

# Recurrence rate of pre-eclampsia in women with thrombophilia influenced by low-molecular-weight heparin treatment?

J.J. Kalk<sup>1\*</sup>, A.J.M. Huisjes<sup>2</sup>, C.J.M. de Groot<sup>3</sup>, E. van Beek<sup>4</sup>, M.G. van Pampus<sup>5</sup>, M.E.A. Spaanderman<sup>6</sup>, J. van Eyck<sup>7</sup>, S.G. Oei<sup>8</sup>, P.D. Bezemer<sup>9</sup>, J.I.P. de Vries<sup>1</sup>

Department of Obstetrics and Gynaecology, <sup>1</sup>VU University Medical Centre, PO Box 7057, 1007 MB Amsterdam, tel.: +31 (0)20-444 30 41, fax: +31 (0)20-444 29 54, e-mail JJ.Kalk@VUmc.nl, <sup>2</sup>University Medical Centre Utrecht, <sup>3</sup>Leiden University Medical Centre, <sup>4</sup>University Medical Centre St Radboud, Nijmegen. <sup>5</sup>Academic Medical Centre, Amsterdam, <sup>6</sup>University Hospital Maastricht, <sup>7</sup>Isala Hospital, location Sophia, Zwolle, <sup>8</sup>St. Joseph Hospital, Veldhoven, <sup>9</sup>Department of Clinical Epidemiology and Biostatistics, Free University, Amsterdam, \* corresponding author

## ABSTRACT

**Objectives:** (1) To assess the recurrence rate of pre-eclampsia in women with this history before 34 weeks of pregnancy and thrombophilia. (2) To evaluate the effects of low-molecular-weight heparin (LMWH) on pregnancy outcome.

**Methods:** In a multicentre retrospective study subsequent pregnancies of women with a history of pre-eclampsia necessitating birth before 34 weeks and thrombophilia were analysed. Of 58 women, 26 received LMWH and aspirin (ASA) and 32 ASA (22) or no (10) medication in their subsequent pregnancies.

**Results:** In eight women treated with LMWH and ASA and in 16 women receiving ASA or no medication pre-eclampsia recurred in the subsequent pregnancy. (OR 0.55, 95% CI 0.15-1.31) There were no significant differences in birth weight or gestational age between both groups.

**Conclusions:** The recurrence rate of pre-eclampsia in women with thrombophilic disorders is high in this small retrospective study. No positive effect was found for LMWH treatment. A multicentred randomised study has been started to reach an adequate number of patients to evaluate the influence of LMWH treatment.

## INTRODUCTION

Pre-eclampsia is a major problem in perinatal medicine especially in early onset pre-eclampsia before 34 weeks gestation. The exact cause of pre-eclampsia is unknown and a multifactorial origin is suggested. Maladaptation of the maternal immune system to the foetal allograft as well as genetic factors are probably involved in its aetiology.<sup>1</sup> More recently, several investigators confirmed the presence of thrombophilic disorders (hereditary coagulation abnormalities, anticardiolipin antibodies, hyperhomocysteinaemia) in a substantial percentage (up to 60%) of women with a history of severe early onset pre-eclampsia and small-for-gestational-age (SGA) infants.<sup>2-4</sup>

The recurrence rate of pre-eclampsia in women with this history necessitating delivery before 34 weeks and documented thrombophilia without treatment with low-molecular-weight heparin is still unknown. Riyazi *et al.* tested a total of 276 patients with a history of pre-eclampsia and/or foetal growth restriction for the presence of hereditary coagulation abnormalities and anticardiolipin antibodies. Ninety patients with pre-eclampsia and 15 patients with isolated foetal growth restriction had haemostatic abnormalities. In 26 patients a subsequent pregnancy occurred and they were treated with low-molecular-weight heparin (started directly after confirmation of a viable intrauterine pregnancy) and low-dose aspirin (started at 10 to 12 weeks gestational age). Pre-eclampsia recurred in 38%, and intrauterine growth restriction in 15% of pregnancies.<sup>5</sup>

The recurrence rate in this population with known thrombophilia is lower than two studies reporting the recurrence rate of severe pre-eclampsia or HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome in a population with unknown thrombophilic status. Sibai *et al.*<sup>6</sup> described a group of 125 women with a history of severe pre-eclampsia in the second trimester (range 18 to 27 weeks gestation), of which 108 women had 169 subsequent pregnancies (range 1 to 4 per woman): 59 (35%) had a normotensive pregnancy and 110 (65%) developed pre-eclampsia. Sullivan *et al.*<sup>7</sup> studied 481 patients with a history of HELLP syndrome. Subsequent gestations (n=195) occurred in 122 of 481 patients. Available data on 161 pregnancies showed a recurrence rate of 43%.

There is still no treatment to reduce the recurrence of pre-eclampsia in women with thrombophilia. Rai *et al.*<sup>8</sup> did perform a randomised study on women with pregnancies complicated by intrauterine foetal death before 28 weeks associated with anticardiolipin antibodies and unknown hereditary coagulation status. Women treated with unfractionated heparin with aspirin had better pregnancy outcome compared with women treated with aspirin only. However, in his study the entry criterion was recurrent foetal death associated with anticardiolipin antibodies and primary endpoint in this population was number of live births. Recently Kupferminc *et al.*<sup>9</sup> published the results of an uncontrolled study of 33 women with an earlier pregnancy complicated by severe pre-eclampsia, abruptio placentae, intrauterine growth retardation or intrauterine foetal death. These women received LMWH in their subsequent pregnancies and only 9.1% of the women developed pregnancy complications.

The study presented here concerned a retrospective study of subsequent pregnancies of women with a history of pre-eclampsia necessitating birth before 34 weeks. The aims of this study were to evaluate the recurrence rate of pre-eclampsia in women with thrombophilia and to test the hypothesis if LMWH is beneficial in reducing the recurrence of pre-eclampsia. The different treatments consisted of low-molecular-weight heparin (LMWH) in combination with aspirin or aspirin only or no medication. This retrospective study was performed in advance of a prospective randomised study to evaluate whether a study for the effects of LMWH treatment in women with thrombophilia would be beneficial.

## MATERIALS AND METHODS

In a retrospective study subsequent pregnancies of women with a history of pre-eclampsia necessitating birth

before 34 weeks were analysed. Inclusion criteria were women with an index pregnancy of pre-eclampsia leading to birth before 34 weeks gestation and thrombophilia. Between the period 1991 and 1998, 1146 women were tested for thrombophilic disorders in eight Dutch hospitals (*table 1*). The hereditary coagulation abnormalities included were antithrombin deficiency, protein C deficiency, activated protein C resistance with and without factor V Leiden mutation, protein S deficiency and factor II mutation.

**Table 1**

*Results in 1146 women with a history of pre-eclampsia necessitating delivery before 34 weeks in the period between 1991 and 1998 in eight Dutch hospitals (some women had more than one thrombophilic disorder)*

	TESTED	ABNORMAL	
	n	n	%
Antithrombin deficiency	1146	6	0.5
Protein C deficiency	1146	13	1
Activated protein C resistance (APCr)	1146	66	5
APCr+ factor V Leiden mutation	1146	96	8
Protein S deficiency	1146	88	8
Factor II mutation	1033	5	0.4
Anticardiolipin antibodies	990	95	9
Hyperhomocysteinaemia	990	99	10

The acquired anticardiolipin antibodies were tested as well as hereditary/acquired hyperhomocysteinaemia. In this period not all hospitals tested for all thrombophilic disorders; one hospital did not test for factor II mutation (n=113) and two hospitals did not test for anticardiolipin antibodies and hyperhomocysteinaemia (n=156). In case of coagulation abnormalities and anticardiolipin antibodies five hospitals gave aspirin or no medication and three hospitals treated with LMWH and aspirin in the subsequent pregnancy. Hyperhomocysteinaemia was treated with vitamin B6 and folic acid supplementation throughout gestation in all hospitals. For each patient, the medical records were checked to establish which treatment was applied in the subsequent pregnancy. Outcome measurement was recurrence rate of pre-eclampsia. Birth weight and gestational age in index and subsequent pregnancy were also compared between both groups.

Definitions of pre-eclampsia and eclampsia were used according to the standards of the International Society for the Study of Hypertension in Pregnancy (ISSHP).<sup>10</sup> Pre-eclampsia was defined as pregnancy-induced hypertension plus significant proteinuria after 20 weeks of

gestational age. Proteinuria was defined as excretion of 300 mg or more in 24 h or two readings of 2+ or higher on dipstick analysis of midstream or catheter urine specimens. HELLP syndrome was defined as the presence of (1) haemolysis, defined by increased LDH (>600 IU/l) and (2) elevated liver enzymes, defined as increased SGOT (>70 IU/l) and (3) thrombocytopenia (<100 x 10<sup>9</sup>/l). Eclampsia was defined as the occurrence of generalised convulsions during pregnancy, during labour, or within seven days of delivery and not caused by epilepsy or other convulsive disorders.

#### Laboratory tests

Normal values of each centre were tested, applying the International Thrombophilia External Quality Assessment within the European Concerted Action on Thrombosis (ECAT) Foundation. The measurement procedures were standardised for each laboratory. For details of hereditary coagulation abnormalities see *table 1*. All tests were performed at least ten weeks post partum, and women were not on oral contraceptives. Anticardiolipin antibodies, immunoglobulin (Ig)G and IgM, were determined by enzyme-linked immunosorbent assay according to the Harris directives (all centres).<sup>11</sup>

Hyperhomocysteinaemia was diagnosed using a methionine loading test: a blood sample for determination of the fasting homocysteine concentration is drawn at 8 a.m. after an overnight fast. Subsequently, an oral dose of L-methionine (0.1g/kg body weight) is administered in orange juice. The patients had a standardised low-methionine breakfast and lunch. Patients were considered hyperhomocysteinaemic when fasting normal values and/or postloading normal values exceeded the 97.5 percentile (all centres).<sup>12</sup>

#### Statistical analysis

Analysis was carried out with SPSS for Windows (version 8.0, SPSS Inc., Chicago II) and Excel for Windows (version 5.0c, Microsoft Corporation). Odds ratios with 95%

confidence intervals were calculated by logistic regression analysis. Statistical significance was defined as  $p < 0.05$ .

## RESULTS

In the total group of 1146 tested women, 407 women were found to have 468 thrombophilic disorders i.e. hereditary coagulation abnormalities (n=274) and/or anticardiolipin antibodies (n=95) and/or hyperhomocysteinemia (n=99) (*table 1*). In 48 women more than one thrombophilic disorder was found.

In this period 58 women had a subsequent pregnancy. Twenty-six patients who had a pregnancy after the index pregnancy received LMWH (nadroparin 2 dd 2850 IU anti-Xa sc a day) plus aspirin (80 mg) starting between six and 12 weeks gestational age, the other 32 patients received aspirin (n=22) or no medication (n=10). In the 26 patients who received LMWH in combination with aspirin, pre-eclampsia recurred in eight patients (30%). In the 32 patients who received aspirin or no medication, pre-eclampsia recurred in 16 patients (50%) (OR 0.55, 95% CI 0.15-1.31). The recurrence of pre-eclampsia *before* 34 weeks in the subsequent pregnancy was 2/26 (8%) *versus* 7/32 (22%) (OR 0.3, 95% CI 0.05-1.58) No difference was found in recurrence rate in women treated with aspirin (27%, 6/22) *versus* women without aspirin (40%, 4/10) (OR 0.56, 95% CI 0.11-2.72). In subsequent pregnancies the number of babies under the 10<sup>th</sup> percentile of birth weight was one of 26 in women receiving LMWH and ASA *versus* two of 12 in women receiving ASA alone and one of 10 women receiving no medication. The number of preterm deliveries before 34 weeks of gestational age was three of 26, three of 12 and two of 10, respectively.

In *table 2* the mean birth weights and mean gestational ages of the index pregnancies and subsequent pregnancies in the three groups are presented.

**Table 2**

*Index (i) and subsequent (s) outcome of pregnancies in women receiving low-molecular-weight heparin (LMWH) and aspirin versus women receiving aspirin only or no medication (data presented as mean with standard deviation)*

	LMWH + ASA N=26	ASA N=22	NO MEDICATION N=10
Mean birth weight (gram) (i)	1004 (±437)	886 (±554)	1272 (±437)
Mean birth weight (gram) (s)	2956 (±583)	2497 (±954)	2697 (±1415)
Mean gestational age (days) (i)	205 (±19)	198 (±24)	204 (±26)
Mean gestational age (days) (s)	264 (±13)	257 (±23)	260 (±38)

## DISCUSSION

This study demonstrated that women with a history of early onset pre-eclampsia in their index pregnancy do have a high recurrence rate in subsequent pregnancies. This was found for women receiving LMWH, aspirin or no medication. As far as percentages can be reliably presented for the small study population, the percentages found are comparable with the study by Riyazi *et al.*<sup>5</sup> She reported from one hospital the recurrence rate of early onset pre-eclampsia and SGA babies in women with thrombophilia receiving LMWH and aspirin. Our study showed a low recurrence rate of pre-eclampsia in comparison with the studies by Sibai *et al.*<sup>6</sup> and Sullivan *et al.*<sup>7</sup> of women with unknown thrombophilia. Our study did not demonstrate significant benefit from LMWH in the recurrence rate. The drawn conclusion should be seen within the context of the retrospective character of the study and the limited number of subsequent pregnancies in this population. The insignificance can be merely a power problem.

In our study we report on subsequent pregnancies in women checked in the hospital in which they had their index pregnancy and thrombophilia analysis. The low percentage of found subsequent pregnancies may in part be responsible for this procedure. For practical reasons we did not contact the 407 women with thrombophilic disorders personally. From the work by Van Pampus *et al.* who did consequently contact all the patients she included in her study, we know that she found that 66% of women with a history of HELLP syndrome had subsequent pregnancies.<sup>13</sup> Concerning the direction of a possible bias it is plausible that we did not miss the severe early onset pre-eclampsia. This is thanks to the Dutch healthcare organisation. Preterms (<32 weeks) deliver in hospitals with neonatal intensive care units and severe pre-eclamptic women are advised to be treated in tertiary centres. All Dutch hospitals with neonatal intensive care units and tertiary centres participated in this study with the exception of one, which was not systematically examining thrombophilic factors in these patients at that time.

The distribution of thrombophilic factors of this study is in accordance with other Dutch studies.<sup>14</sup> Various investigators have found that the distribution of thrombophilic factors varies per population.<sup>4,15</sup> Factor V Leiden mutation is common in Caucasian populations, but in African and Asian countries the frequency is lower.<sup>14</sup>

The occurrence of pre-eclampsia in women with thrombophilia can be explained by excessive microthrombic deposition within the maternal placental circulation.<sup>16</sup> Therefore, thromboprophylaxis seems to be a logical preventive therapy. Recently more studies have been

published of LMWH treatment in women with thrombophilia and recurrent foetal loss.<sup>17</sup> However, no large studies have been performed in women with a history of severe pregnancy complications such as pre-eclampsia. For years LMWH has been used as thromboprophylaxis during pregnancy.<sup>18</sup> LMWH does not cross the placental barrier.<sup>19</sup> In several studies the authors concluded that the use of LMWH appears to be relatively safe and well tolerated during pregnancy, delivery and the immediate postpartum period.<sup>19</sup> It has a longer half-life, better bioavailability and less effect on platelets than unfractionated heparin. Furthermore, it is considered to have a better thromboprophylactic effect and a lower risk on bleeding complications. As the long-term use of heparin is associated with the development of osteoporosis, bone density measurements performed by pregnant women treated with LMWH and untreated pregnant women showed similar bone density loss in both groups.<sup>20</sup> Furthermore, heparin-induced osteoporosis is reversible when heparin is stopped.

Despite the above-mentioned items as possible therapeutic effect and safety aspects for mother and foetus, the benefit of LMWH treatment still has to be demonstrated. For this reason an international multicentred trial has been started called FRactionated heparin in women with a history of Uteroplacental Insufficiency and Thrombophilia (FRUIT study) in which 13 Dutch centres and two Australian centres are participating. To enable an optimal inclusion of patients, all gynaecologists in the Netherlands receive information about the FRUIT study through newsletters and from the website of the Dutch Society of Obstetrics and Gynaecology.

## CONCLUSION

This study demonstrates a high recurrence rate of pre-eclampsia in women with such a history and documented thrombophilia and found no effect of LMWH on pregnancy outcome. These findings support the need for an adequately sized randomised study to evaluate the effects of treatment with LMWH.

## REFERENCES

1. Beek E van, Peeters LL. Pathogenesis of preeclampsia: a comprehensive model. *Obstet Gynecol Surv* 1998;53(4):233-9.
2. Dekker GA, Vries JIP de, Doelitzsch PM, et al. Underlying disorders associated with severe early-onset preeclampsia. *Am J Obstet Gynecol* 1995;173(4):1042-8.
3. Vries JIP de, Dekker GA, Huijgens PC, Jakobs C, Blomberg BM, Geijn HP van. Hyperhomocysteinaemia and protein S deficiency in complicated pregnancies. *Br J Obstet Gynaecol* 1997;104(11):1248-54.

4. Kupferminc M, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy [see comments]. *N Engl J Med* 1999;340(1):9-13.
5. Riyazi N, Leeda M, Vries JIP de, Huijgens PC, Geijn HP van, Dekker GA. Low-molecular-weight heparin combined with aspirin in pregnant women with thrombophilia and a history of preeclampsia or fetal growth restriction: a preliminary study. *Eur J Obstet Gynecol Reprod Biol* 1998;80(1):49-54.
6. Sibai BM, Mercer B, Sarinoglu C. Severe preeclampsia in the second trimester: recurrence risk and long-term prognosis. *Am J Obstet Gynecol* 1991;165(5 Pt 1):1408-12.
7. Sullivan CA, Magann EF, Perry KGJ, Roberts WE, Blake PG, Martin JN. The recurrence risk of the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) in subsequent gestations. *Am J Obstet Gynecol* 1994;171(4):940-3.
8. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies) [see comments]. *BMJ* 1997;314(7076):253-7.
9. Kupferminc M, Fait G, Many A, et al. Low-molecular-weight heparin for the prevention of obstetric complications in women with thrombophilias. *Hypertens Pregnancy* 2001;20:35-44.
10. Rai R, Shlebak A, Cohen H, et al. Factor V Leiden and acquired activated protein C resistance among 1000 women with recurrent miscarriage. *Hum Reprod* 2001;16(5):961-5.
11. Harris EN. Special report. The Second International Anti-cardiolipin Standardization Workshop/the Kingston Anti-Phospholipid Antibody Study (KAPS) group. *Am J Clin Pathol* 1990;94(4):476-84.
12. Steegers-Theunissen RP, Boers GH, Blom HJ, Trijbels FJ, Eskes TK. Hyperhomocysteinaemia and recurrent spontaneous abortion or abruptio placentae [letter]. *Lancet* 1992;339(8801):1122-3.
13. Pampus MG van, Wolf H, Mayruhu G, Treffers PE, Bleker O.P. Long-term follow-up in patients with a history of (H)ELLP syndrome. Hypertension in Pregnancy. In press.
14. Pampus MG van, Dekker GA, Wolf H, et al. High prevalence of hemostatic abnormalities in women with a history of severe preeclampsia. *Am J Obstet Gynecol* 1999;180(5):1146-50.
15. Groot CJM de, Bloemenkamp KW, Duvekot EJ, et al. Preeclampsia and genetic risk factors for thrombosis: a case-control study. *Am J Obstet Gynecol* 1999;181(4):975-80.
16. Dekker GA. Risk Factors For Preeclampsia; How Do They Link With Current Concepts on Its Etiology and Pathogenesis. *Lancet*. In press.
17. Younis JS, Ohel G, Brenner B, Haddad S, Lanir N, Ben-Ami M. The effect of thrombophylaxis on pregnancy outcome in patients with recurrent pregnancy loss associated with factor V Leiden mutation [In Process Citation]. *BJOG* 2000;107(3):415-9 [MEDLINE record in process].
18. Sanson BJ, Lensing AW, Prins MH, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review [In Process Citation]. *Thromb Haemost* 1999;81(5):668-72.
19. Melissari E, Parker CJ, Wilson NV, et al. Use of low molecular weight heparin in pregnancy. *Thromb Haemost* 1992;68(6):652-6.
20. Shefras J, Farquharson RG. Bone density studies in pregnant women receiving heparin. *Eur J Obstet Gynecol Reprod Biol* 1996;65(2):171-4.

