**LMWH in the prevention of preeclampsia and fetal growth restriction in women without thrombophilia**

A systematic review and meta-analysis

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**Summary**

Placental mediated pregnancy complications such as preeclampsia and fetal growth restriction (FGR) are common, serious, and associated with increased morbidity and mortality. We conducted a systematic review and meta-analysis to determine the effect of treatment with low-molecular-weight heparins (LMWHs) for secondary prevention of these complications in non-thrombophilic women. We searched the electronic databases PubMed, Scopus, and Cochrane Library for randomised controlled trials addressing this question. Five studies including 403 patients met the inclusion criteria, 68 developed preeclampsia and 118 FGR. The studies were very heterogeneous in terms of inclusion criteria, LMWH preparation, and dosage. Meta-analyses were performed using random-effect models. The overall use of LMWHs was associated with a risk reduction for preeclampsia (Relative risk (RR) 0.366; 95% confidence interval (CI), 0.219–0.614) and FGR (RR 0.409; 95% CI, 0.195–0.932) vs. no treatment. From the data available for analysis it appears that the use of Dalteparin is associated with a risk reduction for preeclampsia (p=0.002) and FGR (p=0.001); while Enoxaparin is associated with risk reduction for preeclampsia (p=0.013) but not for FGR (p=0.3). In spite of the small number of studies addressing the research question, and the high variability among them, our meta-analysis found a modest beneficial effect of LMWH for secondary prevention of preeclampsia and FGR. Further studies are needed to address these questions before a definite conclusion can be reached.

**Keywords**

Dalteparin, Enoxaparin, placental mediated pregnancy complications, randomized controlled trial, secondary prevention

**Introduction**

Placenta mediated pregnancy complications (PMPC) are common and serious. Indeed, preeclampsia, placental abruption, fetal growth restriction (FGR), and fetal death are associated with increased maternal, fetal and neonatal morbidity and mortality (1, 2). Preeclampsia is associated with increased maternal risk for chronic hypertension and cardiovascular morbidity later in life (3–5). Offspring of women with preeclampsia have a double rate of cerebral palsy than children of normotensive patients (6), and early onset preeclampsia is an independent risk factor for future cerebral palsy (6, 7). In addition, growth restriction is now recognised as a major risk factor for premature atherosclerosis (8, 9), in adult age.

All these placental mediated complication tend to reoccur (10–16). Therefore, in light of the severe morbidity they are associated with and their risk of recurrence, modern obstetrics is looking for adequate primary and secondary preventive strategies for these obstetrical syndromes.

This task is challenging since all PMPC are syndromic in nature (17, 18) and a single treatment may not be suitable for all patients developing a specific syndrome. In preeclampsia, there is a debate regarding the diagnostic tools that will identify patients at risk for primary or recurrent disease, and therefore there is a lack of agreement on treatment that will prevent this syndrome. The Task Force on Hypertension in Pregnancy of the American College of Obstetricians and Gynecologists (19) suggested the use of low-dose aspirin (60–80 mg) for the secondary prevention in women with a history of preeclampsia, starting in late first trimester.
The role of heparin and low-molecular-weight heparin (LMWH) for the prevention of preeclampsia is under constant debate (20–24), nevertheless there is preliminary evidence that it might be beneficial (20, 21). The rationale for using heparins to prevent preeclampsia and other placental mediated syndromes is based on the fact that thrombosis and placental vascular pathology, as well as different degrees of failure in implantation are regarded as leading mechanisms of disease in preeclampsia (2, 17, 24, 25). Heparins play a major role in the prevention of thrombosis (26–28) and the fact that they do not cross the placenta make them an ideal candidate for this purpose (29). Moreover, heparins also have an anti-inflammatory effect (22, 30–33) which has relevance in patients with preeclampsia since it is associated with an exaggerated maternal inflammatory status (34–37).

Several randomised controlled trials studied the role of heparin in the prevention of preeclampsia in patients at risk for this syndrome as well as in thrombophilic patients (38–40). However, the evidence thus far is not conclusive, and there is much confusion regarding the role of heparins in the prevention of PMPC. Moreover, the significant association between inherited thrombophilia and the development of PMPC is under debate, since not all patients with inherited thrombophilia develop PMPC, and most patients with PMPC screen negative for inherited thrombophilia (41–45). Therefore, we conducted a systematic review and meta-analysis aimed at answering the question: are LMWHs effective in the secondary prevention of placental mediated obstetrical syndromes in non thrombophilic pregnant women?

Materials and methods

Study protocol

The systematic review was conducted and reported according to the PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses (46). Study objectives, inclusion criteria, definition of outcome, search strategy, data extraction process, statistical analyses, and method of study quality assessment were all pre-specified in a protocol.

Eligibility criteria

Randomised controlled trials (RCTs) assessing the effect of LMWHs (Dalteparin, Enoxaparin, Nadroparin, Tinzaparin, Bemiparin) vs placebo or no treatment for the secondary prevention of preeclampsia, intrauterine growth restriction (IUGR), placental abruption, spontaneous preterm delivery and fetal death, in pregnant women at risk for these complications who carry a singleton gestation, were included.

Studies including patients with inherited or acquired thrombophilia, or in which patients were randomised to aspirin, were excluded in order to test whether or not the beneficial preventive effect belongs to LMWH alone. We also excluded studies in which unfractionated heparin (UFH) or any other treatments were employed. In addition, non randomised trials, reviews and meta-analyses, letters to Editor and expert opinions were excluded.

Outcomes definition

We divided our analysis according to the pregnancy complications using preeclampsia, FGR, fetal death, placental abruption, as outcome measures (clinical definitions for the outcome measures are detailed in Suppl. Table 1, available online at www.thrombosis-online.com).

Data source and literature search

To identify potentially eligible studies, we searched PubMed, Scopus, Cochrane Library (all from inception to January 31, 2015). Reference lists of identified studies were searched. No language restrictions were initially applied. We used a combination of key words and text words represented by "heparin", "low-molecular-weight heparin", "Dalteparin", "Enoxaparin", "Tinzaparin", "Bemiparin", "Nadroparin", "pregnancy", "gestation", "pregnancy complications", "preeclampsia", "IUGR", "SGA", "fetal growth retardation", "placental abruption", "abruption placentae", "fetal death", "randomised controlled trial", "randomised trial", and "randomised study". An example for the complete search strategy used for the PubMed search is presented in Suppl. Table 2 (available online at www.thrombosis-online.com).

Two reviewers (S.A.M, O.E.) independently screened the titles and abstracts of records retrieved through database searches. Both reviewers recommended studies for the full-text review. The screen of full-text articles recommended by at least one reviewer was done independently by the same two reviewers and assessed for inclusion in the systematic review. Disagreements between reviewers were resolved by consensus.

Data extraction

Data were extracted using a specifically designed form for capturing information on study and characteristics (inclusion and exclusion criteria, sample size, endpoints, employed treatment, gestational age at the beginning of treatment and LMWH preparation and dosage).

We assessed the methodological quality of the studies using a scoring system proposed by Jadad et al. (47), which is based on three items related to the control of bias (randomisation, blinding, and follow-up). The description of the method is reported in Suppl. Table 3 (available online at www.thrombosis-online.com).

Statistical analysis

Due to the small number of patients in each of the outcomes we decided a priori to group together all patients with preeclampsia regardless of severity or time of diagnosis. Similarly, we grouped all growth restricted neonates regardless to the severity of the growth restriction.

Study findings were summarised as relative risk of developing a complication between the study groups and combined into an overall effect estimate using fixed and random effects model by DerSimonian and Laird (48, 49). Heterogeneity of effects across
studies was tested using Cochran Q and $I^2$ statistics (50). Departure from homogeneity was concluded at p-value <0.05 of the Cochran Q estimate. In these cases, only the estimates based on the random effects were considered valid. The primary analysis was based on random effects modelling, a conservative approach assuming variability of an effect between the studies. We calculated the number needed to treat (NNT) for the prevention of one harmful outcome. The analysis was performed in two steps. We initially analysed the entire group of LMWHs alone in comparison to placebo or no treatment. In the second step we studied the efficacy of each of the LMWH subtypes in the prevention of pre-eclampsia and FGR.

The likelihood of publication bias was assessed by funnel plots for each of the main outcomes, separately. Analyses were performed using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium) and Comprehensive Meta-Analysis version 2.

**Results**

**Study population**

The electronic database search provided a total of 8358 results (Figure 1). After duplicate exclusion there were 5407 citations left. Of these, 5337 were not relevant to the review based on title and abstract screening. Seventy studies were considered for full text assessment, of which 65 were excluded for the following reasons: there were 12 conference abstracts, we could not translate three articles (one Russian, two German), seven studies were retrospective, six were review papers, two were Letters to the Editor, 16 were prospective not randomised or quasi randomised, seven studies did not assess placental mediated pregnancy complications, seven included thrombophilic patients or patients randomised to aspirin, one study randomised patients to UFH, two papers included twin pregnancies, one was a case report, and outcomes were already present at the beginning of therapy in one study. Overall, five studies (51–55) met the inclusion criteria and were incorporated for further assessment. The main characteristics of these studies and their individual results are listed in Table 1A and B. Outcome definitions, as used by each study, are listed in Suppl. Table 1 (available online at www.thrombosis-online.com). All the studies included were non blinded randomised controlled trials. They included small numbers of patients, that resulted in relatively small outcome groups (preeclampsia n=68, FGR n=118). None of the studies included used Nadroparin, Tinzaparin or Bemiparin.

The studies included were very heterogenic clinically. Different inclusion criteria were used (Table 1A), resulting in differences in the populations analysed: two studies (52, 53) included women with recurrent pregnancy loss, also employing different clinical definitions (see Suppl. Table 1, available online at www.thrombosis-online.com); two studies (51, 55) included women with previous pregnancy complications: one took into consideration women with a history of preeclampsia (51), the other women with a history of placental abruption (55); and, finally, one study (54) was recruiting women with both a history of unexplained pregnancy loss, as well as placental mediated late pregnancy complications. The interventions employed also differed among studies: different LMWH were given (Dalteparin in two studies (51, 54), Enoxaparin in three (52, 53, 55) as well as different dosage of the LMWHs were administered. In the control arms four studies (51, 52, 54, 55) compared the effect of LMWH to no treatment and one (53) had a placebo arm.

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**Figure 1: Study selection process.**
Table 1A: Characteristics of the studies included in the analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Centre</th>
<th>Patients included in the analysis</th>
<th>Inclusion criteria</th>
<th>Intervention group</th>
<th>Treatment duration</th>
<th>Control group</th>
<th>Primary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mello et al., 2005 (50)</td>
<td>Italy</td>
<td>Single centre</td>
<td>80</td>
<td>Prior preeclampsia; ACE DD mutation; negative thrombophilia workup</td>
<td>Dalteparin 5000 IU</td>
<td>From positive pregnancy testing, and then throughout the pregnancy, with no further specification regarding gestational week</td>
<td>No treatment</td>
<td>Preeclampsia with or without fetal growth restriction*; fetal growth restriction without preeclampsia; gestational age at delivery; birth weight</td>
</tr>
<tr>
<td>Badawy et al., 2008 (51)</td>
<td>Egypt</td>
<td>Single centre</td>
<td>340</td>
<td>Recruitment before 8 weeks’ gestation, history of three or more consecutive first trimester (first 12 weeks of gestation) miscarriages without identifiable aetiology after full investigation.</td>
<td>Enoxaparin sodium 20 mg</td>
<td>From sonographic pregnancy visualisation until 34 weeks of gestation</td>
<td>Folic acid tablets 0.5 mg daily until 13 weeks’</td>
<td>All maternal and fetal complications during pregnancy</td>
</tr>
<tr>
<td>Fawzy et al., 2008 (52)</td>
<td>Egypt</td>
<td>Single centre</td>
<td>107</td>
<td>Three or more previous spontaneous consecutive pregnancy losses in the first or second trimesters before 24 weeks’ gestation with the same partner</td>
<td>Enoxaparin 20 mg</td>
<td>From sonographic pregnancy visualisation until term or spontaneous onset of labour</td>
<td>Placebo</td>
<td>Live birth rate and pregnancy outcome</td>
</tr>
<tr>
<td>Rey et al., 2009 (53)</td>
<td>Canada</td>
<td>Multi-centre</td>
<td>110</td>
<td>Gestational age &lt; 17 weeks at randomisation, normal thrombophilia screen; one or more of the following complications in the immediate previous pregnancy: severe PET resulting in delivery before 34 6/7 weeks, unexplained newborn weight less than the 5th percentile, placental abruption resulting in delivery before 34 6/7 weeks or in fetal death after 19 6/7 weeks, one or more episodes of unexplained intrauterine death after 19 6/7 weeks or two episodes of unexplained fetal death between 12 and 19 6/7 weeks.</td>
<td>Dalteparin (dose adjusted for maternal weight at randomisation)</td>
<td>No information on initiation of therapy. Therapy administered until 36 weeks of gestation</td>
<td>No treatment</td>
<td>Composite outcome, defined as one or more of the following: severe PET, newborn weight ≤ 5th percentile, major placental abruption resulting in delivery before 34 weeks of pregnancy or fetal death after 20 weeks of gestation.</td>
</tr>
<tr>
<td>Gris et al., 2010 (54)</td>
<td>France</td>
<td>Single centre</td>
<td>160</td>
<td>Placental abruption without fetal loss during the first pregnancy; negative workup for thrombophilia</td>
<td>Enoxaparin 4000 IU</td>
<td>From around two days after positive pregnancy test until delivery or 36 weeks of pregnancy</td>
<td>No treatment</td>
<td>One or more of the following: preeclampsia, IUGR restricted to newborn birthweight ≤ the 5th percentile, placental abruption, fetal demise after 20 weeks of gestation</td>
</tr>
</tbody>
</table>

* defined as birth weight below 10th percentile for the reference chart in the absence of chromosome or congenital anomalies. ACE, angiotensin converting enzyme; PET, pre-eclamptic toxaemia; IUGR, intrauterine growth restriction.
The assessment of the methodological quality of the included studies is reported in Suppl. Table 3 (available online at www.thrombosis-online.com). All studies were of high quality according to Jadad score (Table 2).

The pooled study population for the analysis of the effect of all LMWHs in the prevention of preeclampsia and FGR included 797 women divided into two groups: interventions (n=403), and controls (n=394) (Table 1B). Due to insufficient data regarding

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups</th>
<th>Outcomes</th>
<th>Group 1 (LMWH)</th>
<th>Group 2 (Placebo or no treatment)</th>
<th>P-value</th>
<th>OR</th>
<th>HR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mello et al., 2005 (50)</td>
<td>Dalteparin (n=41) vs. No treatment (n=39)</td>
<td>Preeclampsia</td>
<td>3 (7.3)</td>
<td>11 (28.2)</td>
<td>&lt;0.01</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Badawy et al., 2008 (51)</td>
<td>Enoxaparin (n=170) vs. No treatment (n=170)</td>
<td>Preeclampsia</td>
<td>6 (3.5%)</td>
<td>9 (5.2%)</td>
<td>0.42</td>
<td>0.65</td>
<td>n/a</td>
<td>0.2–2.07</td>
</tr>
<tr>
<td>Fawzy et al., 2008 (52)</td>
<td>Enoxaparin (n=57) vs. Placebo (n=50)</td>
<td>Preeclampsia</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>ns</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Rey et al., 2009 (53)</td>
<td>Dalteparin (n=55) vs. No treatment (n=55)</td>
<td>Severe Preeclampsia</td>
<td>1 (1.8%)</td>
<td>8 (14.5%)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Gris et al., 2010 (54)</td>
<td>Enoxaparin (n=80) vs. No treatment (n=80)</td>
<td>Preeclampsia</td>
<td>6 (7.5%)</td>
<td>18 (22.5%)</td>
<td>0.009</td>
<td>n/a</td>
<td>0.30</td>
<td>0.12–0.76</td>
</tr>
</tbody>
</table>

ns, not significant; OR, odds ratio; HR, hazard ratio; IUGR, intrauterine growth restriction; SGA, small for gestational age. Clinical definitions, as provided in the included studies, are available in the Supplementary material.

### Table 1B: Outcome measures of the included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups</th>
<th>Outcomes</th>
<th>Group 1 (LMWH)</th>
<th>Group 2 (Placebo or no treatment)</th>
<th>P-value</th>
<th>OR</th>
<th>HR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mello et al., 2005 (50)</td>
<td>Dalteparin (n=41) vs. No treatment (n=39)</td>
<td>Preeclampsia</td>
<td>3 (7.3)</td>
<td>11 (28.2)</td>
<td>&lt;0.01</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Badawy et al., 2008 (51)</td>
<td>Enoxaparin (n=170) vs. No treatment (n=170)</td>
<td>Preeclampsia</td>
<td>6 (3.5%)</td>
<td>9 (5.2%)</td>
<td>0.42</td>
<td>0.65</td>
<td>n/a</td>
<td>0.2–2.07</td>
</tr>
<tr>
<td>Fawzy et al., 2008 (52)</td>
<td>Enoxaparin (n=57) vs. Placebo (n=50)</td>
<td>Preeclampsia</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>ns</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Rey et al., 2009 (53)</td>
<td>Dalteparin (n=55) vs. No treatment (n=55)</td>
<td>Severe Preeclampsia</td>
<td>1 (1.8%)</td>
<td>8 (14.5%)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Gris et al., 2010 (54)</td>
<td>Enoxaparin (n=80) vs. No treatment (n=80)</td>
<td>Preeclampsia</td>
<td>6 (7.5%)</td>
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<td>0.009</td>
<td>n/a</td>
<td>0.30</td>
<td>0.12–0.76</td>
</tr>
</tbody>
</table>

ns, not significant; OR, odds ratio; HR, hazard ratio; IUGR, intrauterine growth restriction; SGA, small for gestational age. Clinical definitions, as provided in the included studies, are available in the Supplementary material.

### Table 2: Jadad score for assessment of methodological quality of the studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Methodology item</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomisation</td>
<td>Mello et al., 2005 (50)</td>
</tr>
<tr>
<td></td>
<td>Badawy et al., 2008 (51)</td>
</tr>
<tr>
<td></td>
<td>Fawzy et al., 2008 (52)</td>
</tr>
<tr>
<td></td>
<td>Rey et al., 2009 (53)</td>
</tr>
<tr>
<td></td>
<td>Gris et al., 2010 (54)</td>
</tr>
<tr>
<td>Method to generate randomisation clear and appropriate</td>
<td>Mello et al., 2005 (50)</td>
</tr>
<tr>
<td></td>
<td>Badawy et al., 2008 (51)</td>
</tr>
<tr>
<td></td>
<td>Fawzy et al., 2008 (52)</td>
</tr>
<tr>
<td></td>
<td>Rey et al., 2009 (53)</td>
</tr>
<tr>
<td></td>
<td>Gris et al., 2010 (54)</td>
</tr>
<tr>
<td>Double blind</td>
<td>Mello et al., 2005 (50)</td>
</tr>
<tr>
<td></td>
<td>Badawy et al., 2008 (51)</td>
</tr>
<tr>
<td></td>
<td>Fawzy et al., 2008 (52)</td>
</tr>
<tr>
<td></td>
<td>Rey et al., 2009 (53)</td>
</tr>
<tr>
<td></td>
<td>Gris et al., 2010 (54)</td>
</tr>
<tr>
<td>Method for blinding appropriate</td>
<td>Mello et al., 2005 (50)</td>
</tr>
<tr>
<td></td>
<td>Badawy et al., 2008 (51)</td>
</tr>
<tr>
<td></td>
<td>Fawzy et al., 2008 (52)</td>
</tr>
<tr>
<td></td>
<td>Rey et al., 2009 (53)</td>
</tr>
<tr>
<td></td>
<td>Gris et al., 2010 (54)</td>
</tr>
<tr>
<td>Description of withdrawal or dropout</td>
<td>Mello et al., 2005 (50)</td>
</tr>
<tr>
<td></td>
<td>Badawy et al., 2008 (51)</td>
</tr>
<tr>
<td></td>
<td>Fawzy et al., 2008 (52)</td>
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<tr>
<td></td>
<td>Rey et al., 2009 (53)</td>
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<tr>
<td></td>
<td>Gris et al., 2010 (54)</td>
</tr>
<tr>
<td>Total score</td>
<td>Mello et al., 2005 (50)</td>
</tr>
<tr>
<td></td>
<td>Badawy et al., 2008 (51)</td>
</tr>
<tr>
<td></td>
<td>Fawzy et al., 2008 (52)</td>
</tr>
<tr>
<td></td>
<td>Rey et al., 2009 (53)</td>
</tr>
<tr>
<td></td>
<td>Gris et al., 2010 (54)</td>
</tr>
</tbody>
</table>

n/a, not applicable. The definition of the points awarding method for this scoring system is provided in the Suppl. Material (available online at www.thrombosis-online.com).
the use of LMWH in the prevention of placental abruption and fetal death, the main analysis focused on preeclampsia and FGR.

What is the effect of low molecular heparin in the prevention of preeclampsia?

In the comparison of LMWH vs placebo or no treatment, five studies (51–55) were included in the analysis (Figure 2A). There was a statistically significant risk reduction in the treatment group vs the control group (relative risk (RR) 0.366; 95% confidence interval (CI), 0.291–0.614, p<0.001). The heterogeneity score I² was 0% (p=0.74). The number of patients needed to treat one case of preeclampsia was 11 (Table 3).

When we studied the individual effect of each LMWH for the prevention of preeclampsia, Dalteparin was used in two studies [48, 51] with 96 patients in the intervention group and 94 patients in the control group and a RR of 0.266 (95% CI, 0.153–0.625, p=0.002). The heterogeneity score I² was 0% (Figure 2B). The number of patients needed to treat by Dalteparin for the prevention of one case of preeclampsia was 5 (Table 3).

What is the effect of low molecular heparin in the prevention of FGR?

The analysis comparing Enoxaparin alone vs placebo or no treatment included three studies (49, 50, 52). Altogether there were 307 patients in the intervention group and 300 controls. The RR for preeclampsia was 0.44 (95% CI, 0.231–0.839, p=0.013) and the heterogeneity I² score was 0% (Figure 2C). The number of patients needed to treat by Enoxaparin for the prevention of one case of preeclampsia was 22 (Table 3).

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Figure 2: A) Effect of the combination of all LMWH vs placebo or no treatment on the prevention of preeclampsia; B) Effect of the Dalteparin alone vs placebo or no treatment for the prevention of preeclampsia; C) Effect of the Enoxaparin alone vs placebo or no treatment for the prevention of preeclampsia; D) Funnel plot for assessment of publication bias regarding preeclampsia.
three studies (52, 53, 55) with a RR of 0.589 (95% CI, 0.206–1.269, p=0.3) (Figure 3C). The I² was 0% and 70.78% in the analyses of Dalteparin, and Enoxaparin respectively. The number of patients needed to treat by Dalteparin for the prevention of one case of FGR was 4, while the number needed to treat by Enoxaparin was 19 (Table 3).

Side effects of LMWH treatment and their influence on patient’s adherence to treatment

Out of the five studies included, only two studies describe side effects of treatment (53, 54). Fawzy et al. (53) describe minor bleeding complication in two patients, one in the Enoxaparin and one in the combined treatment group, and thrombocytopenia (platelet count <150,000/µl) in one patient in the Enoxaparin group, the authors did not report any event of massive bleeding or thrombosis. In addition, Rey et al. (54), report no cases of such complications but only local bruising at the injection site. There was no report on any patient who stopped her participation in any of the studies due to side effects of heparin treatment, suggesting that such treatment was well tolerated.

Figure 2D and Figure 3D show the results of our assessment of publication bias. The funnel plots for both pathological conditions suggest that publication bias cannot be ruled out. However, in light of the small number of studies that met the inclusion criteria for this meta-analysis, accurate assessment of such bias is not possible. For the same reason we were unable to assess publication bias for each of the different LMWHs.

Discussion

We reviewed the available evidence for the effectiveness of LMWHs in the secondary prevention of PMPC. Five studies were included yielding the following results: 1) Prophylactic LMWH administration reduces the risk for preeclampsia in non-thrombophilic patients with a history of placental mediated diseases or recurrent pregnancy loss; 2) LMWHs appear to reduce the risk for FGR in these patients; and 3) The specific LMWH preparation used may have a differential effect in the prevention of these complications. It should be stressed that these findings are based on relatively small studies using different inclusion criteria and administering different types and dosages of LMWH. Hence, our results should be taken as pointing towards a direction for further investigation, acknowledging the limited data available thus far.

What is the importance of prevention of placental mediated obstetrical syndromes?

Placental mediated pregnancy complications are common and serious (1, 2), with a significant impact on short- and long-term outcomes for both the mother and her fetus. For this reason, during the last decades efforts have been focused on: 1) understanding the underlying mechanisms leading to PMPC; 2) studying if there is a real benefit arising from the use of treatments like LMWHs and aspirin in the prevention of these complications; and 3) If this beneficial effect does exist, how can it be translated into a valid preventive strategy?

Currently, we have no efficient strategy for primary or secondary prevention of these complications, although there is a recommendation for the administration of low-dose aspirin in order to prevent preeclampsia in patients at risk (19, 20, 56–64). The development of a strategy to prevent preeclampsia is complicated further by the fact that the early identification of patients at risk for preeclampsia is based merely on maternal risk factors, but this method is not sensitive and specific enough.

In addition, increasing evidence today suggest that early onset preeclampsia (prior to 34 weeks) may be a different disease than late onset phenotype and might differ in the needed preventive

Table 3: Summary findings and number needed to treat (NNT) to prevent one case of preeclampsia or IUGR/SGA, by study treatments.

<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>Control arm</th>
<th>Experimental arm</th>
<th>Absolute Risk Reduction (ARR)*</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of events</td>
<td>Number of subjects</td>
<td>Control Event Rate (CER)</td>
<td>Number of events</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All heparin</td>
<td>50</td>
<td>394</td>
<td>0.127</td>
<td>18</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>22</td>
<td>94</td>
<td>0.234</td>
<td>6</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>28</td>
<td>300</td>
<td>0.093</td>
<td>12</td>
</tr>
<tr>
<td>IUGR/SGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All heparin</td>
<td>79</td>
<td>394</td>
<td>0.201</td>
<td>45</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>29</td>
<td>94</td>
<td>0.309</td>
<td>8</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>50</td>
<td>300</td>
<td>0.167</td>
<td>37</td>
</tr>
</tbody>
</table>

* Based on random effects model. IUGR, Intrauterine growth restriction; SGA, small for gestational age.
measures in comparison to those to be used for the prevention of preeclampsia at term (39, 66, 67). A good example was the FRUIT study by De Vries et al. (39) that demonstrated that treatment with LMWH plus aspirin reduces the rate of early onset preeclampsia but not the overall occurrence of the disease.

**What is the role of heparin in prevention of preeclampsia and FGR?**

When we designed our meta-analysis we decided a priori that, since LMWHs are the main heparins in routine obstetrical care, only studies using these drugs would be included. Moreover, to avoid the unclear effect of thrombophilia on placental mediated pregnancy complications, only studies that did not include women with thrombophilia were selected. The role of thrombophilia in the pathogenesis of PMPC was questioned already in 2008 by Rodgers et al. (68) who stated that inherited thrombophilias are not yet established as a cause of PMPC, such as FGR, preeclampsia, abortion, and pregnancy loss. In addition, these authors suggested that inherited thrombophilia is only one of many factors that lead to development of these diseases and is unlikely to be the unique factor that should drive management in subsequent pregnancies.

Further studies failed to yield more evidence to support the role of thrombophilia as a specific risk factor for PMPC, and a systematic review and meta-analysis in 2010 concluded that women with Factor V Leiden mutation and prothrombin gene mutation appear not to be at increased risk of preeclampsia or birth of growth restricted infants. Finally, the American College of Obstetricians and Gynecologists, in its practice bulletin, concluded that a definitive causal link cannot be made between inherited thrombophilias and adverse pregnancy outcomes since most of the available studies are small case control and cohort studies assembled in heterogeneous populations, frequently contradictory, and reporting potential biases (69). Also other authors support this concept (68, 70–72). Therefore, we were concerned that including studies with thrombophilic patients without information regarding prior PMPC might introduce further bias and mask the actual effect of LMWH in the secondary prevention of PMPC.

Indeed, we identified a risk reduction of preeclampsia by treatment with LMWH. We were not able to ascertain whether this treatment affects differently early or late disease because the

**Figure 3:** A) Effect of the combination of all LMWH vs placebo or no treatment on the prevention FGR; B) Effect of Dalteparin vs placebo for the prevention FGR; C) Effect of Enoxaparin vs placebo for the prevention FGR; D) Funnel plot for assessment of publication bias regarding FGR.
studies included in our meta-analysis did not discriminate between early and late onset preeclampsia. Similarly, we identified a significant reduction in the risk for FGR in the treatment group vs the placebo or no treatment arm. In comparison to other meta-analyses, Rodger et al. (73) included thrombophilic and non-thrombophilic patients, and studies that were comparing LMWH plus aspirin vs no treatment and LMWH plus aspirin vs aspirin alone, while Dodd et al. (21) included thrombophilic and non-thrombophilic patients who received either UFH, or LMWH, vs no treatment, placebo, or aspirin. Our study and the other two meta-analyses (21, 73) demonstrate that heparin may prevent the development of preeclampsia. However, only in our study this effect is based solely on the comparison of LMWH vs placebo/no treatment.

The effect size of LMWH in our meta-analysis is modest. However, it has to be noted that we pooled together different degrees of severity of both preeclampsia and FGR, that might respond in a differential manner to treatment, and it could be that the effect of the treatment is influenced by the severity of the disease. We cannot rule out that only the most severe forms of the different syndromes show a significant benefit from treatment with LMWH.

Collectively, the evidence brought herein, although based on small numbers of patients, supports the beneficial effect of treatment with LMWH to prevent preeclampsia and FGR. However, significant clinical heterogeneity among studies raises the question of whether there is a difference in the efficacy of the different types of LMWHs? How long should we treat patients, throughout gestation or only through the first half of it? Would treatment with LMWHs be effective in the prevention of both early vs late onset preeclampsia or all FGR or just the severe forms below the 5th centile?

Do the various LMWH differ in their efficacy to prevent obstetrical syndromes?

We report herein for the first time an individual analysis of LMWH. Dalteparin appeared to have a significant effect on the prevention of preeclampsia and FGR vs placebo or no treatment. Enoxaparin had a modest but significant effect in the secondary prevention of preeclampsia but not of FGR. This is based on the limited data derived from two studies using Dalteparin and three that were using Enoxaparin. When we tested the NNT (Table 3) for all LMWHs, 11 women needed to be treated in order to prevent one case of preeclampsia vs six when only Dalteparin was considered.

These findings need to be interpreted with caution, since there was a substantial difference between studies using Dalteparin and Enoxaparin. In the studies using Dalteparin, similar patient populations were included (one with a history of preeclampsia, the other with history of PMPC), while those using Enoxaparin were more diverse in term of their selected populations (two studies included women with recurrent pregnancy loss, and one those with a history of abruption). Of interest, the summary RR showing a beneficial effect of Enoxaparin was mainly driven by the study by Gris et al. (55) that included women with a history of placental abruption. It cannot be excluded that application of standardised and specific inclusion criteria would have led to a more homogeneous study population, with different results.

Our findings raise the question of whether there is a difference in the effectiveness of the various LMWHs for the prevention of preeclampsia. Differences in design and participants of included studies inhibit direct comparisons; further studies are needed to clarify this subject.

Strengths and limitations of the study

The limitations of our study derive from several fields. Firstly, obstetrical complications may often overlap and sometimes one woman may have more than one specific complication in the same gestation or different complications in each pregnancy. The second point is the high heterogeneity among the studies included, which leads to the fact that we cannot be sure that all women included had a similar risk for developing the complication. As a consequence it is uncertain that the outcomes reported would be similar between studies. This is a common limitation to all meta-analysis performed on the effect of heparins in the prevention of placental mediated obstetrical syndromes. The outcome definitions also differed among studies, making the comparison of their results harder. The small numbers of patients and the fact that all included studies are non blinded studies are additional limitations. In addition, as derived from our funnel plots, the assessment of
publication bias of the individual LMWH is impossible because of the low number of studies in each group. Therefore, this point may need to be addressed when more data regarding specific LMWHs in the prevention of PMPC will be available.

There are several strengths of our study: 1) the studies that met the inclusion criteria also scored as high quality RCTs in the assessment of risk of bias, according to Jadad score (47); 2) in contrast to prior meta-analyses, we excluded studies that were either treating with aspirin or comparing with effect of LMWH vs aspirin in order to overcome the bias of its administration and to test whether or not the beneficial preventive effect belongs to LMWH alone or it could be attributed to the addition of aspirin; 3) we also did not include UFH in order to see whether or not the effect could be attributed to LMWH alone; and 4) we excluded women with inherited or acquired thrombophilia, since this heterogeneous group might introduce bias as for the specific risk of each patient.

Conclusions

Our systematic review and meta-analysis found evidence for a beneficial effect of LMWHs in the secondary prevention of pre-eclampsia and FGR. Moreover, our study raises the question of whether various LMWH preparations differ in their effectiveness for preventing these serious complications.

The effect of LMWH in the secondary prevention of PMPC needs to be studied in a specifically targeted RCT before further conclusions regarding its use can be made. Our observations need further confirmation in future studies.

Conflicts of interest

None declared.

References