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Prevention of pre-eclampsia by low-molecular-weight heparin in addition to aspirin: a meta-analysis

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KEYWORDS: aspirin; heparin; meta-analysis; pre-eclampsia; small-for-gestational age

ABSTRACT

Objective *To estimate the impact of adding low-molecular-weight heparin (LMWH) or unfractionated heparin to low-dose aspirin started ≤ 16 weeks' gestation on the prevalence of pre-eclampsia (PE) and the delivery of a small-for-gestational-age (SGA) neonate.*

Methods *A systematic review and meta-analysis of randomized controlled trials (RCTs) was performed by searching the medical databases PubMed, EMBASE, Web of Science and Cochrane Central. Pregnant women randomized to receive LMWH or unfractionated heparin in addition to low-dose aspirin were compared with those who received low-dose aspirin alone. Outcome measures were PE, severe PE, early-onset PE and SGA. Pooled relative risks (RRs) with 95% CI were calculated using a random-effects model.*

Results *Eight RCTs met the inclusion criteria; the indication for recruitment was previous recurrent miscarriage in five studies (three included women with thrombophilia) and a history of severe or early-onset PE in three studies (including women with thrombophilia in one). LMWH was administered in seven studies and unfractionated heparin in one. In women with a history of PE, treatment with LMWH and aspirin, compared with aspirin alone, was associated with a significant reduction in development of PE (three trials (*n = *379); RR, 0.54 (95% CI, 0.31–0.92);* P = *0.03) and in delivery of SGA neonates (two trials (*n = *363); RR, 0.54 (95% CI, 0.32–0.91);* P = *0.02). These outcomes were not significantly reduced in women with recurrent miscarriage who received LMWH and aspirin, compared with aspirin alone. The small number of studies precluded sensitivity analyses and the evaluation of publication biases. Blinding to the allocation treatment was absent in all RCTs.*

Conclusions *Based on limited evidence, the addition of LMWH to low-dose aspirin could reduce the prevalence of PE and SGA in women with a history of PE. This observation should be the basis of a well-conducted future trial rather than a recommendation for immediate clinical application. Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Pre-eclampsia (PE), which occurs in 2–8% of pregnancies, is associated with evidence of impaired placentation[1,2]. Placental vascular lesions and incomplete transformation of uterine spiral arteries are also found in some pregnancies that are complicated by the delivery of small-for-gestational-age (SGA) neonates[2]. Meta-analyses of randomized controlled trials (RCTs) have reported that, in pregnancies at high risk of PE, the prophylactic use of low-dose aspirin started ≤ 16 weeks' gestation can reduce the prevalence of PE and SGA[3–5]. The role of heparin in prevention of these conditions is becoming increasingly apparent, mainly due to its antithrombotic and anti-inflammatory effects, similar to those of aspirin[6]. A Cochrane review concluded that prophylactic use of heparin in high-risk pregnancies may reduce the prevalence of PE and SGA; however, the study included women who did not receive low-dose aspirin[7]. A recent randomized trial in 292 pregnant women with thrombophilia, not included in the Cochrane review, reported that prophylactic use of low-molecular-weight heparin (LMWH) does not reduce the occurrence of placenta-mediated pregnancy complications; however, the relative risk (RR) for women who were concomitantly taking low-dose aspirin was 0.30 (95% CI, 0.1–1.1) compared with 1.20 (95% CI, 0.7–2.2) for those who were not taking aspirin[8].

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As it has been demonstrated that aspirin is effective in early gestation, the objective of this meta-analysis was to determine if the combined treatment of LMWH and low-dose aspirin starting ≤ 16 weeks' gestation is superior to the administration of low-dose aspirin alone in the prevention of PE and SGA in women at risk[9].

METHODS

Information sources

Included in this meta-analysis were RCTs that compared the administration of a combination of any type of LMWH or unfractionated heparin and aspirin with the administration of aspirin alone, started ≤ 16 weeks' gestation in women at risk of hypertensive disorders. Studies that included other treatment or cotreatment were excluded. An electronic search was made of PubMed, EMBASE, Web of Science and Cochrane Central to identify studies published from 1945 to March 2015; references of systematic reviews were investigated to identify further articles. No language restriction was imposed. A combination of the following keywords and MeSH terms were included: 'heparin', 'bemiparin', 'certoparin', 'dalteparin', 'enoxaparin', 'nadroparin', 'parnaparin', 'reviparin', 'tinzaparin', 'LMWH', 'aspirin', 'acetylsalicylic acid', 'preeclampsia', 'pre-eclampsia', 'PE', 'toxaemia', 'toxemia' and 'eclampsia'.

Study selection

Screening of the titles of identified articles was performed by one reviewer (S.R.). The relevant selected abstracts were screened separately by two reviewers (S.R. and M.B.). Final selection and data extraction from the complete articles was performed independently by two reviewers (M.B. and E.B.) and any discrepancies were resolved by discussion. The quality of studies was evaluated using the Cochrane Handbook Criteria tool for judging risk of bias, and studies with high risk of bias were considered for sensitivity analysis[10]. The quality and integrity of this review were validated with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[11].

The outcome measures were PE, early-onset PE and SGA. The definition of PE was that of the American College of Obstetricians and Gynecologists as systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg occurring > 20 weeks' gestation in a woman with previously normal BP plus proteinuria, defined as urinary excretion of ≥ 0.3 g protein in a 24-h urine specimen or 2+ protein on dipstick[12]. Considering the variations in the definition of PE around the world, similar definitions were accepted[13]. Early-onset PE was defined as PE ≤ 34 weeks of gestation. The definition of SGA was a neonatal birth weight below the 10th, 5th or 3rd percentile (the first available in this order) for gestational age at delivery, or an equivalent.

Pooled RRs were computed for dichotomous outcomes, using Review Manager 5.2.3 software. Global RRs were calculated according to the DerSimonian and Laird random-effects model in case of significant heterogeneity and variance, and fixed-effects model in case of homogeneity between studies. Heterogeneity between studies was analyzed using the Higgins I^2 statistic[14,15]. The distribution of trials was examined using funnel plots to assess publication bias[16]. It was planned to conduct sensitivity analyses to investigate robustness of the findings and to assess heterogeneity between studies, with comparison of the inclusion criteria, blinding, study quality and trial size.

RESULTS

The search of databases identified 1807 potentially eligible studies and 250 were selected for further evaluation. Eight (885 participants) met the selection criteria and were included in the analysis (Figure 1). Gestational age at treatment randomization varied among the trials but all women were randomized between the time of a positive pregnancy test and 14 weeks' gestation. Three RCTs used dalteparin[17–20], two used enoxeparin[21,22], two did not specify the type of LMWH[23,24] and one used unfractionated heparin[25]. Three studies recruited women with a history of PE, one of which included only women with thrombophilia, and five studies recruited women with at least two consecutive miscarriages, three of which included only women with thrombophilia. The dose of aspirin varied between 75 and 100 mg/day. The characteristics of each trial, including the number of patients, inclusion criteria, treatment and outcome measures are summarized in Table 1.

Due to the wide heterogeneity between inclusion criteria for the two subgroups of women, we stratified our results according to the entry criteria and used a random-effects model. We observed that, in women with a history of PE, the addition of LMWH to low-dose aspirin reduced the risk of PE (three trials ($n = 379$); RR, 0.54 (95% CI, 0.31–0.92); $P = 0.03$) and SGA (two trials ($n = 363$); RR, 0.54 (95% CI, 0.32–0.91); $P = 0.02$), whereas the risks for these outcomes were not significantly reduced in the subgroup of women with recurrent miscarriage (PE: two trials ($n = 211$); RR, 0.57 (95% CI, 0.08–4.35); $P = 0.59$; SGA: three trials ($n = 337$); RR, 0.73 (95% CI, 0.18–2.99); $P = 0.66$ (Figures 2 and 3)). Moreover, LMWH with low-dose aspirin appears to show a trend in the reduction of early-onset PE (two trials ($n = 155$); RR, 0.14 (95% CI, 0.02–1.10); $P = 0.06$) but not late-onset PE (two trials ($n = 155$); RR, 1.20 (95% CI, 0.53–2.72); $P = 0.65$) in women with a history of PE.

The Higgins I^2 statistic demonstrated no heterogeneity between studies for PE and early-onset PE ($I^2 = 0\%$) and low heterogeneity for SGA ($I^2 = 22\%$). The small number of included RCTs precluded appropriate analysis of the funnel plot and other sensitivity analysis and therefore we cannot exclude selection biases. According to the Cochrane Handbook Criteria tool for judging risk of bias, the majority of included studies were judged to have low or unclear risk of bias, except for the blinding of the participants as no study used a placebo in the control group (Figure 4)[10].

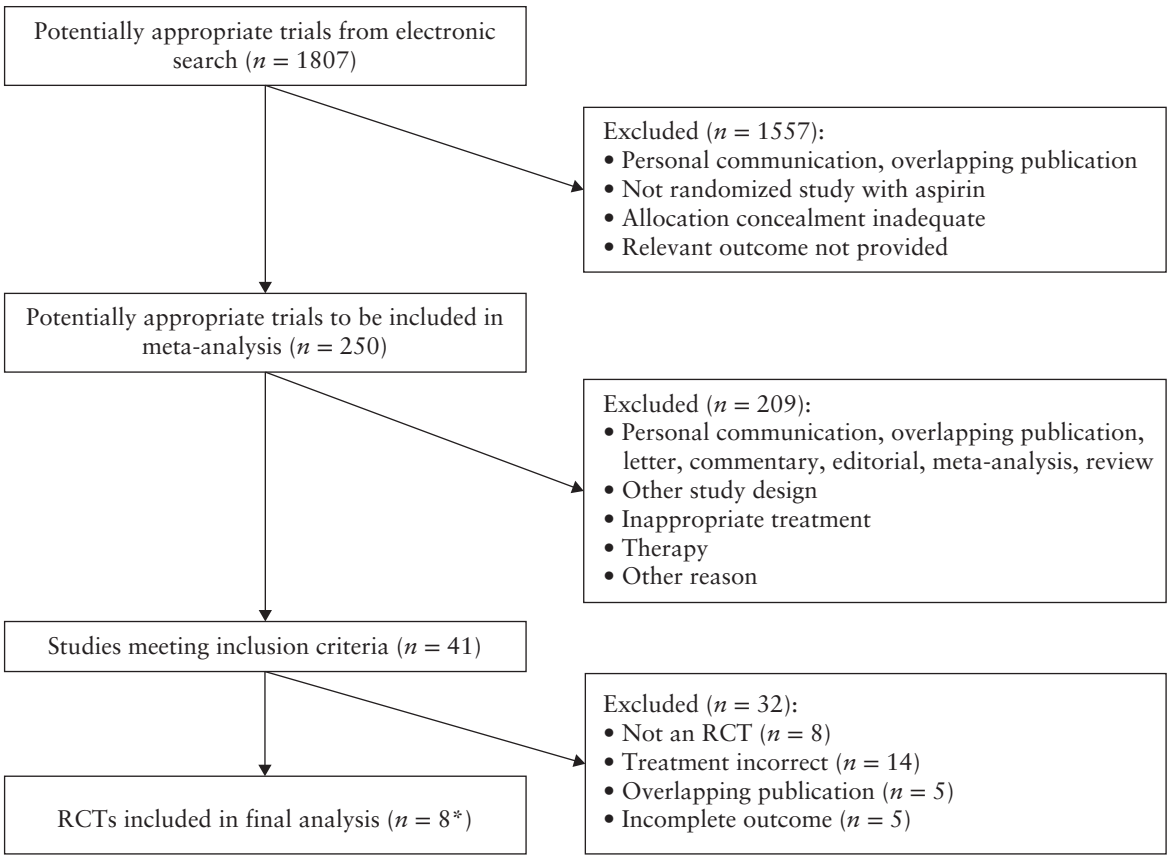

Figure 1 Flowchart summarizing study selection of randomized controlled trials (RCTs) comparing combination of low-molecular-weight heparin and aspirin with aspirin alone for prevention of pre-eclampsia. *One study reported in two publications.

Table 1 Characteristics of eight randomized controlled trials comparing the combination of low-molecular-weight heparin (LMWH) and low-dose aspirin with aspirin alone for prevention of pre-eclampsia (PE) in high-risk women, which were included in the meta-analysis

				Intervention		
Reference	n	*GA at recruitment*	*Inclusion criteria*	*Heparin*	*Aspirin (mg)*	*Outcome*
Farquharson (2002)[24]	98	<12 weeks	History of ≥ two consecutive miscarriages and thrombophilia, positive for lupus anticoagulant and/or anticardiolipin immunoglobulin	Unspecified LMWH, 5000 IU	75	Perinatal death
Ferrier (2000)[17]	16	10–12 weeks	History of severe PE, renal disease or chronic hypertension	Dalteparin, 5000 IU	100	PE, severe PE, early/late PE, perinatal death
de Vries (2012)[19,20]	139	< 12 weeks	History of early-onset PE and thrombophilia	Dalteparin, 2500–7500 IU	75–100	PE, SGA, early/late PE
Goel (2006)[25]	72	< 10 weeks	History of ≥ two miscarriages and anticardiolipin antibodies	Unfractionated heparin, 5000 IU	80	PE, early/late PE, perinatal death
Gris (2011)[22]	224	< 12 weeks	History of severe PE	Enoxaparin, 4000 IU	100*	PE, severe PE, SGA, perinatal death
Laskin (2009)[18]	88	First trimester	History of ≥ two consecutive miscarriages and thrombophilia	Dalteparin, 5000 IU	81	SGA, perinatal death
Malinowski (2003)[23]	109	Day 16 of menstrual cycle	History of ≥ three consecutive miscarriages and thrombophilia	Unspecified LMWH, 20 mg	75	SGA
Visser (2011)[21]	139	< 7 weeks	History of ≥ three consecutive miscarriages without thrombophilia	Enoxaparin, 40 mg	100	PE, SGA

Only the first author of each study is given. *Taken at bedtime. GA, gestational age; SGA, small-for-gestational age.

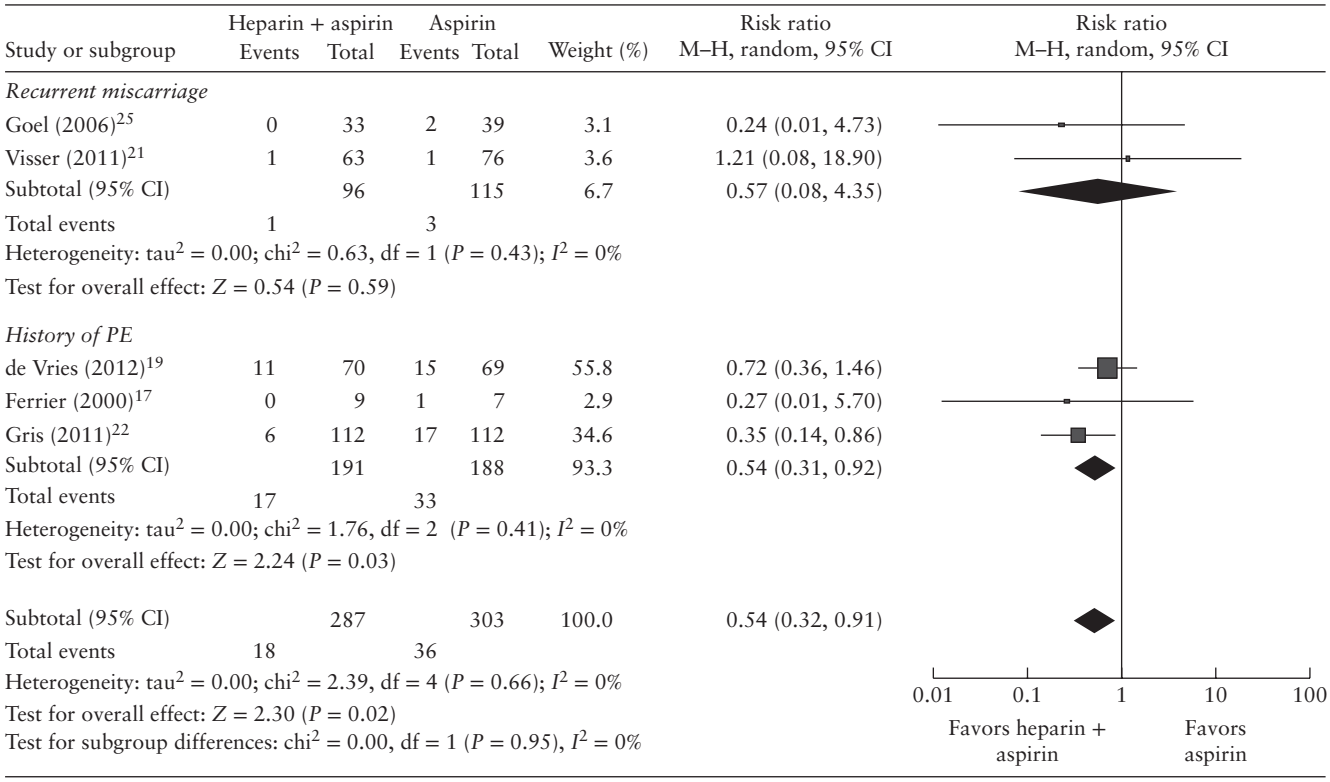

Figure 2 Forest plots of risk of pre-eclampsia (PE) in women with recurrent miscarriage and those with history of PE when randomized to receive low-molecular-weight heparin and low-dose aspirin or aspirin alone. M–H, Mantel–Haentszel. Studies are stratified according to inclusion criteria. Only the first author of each study is given.

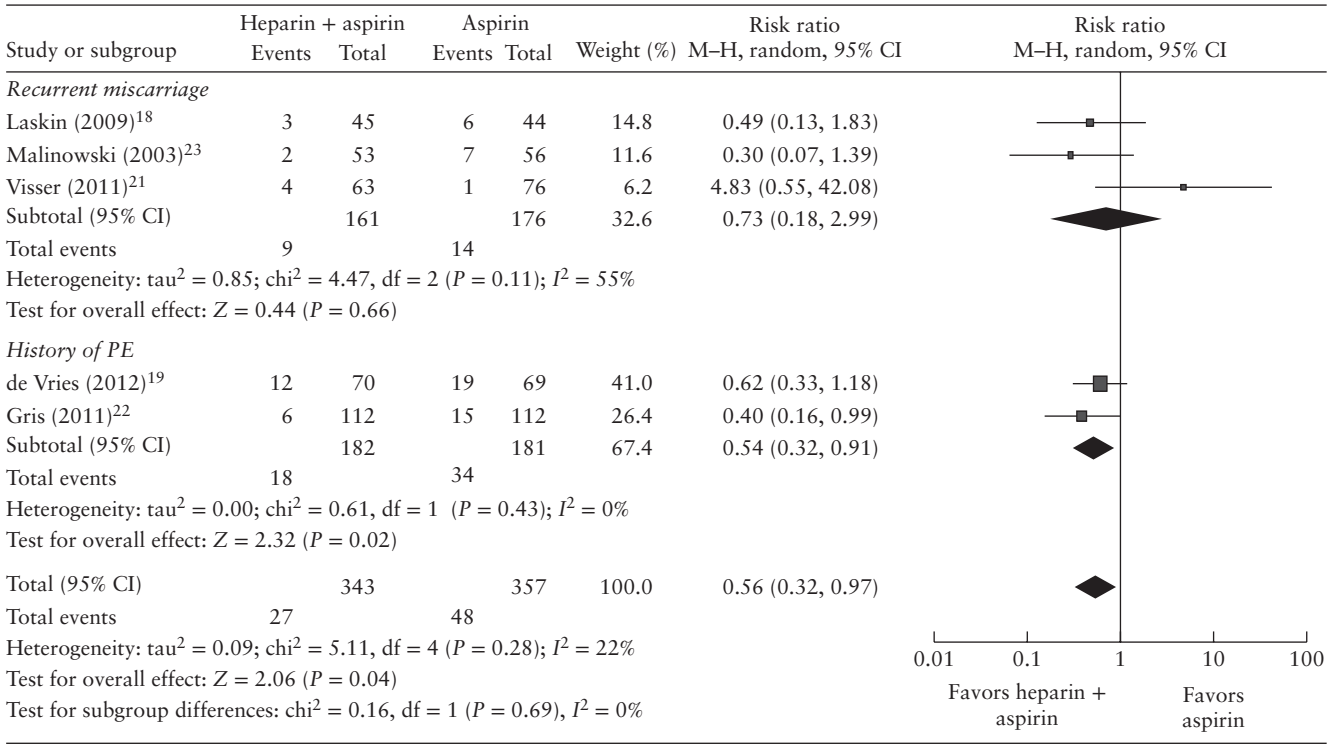

Figure 3 Forest plots of risk of small-for-gestational-age neonate in women with recurrent miscarriage and those with history of pre-eclampsia (PE) when randomized to receive low-molecular weight heparin and low-dose aspirin or aspirin alone. M–H, Mantel–Haentszel. Studies are stratified according to inclusion criteria. Only the first author of each study is given.

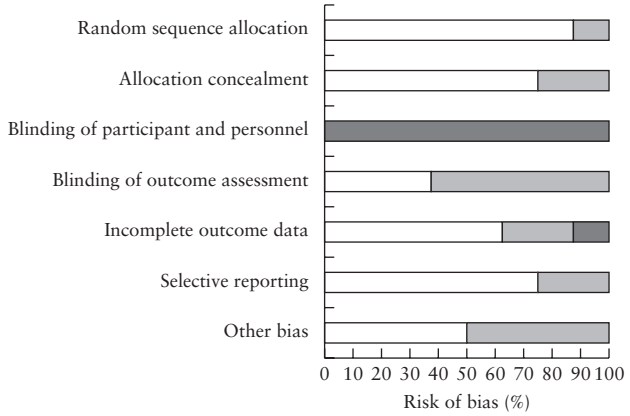

Figure 4 Risk of bias following The Cochrane Handbook[10] across studies included in the meta-analysis. □, Low; ▒, unclear; ■, high.

DISCUSSION

Main findings

The findings of this systematic review and meta-analysis suggest that, in women who developed PE in a previous pregnancy, the combination of LMWH and low-dose aspirin started in early pregnancy is superior to low-dose aspirin alone for the prevention of early-onset PE and the delivery of a SGA neonate. In women with recurrent miscarriage, there appeared to be no benefit, in terms of occurrence of PE or SGA, of adding LMWH compared with treatment by aspirin alone.

Comparison of results with those of previous studies

A trial including 135 participants that evaluated LMWH without low-dose aspirin *vs* no treatment did not find a significant reduction in adverse perinatal outcome (risk difference, 2.2 (95% CI, −11.6 to 16.0); $P = 0.76$)[26]. Similarly, as mentioned earlier, the TIPPS trial including 292 participants showed that LMWH without aspirin had no effect on adverse outcome, whereas LMWH with aspirin was associated with a non-significant reduction in adverse outcomes[8]. However, in a trial by Rey *et al.*[27] evaluating LMWH *vs* no treatment in 116 participants, but in which about 90% of women randomized to LMWH also received low-dose aspirin, a significant reduction in PE (odds ratio (OR), 0.15 (95% CI, 0.03–0.70)) and severe PE (OR, 0.11 (95% CI, 0.01–0.90)) was reported. Mello *et al.*[28] reported a beneficial effect of LMWH in reducing severe PE (RR, 0.25 (95% CI, 0.08–0.86)) in a trial including 85 participants, but it was not specified whether or not the participants were taking aspirin. Finally, Schleussner *et al.*[29] did not observe a reduction in intrauterine growth restriction, placental insufficiency or PE with administration of LMWH alone, started between 5 and 8 weeks' gestation, in a trial of 449 women with recurrent miscarriage.

On the basis of the results of the above trials and our meta-analysis, it could be suggested that, in high-risk pregnancies, the prophylactic use of LMWH is beneficial in reducing adverse pregnancy outcome only when there is concomitant therapy with low-dose aspirin.

Limitations of the study

The main limitation to our analysis relates to the small number of studies and patients fulfilling the inclusion criteria. Consequently, the possibility of bias in results could not be assessed by funnel plot and sensitivity analysis, and therefore we cannot exclude the possibility of publication bias. Other limitations include heterogeneity in inclusion criteria, dose of aspirin and outcome measures. Half (4/8) of the studies included women with thrombophilia. Finally, our study did not allow for evaluation of the cost benefits or side effects of LMWH, or its impact on perinatal mortality and long-term maternal or infant outcomes.

Implications for practice and future research

There is good evidence that, in women with a history of previous PE, the prophylactic use of low-dose aspirin starting ≤ 16 weeks' gestation can substantially reduce the rate of preterm PE, SGA and perinatal death[9]. There is some evidence that, to maximize the beneficial effect of aspirin, it would be preferable to use 100–160 mg rather than 75–81 mg, and that the drug should be administered at bed time[30–32]. The limited evidence presented in this study that the use of LMWH may have a beneficial effect in addition to that of low-dose aspirin should be the basis of a well-conducted future trial rather than a recommendation for immediate clinical application.

We observed that the benefits of adding LMWH to aspirin are potentially limited to the reduction of early-onset PE and SGA, two disorders typically related to impaired placentation, in comparison with late-onset PE that does not have the same etiology[33]. Any strategy aiming at the prevention of early-onset PE, a disease affecting only a very small number of pregnant women, should rely on an effective method of screening that would identify the high-risk group in the first trimester of pregnancy. A large population-based study has reported that only about 15% of pregnancies that develop preterm PE have a history of previous PE[34]. Moreover, the prevalence of early-onset PE has been reported to be as low as 2% in women with previous history of PE but increasing to 14% when such history was combined with an abnormal first-trimester uterine artery Doppler assessment[35]. Therefore, future trials evaluating the impact of LMWH should focus on women at high risk of early-onset placenta-mediated complications of pregnancy based on such previous history or using a combined screening with adequate positive predictive values. It has been reported that a combination of maternal characteristics and medical history, uterine artery Doppler, mean arterial pressure and serum placental growth factor at 11–13 weeks' gestation can identify more than 90% of cases of early-onset PE[36]. Larger clinical trials, including women at risk of PE, should consider combining LMWH with aspirin for its prevention.

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REFERENCES

1. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet* 2010; **376**: 631–644.
2. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. *Am J Obstet Gynecol* 2011; **204**: 193–201.
3. Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux X, Forest JC, Giguère Y. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010; **116** (2 Pt 1): 402–414.
4. Roberge S, Giguere Y, Villa P, Nicolaides K, Vainio M, Forest JC, von Dadelszen P, Vaiman D, Tapp S, Bujold E. Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: a systematic review and meta-analysis. *Am J Perinatol* 2012; **29**: 551–556.
5. Roberge S, Villa P, Nicolaides K, Giguère Y, Vainio M, Bakthi A, Ebrashy A, Bujold E. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis. *Fetal Diagn Ther* 2012; **31**: 141–146.
6. Mastrolia SA, Mazor M, Holcberg G, Leron E, Beharier O, Loverro G, Erez O. The physiologic anticoagulant and anti-inflammatory role of heparins and their utility in the prevention of pregnancy complications. *Thromb Haemost* 2015; **113**: 1236–1246.
7. Dodd JM, McLeod A, Windrim RC, Kingdom J. Antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction. *Cochrane Database Syst Rev* 2013; **7**: CD006780.
8. Rodger MA, Hague WM, Kingdom J, Kahn SR, Karovitch A, Sermer M, Clement AM, Coat S, Chan WS, Said J, Rey E, Robinson S, Khurana R, Demers C, Kovacs MJ, Solymoss S, Hinshaw K, Dwyer J, Smith G, McDonald S, Newstead-Angel J, McLeod A, Khandelwald M, Silver RM, Le Gal G, Greer IA, Keely E, Rosene-Montella K, Walker M, Wells PS, TIPPS Investigators. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): A multinational open-label randomised trial. *The Lancet* 2014; **384**: 1673–1683.
9. Roberge S, Nicolaides KH, Demers S, Villa P, Bujold E. Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis. *Ultrasound Obstet Gynecol* 2013; **41**: 491–499.
10. Cochrane Handbook for Systematic Reviews of Interventions. In *The Cochrane Collaboration*, Higgins J, Green S (eds). 2011. www.cochrane-handbook.org
11. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PG, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009; **6**: e1000100.
12. *Diagnosis and Management of Preeclampsia and Eclampsia*. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin #33, January 2002 and Working Group Report on High Blood Pressure in Pregnancy. National Instititutes of Health: Washington, 2000.
13. Magee LA, Helewa M, Moutquin JM, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *J Obstet Gynaecol Can* 2008; **30**: S1–48.
14. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
15. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods* 2006; **11**: 193–206.
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–634.
17. Ferrier C, Koferl U, Durig P, Schneider H. LMW-heparin and low-dose aspirin for prevention of preeclampsia: preliminary data of a randomized prospective study [abstract]. *Hypertens Pregnancy* 2000: 82. http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/939/CN-00323939/frame.html
18. Laskin CA, Spitzer KA, Clark CA, Crowther MR, Ginsberg JS, Hawker JA, Kingdom JC, Barrett JA, Gent M. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA trial. *J Rheumatol* 2009; **36**: 279–287.
19. de Vries JI, van Pampus MG, Hague WM, Bezemer PD, Joosten JH. Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT. *J Thromb Haemost* 2012; **10**: 64–72.
20. de Vries JI, van Pampus MG, Hague WM, Bezemer PD, Joosten JH, FRUIT Investigators. Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT (vol 10, pg 64, 2012) Erratum in. *J Thromb Haemost* Feb 2015; **13**: 327.
21. Visser J, Ulander VM, Helmerhorst FM, Lampinen K, Morin-Papunen L, Bloemenkamp KW, Kaaja RJ. Thromboprophylaxis for recurrent miscarriage in women with or without thrombophilia. HABENOX: a randomised multicentre trial. *Thromb Haemost* 2011; **105**: 295–301.
22. Gris JC, Chauleur C, Molinari N, Marès P, Fabbro-Peray P, Quéré I, Lefrant JY, Dauzat M. Addition of enoxaparin to aspirin for the secondary prevention of placental vascular complications in women with severe pre-eclampsia. The pilot randomised controlled NOH-PE trial. *Thromb Haemost* 2011; **106**: 1053–1061.
23. Malinowski A, Dynski MA, Maciolek-Blewniewska G, Glowacka E, Pawlowski T, Babula G. [Treatment outcome in women suffering from recurrent miscarriages and antiphospholipid syndrome.] *Ginekol Pol* 2003; **74**: 1213–1222.
24. Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: A randomized, controlled trial of treatment. *Obstet Gynecol* 2002; **100**: 408–413.
25. Goel N, Tuli A, Choudhry R. The role of aspirin versus aspirin and heparin in cases of recurrent abortions with raised anticardiolipin antibodies. *Med Sci Monitor* 2006; **12**: CR132–CR136.
26. Martinelli I, Ruggenenti P, Cetin I, Pardi G, Perna A, Vergani P, Acaia B, Facchinetti F, La Sala GB, Bozzo M, Rampello S, Marozio L, Diadei O, Gherardi G, Carminati S, Remuzzi G, Mannuzzi PM, HAPPY Study Group. Heparin in pregnant women with previous placenta-mediated pregnancy complications: a prospective, randomized, multicenter, controlled clinical trial. *Blood* 2012; **119**: 3269–3275.
27. Rey E, Garneau P, David M, Gauthier R, Leduc L, Michon N, Morin F, Demers C, Kahn SR, Magee L, Rodger M. Dalteparin for the prevention of recurrence of placental-mediated complications of pregnancy in women without thrombophilia: a pilot randomized controlled trial. *J Thromb Haemost* 2009; **7**: 58–64.
28. Mello G, Parretti E, Fatini C, Riviello C, Gensini F, Abbate R. Low-molecular-weight heparin lowers the recurrence rate of preeclampsia and restores the physiological vascular changes in angiotensin-converting enzyme DD women. *Hypertension* 2005; **45**: 86–91.
29. Schleussner E, Kamin G, Seliger G, Rogenhofer N, Ebner S, Toth B, Schenk M, Henes M, Bohlmann MK, Fischer T, Brosteanu O, Bauersachs R, Petroff D, ETHIG II group. Low-molecular-weight heparin for women with unexplained recurrent pregnancy loss: a multicenter trial with a minimization randomization scheme. *Ann Intern Med* 2015; **162**: 601–609.
30. Caron N, Rivard GE, Michon N, Morin F, Pilon D, Moutquin J, Rey E. Low-dose ASA response using the PFA-100 in women with high-risk pregnancy. *J Obstet Gynaecol Can* 2009; **31**: 1022–1027.
31. Ayala DE, Ucieda R, Hermida RC. Chronotherapy with low-dose aspirin for prevention of complications in pregnancy. *Chronobiol Int* 2013; **30**: 260–279.
32. Rey E, Rivard GE. Is testing for aspirin response worthwhile in high-risk pregnancy? *Eur J Obstet Gynecol Reprod Biol* 2011; **157**: 38–42.
33. Ogge G, Chaiworapongsa T, Romero R, Hussein Y, Kusanovic JP, Yeo L, Kim CJ, Hassan SS. Placental lesions associated with maternal underperfusion are more frequent in early-onset than in late-onset preeclampsia. *J Perinat Med* 2011; **39**: 641–652.
34. Wright D, Syngelaki A, Akolekar R, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *Am J Obstet Gynecol* 2015; **213**: 62.e1–10.
35. Demers S, Bujold E, Arenas E, Castro A, Nicolaides KH. Prediction of recurrent preeclampsia using first-trimester uterine artery Doppler. *Am J Perinatol* 2014; **31**: 99–104.
36. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther* 2013; **33**: 8–15.

