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Outcomes of threatened abortions after anticoagulation treatment to prevent recurrent pregnancy loss

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KEY MESSAGE
For women who are under threat of abortions, continuation of low-molecular weight heparin indicated to prevent recurrent pregnancy loss was negatively associated with live birth rates. This deleterious effect is worrisome in light of the widely adopted practice of prescribing low-molecular weight heparin in this group of women, despite lack of evidence of benefit.

A B S T R A C T

We aimed to determine the outcome of threatened abortion in women treated with low-molecular weight heparin (LMWH) for recurrent pregnancy loss (RPL). Data of women with RPL who experienced threatened abortion while taking LMWH between 2007 and 2016 were retrospectively reviewed. All patients received the LMWH, enoxaparin (40 mg). Thrombophilia was present in 38 (33.3%) women, including 11 (9.6%) with antiphospholipid syndrome (APLS). The overall live birth rate was 58.8% (67/114). Live birth rates were 87.2% (41/47 patients) and 38.8% (26/67 patients) among those who discontinued versus those who continued LMWH treatment, respectively ($P < 0.0001$). Among APLS patients, live births resulted in eight of the nine women who continued LMWH. In multivariate analysis, discontinuation of LMWH was the only significant predictor of live birth outcome ($P < 0.0001$). Thrombophilia, presence of subchorionic haematoma, and severity of bleeding were not found to be associated with live birth outcomes. For women with threatened abortions, continuation of LMWH indicated to prevent RPL was negatively associated with live birth rates. Therefore, we support its discontinuation in this setting. Among women with APLS, LMWH continuation resulted in a relatively high live birth rate; we advocate against its withdrawal in this subset of patients.

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Introduction

Recurrent pregnancy loss (RPL), defined as two or more consecutive miscarriages, affects 1–5% of women who become pregnant (Branch et al., 2010; Rai and Regan, 2006). Even after comprehensive investigations, an identifiable cause is revealed in less than one-half of cases (Rai and Regan, 2006; Tulppala et al., 1993). Placental insufficiency caused by inappropriate coagulation activation has been postulated to play an important role in the pathogenesis of pregnancy loss (Kwak-Kim et al., 2009). This potential mechanism has led to the hypothesis that antithrombotic treatment might prevent RPL. Some studies have suggested a beneficial effect of antithrombotic treatment in the prevention of RPL (Brenner et al., 2005; Dolitzky et al., 2006; Fawzy et al., 2008; Grandone et al., 2002; Gris et al., 2004; Kupferminc et al., 2001). In contrast, however, a recent meta-analysis and a randomized trial concluded that such treatment yields no benefit (Pasquier et al., 2015; Skeith et al., 2016). Despite its unproven benefit, antithrombotic treatment is often prescribed by clinicians who face women eagerly seeking treatment that may potentially improve their distressing situation.

Low-molecular-weight heparin (LMWH) is the thromboprophylactic drug of choice in pregnancy (pregnancy category B according to the US Food and Drug Administration) because it does not cross the placenta and has a relatively favourable maternal safety profile (Greer and Nelson-Piercy, 2005). Nevertheless, antepartum LMWH use is not a benign intervention. It is associated with significant costs, burdensome daily subcutaneous injections and the potential for causing various adverse events. Most importantly, it is associated with higher bleeding rates, with most events occurring antepartum (Greer and Nelson-Piercy, 2005; Rodger *et al*, 2014a).

Threatened abortion is defined as the occurrence of vaginal bleeding before 20 gestational weeks. It is the most common complication in pregnancy, occurring in about one-fifth of cases (Everett, 1997). The management and outcome of threatened abortion in patients while taking anticoagulant treatment to prevent RPL have not been studied to date.

Given the paucity of published research, we studied the outcome of threatened abortion in patients treated with LMWH caused by RPL. We aimed to evaluate the management of anticoagulation treatment among such patients, and its effect on pregnancy outcomes.

Materials and methods

Patients

The data set derives from patients treated between January 2007 and September 2016 in two university hospitals. Patients were included in the study if they had experienced threatened abortion while taking prophylactic anticoagulant treatment to prevent RPL. Threatened abortion was defined as vaginal bleeding in the presence of a closed cervix before 20 gestational weeks, and documented fetal cardiac activity on ultrasound (Saraswat et al., 2010). Patients were eligible for inclusion in the study if they had previously experienced recurrent early pregnancy loss (≥2 consecutive losses at <12 weeks of gestation) (de Jong et al., 2013).

Patients who received anticoagulation treatment because they were at high risk of venous thromboembolism, or had a cardiovascular condition, were excluded from the study. In all includeld patients, previous pregnancy losses could not be accounted for by chromosomal abnormalities, fetal structural anomalies, maternal infection, uterine anatomical abnormality, cervical insufficiency or an intentional termination of pregnancy.

Data collection

A retrospective analysis was conducted using the Electronic Medical Record database of the maternal–fetal unit of two university hospitals in Israel. Emergency room encounters, hospital admissions and outpatient clinic follow-up visits were analysed. Records were reviewed between October and December 2016. The following data were extracted: patient characteristics (demographics, gravity, parity, number of previous spontaneous abortions, thrombophilic evaluation), gestational week at the time of the threatened abortion, use of antithrombotic treatment, severity and duration of bleeding, laboratory parameters (complete blood count), sonographic parameters and pregnancy outcome. Gestational age at presentation was determined by the date of the last menstruation; this was corrected if the crown–rump length observed in ultrasonography differed from the calculated gestational age by more than one week.

Bleeding was categorized according to patients' subjective assessment at presentation. The categories were mild, moderate and severe, and defined as less than, equal to, and more than regular menstrual bleeding, respectively. Thrombophilic evaluation included prothrombin 20210, factor V Leiden (FVL), antithrombin, protein C and S, and antiphospholipid antibodies. All patients who were diagnosed with antiphospholipid syndrome (APLS) fulfilled the current diagnostic criteria-Sydney revision of Sapporo Criteria (Miyakis et al., 2006). The antiphospholipid antibodies tested included lupus anticoagulant, anticardiolipin IgM and IgG, anti beta2-glycoprotein1 IgM, and IgG. The diagnosis of protein S deficiency was accepted only when testing was carried out at least twice, from 6 months after pregnancy, following a period without anticoagulation treatment. Institutional review board approval waiving informed consent was obtained for this retrospective study from Hadassah Medical Center Helsinki Committee (No. HMO 0662-15, approved in September 2015).

Statistical analysis

Patient characteristics are described as proportions for categorical variables and medians and interquartile range for continuous variables without a normal distribution. Significance between groups was assessed by the chi-square test and Fisher's exact test for categorical variables, and the Mann–Whitney U test for continuous variables. A multivariable logistic regression analysis (reported as odds ratios and 95% confidence intervals), using a stepwise method, was carried out to assess factors independently associated with live birth outcome. A two-sided P-value < 0.05 indicated statistical significance. Software Package for Statistics and Simulation (IBM SPSS version 22, IBM Corp, Armonk, NY) was used for statistical analyses.

Results

Patient characteristics

A total of 114 patients met study inclusion criteria. Demographic and clinical characteristics of these patients are presented in **Table 1**,