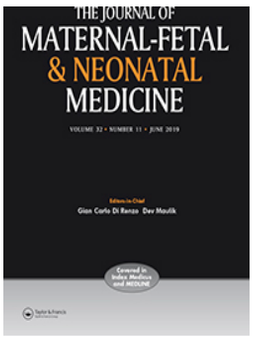

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REVIEW ARTICLE

Low molecular weight heparin use during pregnancy and risk of postpartum hemorrhage: a systematic review and meta-analysis

Angelo Sirico[a], Gabriele Saccone[a], Giuseppe Maria Maruotti[a], Elvira Grandone[b], Laura Sarno[a], Vincenzo Berghella[c], Fulvio Zullo[a] and Pasquale Martinelli[a]

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ABSTRACT

Introduction: Postpartum hemorrhage (PPH) is the leading cause of maternal mortality worldwide with a prevalence rate of approximately 6%. Although most cases of PPH have no identifiable risk factors, the incidence of PPH has been associated to the thromboprophylaxis in pregnancy with low molecular weight heparin (LMWH). Thus, the aim of the study is to evaluate the risk of PPH in cases of pregnant women exposed to LMWH.

Materials and methods: Electronic research was performed in OVID, Scopus, ClinicalTrials.gov, MEDLINE, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, and the Cochrane Central Register of Controlled Trials through April 2016. We included randomized controlled trials, cohort and case-control studies of women who underwent thromboprophylaxis with LMWH during pregnancy compared to a control group (either placebo or no treatment). The primary outcome was the incidence of PPH. The summary measures were reported as relative risk (RR) or as mean differences (MD) with 95% confidence interval (CI).

Results: Eight studies including 22,162 women were analyzed. Of the 22,162 women, 1320 (6%) were administered LMWH, 20,842 (94%) women formed the nonexposed group (control group). Women treated with LMWH had a higher risk of PPH (RR 1.45, 95%CI 1.02–2.05) compared to controls; there was no difference in mean of blood loss at delivery (MD −32.90, 95%CI 68.72–2.93) and in risk of blood transfusion at delivery (RR 1.24, 95%CI 0.62–2.51), respectively.

Conclusions: Women who receive LMWH during pregnancy have a significantly higher risk of developing PPH. Women who receive LMWH during pregnancy have neither significantly higher mean blood loss at delivery nor higher risk of blood transfusion.

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Heparin; bleeding; prevention; pregnancy; post-partum hemorrhage; PPH; LMWH

Introduction

Postpartum hemorrhage (PPH) is the leading cause of maternal mortality worldwide with a prevalence rate of approximately 6% [1]. PPH is responsible for about 25% of maternal deaths worldwide, and 12% of survivors will have severe anemia. Clinically, it is associated with weakness, sweating, and tachycardia, and with hemodynamic collapse occurring at losses of between 35 and 45% of blood volume [2]. According to the World Health Organization (WHO), PPH is defined as "blood loss from the birth canal in excess of 500 mL during the first 24 h after delivery", although currently there is a debate about what definition to use [3].

The most common risk factors for PPH are the presence of suspected or proven placental abruption, placenta previa, multiple pregnancy, macrosomia and prolonged labor, retained placenta or cotyledons, uterine hypotonia, major perineal lacerations and vaginal hematoma, coagulation disorders, and prolonged oxytocin use [4]. On the other hand, most cases of PPH have no identifiable risk factors. The incidence of PPH has been also associated to the use of thromboprophylaxis in pregnancy with low molecular weight heparin (LMWH). LMWHs are anticoagulants used mostly in pregnant women with risk factors for deep venous thrombosis (DVT) or pulmonary embolism (PE) in order to avoid the incidence of venous thromboembolism (VTE) and the related adverse outcomes in pregnancies [5]. The safety of LMWH for the fetus has been assessed since it does not pass the placental barrier [6]; nevertheless, the role of anticoagulant has been postulated to determine a higher risk of PPH.

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In 2005, a systematic review of safety and efficacy assessed that LMWHs are not associated with an increased risk of severe peripartum bleeding [7]. However, so far the risk of PPH in women using LMWH during pregnancy is still the subject of debate and up-to-date literature include different studies with opposing results. Thus, the aim of this meta-analysis is to evaluate the risk of PPH in cases of pregnant women exposed to LMWHs.

Materials and methods

Search strategy

The research protocol was designed *a priori* [8], and registered on Prospero (registration number: CRD42016049373). We performed electronic research in OVID, Scopus, ClinicalTrials.gov, MEDLINE, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, and the Cochrane Central Register of Controlled Trials with the use of a combination of text words related to "heparin", "low molecular weight heparin", "lmwh", "postpartum hemorrhage", "pph", "anticoagulation", "thromboprophylaxis", and "pregnancy" through April 2016. No restrictions for language or geographic location were applied.

Study selection

We included all randomized controlled trials (RCTs), cohort, and case-control studies of women who underwent thromboprophylaxis with LMWH during the third trimester of pregnancy compared to a control group (either placebo or no treatment). All the studies were eligible if they reported the incidence of PPH after any exposure to LMWHs and had a comparison group of unexposed pregnant women. Studies without a control group were excluded. Only studies reporting the incidence of PPH as outcome were included. Studies on LMWH during delivery or after delivery were not included in the meta-analysis.

Risk of bias

The risk of bias of the included studies was assessed via the Methodological Index for Non-Randomized Studies (MINORS) [9]. Seven domains related to risk bias were assessed in each study: (1) aim (i.e. clearly stated aim), (2) rate (i.e. inclusion of consecutive patients and response rate), (3) data (i.e. prospective collection of data), (4) bias (i.e. unbiased assessment of study end points), (5) time (i.e. follow-up time appropriate), (6) loss (i.e. loss to follow-up), and (7) size (i.e. calculation of the study size). Review authors' judgments were categorized as "low risk", "high risk", or "unclear risk of bias".

Data extraction

Two authors (AS, GS) independently assessed inclusion criteria, risk of bias and data extraction. Disagreements were resolved by consensus through discussion. Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. Differences were reviewed, and further resolved by common review of the entire process.

The primary outcome was the incidence of PPH, as defined by the original studies. Secondary outcome were mean blood loss and incidence of blood transfusion at delivery. We planned sensitivity analysis according to the study design of the included studies. All analyses were performed using an intention-to-treat approach, evaluating women according to the group of allocation in the original studies.

All authors of the original studies were contacted in case of missing data.

The following *post hoc* subgroup analyses were assessed for the primary outcome:

- According to mode of delivery
- According to type of LMWH
- According to dose of LMWH
- According to indication of LMWH

Data analysis

The data analysis was completed independently by two authors (AS, GS) using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014). The completed analyses were then compared, and any difference was resolved with review of the entire data and independent analysis. Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance [8]. A value of 0% indicates no observed heterogeneity, whereas I^2 values of $\geq$50% indicate a substantial level of heterogeneity. A fixed effects model was used if substantial statistical heterogeneity was not present. On the contrary, if there was evidence of significant heterogeneity between studies included, a random effect model was used [7]. We planned to assess potential publication biases by using Begg's and Egger's tests statistically, and by using the funnel plot graphically.

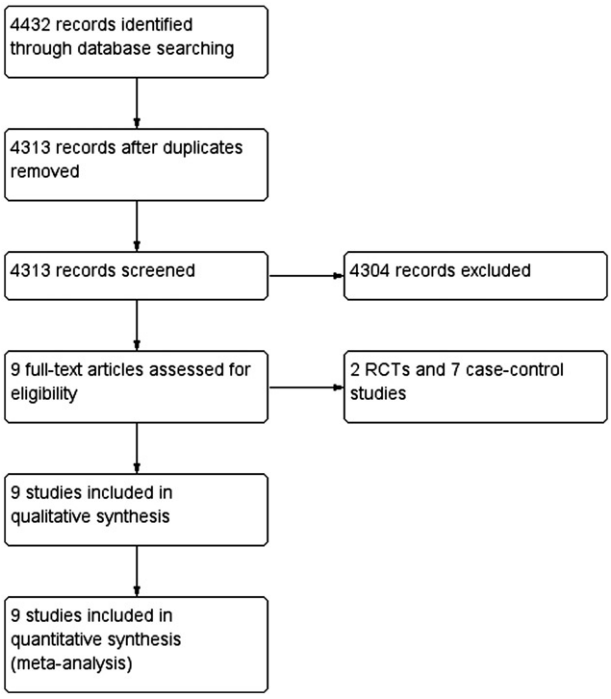

Figure 1. Flow diagram of studies identified in the systematic review. (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).

The summary measures were reported as relative risk (RR) or as mean differences (MD) with 95% confidence interval (CI). p Value $<.05$ was considered as statistically significant. The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [10].

Results

Study selection and study characteristics

Nine articles were assessed for eligibility [11–19]. The RCT of Howell et al. was excluded since they used unfractionated heparin and not LMWH [19]. Eight studies including 22,162 women were therefore analyzed (Figure 1) [11–18].

Risk of publication bias was assessed by visual inspection of the funnel plot, and the symmetric plot suggested no publication bias (Figure 2). Publication bias, assessed statistically using Begg's and Egger's tests, showed no significant bias ($p = .47$ and $p = .51$, respectively). The statistical heterogeneity between the studies was low.

Most of the included studies had low risk of bias in "aim", "rate", "time", and "follow-up". Two of them were prospective. Four studies were large retrospective cohort studies. The most used types of LMWH were dalteparin, enoxaparin, tinzaparin, and nadroparin (Figure 3).

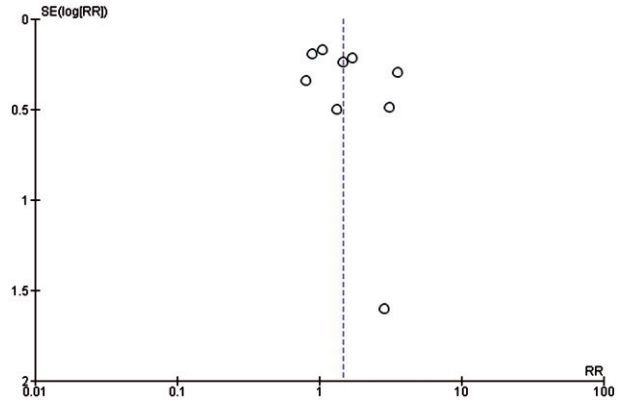

Figure 2. Funnel plot for assessing publication bias. OR: odds ratio; SE: standard error.

Table 1 shows the characteristics of the included studies. Of the 22,162 women, 1320 (6%) were administered LMWH during pregnancy, and 20,842 (94%) women formed the nonexposed group (control group). One study came from the UK [18], two from the Netherlands [14,16] one from the US [12], one from France [17], and the rest from the northern Europe [11,13,15]. All the included studies had PPH as primary outcome.

In the eligible studies, PPH was defined as blood loss >600 mL [11], blood loss >500 mL for vaginal delivery and >1000 mL for cesarean delivery (CD) [12,16], blood loss ≥1000 mL [13,15,17], and blood loss ≥500 mL [14,18]. In the eligible studies, blood loss was assessed during delivery [11–13,15] or within 24 hours of delivery [14,16–18].

The indications for therapy with LMWH were mostly history of VTE or adverse obstetric outcome, the presence of thrombophilia or a mechanical valve replacement.

Regarding the LMWH therapy, in Lindqvist et al. [11] Boilot et al. [17], and Galambosi et al. [15] women were treated with dalteparin 5000 IU/day or enoxaparin 40 mg/day; Andersen et al. used tinzaparin 4500 IU/day or dalteparin 5000 IU/day [13]; Knol et al. therapeutic dose of nadroparin 95 UI/kg twice daily [16]; Kominiarek et al. Enoxaparin 40 mg twice/day; dalteparin 5000 UI twice/day in case of prosthetic mitral valve [12]; while Roshani et al. used various type of LMWH including enoxaparin, dalteparin, nadroparin, danaparoid, and tinzaparin [14].

In all studies, women in the control group received no anticoagulation or antiplatelet therapy.

Gestational age at onset of therapy was various, but all studies excluded those women who did not receive LMWH in the third trimester. In most of the included studies therapy was discontinued at onset of labor or

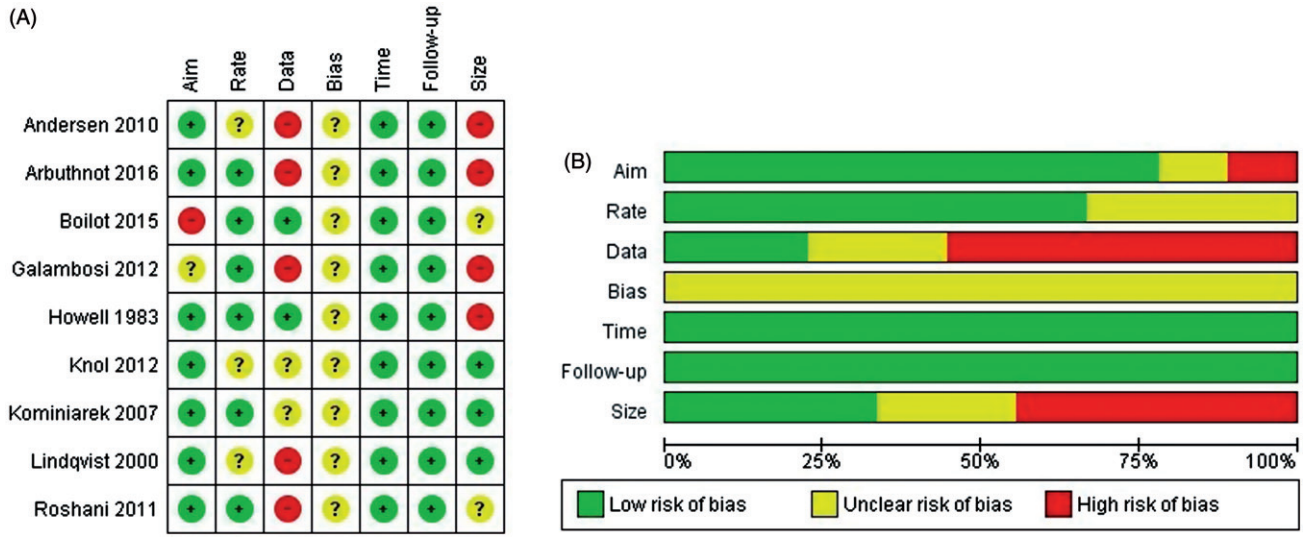

Figure 3. Assessment of risk of bias. Aim, clearly stated aim; Rate, inclusion of consecutive patients and response rate; Data, prospective collection of data; Bias, unbiased assessment of study end points; Time, follow-up time appropriate; Loss, loss to follow-up; Size, calculation of the study size. (A) Summary of risk of bias for each study. Plus sign, low risk of bias; minus sign, high risk of bias; question mark, unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

at time of induction or at least 12 or 24 hours before scheduled CD (Table 2).

Synthesis of results

We found that women treated with LMWH during pregnancy had a significantly higher risk of PPH (RR 1.45, 95%CI; 1.02–2.05; Figure 4) compared to controls; while no differences were found in the mean of blood loss at delivery (MD −32.90, 95%CI; −68.72to 2.93; Figure 5) and in risk of blood transfusion at delivery (RR 1.24, 95%CI; 0.62–2.51; Figure 6).

Sensitivity analyses according to the study design of the included studies, concurred with the overall analysis for prospective (RR 3.42, 95%CI; 2.09–5.61) but not for retrospective studies (RR 1.16, 95%CI; 0.92–1.47).

Subgroup analyses in cesarean delivery only (RR 1.52, 95% CI; 1.22–1.88) and vaginal delivery (RR 1.20, 95% CI; 1.17–1.64) only concurred with the overall analysis.

Discussion

Main findings

This meta-analysis shows that women who received LMWH during pregnancy had a significantly higher risk of developing PPH. Women who received LMWH during pregnancy had neither significantly higher mean blood loss at delivery nor higher risk of blood transfusion.

Comparison with existing literature

To date, most meta-analyses have investigated the role of LMWH in reducing the risk of miscarriage in women with recurrent pregnancy loss [20] or in reducing the prevalence of preeclampsia and small for gestational age babies in women with a history of preeclampsia [21]. To our knowledge, this is the first systematic review evaluating the possible association between the administration of LMWH during pregnancy and the risk of PPH.

Strengths and limitations

The most important strength of our work rest on the large number of women included. When considering the incidence of PPH for each single study, only two studies included reach a significant result but with a moderate number of women included [16,18]. Most of the included studies have a low risk of bias. All the eight studies had PPH as primary outcome.

Although meta-analytical techniques pool all available data, limitations include those of the original articles. Only two studies were prospective and six were retrospective cohort studies. Furthermore, five studies did not report the exact dosage of LMWH administered to pregnant women and two studies did not report the definition of PPH. None of the included studies adjusted data for confounders and this is the major shortcoming of this review. As LMWH use occurs mainly in the context of maternal risk of thromboembolic events, we were not able to study the effects

Table 1. Characteristics of included studies.

	Study location	Type of study	Number of included women	Indication for LMWH use	Type of LMWH used in pregnancy	Definition of PPH
Lindqvist 2000 [11]	Sweden	Prospective cohort	1731 (34 versus 1697)	APCR	Dalteparin 5000 IU/day; Enoxaparin 40 mg/day	Blood loss >600 mL during delivery
Kominiarek 2007 [12]	USA	Retrospective case-control	165 (55 versus 110)	History of VTE, inherited or acquired thrombophilia, mitral valve replacement, coronary aneurysm	Enoxaparin 40 mg twice/day; Dalteparin 5000 UI twice/day in case of prosthetic mitral valve	Blood loss >500 mL during vaginal delivery mL; Blood loss >1000 mL during CD
Andersen 2010 [13]	Denmark	Retrospective cohort	461 (155 versus 306)	History of VTE, prior adverse obstetric outcomes, inherited or acquired thrombophilia	Tinzaparin 4500 IU/day; Dalteparin 5000 IU/day	Blood loss ≥1000 mL during delivery
Roshani 2011 [14]	Netherlands	Retrospective cohort	619 (95 versus 524)	History of VTE, inherited or acquired thrombophilia, prior preeclampsia, prosthetic heart valve	Various types[a]	Blood loss >500 mL within 24 hours of delivery
Galambosi 2012 [15]	Finland	Retrospective Cohort	1274 (648 versus 626)	History of VTE or stroke, prior adverse obstetric outcome, mechanical heart valve, inherited or acquired thrombophilia	Enoxaparin 40 mg/day; Dalteparin 5000 IU/day	Blood loss >1000 mL during delivery
Knol 2012 [16]	Netherlands	Retrospective case-control	440 (88 versus 352)	History of VTE, inherited or acquired thrombophilia	Nadroparin 95 IU/kg/day twice daily	Blood loss >500 mL within 24 hours of vaginal delivery; Blood loss >1000 mL within 24 hours of CD
Boilot 2015 [17]	France	Prospective case-control	942 (130 versus 812)	Prior adverse obstetric outcomes, inherited or acquired thrombophilia	Dalteparin 5000 IU/day; Enoxaparin 40 mg/day	Blood loss >1000 mL within 24 hours of delivery
Arbuthnot 2016 [18]	UK	Retrospective cohort	16,530 (115 versus 16,415)	History of VTE, inherited or acquired thrombophilia, recurrent miscarriage	Not reported	Blood loss ≥500 mL within 24 hours of delivery

Data are presented as total number (number of exposed versus number of nonexposed).
LMWH: low molecular weight heparin; PPH: postpartum hemorrhage; APCR: activated protein C resistance; VTE: venous thromboembolism; CD: cesarean delivery.
[a]Various types of LMWH including enoxaparin, dalteparin, nadroparin, danaparoid, tinzaparin.

Table 2. Gestational age at therapy and mode of delivery in women treated with LMWH.

	No. of women treated with LMWH	GA starting LMWH	GA discontinued LMWH	LMWH postpartum	Vaginal delivery	Cesarean delivery
Lindqvist 2000 [11]	34	14/34 only 3rd trimester 15/34 2nd and 3rd trimester 5/34 all three trimesters	At induction or onset of labor	12 hours after delivery and until 6 weeks post-partum	34/34	0/34
Kominiarek 2007 [12]	55	All three trimesters	At induction or onset of labor	Not reported	35/55 (63.6%)	20/55 (36.4%)
Andersen 2010 [13]	155	76/155 only third or second and third trimester 79/155 all three trimesters	At induction or onset of labor	12 hours after delivery and until 6 weeks post-partum	Not reported	Not reported
Roshani 2011 [14]	95	Not reported[a]	At onset of labor, or rupture of membranes, or 24 hours before induction or planned cesarean delivery	Not reported	73/95 (76.8%)	22/95 (23.2%)
Galambosi 2012 [15]	648	Not reported[a]	At induction or onset of labor	12 hours after delivery and until 6 weeks post-partum	Not reported	Not reported
Knol 2012 [16]	88	88/88 all three trimesters	At onset of labor, or 12 hours before induction or planned cesarean delivery, or at 37th weeks of gestation	8 hours after delivery and until 6 weeks post-partum	71/88 (80.7%)	17/88 (19.3%)
Boilot 2015 [17]	130	Not reported[a]	At onset of labor, or 12 hours before induction or planned cesarean delivery	12 hours after delivery and until 6 weeks post-partum	Not reported	Not reported
Arbuthnot 2016 [18]	115	115/115 all three trimesters	At onset of labor, or 12 hours before induction or planned cesarean delivery	Not reported	83/115 (72.2%)	32/115 (27.8%)

LMWH: low molecular weight heparin; GA: gestational age.
[a]Women who did not receive LMWH in the third trimester were excluded.

of LMWH exposure independent of exposure to thromboembolic risk. This bias cannot be reliably eliminated with a multivariable analysis. Based on the characteristics of the included studies and the summary statistics for heterogeneity there was a large amount of both statistical and clinical heterogeneity. The studies vary markedly by overall study design, analysis, drug exposure, drug type, and definition of the main outcome. The statistical heterogeneity within the studies for the primary outcome was high ($I^2 = 71\%$). For this reason, random effects models were used in the analysis performed. Another major issue is the small OR (1.45 for the primary outcome). The primary outcome may be statistically, but not clinical significant. Maybe the existing studies pooled together for this review did not adequately address the question, especially as no RCTs were included. No data were available on the assessment methods of mean blood loss at delivery and on the indications and hemoglobin thresholds for red blood cell transfusion. Subgroup analyses were *post hoc* and not planned *a priori*.

Interpretation

Metabolic changes during pregnancy enhance the risk of venous thromboembolic events (VTE) [21,22]. For this reason women with history of VTE, thrombophilia or other conditions at risk, such as a mechanical heart valve, undergo an anticoagulant prophylaxis during pregnancy to reduce the risk of VTE. LMWH is considered as the gold standard drug for prophylaxis and therapy of VTE during pregnancy because it does not pass through the placenta and thus there is no teratogenic risk for the fetus [7]. Furthermore, since preeclampsia has been shown to be linked to an increased risk of VTE and at the same time the thrombophilic state in preeclampsia has been linked to a worsened perinatal outcome of the pregnancy, also women with history of preeclampsia or fetal growth restriction usually undergo a thromboprophylaxis during pregnancy, even if at the moment there is no unanimous consensus on this strategy. However, a recent meta-analysis showed that the addition of LMWH to low-dose aspirin could reduce the prevalence of preeclampsia and small for gestational age babies in women with a history of preeclampsia [20]. Simonazzi et al. found that prophylactic tranexamic acid given before cesarean skin incision in women undergoing cesarean delivery, under spinal or epidural anesthesia, significantly decreases blood loss, including PPH and severe PPH, in addition to the standard prophylactic oxytocin given after delivery of the neonate, but women receiving LMWH therapy were not included in this study [4,23].

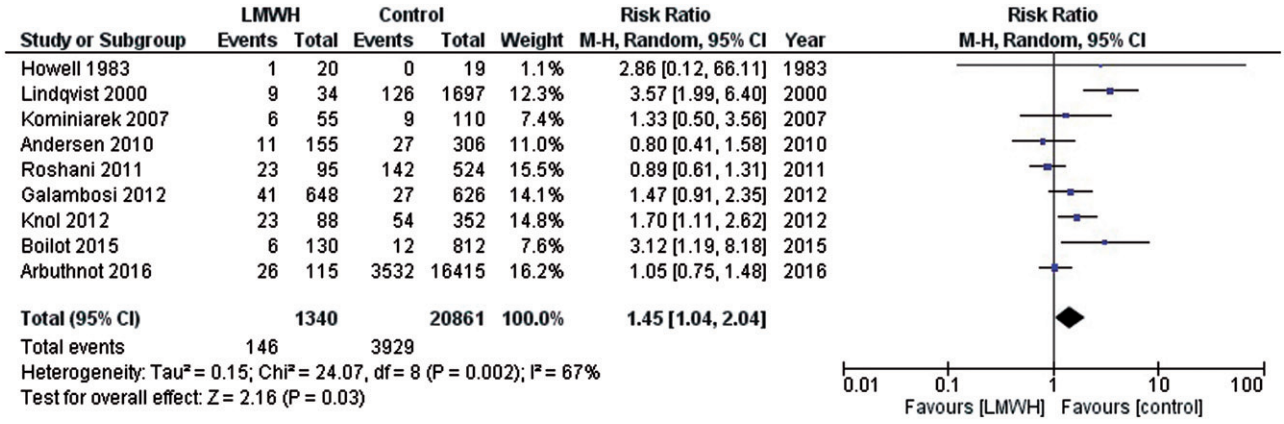

Figure 4. Forest plot for the risk of postpartum hemorrhage. M-H: Mantel–Haenszel test; CI: confidence interval.

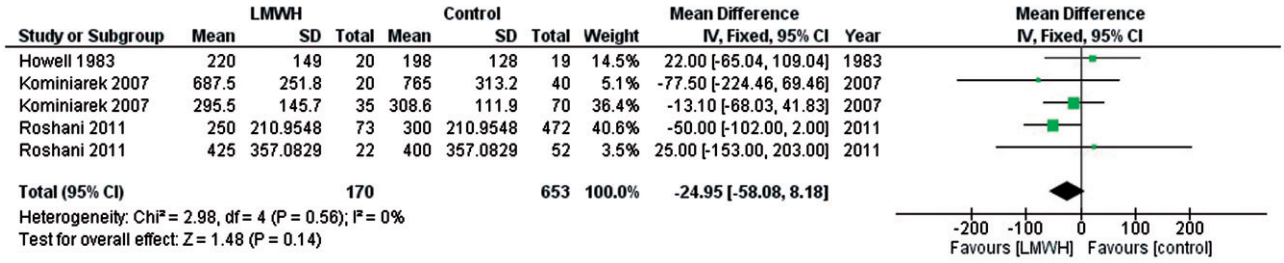

Figure 5. Forest plot for the mean of blood loss. M-H: Mantel–Haenszel test; CI: confidence interval.

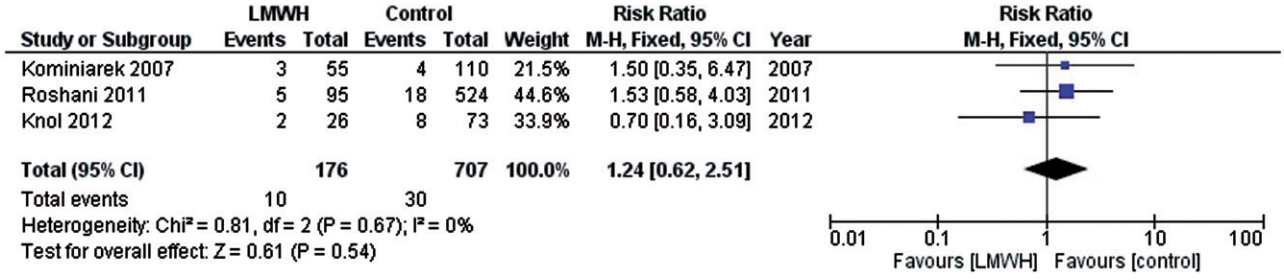

Figure 6. Forest plot for the risk of blood transfusion at delivery. M-H: Mantel–Haenszel test; CI: confidence interval.

The biological plausibility of our findings is not completely clear. With respect to PPH, LMWH-related risk of bleeding is usually considered low when administration is suspended 12 hours before delivery [24,25]. It is not clear whether a chronic exposure to LMWH during pregnancy may lead to modifications on the decidual architecture and the uterine wall at term, thus increasing the hemorrhagic risk even if LMWH is suspended according to the present recommendations. On the other hand, untreated women with increased thromboembolic risk may be at higher risk for VTE.

Furthermore, the significant increased incidence of PPH but not of mean blood loss at delivery or transfusion could be explained considering the small number of women included in the secondary analysis (784 for mean blood loss at delivery, 883 for blood transfusion) compared to the women included in the primary analysis (22,162). Since no data were available on the assessment methods of mean blood loss at delivery and on the indications and hemoglobin thresholds for red blood cell transfusion, it seems difficult to evaluate the clinical significance of these findings.

Conclusions

In summary, based on this findings treatment with LMWH during pregnancy may be associated with an increased risk of PPH. Hence, in situations where it may be necessary to use LMWHs in pregnancy (prior history of VTE, thrombophilia, mechanical heart valve, previous obstetric complications), the decision to use

LMWHs during pregnancy must be weighed against this risk/benefit ratio, including the risk of PPH. This must be carefully discussed with the woman, and should ideally be done in collaboration with the expert in hemostasis and thrombosis.

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Disclosure statement

The authors report no conflicts of interest

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