Recurrent pregnancy loss and inherited thrombophilias: Does low molecular weight heparin improve the live birth rate?

FAST TRACK

Women with RPL have endured overzealous evaluations and management despite a lack of proven efficacy

The **use of low molecular weight heparin** (LMWH) in women with recurrent pregnancy loss (RPL) and confirmed inherited thrombophilias **does not improve the live birth rate when compared with a control group,** according to results of a randomized trial that followed 164 pregnant women treated with LMWH plus standard care and 162 women treated with standard care alone. In the LMWH-treated group, 116 (72%) of 162 women with primary outcome data had live births, while 112 (71%) of 158 women in the standard care group had live births (odds radio [OR], 1.04; 95% confidence interval [CI], 0.64–1.68).

Quenby S, Booth K, Hiller L, et al; ALIFE2 Block Writing Committee and ALIFE2 Investigators. Heparin for women with recurrent miscarriage and inherited thrombophilia (ALIFE2): an international open-label, randomised controlled trial. Lancet. 2023;402:54-61. doi:10.1016/S0140-6736(23)00693-1.

EXPERT COMMENTARY
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> "Follow the evidence to where it leads, even if the conclusion is uncomfortable."
>
> —*Steven James, author*

Women with RPL have endured overzealous evaluations and management despite a lack of proven efficacy. From alloimmune testing that results in paternal leukocyte immunization[1] and the long-entrusted metroplasty for a septate uterus recently put under fire[2] to the "hammer and nail" approach of preimplantation genetic testing for embryo aneuploid screening,[3] patients have been subjected to unsubstantiated treatments.

While the evaluation of RPL has evolved, guidelines from the American Society for Reproductive Medicine (ASRM), American College of Obstetricians and Gynecologists (ACOG), and Royal College of Obstetricians and Gynaecologists (RCOG) do not recommend testing for inherited thrombophilias outside of a history for venous thromboembolism.[4-6] These 3 societies support treating acquired thrombophilias that represent the antiphospholipid antibody syndrome.

Citing insufficient evidence for reducing adverse pregnancy outcomes, ACOG recommends the use of prophylactic- or intermediate-dose LMWH or unfractionated heparin (UFH) for patients with "high-risk" thrombophilias only to prevent venous thromboembolism during pregnancy and continuing postpartum.[4] (High-risk thrombophilias are defined as factor V Leiden homozygosity, prothrombin gene G20210A mutation homozygosity, heterozygosity for both factor V Leiden homozygosity and prothrombin gene G20210A mutation, or an antithrombin deficiency.[4])

To determine the impact of LMWH treatment versus no treatment on live birth rate, Quenby and colleagues conducted a prospective randomized controlled trial of women with RPL and inherited thrombophilias (the ALIFE2 trial). This was a follow-up to their 2010 randomized controlled trial that demonstrated no effect of LMWH with low-dose aspirin versus low-dose aspirin alone compared with placebo in women with unexplained RPL.[7]

Details of the study

The ALIFE2 study took place over 8 years and involved 5 countries, including the United States, with the 2 main centers in the Netherlands and the United Kingdom. Women eligible for the study were aged 18 to 42 years, had an inherited thrombophilia (confirmed by 2 tests), experienced recurrent miscarriages (2 or more consecutive miscarriages, nonconsecutive miscarriages, or intrauterine fetal deaths, irrespective of gestational age), and were less than 7 weeks' estimated gestational age. Study patients were randomly allocated with a positive pregnancy test to either surveillance or LMWH treatment, which was continued throughout pregnancy.

The primary outcome was live birth rate, and secondary outcomes were a history of miscarriage, ectopic pregnancy, and obstetric complications. A total of 164 women were allocated to LMWH plus standard care, and 162 women to standard care alone. LMWH was shown to be safe without major/minor

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FAST TRACK

The ALIFE2 study was a follow-up to a 2010 randomized trial that demonstrated no effect of LMWH with low-dose aspirin alone compared with placebo in women with unexplained RPL

bleeding or maternal heparin-induced thrombocytopenia.

The statistical calculation was by "intention to treat," which considers all enrolled participants, including those who dropped out of the study, as opposed to a "per protocol" analysis in which only patients who completed the study were analyzed.

Results. Primary outcome data were available for 320 participants. Of the 162 women in the LMWH-treated group, 116 (72%) had live birth rates, as did 112 (71%) of 158 in the standard care group. There was no significant difference between groups (OR, 1.04; 95% CI, 0.64–1.68).

Study strengths and limitations

The outcome of the ALIFE2 study is consistent with that of a Cochrane review that found insufficient evidence for improved live birth rate in patients with RPL and inherited thrombophilias treated with LMWH versus low-dose aspirin. Of their review of the studies at low risk of bias, only 1 was placebo controlled.[8]

This study by Quenby and colleagues was well designed and ensured a sufficient number of enrolled participants to comply with their power analysis. However, by beginning LMWH at 7 weeks' gestation, patients may not have received a therapeutic benefit as opposed to initiation of treatment with a positive pregnancy test. The authors did not describe when testing for thrombophilias occurred or explain the protocol and reason for repeat testing.

Study limitations included a deviation from protocol in the standard care group, which was the initiation of LMWH after 7 weeks' gestation. In the standard care group, 30 participants received LMWH, 18 of whom started heparin treatment before 12 weeks of gestation. The other 12 participants received LMWH after 12 weeks' gestation, and 6 of those 12 started after 28 weeks' gestation, since they were determined to need LMWH for thromboprophylaxis according to RCOG guidelines. While this had the potential to influence outcomes, only 18 of 162 (11%) patients were involved.

The authors did not define RPL based on a clinical versus a biochemical pregnancy loss as the latter is more common and is without agreed upon criteria for testing. Additionally, a lack of patient masking to medication could play an undetermined role in affecting the outcome. ●

FAST TRACK

There is no significant difference in live birth rate from LMWH treatment in women with RPL and inherited thrombophilias compared with surveillance

WHAT THIS EVIDENCE MEANS FOR PRACTICE

This elegant, and vital, randomized controlled trial provides double take-home messages: There is no value in testing for inherited thrombophilias in RPL, as they occur in a similar prevalence in the general population, and there is no significant difference in live birth rate from LMWH treatment in women with RPL and inherited thrombophilias compared with surveillance. Consequently, the increased cost of medication and testing can be averted.

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