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Low molecular weight heparin for repeated pregnancy loss: is it based on solid evidence?

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See also Brenner B, Hoffman R, Carp H, Dulitsky M, Younis J for the LIVE-ENOX Investigators. Efficacy and safety of two doses of enoxaparin in women with thrombophilia and recurrent pregnancy loss: the LIVE-ENOX study. This issue, pp. 227–9; Gris JC, Marés P. The long and winding road ... towards LMWH for pregnancy loss. This issue, pp 224–6.

The subject of the study by Brenner and coworkers in this issue of *Journal of Thrombosis and Haemostasis* [1] is of the outmost importance. Between 0.5% and 1% of women have repeated pregnancy loss (RPL), which represents both an individual misfortune and medical concerns. The uteroplacental circulation resembles venous circulation in terms of its low pressure and low flow velocity, and may be particularly susceptible to thrombotic complications in thrombophilic women. Therefore, it is reasonable to believe that prophylactic treatment to combat the thrombophilic process may be useful in women with RPL. The Brenner study finds that treatment with enoxaparin was effective and safe, and that both 40 mg and 80 mg enoxaparin doses were equally effective. Nevertheless, even if a therapeutic option is greatly desired and the results are encouraging, it needs to be judged according to the strength of its clinical evidence. This is especially important with regard to low molecular weight heparin (LMWH) treatment during pregnancy, which has been related to a 4-fold increased risk of profuse blood loss at delivery [2].

To place the paper by Brenner and coworkers in perspective, a number of critical comments regarding the background, design and conclusions of this study may be offered. Readers may find that the Brenner study is, in fact, not an investigation of the effect of enoxaparin in the prevention of RPL, for it assumes that its efficacy is already evident. The study compares the efficacy and safety of two different doses of enoxaparin. No arm of this clinical trial represents absence of treatment (the most common therapeutic alternative today). The main argument offered by the authors for performing their clinical trial is a previous observational study led by the same principal author [3] in which 50 women with RPL and thrombophilia were

followed through 61 pregnancies. These women were treated with either 40 mg or 80 mg of enoxaparin daily. In comparing the outcomes of these 61 treated pregnancies with those of historical pregnancies in the same 50 women, the risk of RPL appeared lower in the pregnancies treated with enoxaparin.

In our view this observational study presents such weaknesses that make it inappropriate to use as a source of reference. First, the study did not consider that some pregnancies were actually carried by the same women, a circumstance requiring special analytical handling [4]. Secondly, by comparing women with themselves using a 'before–after' approach there is a clear risk of regression towards the mean. This phenomenon expresses itself as a higher prospective probability of pregnancy success in women with the worst history and their expected pregnancy success rate in next pregnancy will be about 60–80% [5,6]. Thus, the results of the previous observational study appears heavily biased and gives no evidence for concluding that LMWH prevent fetal loss in women with RPL. The authors also cited a study by Gris and coworkers [7] that did not deal with RPL. In fact, there are currently no randomized studies providing evidence of efficacy of LMWH treatment in women with RPL.

The earlier observational study may, however, suggest the hypothesis that LMWH treatment prevents pregnancy loss in women with RPL. The logical design to test this hypothesis would therefore be to compare treatment and no treatment. Surprisingly, the authors make an equivalence trial by comparing two different doses of enoxaparin, something which is obviously out of place. For example, using the design applied by the authors, one cannot validate whether enoxaparin increases the risk of bleeding or decreases the risk of pregnancy loss. The fact that the risk of bleeding and the risk of pregnancy loss were similar in women with different doses of enoxaparin is not informative in this context.

In summary, the fundamental appropriateness of the trial performed by Brenner and coworkers appears open to question. The trial does not follow the CONSORT recommendations (a statement that lists 21 items that should be included in a randomized trial) regarding clinical trials and has

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Table 1 First trimester repeated pregnancy loss and FVL Leiden (FVL)

	Study Group (FVL +/-)	Control Group (FVL +/-)	Odds ratios (95% CI)	Power (β)*
Repeated first trimester pregnancy loss				
Rai (2001)	59/904	12/150	0.8 (0.4-2.0)	63%
Reznikoff-Etiévant (2001)	27/260	11/240	2.4 (1.2-5.0)	45%
Finan (2002)	45/110	11/67	3.5 (1.7-7.5)	42%
Younis (2000)	6/37	8/139	3.1 (1.0-10.0)	23%
Fatini (2000)	6/59	8/121	1.6 (0.5-4.8)	27%
Carp (2002)	2/70	5/82	0.5 (0.1-2.4)	22%
Foka (2000)	9/61	4/100	4.2 (1.2-14.1)	18%
Grandone (1997)	2/27	5/118	1.8 (0.3-9.8)	17%
Balash (1997)	1/55	1/50	0.9 (0.06-14.9)	12%

*Power to detect a doubled carriership rate in study group as compared to given control group

Figures recalculated to only include first trimester fetal loss

a poor transparency [8]. The main flaw of the paper remains, however, that there is no control group. Thus, it is impossible to validate whether the treatment had any effect at all. In this context, we would like to add some additional concerns.

An essential aspect of the paper by Brenner and coworkers is whether the assumption that there is an increased risk of RPL among thrombophilic women is correct. This is true for antiphospholipid syndrome [9], where the combination of LMWH and low-dose aspirin is the therapy of choice. However, there is no clear evidence that RPL is associated with all included thrombophilias. There is controversy as to whether two of the most prevalent thrombophilias in the population, coagulation factor V Leiden (FVL) and homozygous MTHFR C677T polymorphism (which is not a thrombophilia), are related to RPL. Regarding homozygous MTHFR C677T polymorphism, we have not found proof of increased risk of RPL in the literature consulted [10–14]. Of the possible relation between FVL and first-trimester fetal loss, there is solid evidence that FVL is unrelated to first-trimester fetal loss in the general population [15]. Moreover, it is unlikely that there exists a strong link with fetal loss, given the known evolutionary advantage that FVL has conferred to the carriers [16]. This does not, however, rule out a relation between FVL and small subgroups of fetal loss such as RPL. None of the studies in Table 1 that we present in this commentary were designed to identify a doubled risk of RPL with reasonable power [$\beta \geq 80\%$] [9,11,13,17–22]. In considering Table 1, we realize that in small retrospective case-control studies any selection bias will have a large impact on the results. The largest study points in a different direction than most small studies, indicating that publication bias may be present. Even if several published meta-analyses have shown a relationship between RPL and thrombophilias, we need to keep in mind the potential of publication bias in the papers surveyed. It becomes obvious that the results of meta-analysis of small observational studies do not have close to the same validity as in controlled, randomized trials.

Let us now assume that the efficacy of enoxaparin was already established and the approach of comparing two different doses was a plausible one. The authors state that their 'data demonstrate, in a large study population of women with thrombophilia: that both doses of enoxaparin are equally

effective'. Conclusions of 'equality' convey special difficulties, as they need be grounded on extremely well-executed trials having no risk of therapeutic contamination and possessing sufficient statistical power. The authors fail to show a power estimation, which is vital in equivalent study. It is an accepted axiom that 'absence of evidence is not evidence of absence' [23,24]. Although the authors have performed a multicenter trial, we do not know if randomization was conducted at the patient or hospital level. This aspect is very relevant. If at the patient level, there is a high risk of therapeutic 'contamination' of the patients within the same hospitals, which will produce dilution bias and an underestimation of the possible effects of the different enoxaparin doses. To counteract the effect of contamination requires a larger sample. Because the design was a multicentre study, the appropriate sample size also needs to be larger than the estimated for a common trial on individual patients because of the existence of intracluster correlation [25].

A final concern is that of heterogeneity. The definition of RPL used by the authors is heterogeneous: at least three first-trimester losses, at least two second-trimester losses or at least one third-trimester loss. With such wide inclusion criteria and with different prognoses in terms of live birth rates for these different categories, it is difficult to draw any clear conclusions. In addition, including women with one previous stillbirth among those with recurrent pregnancy loss also seems inappropriate. Similarly, 'thrombophilia' itself has a wide definition that includes conditions with very different prognoses of pregnancy success.

We conclude that the use of LMWH in the prevention of RPL is not based on solid evidence and that it is as yet too early for clinical implementation. Further studies are needed to determine which thrombophilias are related to RPL and if LMWH is beneficial in the prevention of RPL.

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