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Concerns on the ALIFE2 trial

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Author Comments:	This is a correspondence letter to the recent Lancet article entitled "Heparin for women with recurrent miscarriage and inherited thrombophilia (ALIFE2): an international open-label, randomised controlled trial" by Quenby S et al (Lancet 2023; 402: 54–61).

Title

Concerns on the ALIFE2 trial

Text

The ALIFE2 trial showed no benefit of low-molecular-weight heparin (LMWH) for women with recurrent miscarriages and inherited thrombophilia.¹ Our concerns are as follows.

First, the open-label design might have negatively affected the results, leading to altered “standard care” especially directed by physicians convinced of LMWH efficacy. In the double-blind PREFIX trial, investigating the preventive effect of LMWH among non-thrombophilic women with recurrent miscarriages in France, the physicians’ convincement caused a suspected delay of patient recruitment.² Moreover, psychological support can be beneficial for that population in improving the live-birth rate.³ To prove the possibility, a subgroup analysis by recruitment types seems important; health-care providers for patients with post-conception recruitment strategy (Dutch) can be more biased than those for patients with pre-conception strategy (UK).

Second, contribution of genetic mutations in the trial patients to recurrent miscarriage is uncertain; over 80% of the trial patients were Caucasians carrying heterozygous mutations of Factor V Leiden (FVL) or prothrombin G20210A (Table 1).¹ A recent meta-analysis revealed a significant association of recurrent miscarriage with heterozygous FVL and prothrombin mutations (odds ratios; 2.07 and 1.69, respectively).⁴ But surprisingly, the live-birth rate in the standard-care group (71%)¹ was comparable to that in the placebo group (72.9%) of the PREFIX trial.²

Considering the possible LMWH efficacy in reducing miscarriage rate among women with ≥ 3 miscarriages,⁵ we believe that it is premature to conclude LMWH is not beneficial and that further studies are warranted among the African and/or Asian populations, who are at higher risk of recurrent miscarriage than Caucasians.⁴

References

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unexplained recurrent pregnancy loss: a meta-analysis of randomized controlled trials. *J Matern Neonatal Med* 2021; **35**: 7601–8.

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We declare no competing interests.

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