European Journal of Obstetrics & Gynecology and Reproductive Biology 197 (2016) 168–173

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Low-molecular-weight heparin and aspirin in the prevention of recurrent early-onset pre-eclampsia in women with antiphospholipid antibodies: the FRUIT-RCT

Marion E. van Hoorn [a,*], William M. Hague [b], Mariëlle G. van Pampus [c], Dick Bezemer [d], Johanna I.P. de Vries [a] for the FRUIT investigators

[a] Department of Obstetrics and Gynecology, VU University Medical Center, Amsterdam, The Netherlands
[b] Robinson Research Institute, University of Adelaide, Women's and Children's Hospital, Adelaide, Australia
[c] Department of Obstetrics and Gynecology, University Medical Center, Groningen, The Netherlands
[d] Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 2 July 2015
Received in revised form 26 November 2015
Accepted 10 December 2015

Keywords:
Antiphospholipid antibodies
Aspirin
Low-molecular-weight heparin
Pre-eclampsia
Randomised controlled trial

ABSTRACT

Objective: To examine whether combined treatment with low-molecular-weight heparin (LMWH) and aspirin reduces recurrent hypertensive disorders of pregnancy (HD: pre-eclampsia, eclampsia or HELLP syndrome) in women with antiphospholipid antibodies (aPLA) and a previous delivery for HD and/or small-for-gestational-age (SGA) birthweight before 34 weeks gestation.

Study design: This multicentre randomised controlled trial was performed between December 2000 and December 2009. Women were recruited from all eight university and six non-university/teaching hospitals in The Netherlands, two university hospitals in Australia and one university hospital in Sweden. Thirty two women with a previous delivery <34 weeks gestation with HD and/or SGA and aPLA were included before 12 weeks gestation. The intervention was daily LMWH with aspirin or aspirin alone. Primary outcomes: recurrent HD onset <34 weeks and recurrent HD irrespective of gestational age. Analysis by intention-to-treat.

Results: After an interim analysis, recruitment was ceased: accrual was low and the incidence of recurrent HD was far lower (3%) than expected (60%). The final analysis, performed on 32 women, shows no difference in the primary outcomes (LMWH and aspirin 0/16 versus aspirin only 1/16, risk difference 6.25% [CI −17 to 27%] for recurrent HD onset <34 weeks and 0/16 for LMWH and aspirin versus 2/16 for aspirin only, risk difference 12.5% [CI −15 to 35%] for HD irrespective of gestational age).

Conclusion: In this population of women with aPLA, who had previously had an early delivery for HD and/or SGA prior to 34 weeks gestation, combined LMWH and aspirin treatment started before 12 weeks gestation in a subsequent pregnancy did not show reduction of onset of recurrent HD either <34 weeks gestation or irrespective of gestational age, compared with aspirin alone.

Introduction

Antiphospholipid antibody syndrome (APS) is characterised as vascular thrombosis or obstetric complications associated with the presence of persistent moderate to high titres of antiphospholipid antibodies (aPLA). Such obstetric complications include a history of three unexplained consecutive miscarriages ≤10 weeks gestation, one unexplained foetal death ≥10 weeks gestation or a history of preterm delivery ≤34 weeks gestation associated with pre-eclampsia or uteroplacental insufficiency [1–3]. Women with aPLA and recurrent pregnancy loss (first and second trimester) have a better pregnancy outcome when treated with a combination of aspirin and unfractionated heparin (UH) than when treated with aspirin alone (OR 3.37 [CI: 1.40–8.10]) [4]. However, studies of such women treated with aspirin combined with low-molecular-weight heparin (LMWH) have shown no benefit from the treatment (OR 2.00 [CI: 0.56–7.14] [5] and 79.1% versus 77.8% live birth in the HepASA trial (OR 1.13 [CI:0.26–5.00]) [6]. Women with APS are at increased risk for hypertensive disorders of pregnancy (HD) [7–9]. One quasi-randomised trial did not show

* Corresponding author at: Department of Obstetrics and Gynecology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands. Tel.: +31 20 4442585; fax: +31 20 4441485.
E-mail address: m.vanhoorn@vumc.nl (M.E. van Hoorn).

http://dx.doi.org/10.1016/j.ejogrb.2015.12.011
0301-2115/

benefit of combined aspirin and UH in relation to HD [10]. There are, however, no randomised data in relation to HD in respect of treatment with LMWH combined with aspirin in pregnant women with APS. Despite this, since the publication of Rai et al. [4], LMWH has been prescribed frequently to women with aPLA and various complications in pregnancy.

A multicentre randomised controlled trial was therefore designed to test the hypothesis that LMWH added to aspirin would prevent recurrent early-onset pre-eclampsia in women with thrombophilia more than aspirin alone (ISRCTN 87325378). Within this overall aim, it was planned from the outset to study both women with an inheritable thrombophilia, as well as women with acquired thrombophilia, including those with aPLA. Those eligible for the study were women with a viable pregnancy between 8 and 12 weeks gestation who had had a prior pregnancy complicated by HD and/or small-for-gestational-age (SGA) before 34 weeks gestation, and with a confirmed thrombophilia. It was recognised that some women would have both inheritable and acquired thrombophilic factors, and it was planned ab initio that such women would be studied in the acquired group. The intervention in both groups was the administration from before 12 weeks gestation of either weight-adjusted dalteparin with aspirin or aspirin alone. The choice to perform the study in two separate stratified groups was necessary because of the expected difference in recurrence rate of uteroplacental insufficiency (35% in the inheritable group and 60% in the acquired group). Recruitment to the purely inheritable group within this trial was completed in 2010 and the data were analysed and published in 2012 while the study of the acquired group was still ongoing. In the inheritable group, combination treatment reduced the recurrence of HD before 34 weeks gestation (RD 8.7% [CI: 1.9–15.5%]), NNT 12 [11].

We now present the second group of the FRUIT-RCT, in which women were included with the same pregnancy history, but who had aPLA (with or without an inheritable thrombophilia). As before, the hypothesis was that the combination of weight-adjusted dalteparin and aspirin started before 12 weeks gestation reduces recurrent HD in women with an *acquired* thrombophilia, who had had a previous pregnancy complicated by HD and/or SGA at <34 weeks gestation more than aspirin alone.

Materials and methods

Women were eligible for inclusion, who met the criteria described in Table 1. The presence of HD and/or SGA (birthweight <10th centile) [12] and delivery before 34 weeks gestation in a prior pregnancy was verified by chart review and the presence of aPLA (anticardiolipin antibodies ≥10 GPL and/or ≥10 MPL and/or a lupus anticoagulant on at least two occasions 6 or more weeks apart) following the previous pregnancy was established. Anticardiolipin antibodies were assessed by an ELISA with bovine cardiolipin and calf serum as antigen. The ELISA was calibrated according to Harris et al., 1990 in GPL and MPL and performed in a certified diagnostic laboratory (based on EN/ISO 15189) [13]. Women, who in addition might have other inheritable thrombophilic factors, were included in this acquired thrombophilia group of the FRUIT-RCT. All aPLA tests and all functional thrombophilia tests were carried out while women were not using oral contraceptives, and were at least 10 weeks postpartum.

Between December 2000 and December 2009, women were recruited from all eight university hospitals and six non-university/teaching hospitals in The Netherlands, two university hospitals in Australia and one university hospital in Sweden. Full

Table 1
Inclusion and exclusion criteria, and definitions.

Inclusion criteria	Definition
Pregnancy <12 weeks gestation	
Maternal age ≥18 years	
History of uteroplacental insufficiency and delivery before 34 weeks gestation	
1. Hypertensive disorders of pregnancy (HD)	
1A. Pre-eclampsia	Pregnancy-induced hypertension (diastolic blood pressure of ≥90 mm Hg and ≥20 mm Hg increment as compared with first trimester diastolic blood pressure), together with proteinuria (≥300 mg/24 h urine; or spot urine protein/creatinine ≥30 mg/mmol) after 20 weeks gestation.
1B. Eclampsia	Generalised convulsions in pregnancy, not caused by epilepsy.
1C. HELLP syndrome	The presence of (1) haemolysis, defined by increased LDH (≥600 IU/L), (2) elevated liver enzymes, defined as increased SGOT/ALT (≥70 IU/L), (3) thrombocytopenia (defined as platelet count $<100 \times 10^9\,L^{-1}$).
2. Small-for-gestational age (SGA) infant	Birthweight <10th percentile (12).
Antiphospholipid antibodies	
Anticardiolipin antibodies present	≥10 GPL and/or MPL on at least two occasions. Stratified as: 10–14 GPL and/or MPL 15–19 GPL and/or MPL ≥20 GPL and/or MPL One MPL or GPL is equivalent to 1 μg of affinity-purified ACA, where either IgM or IgG assay is positive.
AND/OR	
Lupus anticoagulant present	Prolongation of the partial thromboplastin time and/or an activated partial-thromboplastin time test in a mixture of 1:1 patient and pooled normal plasma is abnormal on at least two occasions. For confirmation, the thromboplastin dilution test using Thromborel S reagent and the platelet neutralisation procedure was used.
Exclusion criteria: 1 or more of	
Antithrombin deficiency, homozygosity for Factor V Leiden and Prothrombin G20210A mutations, diabetes mellitus, known malignancy, known peptic ulceration, severe renal or hepatic insufficiency, history of venous thrombo-embolism, haemorrhagic diathesis, idiopathic thrombocytopenia, earlier participation in the FRUIT trial, LMWH use in earlier pregnancy.	
Hyperhomocysteinaemia, tested for by a methionine loading test (fasting homocysteine ≥15 μmol/L, post load ≥51 μmol/L) was not an exclusion criteria: such women were treated with folic acid and vitamin B6 supplementation.	