A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia

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Short Running Title: LMWH to prevent pregnancy loss in thrombophilia

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Abstract

We performed a meta-analysis of randomized controlled trials comparing LMWH versus no LMWH in women with inherited thrombophilia and prior late (≥10 weeks) or recurrent early (<10 weeks) pregnancy loss. Eight trials and 483 patients met our inclusion criteria. There was no significant difference in livebirth rates with the use of LMWH compared to no LMWH (RR 0.81, 95% CI, 0.55 to 1.19, p=0.28), suggesting no benefit of LMWH in preventing recurrent pregnancy loss in women with inherited thrombophilia.

Case Presentation

Case 1. A 34-year old woman with three consecutive unexplained miscarriages wants to get pregnant again. Would she benefit from thrombophilia testing?

Case 2. A 25-year old woman with one unexplained pregnancy loss at 16 weeks’ gestation is found to be heterozygote for the Factor V Leiden mutation. She has no personal history of thrombosis. She asks you if taking low-molecular-weight heparin (LMWH) could prevent a second pregnancy loss.

Introduction

Recurrent pregnancy loss, commonly defined as 3 or more consecutive miscarriages, occurs in 1% of all women, with no cause identified in half of cases. Inherited and acquired thrombophilias have been evaluated as a potential cause of pregnancy loss, given the importance of adequate utero-placental circulation on fetal development and survival. Coagulation activation at the maternal-fetal interface plays an important role in placental development. Several meta-analyses have reported an increased risk of pregnancy loss in women with inherited thrombophilia, however, significant heterogeneity attributed to study design and the definition of recurrent pregnancy loss limits firm conclusions. Overall, inherited thrombophilias appear to be, at best, a weak contributor to late or recurrent early pregnancy loss. Our meta-analysis evaluating only prospective cohort studies reported a small increased risk of pregnancy loss in women with Factor V Leiden (FVL) (4.2%) compared to women without FVL (3.2%), suggesting a weak causal effect (OR 1.52, 95% CI, 1.06 to 2.19). There is a lack of data...
on pregnancy loss risk in women with uncommon thrombophilias such as protein C, S or antithrombin deficiency.

When compared to inherited thrombophilias, antiphospholipid syndrome (APS) has been more strongly and consistently associated with pregnancy loss; clinical criteria needed to make a diagnosis of APS includes pregnancy morbidity involving either one pregnancy loss ≥ 10 weeks gestation, three unexplained losses < 10 weeks gestation or other placental complications. Unfortunately, high-quality data to support the use of prophylactic-dose low-molecular-weight heparin (LMWH) and aspirin to prevent pregnancy loss or placental complications in APS is surprisingly limited and warrants further randomized trials. For the purpose of this review, we will focus on inherited thrombophilia and the role of LMWH in preventing future pregnancy loss.

In women with an inherited thrombophilia and prior late or recurrent early pregnancy loss, we sought to determine whether the use of prophylactic-dose LMWH (+/- aspirin) reduced the risk of pregnancy loss when compared to no LMWH (+/- aspirin).

Methods

Study Selection

A systematic search of the literature was conducted on MEDLINE (1946-September 2015), EMBASE (1947-September 2015) and EBM reviews using the Cochrane Database of Systematic Review (2005-September 2015), APC Journal Club (1981-September 2015), Database of Abstracts of Reviews of Effects (2nd Quarter 2015), Cochrane Central Register of Controlled Trials (July 2015), Cochrane Methodology Register (3rd Quarter 2012), Health Technology Assessment (3rd Quarter 2015) and NHS Economic Evaluation (2nd Quarter 2015) using an OVID interface. References of narrative reviews and included trials were reviewed for additional studies, and ClinicalTrials.gov was searched for completed and ongoing studies. The last search was completed on September 6, 2015. There was no restriction on language or date of publication. The systematic search strategy is available in Appendix 1. (PROSPERO Registration Number: CRD42015025697).
Data Extraction and Synthesis

Two investigators independently reviewed all abstracts and the full-text of potentially relevant studies (L.S. and M.C.). Studies were included if they met eligibility criteria outlined as follows: (1) peer-reviewed randomized controlled trials, (2) pregnant women with 1) inherited thrombophilia and 2) prior late (≥10 weeks) or recurrent early (≥2 losses <10 weeks) pregnancy loss, (3) randomly allocated to prophylactic-dose LMWH with or without aspirin, versus no LMWH with or without aspirin and (4) the primary outcome of livebirth rate was reported. Only patients with an inherited thrombophilia were included, women with a diagnosis of APS or women who did not have a thrombophilic disorder were excluded. Secondary outcomes of adverse events such as major and non-major bleeding, HIT, increased liver enzymes, skin or allergic reactions, induction of labor and cesarean section rates were recorded when available13,14.

Of the eligible studies, data was extracted independently by two investigators utilizing a standardized pilot data extraction form (L.S. and M.C.). The data extracted included number of eligible participants, study-level inclusion and exclusion criteria, intervention details and reported outcomes. Disagreements between reviewers were resolved by consensus and reviewed by a third investigator (M.A.R.). Individual study investigators were contacted (M.A.R., R.K., I.M, D.P., E.S., C.A.L.) to provide data clarifications, previous correspondence from P. Clark provided additional data15 and 2 included studies provided all of the required details in the published manuscript16,17. Two additional authors did not respond to queries and hence their studies were excluded after full-text review because the thrombophilia status or primary outcome was unknown18,19. Study quality was independently evaluated by two investigators utilizing the Cochrane Collaboration Risk of Bias Tool (L.S. and M.C.)20.

Outcomes were analyzed according to the intention-to-treat principle. Relative risks (RR) using a random effects model were reported with 95% confidence intervals (CIs). The I² statistic was used to estimate total variation among the pooled estimates across trials. An I² of < 25% was considered low-level heterogeneity. A sensitivity analysis excluding single-center trials was completed. A priori exploratory analyses were planned to
evaluate LMWH prophylaxis in subgroups of 2 versus 3 or more early pregnancy losses, and in prior early (<10 weeks) or late (≥10 weeks) loss. Analyses were performed using StatsDirect software version 2.8.0 (StatsDirect Ltd, Cheshire, UK).

Our treatment recommendations are based on the quality of available evidence, and are outlined using the Grading of Recommendations Assessment Development and Evaluation tool21.

**Results**

Our search strategy identified 1406 article records, of which 8 publications and 483 participants met eligibility criteria (Figure 1)15-17,22-26. Baseline study characteristics are depicted in Table 1. Of the 8 publications included, 4 trials included a LMWH + aspirin arm, and 5 trials included a LMWH only arm. The control groups included 4 trials with an aspirin arm, and 5 trials with a placebo or no treatment arm. One of the trials that compared LMWH versus no LMWH allowed aspirin use in either arm25. The definition of pregnancy loss varied across each trial. Study quality is reported in Table 2. Every trial included had adequate random sequence generation, good allocation concealment and no selective reporting, and most trials (6/8) clearly addressed incomplete outcome data. All trials used open-label LMWH, however, the outcome of livebirth rate is objective and therefore unlikely to increase the risk of bias. Only 2 of the 8 trials reported blinding of outcome assessors24,25.

In our primary outcome analysis, there was no significant difference in livebirth rates with the use of LMWH when compared to no LMWH (RR 0.81, 95% CI, 0.55 to 1.19 p=0.28, I² 91.9%)15-17,22-26. Given the high heterogeneity, we performed a sensitivity analysis to explore multi-center versus single-center trials as a cause of heterogeneity. When evaluating only multi-center trials there was no difference in livebirth rates between groups, with reduced heterogeneity (RR 1.04, 95% CI, 0.93 to 1.16, p=0.52, I² 12.9%) (Figure 2, Table 3)15,17,22-26.
When evaluating outcomes in the subgroup of 308 women with inherited thrombophilia and late (≥10 weeks) pregnancy loss in 5 trials, there was no significant difference in livebirth rates between the LMWH and the control group (RR 0.81, 95% CI, 0.38 to 1.72, p=0.58, I² 95.3%)\(^{16,23-26}\). Again, given the high heterogeneity in this subgroup analysis we performed a multi-center versus single-center sensitivity analysis. When only multi-center trials were analyzed, there was no significant difference between the LMWH versus no LMWH group (RR 1.12, 95% CI, 0.97 to 1.30, p=0.13) with no heterogeneity (I²=0%) (Table 3)\(^{23-26}\).

When evaluating early recurrent pregnancy loss (≥ 2 losses <10 weeks) in 2 trials, there was no significant difference in livebirth rates between the LMWH and the control group in 66 participants with inherited thrombophilia (RR 0.97, 95% CI, 0.80 to 1.19, p=0.79) (Table 3)\(^{25,26}\).

Safety outcomes were not uniformly reported for our population of interest, all adverse events reported have been described in the context of larger clinical trials. There was not enough data available to compare 2 versus 3 or more losses in women with thrombophilia.

**Discussion**

In this systematic review and meta-analysis, prophylactic-dose LMWH (with or without aspirin) did not reduce the risk of pregnancy loss in women with inherited thrombophilia with prior late or recurrent early pregnancy loss, when compared to no treatment or aspirin alone. This finding was consistent across subgroups of either previous late loss (≥10 weeks) or previous recurrent early (<10 weeks) pregnancy loss. To our knowledge, this is the largest study published to date that evaluates LMWH in women with inherited thrombophilia and previous pregnancy loss, made possible by international collaboration with investigators who provided additional data in 6 of the 8 trials.
We did not see evidence of a beneficial effect of LMWH in preventing future pregnancy loss in thrombophilic women with prior recurrent early loss. However, given our limited sample size (n=66), we cannot exclude a beneficial effect of LMWH in this subgroup. There is an ongoing randomized controlled trial, ALIFE2 (Netherlands Trial Registration Identifier: NTR3361) that is evaluating LMWH in women with inherited thrombophilia and a history of 2 or more miscarriages and/or intrauterine fetal death, which we hope will provide definitive answers to this question.

In the era of responsible testing and prescribing practices, the results of our meta-analysis provide further evidence that there is no benefit of LMWH in preventing future pregnancy loss in women with inherited thrombophilia, with the potential for adverse side effects and significant cost of LMWH. By extension, this also significantly limits the benefit of thrombophilia testing in women with pregnancy loss. If LMWH intervention is not going to be offered (outside of clinical trials) then why test? One could argue that because there is a higher prevalence of inherited thrombophilia in women with prior pregnancy loss, testing offers an opportunity to identify women with thrombophilia. However, the benefits of identifying thrombophilia would be limited to alerting these women and their health care providers to their lifetime risks of venous thrombosis with an opportunity for thromboprophylaxis during high-risk periods (including the post-partum interval). The associated cost of testing to identify one case would be significant given the weak association with pregnancy loss.

There are several limitations to our meta-analysis. We included the use of aspirin in either treatment arm, as we were primarily evaluating the role of LMWH versus no LMWH. We cannot exclude the possibility that a combined treatment effect of LMWH and aspirin was lost by combining results with LMWH alone, or that aspirin in the control group mitigated any differences seen between groups. Unfortunately, the number of patients included was too small to evaluate outcomes from trials that did not include aspirin in either treatment arm. Reassuringly, a recent Cochrane Review found no difference in livebirth rates in women with or without inherited thrombophilia treated with LMWH and aspirin versus no treatment (RR 1.01, 95% CI, 0.87 to 1.16), and no
difference between aspirin versus no treatment (RR 0.94, 95% CI, 0.80 to 1.11)\cite{29}. This is further supported by the EAGeR trial, where there was no difference in livebirth rates between aspirin and placebo in women with previous pregnancy loss\cite{30}.

There were 2 trials that were excluded from our meta-analysis because we could not extract the necessary data from the published manuscripts and the authors could not be contacted. The trials were excluded because we either did not know if the patients were tested for an inherited thrombophilia\cite{18}, or outcomes based on an inherited thrombophilia subgroup were not available\cite{19}. In the worst-case scenario we missed data from 111 women with inherited thrombophilia, but very likely this number is less than 50. It is unlikely that our study conclusions would have differed with this number of patients.

Because the inclusion criterion for prior pregnancy loss was different in every trial, we could only pool data from a limited number of trials to evaluate LMWH in the subgroups of prior late or recurrent early pregnancy loss. Furthermore, we could not specifically evaluate subgroups of later pregnancy loss in women with prior loss of >16 weeks or >24 weeks. Standardization of a definition for early and late pregnancy loss is urgently needed across disciplines to guide future clinical trials and permit meaningful meta-analysis. The European Society of Human Reproduction and Embryology published a 2014 consensus statement on the research definition of pregnancy loss, recommending early pregnancy loss be defined as less than 10 weeks gestation when organogenesis is complete\cite{31}. Furthermore, the definition of ‘recurrent pregnancy loss’ (i.e. 2 or 3 losses) is still debated and remains undefined\cite{31}.

There were also differences across trials in the types of inherited thrombophilia included and the method in which thrombophilia testing was performed. A patient-level meta-analysis could provide additional data on the outcomes for specific thrombophilias, as well as address the issue of heterogeneity in the varying definitions of pregnancy loss.

In conclusion, we found no difference in preventing future pregnancy loss with LMWH when compared to no LMWH in women with inherited thrombophilia and prior late or
recurrent early pregnancy loss. Further research evaluating LMWH prophylaxis in women with thrombophilia and recurrent early pregnancy loss is still needed.

**Recommendations**

1) In women with prior late or recurrent early pregnancy loss, we suggest not testing for inherited thrombophilia over testing for inherited thrombophilia. (Grade 2B, weak recommendation with moderate-quality evidence)

2) We recommend against the use of LMWH to prevent recurrent pregnancy loss in women with inherited thrombophilia and prior late pregnancy loss (≥10 weeks) over the use of LMWH. (Grade 1B, strong recommendation with moderate-quality evidence)

3) We suggest against the use of LMWH to prevent recurrent pregnancy loss in women with inherited thrombophilia and prior recurrent early pregnancy loss (<10 weeks) over the use of LMWH. (Grade 2B, weak recommendation with moderate-quality evidence).

**Cases Revisited**

*Case 1.* We would advise against testing for inherited thrombophilia.

*Case 2.* We would not recommend the use of LMWH to prevent future pregnancy loss.

**Acknowledgments**

L.S. was the recipient of the 2015 Thrombosis Canada Fellowship award. M.C. was supported by a Heart and Stroke Foundation New Investigator Award and a University of Ottawa Faculty of Medicine Clinical Research Chair in Venous Thromboembolism and Cancer. M.A.R. was supported by a Heart and Stroke Foundation Career Investigator Award (CI6225 and CI7441) and a University of Ottawa Faculty of Medicine Clinical Research Chair in Venous Thrombosis and Thrombophilia.

**Authorship**

Contribution: L.S. developed the methods for the systematic review and meta-analysis, participated in review and selection of included publications, data extraction, data analysis, wrote the first draft of the manuscript, and approved the final draft of the manuscript. M.C. developed the methods for the systematic review and meta-analysis,
participated in review and selection of included publications, data extraction, data analysis, reviewed drafts of the manuscript, and approved the final version of the manuscript. R.K., I.M., D.P., E.S, and C.A.L. were all investigators for a component study, provided additional data, reviewed drafts of the manuscript, and approved the final version of the manuscript. M.A.R. had the initial idea for the study, developed the methods for the systematic review and meta-analysis, participated in review and selection of included publications, data analysis, reviewed drafts of the manuscript, and approved the final version of the manuscript.

Conflict-of-interest disclosure: L.S. No competing financial interests. M.C. received honoraria from Pfizer and Leo Pharma. R.K. received grant funding from Sanofi Aventis. I.M. No competing financial interests. D.P. No competing financial interests. E.S. received grant funding from Pfizer Pharma GmbH Germany. C.A.L. No competing financial interests. M.A.R. received grant funding from Boehringer Ingelheim. He was a paid expert for the Canadian Agency for Drugs and Technologies in Health (CADTH).

References


Figure 1. Study flow diagram

1399 of records identified through MEDLINE (n=399), EMBASE (n=945) and the Cochrane database (n=55)

7 Additional records identified through other sources

1369 Records screened by abstract after 37 exact duplicates removed

1300 records excluded
36 near duplicates excluded

33 Full-text reviewed for eligibility

25 Full-text articles excluded:
13 Study design
12 Population
7 Thrombophilia excluded or status unknown
4 No previous pregnancy loss
1 Assisted reproductive technology

8 Studies included in quantitative synthesis (meta-analysis)
### Table 1. Study Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of patients</th>
<th>Mean Gestational Age at Entry (weeks)</th>
<th>Thrombophilia included</th>
<th>Inclusion Criteria for Pregnancy Loss</th>
<th>Treatment Arm 1</th>
<th>Treatment Arm 2</th>
<th>Treatment Arm 3</th>
</tr>
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<tr>
<td>Gris et al.\textsuperscript{16}</td>
<td>2004</td>
<td>160</td>
<td>8.0*</td>
<td>FVL, PGM, PS</td>
<td>1 loss ≥10 wks</td>
<td>Enoxaparin 40 mg</td>
<td>ASA 100 mg</td>
<td>N/A</td>
</tr>
<tr>
<td>HepASA\textsuperscript{22}</td>
<td>2009</td>
<td>19</td>
<td>5.7</td>
<td>FVL, PGM, PC, PS, MTHRF</td>
<td>2 losses &lt;32 wks</td>
<td>Dalteparin 5000 IU + ASA 81 mg</td>
<td>ASA 81 mg</td>
<td>N/A</td>
</tr>
<tr>
<td>ALIFE\textsuperscript{17}</td>
<td>2010</td>
<td>47</td>
<td>6.0*</td>
<td>FVL, PGM, PC, PS, AT</td>
<td>2 losses ≤20 wks</td>
<td>Dalteparin 2850 IU + ASA 80 mg</td>
<td>ASA 80 mg†</td>
<td>Placebo</td>
</tr>
<tr>
<td>SPIN\textsuperscript{15}</td>
<td>2010</td>
<td>10</td>
<td>6.0\‡</td>
<td>FVL, PGM, PC, PS, AT</td>
<td>2 losses ≤24 wks</td>
<td>Enoxaparin 40 mg + ASA 75 mg</td>
<td>No treatment</td>
<td>N/A</td>
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<tr>
<td>HABENOX\textsuperscript{23}</td>
<td>2011</td>
<td>26</td>
<td>5.2</td>
<td>FVL, PGM, PC, PS</td>
<td>3 losses &lt;13 wks, 2 losses 13-24 wks, 1 loss &gt;24 wks + 1 loss &lt;13 wks</td>
<td>Enoxaparin 40 mg + ASA 100 mg</td>
<td>Enoxaparin 40 mg + Placebo</td>
<td>ASA 100 mg</td>
</tr>
<tr>
<td>HAPPY\textsuperscript{24}</td>
<td>2012</td>
<td>23</td>
<td>11.0</td>
<td>FVL, PGM, PC, PS, AT</td>
<td>1 loss &gt;15 wks</td>
<td>Nadroparin 3800 IU</td>
<td>No treatment</td>
<td>N/A</td>
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<tr>
<td>TIPPS\textsuperscript{25}</td>
<td>2014</td>
<td>143</td>
<td>11.9</td>
<td>FVL, PGM, PC, PS, AT</td>
<td>3 losses &lt;10 wks, 2 losses 10-16 wks, 1 loss ≥16 wks</td>
<td>Dalteparin 5000 IU(\textsuperscript{§}) (ASA allowed)</td>
<td>No treatment (ASA allowed)</td>
<td>N/A</td>
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<tr>
<td>ETHIG II\textsuperscript{26}</td>
<td>2015</td>
<td>55</td>
<td>7.0</td>
<td>FVL, PGM, PC, PS, AT</td>
<td>2 losses &lt;12 wks, 1 loss ≥12 wks</td>
<td>Dalteparin 5000 IU</td>
<td>No treatment</td>
<td>N/A</td>
</tr>
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</table>

\*Gestational age when low-molecular-weight heparin was initiated  
†Calcium carbasalate 100 mg daily is equivalent to aspirin 80 mg daily  
‡Mean gestational age at study entry reported as median  
§Dalteparin 5000 IU dosed once daily until 20 weeks, and then twice daily until at least 37 weeks gestation  
Wks indicates Weeks; FVL, Factor V Leiden mutation; PGM, Prothrombin gene mutation; PC, Protein C deficiency; PS, Protein S deficiency; AT, Antithrombin deficiency; MTHRF, Methylene tetrahydrofolate reductase; ASA, Aspirin
Table 2. Quality assessment of included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Random 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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<td>Gris et al.16</td>
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</table>

(+) indicates Low risk of bias; (?), Unclear risk of bias; (-), High risk of bias
### Table 3. Results of a meta-analysis of eligible trials comparing LMWH versus no LMWH in preventing future pregnancy loss in women with inherited thrombophilia

<table>
<thead>
<tr>
<th></th>
<th>Proportion with outcome in the treatment group</th>
<th>Proportion with outcome in the control group</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
<th>I² (%)</th>
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</thead>
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<td><strong>Primary outcome</strong></td>
<td></td>
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<tr>
<td>Livebirth rate</td>
<td>84.5 (201/238)</td>
<td>64.9 (159/245)</td>
<td>0.81</td>
<td>0.55-1.19</td>
<td>0.28</td>
<td>91.9</td>
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<td>Livebirth rate (multi-center trials)</td>
<td>83.5 (132/158)</td>
<td>82.4 (136/165)</td>
<td>1.04</td>
<td>0.93-1.16</td>
<td>0.52</td>
<td>12.9</td>
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<td><strong>Prior late loss†</strong></td>
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<td></td>
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<tr>
<td>Livebirth rate</td>
<td>84.2 (128/152)</td>
<td>59.0 (92/156)</td>
<td>0.81</td>
<td>0.38-1.72</td>
<td>0.58</td>
<td>95.3</td>
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<td>Livebirth rate (multi-center trials)</td>
<td>81.9 (59/72)</td>
<td>90.8 (69/76)</td>
<td>1.12</td>
<td>0.97-1.30</td>
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<tr>
<td>Livebirth rate‡</td>
<td>86.5 (32/37)</td>
<td>86.2 (25/29)</td>
<td>0.97</td>
<td>0.80-1.19</td>
<td>0.79</td>
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</table>

*One participant in the control group (aspirin alone) had a twin pregnancy with 1 livebirth and 1 stillbirth
†Late loss is defined as 1 loss ≥ 10 weeks; Recurrent early loss is defined as 2 losses < 10 weeks
‡All trials included were multi-center trials

LMWH indicates Low-molecular-weight heparin; RR, Relative risk; n/N, number (n) with outcome/number (N) in treatment group
Figure 2. Forest plot of the relative risk of pregnancy loss comparing LMWH versus no LMWH. Top panel: All trials included; Bottom panel: Multi-center trials included. ‘Favor LMWH’ suggests a benefit of LMWH in preventing pregnancy loss; ‘Favor Control’ suggests a benefit of no LMWH in preventing pregnancy loss.

*The relative risk is indeterminate because there were no pregnancy losses among the 23 women from the HAPPY trial.24
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