 weeks) was observed. Likely recurrent pregnancy loss/early pregnancy loss has different pathophysiological mechanisms than late placenta-mediated pregnancy complications and LMWH does not influence these other mechanisms. Perhaps the effect of LMWH is isolated to preventing late complications by preventing placental thrombosis only in the later stages of pregnancy. Regardless, early or recurrent pregnancy loss was not the primary focus of this meta-analysis.

It is also noteworthy that while some studies only included thrombophilic participants, others permitted inclusion of thrombophilic participants and others excluded participants with known thrombophilia. We felt that it was reasonable to combine these studies because of recent cumulative evidence that does not support an association between thrombophilia and the late placenta-mediated pregnancy complications. Pooled results from ten studies, allowing for analyses including more than 20,000 women, showed a small absolute increased risk of pregnancy loss for women with factor V Leiden but not for those with prothrombin G20210A mutation. No association was found for the two mutations with PE, placental abruption, or birth of SGA infants. Hence, it appears unlikely that the effect of LMWH on reducing placenta-mediated pregnancy complications would be modified by thrombophilia. Nonetheless, it is possible that the more severe, and less common, placenta-mediated pregnancy complications are associated with thrombophilia while the more common milder forms of placenta-mediated pregnancy complications are not. By extension, it may be that LMWH prevents recurrent severe placenta-mediated pregnancy complications in the thrombophilic sub-group. Given that thrombophilia may be an effect modifier, future studies, including individual patient meta-
analysis or RCTs in thrombophilic women with prior placenta-mediated pregnancy complications should be conducted and may shed further light on this possibility.

Similarly, it maybe that prophylactic LMWH is mainly of benefit in the sub-group of patients with prior severe placenta-mediated pregnancy complications and that the beneficial effect is limited to only preventing severe placenta-mediated pregnancy complications. This hypothesis is supported by our finding that the larger relative risk reductions were observed for the more severe pregnancy complications (e.g. severe composite outcome (RR 0.39) vs primary milder composite outcome (RR 0.52), severe pre-eclampsia (RR 0.16) vs any pre-eclampsia (RR 0.46), pre-term labor <34 weeks (RR 0.45) vs pre-term labor <37 weeks (RR 0.77), late pregnancy loss (RR 0.41) vs earlier pregnancy loss (RR 0.89). Also, LMWH did not have a beneficial effect in the trial that included women with “any prior pre-eclampsia” (that is mild or severe) while LMWH did generally have a positive effect in the trials including women with only severe or early onset pre-eclampsia. That is, it is plausible that LMWH is only beneficial in preventing recurrent severe placenta-mediated pregnancy complications.

The major strengths of our systematic review and meta-analysis are that we adhered to all of the PRISMA guidelines in the conduct and reporting of our systematic review and meta-analysis and we were able to obtain data clarifications from five out of six 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.

Several limitations are worthy of note. First, the placenta-mediated pregnancy complications often overlap, that is women with one of the prior placenta-mediated pregnancy complications may have also had one or more other placenta-mediated pregnancy complications (e.g. women...
with prior PE may have concomitant abruption and give birth to an SGA newborn). Some of the component studies of our meta-analysis included women with any of the placenta-mediated pregnancy complications whereas others limited inclusion to women with a sub-set of the placenta-mediated pregnancy complications. As such it is difficult to tease out if our findings apply to all patients with placenta-mediated pregnancy complications or a limited sub-set of these patients. Indeed, as noted above, it maybe that the benefit of LMWH will only be to prevent recurrent severe placenta-mediated pregnancy complications. Further trials with limited inclusion criteria or individual patient-level meta-analysis might answer the specific question of which sub-set benefit or benefit most from LMWH. Second, similarly, the primary composite outcome of our meta-analysis, and many of the component studies, are heterogeneous and we are not able to determine if LMWH reduces the risk of all or some of the component placenta-mediated pregnancy complications of this composite outcome. This may explain the moderate heterogeneity observed in our primary analysis ($I^2 = 69\%$) and the low or no heterogeneity ($I^2 < 25\%$) observed in secondary analyses of severe outcomes. Third, ASA was a co-intervention in over 50% of participants in the component trials raising the possibility that the preventative effect of LMWH is biased by ASA use or interacted with ASA use. However, it is important to note that overall ASA use was balanced and most studies either randomised to ASA use or stratified randomisation by ASA use so it is unlikely that ASA is the sole driver of these findings. Fourth, not all of the component studies were of high quality (as reviewed in Table III); some didn’t have independent adjudication of outcomes or adequate allocation concealment. It is noteworthy that it is very challenging, and some argue unethical, to conduct placebo controlled trials of a long term injectable drug in pregnancy and such a design may not be achievable in studies in this area of research. It is also noteworthy and bears emphasis that the two highest
quality trials\textsuperscript{12;13} demonstrated no effect on our primary outcome, introducing the possibility that our summary effect is driven by low quality and possibly biased studies. Fifth, an incomplete dataset for the meta-analysis is possible and may have resulted from reporting bias and/or unavailable results in our included studies that we could not resolve through data clarification requests. However, five of six authors provided data clarifications and were collaborators in this meta-analysis, thereby limiting the amount of missing data. Finally, a large number of participants were recruited in single center studies\textsuperscript{9;11;14} or multicentre studies where the large majority of patients were recruited from one center;\textsuperscript{10} this raises concerns about external generalisability and potentially introduces selection bias. In light of these limitations, there is currently insufficient evidence to support adoption of this intervention in clinical practice. Specifically, high quality multicentre trials should be conducted with a focus on preventing recurrent severe placenta-mediated pregnancy complications.

In conclusion, LMWH appears to be a promising preventative therapy for recurrent, especially severe, placenta-mediated pregnancy complications. More high quality multicentre trials should be conducted to confirm this potentially important preventative therapy for a group of common conditions with no effective preventive therapy.
Recommendations

We provide the following weak recommendations based on moderate quality evidence as suggested by the GRADE working group (http://www.gradeworkinggroup.org). Weak recommendations are made when the benefits and risks and burdens of therapy are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks. Weak recommendations are offered when across the range of patient values, fully informed patients are liable to make different choices. Moderate quality evidence is noted when further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate.

For prevention of recurrent severe placenta mediated pregnancy complications we suggest ante-partum prophylactic dose LMWH ((GRADE 2B- Weak recommendation, moderate quality evidence (inconsistent results)).

For the prevention of recurrent non-severe placenta mediated pregnancy complications we suggest no ante-partum prophylactic dose LMWH (GRADE 2B- weak recommendation, moderate quality evidence (inconsistent results)).
Acknowledgments

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Authorship Contributions

MAR was the lead investigator for this study, had the initial idea for the study, developed the methods for the systematic review and meta-analysis and participated in review and selection of included publications, data extraction and analysis, wrote the first draft of the paper report and approved the final version of the paper.

MC and GLG developed the methods for the systematic review and meta-analysis and participated in review and selection of included publications, data extraction and analysis and approved the final version of the paper.
AP assisted in data extraction, data interpretation, reviewed drafts of the paper and approved the final version of the manuscript.

IM was the principal investigator for a component study, assisted in data clarification, reviewed drafts of the manuscript and approved the final version of the paper.

ER was the principal investigator for a component study, assisted in data clarification, reviewed drafts of the manuscript and approved the final version of the paper.

JdeV was the principal investigator for a component study, assisted in data clarification, reviewed drafts of the manuscript and approved the final version of the paper.

JCG was the principal investigator for two component studies, assisted in data clarification, reviewed drafts of the manuscript and approved the final version of the paper.

Conflicts of Interest Disclosure

Dr. Rodger has received grant funding >$10,000 from Pfizer and Leo Pharma. Dr. Rodger has served on advisory boards for Sanofi Aventis but not been paid.

Dr. Marc Carrier – consultant for LeoPharma and Sanofi.

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Consultant honorarium from Leo Pharma for CME presentations, 2009-2010.

Dr. Jean-Christophe Gris – Board membership Sanofi, LFB, Stago.

Consultant for Sanofi, Stago, Leo Pharma, LFB.

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Payment for lectures including service on speakers bureaus – Sanofi, Stago, Leo Pharma, LFB, Bristol-Myers Squibb Pfizer, Bayer, Boehringer, Ingelheim.
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Table I: Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Country, Centers</th>
<th>Participants</th>
<th>Intervention /Control</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Vries¹²</td>
<td>2012</td>
<td>Multi-National</td>
<td>Prior early onset PE (n=107) and/or SGA &lt;10th (n=94)</td>
<td>Dalteparin 5000IU+ASA vs ASA</td>
<td>PE prior to 34 weeks GA</td>
</tr>
<tr>
<td>Martinelli¹³</td>
<td>2012</td>
<td>Italy, Multi-center</td>
<td>Prior PE (n=52), Prior loss&gt;15 weeks (n=49), Prior SGA &lt;10th (n=28) or prior abruption (n=5)</td>
<td>Nadroparin 3800IU vs No Nadroparin</td>
<td>PE, Loss &gt;15 weeks GA, SGA&lt; 10th and/or Abruption</td>
</tr>
<tr>
<td>Gris⁹</td>
<td>2011</td>
<td>France, Single Center</td>
<td>Prior Severe PE (n=224)</td>
<td>Enoxaparin 4000IU+ASA vs ASA</td>
<td>PE, SB, Abruption, SGA&lt;5th</td>
</tr>
<tr>
<td>Gris¹¹</td>
<td>2010</td>
<td>France, Single Center</td>
<td>Prior Abruption (n=160; 70 with PE)</td>
<td>Enoxaparin 4000IU+/- ASA vs +/- ASA</td>
<td>PE, SB, Abruption, SGA&lt;5th</td>
</tr>
<tr>
<td>Rey¹⁰</td>
<td>2009</td>
<td>Canada, Multi-center</td>
<td>Prior early PE (n=60)</td>
<td>Dalteparin 5001IU+/- ASA vs +/- ASA</td>
<td>PE, SB, Abruption, SGA&lt;5th</td>
</tr>
<tr>
<td>Mello¹⁴</td>
<td>2005</td>
<td>Italy, Single Center</td>
<td>Prior PE with ACE DD (n=80)</td>
<td>Dalteparin 5000 IU vs No Dalteparin</td>
<td>PE, SGA&lt;10th</td>
</tr>
</tbody>
</table>

PE= Pre-eclampsia, SGA (<xth) = Small for gestational age less than xth percentile, ACE DD= Ace deletion/deletion genotype, GA= Gestational age, SB=stillbirth; ASA=aspirin
Table II: Summary characteristics of participants in the studies included in the meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>LMWH (n=425)</th>
<th>No LMWH (n=423)</th>
<th>Combined (n=848)</th>
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<tr>
<td>Thrombophilia</td>
<td>106/425</td>
<td>107/423</td>
<td>213/848 (25%)</td>
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<tr>
<td>Prior PE</td>
<td>296/425</td>
<td>293/423</td>
<td>593/848 (70%)</td>
</tr>
<tr>
<td>Prior Severe PE</td>
<td>208/304</td>
<td>208/304</td>
<td>416/608 (68%)</td>
</tr>
<tr>
<td>Prior SGA &lt;10th</td>
<td>76/192</td>
<td>67/192</td>
<td>143/384 (37%)</td>
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<tr>
<td>Prior Abruption</td>
<td>91/192</td>
<td>90/203</td>
<td>181/405 (45%)</td>
</tr>
<tr>
<td>Prior Loss &gt;12 weeks</td>
<td>34/122</td>
<td>32/123</td>
<td>66/245 (27%)</td>
</tr>
<tr>
<td>Concomitant ASA use</td>
<td>178/495</td>
<td>260/423</td>
<td>438/848 (52%)</td>
</tr>
</tbody>
</table>

PE= Pre-eclampsia, SGA (<x<sup>th</sup>)= Small for gestational age less than x<sup>th</sup> percentile, ASA= Aspirin
Table III: Quality assessment of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>First Author</th>
<th>Randomn Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Blinding of participant/personnel</th>
<th>Blinding of outcome assessors</th>
<th>Incomplete Outcome data</th>
<th>Selective Reporting</th>
<th>Other bias</th>
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<tr>
<td>DeVries(^{12})</td>
<td>+</td>
<td>+</td>
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<td>Martinelli(^{13})</td>
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<td>Gris(^{9})</td>
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+= Low risk of bias; -= High risk of bias;
Table IV: Results of meta-analysis of eligible studies examining prophylactic LMWH vs no LMWH in prevention of pregnancy complications in women with prior placenta-mediated pregnancy complications

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<thead>
<tr>
<th>Outcome (LMWH=288/ Control=286)</th>
<th>Proportion with Outcome Treatment Group % (n/N)</th>
<th>Proportion with Outcome Control Group % (n/N)</th>
<th>Relative Risk (95% CI) (p value) 95% CI</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite: Any pre-eclampsia, abruption, small for gestational age child (&lt;10th percentile) or pregnancy loss &gt;20 weeks</td>
<td>18.7% (67/358)</td>
<td>42.9% (127/296)</td>
<td>0.52 (0.32-0.86) (p=0.01)</td>
<td>69%</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite: Severe pre-eclampsia (as defined by authors) or early onset (&lt;34 weeks) pre-eclampsia, abruption, small for gestational age child (&lt;5th percentile) or pregnancy loss &gt;20 weeks</td>
<td>7.4% (22/295)</td>
<td>22.9% (59/257)</td>
<td>0.39 (0.23-0.65) (p=0.0004)</td>
<td>20%</td>
</tr>
<tr>
<td>Any Pre-eclampsia</td>
<td>8.6% (34/391)</td>
<td>21.6% (75/348)</td>
<td>0.46 (0.28-0.75) (p=0.0019)</td>
<td>33%</td>
</tr>
<tr>
<td>Severe or early Pre-eclampsia</td>
<td>1.7% (6/352)</td>
<td>13.4% (42/313)</td>
<td>0.16 (0.07-0.36) (p&lt;0.0001)</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Rate 1</td>
<td>Rate 2</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------</td>
<td>--------</td>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>Small for Gestational Age &lt;10th</td>
<td>10.1%</td>
<td>29.4%</td>
<td>0.42</td>
<td>0.29-0.59</td>
</tr>
<tr>
<td></td>
<td>(39/386)</td>
<td>(96/327)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small for Gestational Age &lt;5th</td>
<td>5.0%</td>
<td>9.9%</td>
<td>0.52</td>
<td>0.28-0.94</td>
</tr>
<tr>
<td></td>
<td>(15/302)</td>
<td>(30/302)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abruption</td>
<td>0.8%</td>
<td>2.4%</td>
<td>0.42</td>
<td>0.13-1.4</td>
</tr>
<tr>
<td></td>
<td>(3/381)</td>
<td>(9/375)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Loss &lt;20 weeks</td>
<td>6.7%</td>
<td>7.5%</td>
<td>0.89</td>
<td>0.50-1.6</td>
</tr>
<tr>
<td></td>
<td>(20/297)</td>
<td>(22/294)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Loss &gt;20 weeks</td>
<td>1.9%</td>
<td>5.3%</td>
<td>0.41</td>
<td>0.17-1.02</td>
</tr>
<tr>
<td></td>
<td>(6/311)</td>
<td>(16/300)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal Death</td>
<td>0.6%</td>
<td>2.6%</td>
<td>0.31</td>
<td>0.07-1.3</td>
</tr>
<tr>
<td></td>
<td>(2/315)</td>
<td>(8/308)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery &lt;37 weeks</td>
<td>32.1%</td>
<td>47.7%</td>
<td>0.77</td>
<td>0.62-0.96</td>
</tr>
<tr>
<td></td>
<td>(95/296)</td>
<td>(124/260)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery &lt;34 weeks</td>
<td>7.9%</td>
<td>19.3%</td>
<td>0.45</td>
<td>0.30-0.69</td>
</tr>
<tr>
<td></td>
<td>(28/356)</td>
<td>(62/322)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$\Gamma^2$ = Higgins $\Gamma^2$ measure of heterogeneity
FIGURES

Figure 1: PRISMA Flow Diagram for study selection and review

Figure 2: Primary Outcome Analysis - Relative risk reduction of recurrent placenta-mediated pregnancy complications (any pre-eclampsia, placental abruption, small for gestational age child (<10th percentile) or pregnancy loss >20 weeks) with Low Molecular Weight Heparin in women with prior placenta-mediated pregnancy complications (pre-eclampsia, small for gestational age child (<10th percentile), late pregnancy loss (>12 weeks) or placental abruption)
Figures

Figure 1: PRISMA Flow Diagram for study selection and review
(p=0.01). Heterogeneity I² = 69%

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Meta-analysis of low molecular weight heparin to prevent recurrent placenta-mediated pregnancy complications

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