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COMMENTARY

Thrombophilia and pregnancy loss in first intended pregnancy

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Recurrent pregnancy loss is a common health problem affecting 1–5% of women at the reproductive age and bears significant emotional, social and economical impact [1]. A number of case–control and cohort studies have suggested an association between inherited thrombophilia and recurrent pregnancy loss while others refuted this occurrence [2–6]. Several recently reported meta-analysis support an association between maternal factor V Leiden (FV Leiden) and factor II G20210A genotypes and pregnancy loss [7–9].

These findings have lead to the introduction of thrombophilia workup in women at risk, particularly in those with recurrent or late pregnancy loss. Documentation of thrombophilic risk factors in women with pregnancy complications may have significant therapeutic implications as a number of clinical studies have demonstrated the potential efficacy of prophylaxis with low molecular weight heparin (LMWH) in these settings [10,11]. While interpretation of the results of these studies arose some debate [12–22], it is clear that the field of thrombophilia and pregnancy complications continues to be in the focus of medical research and clinical practice.

Studies on the association of thrombophilia and gestational complications in populations of pregnant women have revealed conflicting results [6,23] partly explained by variance in incidence of thrombophilic polymorphisms in different ethnic backgrounds and studies not powered for evaluation of the potential associations.

Differences in type of pregnancy loss i.e. primary or secondary, isolated or recurrent, consecutive or non-consecutive and timing of its occurrence i.e. first, second or third trimester may also influence the magnitude of these associations [24–26].

In this issue of the *Journal of Thrombosis and Haemostasis* Lissalde-Lavigne *et al*. [27] report findings from the 'NOHA first' study, a large carefully designed case–control study nested in a cohort of nearly 32 700 women of who 18% had pregnancy loss with first gestation. After analyzing the characteristics of 3496 pairs of women with an unexplained pregnancy loss and normal pregnancy controls, the authors describe the incidence of FV Leiden and factor II G20210A in these groups. Notably in this study, the great majority (85%) of losses were after 10 weeks of gestation partly due to careful exclusion of other causes of pregnancy loss. The findings of the multivariate analysis clearly demonstrate an overall association between unexplained first pregnancy loss and the two thrombophilic risks factors (OR = 3.09 and OR = 2.34, respectively). The associations results from the 3065 women with losses after 10 weeks of gestation (OR = 3.46 and OR = 2.60, respectively) but were not found in women with losses between 3 and 9 weeks of gestation. However, the latter should be interpreted with some caution in view of the relatively limited number of women (431) in this group, particularly in view of the low incidence of FV Leiden and factor II G20210A (2% each) in the control population, which is typical for southern France and North Africa [28]. However, In the Middle East, the incidence of FV Leiden is 10–15% and that of factor II G20210A is around 5% [29,30]. It is therefore not unlikely that in these populations early first trimester loss between 6 and 9 weeks of gestation particularly if recurrent may be associated with thrombophilia [31].

The importance of the 'NOHA first' study is in the firm documentation that a first pregnancy loss after 10 weeks of gestation is associated with thrombophilia.

As unexplained first pregnancy loss occurred in about 10% of gestations, the findings of this study may have significant clinical impact.

Firstly, it is now clear, that women with first unexplained pregnancy loss after 10 weeks of gestation should be screened for thrombophilia. This should result in amendment of currently available guidelines such as the CAP Consensus Conference on Thrombophilia [32] and those recently reported by the Seventh ACCP conference on Antithrombotic and Thrombolytic Therapy [33].

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Secondly, a recent study by Gris *et al.* [34] demonstrated that in women with thrombophilia and previous one pregnancy loss after 10 weeks of gestation, enoxaparin at a dose of 40 mg daily, resulted in a significantly better live-borne rate compared with low-dose aspirin (86% vs. 29%, respectively). The differences were found in women with FV Leiden and factor II G20210A as well as in women with protein S deficiency.

The LIVE-ENOX trial [11] has recently demonstrated that in women with thrombophilia and pregnancy loss the live birth rate following enoxaparin 40 mg daily (84%) is equivalent to 40 mg b.i.d. (78%). Thus prophylaxis with LMWH is probably indicated throughout gestation and the *post-partum* period in women with thrombophilia who experienced pregnancy loss after 10 weeks in the first pregnancy. Taken together, it is expected that these new findings will impact clinical management of women with pregnancy loss.

References

1 Miller JF, Williamson E, Glue J, Gordon YB, Grudzinskas JG, Sykes A. Fetal loss after implantation. A prospective study. *Lancet* 1980; **13**: 554–6.

2 Grandone E, Margaglione M, Colaizzo D, d'Addedda M, Cappucci G, Vecchione G, Scianname N, Pavone G, Di Minno G. Factor V Leiden is associated with repeated and recurrent unexplained fetal losses. *Thromb Haemost* 1997; **77**: 822–4.

3 Ridker PM, Miletich JP, Buring JE, Ariyo AA, Price DT, Manson JE, Hill JA. Factor V Leiden mutation as a risk factor for recurrent pregnancy loss. *Ann Intern Med* 1998; **15**: 1000–3.

4 Brenner B, Sarig G, Weiner Z, Younis J, Blumenfeld Z, Lanir N. Thrombophilic polymorphisms are common in women with fetal loss without apparent cause. *Thromb Haemost* 1999; **82**: 6–9.

5 Gris JC, Quere I, Monpeyroux F, Mercier E, Ripart-Neveu S, Tailland ML, Hoffet M, Berlan J, Daures JP, Mares P. Case-control study of the frequency of thrombophilic disorders in couples with late foetal loss and no thrombotic antecedent – the Nimes Obstetricians and Haematologists Study 5 (NOHA5). *Thromb Haemost* 1999; **81**: 891–9.

6 Dizon-Townson DS, Kinney S, Branch DW, Ward K. The factor V Leiden mutation is not a common cause of recurrent miscarriage. *J Reprod Immunol* 1997; **34**: 217–23.

7 Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. *Lancet* 2003; **361**: 901–8.

8 Kovalevsky G, Gracia CR, Berlin JA, Sammel MD, Barnhart KT. Evaluation of the association between hereditary thrombophilias and recurrent pregnancy loss: a meta-analysis. *Arch Intern Med* 2004; **164**: 558–63.

9 Dudding TE, Attia J. The association between adverse pregnancy outcomes and maternal factor V Leiden genotype: a meta-analysis. *Thromb Haemost* 2004; **91**: 700–11.

10 Carp H, Dolitzky M, Inbal. A Thromboprophylaxis improves the live birth rate in women with consecutive recurrent miscarriages and hereditary thrombophilia. *J Thromb Haemost* 2003; **1**: 433–8.

11 Brenner B, Hoffman R, Carp H, Dulitsky M, Younis J, LIVE-ENOX Investigators. Efficacy and safety of two doses of enoxaparin in women with thrombophilia and recurrent pregnancy loss: the LIVE-ENOX study. *J Thromb Haemost* 2005; **3**: 227–9.

12 Walker ID, The use of LMWH in pregnancies at risk: new evidence or perception? *J Thromb Haemost* 2005; **3**: 778–9.

13 Kujovich L. The use of LMWH in pregnancies at risk: new evidence or perception? *J Thromb Haemost* 2005; **3**: 779–80.

14 Greer IA. The use of LMWH in pregnancies at risk: new evidence or perception? *J Thromb Haemost* 2005; **3**: 781–2.

15 Rey E, David M. The use of LMWH in pregnancies at risk: new evidence or perception? *J Thromb Haemost* 2005; **3**: 782–3.

16 Hunt BJ. The use of LMWH in pregnancies at risk: new evidence or perception? *J Thromb Haemost* 2005; **3**: 785–6.

17 Zotz RB, Gerhardt A, Scharf RE. The use of LMWH in pregnancies at risk: new evidence or perception? *J Thromb Haemost* 2005; **3**: 787–8.

18 Middeldorp S. The use of LMWH in pregnancies at risk: new evidence or perception? *J Thromb Haemost* 2005; **3**: 788–9.

19 Martinelli I. The use of LMWH in pregnancies at risk: new evidence or perception? *J Thromb Haemost* 2005; **3**: 789–90.

20 Grandone E. The use of LMWH in pregnancies at risk: new evidence or perception? *J Thromb Haemost* 2005; **3**: 792–3.

21 Salmon JE. The use of LMWH in pregnancies at risk: new evidence or perception? *J Thromb Haemost* 2005; **3**: 783–5.

22 Cetin I. The use of LMWH in pregnancies at risk: new evidence or perception? *J Thromb Haemost* 2005; **3**: 791–2.

23 Lindqvist PG, Svensson PJ, Marsaal K, Grennert L, Luterkort M, Dahlback B. Activated protein C resistance (FV:Q506) and pregnancy. *Thromb Haemost* 1999; **81**: 532–7.

24 Sarig G, Younis JS, Hoffman R, Lanir N, Blumenfeld Z, Brenner B. Thrombophilia is common in women with idiopathic pregnancy loss and is associated with late pregnancy wastage. *Fertil Steril* 2002; **77**: 342–7.

25 Tal J, Schliamser LM, Leibovitz Z, Ohel G, Attias D. A possible role for activated protein C resistance in patients with first and second trimester pregnancy failure. *Hum Reprod* 1999; **14**: 1624–7.

26 Preston FE, Rosendaal FR, Walker ID, Briet E, Berntorp E, Conard J, Fontcuberta J, Makris M, Mariani G, Noteboom W, Pabinger I, Legnani C, Scharrer I, Schulman S, van der Meer FJ. Increased fetal loss in women with heritable thrombophilia. *Lancet* 1996; **348**: 913–6.

27 Lissalde-Lavigne G, Fabbro-Peray P, Cochery-Nouvellon E, Mercier E, Ripart-Neveu S, Balducchi J-P, Daures J-P, Perneger T, Quere I, Dauzant M, Mares P, Gris J-CR. Factor V Leiden and prothrombin G20210A polymorphisms as risk factors for miscarriage during a first intended pregnancy: the matched case-control: 'NOHA first' study. *J Thromb Haemost* 2005; **3**: 2178–84.

28 Mathonnet F, Nadifi S, Serazin-Leroy V, Dakouane M, Giudicelli Y. Absence of factor V Leiden mutation and low prothrombin G 20210 A mutation prevalence in a healthy Moroccan population. *Thromb Haemost* 2002; **88**: 1073–4.

29 Awidi A, Shannak M, Bseiso A, Kailani MA, Kailani MA, Omar N, Anshasi B, Sakarneh N. High prevalence of factor V Leiden in healthy Jordanian Arabs. *Thromb Haemost* 1999; **81**: 582–4.

30 Rosendaal FR, Doggen CJ, Zivelin A, Arruda VR, Aiach M, Siscovick DS, Hillarp A, Watzke HH, Bernardi F, Cumming AM, Preston FE, Reitsma PH. Geographic distribution of the 20210 G to A prothrombin variant. *Thromb Haemost* 1998; **79**: 706–8.

31 Younis JS, Brenner B, Ohel G, Tal J, Lanir N, Ben-Ami M. Activated protein C resistance and factor V Leiden mutation can be associated with first-as well as second-trimester recurrent pregnancy loss. *Am J Reprod Immunol* 2000; **43**: 31–5.

32 Brenner B, Nowak-Gottl U, Kosch A, Manco-Johnson M, Laposata M. Diagnostic studies for thrombophilia in women on hormonal therapy and during pregnancy, and in children. *Arch. Pathol Lab Med* 2002; **126**: 1296–303.

33 Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on antithrombotic and thrombolytic therapy. *Chest* 2004; **126**: 627S–44S.

34 Gris JC, Mercier E, Quere I, Lavigne-Lissalde G, Cochery-Nouvellon E, Hoffet M, Ripart-Neveu S, Tailland ML, Dauzat M, Mares P. Low-molecular-weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder. *Blood* 2004; **103**: 3695–9.