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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**,

Table 1 – Patient characteristics in relation to the management of low-molecular weight heparin after threatened abortion.[a]

	All patients (n = 114)	Discontinued LMWH (n = 47)	Continued LMWH (n = 67)
Age at presentation, years	33 [29–37] (33)	34 [29–38] (34)	32 [28–36] (32)
Gestational age at presentation, weeks	10 [7–13] (10.4)	10 [8–13] (10.6)	10 [7–13] (10.2)
Previous live birth, n (%)	80 (70.2)	35 (74.5)	45 (67.2)
Number of previous miscarriages	3 [2–4] (3.4)	3 [2–5] (3.7)	3 [2–4] (3.1)
≥ 3 miscarriages, n (%)	74 (64.9)	32 (68.1%)	42 (62.7)
Thrombophilian[b] n (%)	38 (33.3)	10 (21.3)	28 (41.8)
Inherited thrombophilia, n (%)	27 (23.7)	8 (17.0)	19 (28.4)
APLA, n (%)	11 (9.6)	2 (4.3)	9 (13.4)
Severity of bleeding, n (%)			
Mild	38 (33.3)	19 (40.4)	19 (28.4)
Moderate	56 (49.1)	21 (44.7)	35 (52.2)
Severe	20 (17.5)	7 (14.9)	13 (19.4)
Hemoglobin at admission (g/dl)	12.5 [11.5–13.1] (12.2)	12.6 [11.3–13.1] (12.3)	12.3 [11.6–13.1] (12.2)
Platelet count at admission (X 10^9/l)	244 [192–285] (246)	248 [177–293] (242)	242 [195–281] (249)
Blood transfusion, n (%)	2 (1.8)	1 (2.1)	1 (1.5)
Aspirin co-therapy at presentation, n (%)	18 (15.8)	5 (10.6)	13 (19.4)
Continued aspirin, n (%)	14 (77.8)	3 (60.0)	11 (84.6)
Multifetal gestation, n (%)	8 (7.0)	3 (6.4)	5 (7.5)
Subchorionic haematoma, n (%)	46 (40.4)	22 (46.8)	24 (35.8)
Length of hospital stay, days	2 [1–3] (2.7)	1 [1–4] (3.0)	2 [1–3] (2.5)

[a] All continuous variables are expressed as medians [interquartile range] (mean).
[b] $P = 0.03$.
APLA, antiphospholipid antibodies; LMWH, low-molecular weight heparin.

according to the continuation or discontinuation of anticoagulation treatment after presentation of threatened abortion, as well as for the cohort as a whole.

For all patients, the LMWH used was enoxaparin at a dose of 40 mg. All patients initiated prophylactic LMWH treatment after receiving a positive pregnancy test and at no later than 6 weeks of gestation. For 18 (15.8%) patients, aspirin was co-administered.

The median age of the study cohort was 33 (29–37) years. The median number of previous miscarriages was three (two to four). Overall, 74 (64.9%) women had experienced three or more previous miscarriages. Eighty women (70.2%) had at least one prior live birth. Thrombophilia was present in 38 (33.3%) women, including heterozygous FVL ($n = 17$), homozygous FVL ($n = 1$), heterozygous prothrombin G20210A ($n = 4$), compound heterozygotes for FVL and prothrombin G20210A ($n = 2$), protein C deficiency ($n = 1$), protein S deficiency ($n = 2$) and antiphospholipid syndrome ($n = 11$).

After the presentation of threatened abortion, LMWH treatment was completely discontinued in 47 (41.2%) patients, whereas, in 67 (58.8%), it was continued. Among the 67 patients for whom LMWH treatment was continued, for 43 (64.2%), LMWH was temporarily withdrawn during hospital stay for 24–72 h; in the remaining 24 (35.8%) patients, it was continuously given. Among the 18 (15.8%) patients for whom aspirin was co-administered, it was discontinued in four (22.2%) after presentation of a threatened abortion, and continued in 14 (77.8%). Demographic characteristics, gestational history, gestational week at the time of diagnosis, severity of bleeding, blood counts, aspirin administration, presence of subchorionic haematoma, and length of stay were comparable between patients for whom LMWH treatment was continued and those for whom it was discontinued (**Table 1**). Patients with thrombophilia (antiphospholipid syndrome or inherited thrombophilia), were more likely to continue LMWH than were patients without thrombophilia ($P = 0.03$) (**Table 1**).

Eleven patients had APLS; aspirin was co-administered to eight patients. LMWH treatment was discontinued in two patients and continued in nine. Aspirin was continued in seven patients and discontinued in one.

Outcomes

Outcome data are presented in **Table 2.** Bleeding completely ceased after discharge in a significantly higher proportion of patients for whom LMWH was discontinued (72.3% versus 43.3%; $P = 0.002$). Overall, 67 (58.8%) of the pregnancies ended in live births and 47 (41.2%) in miscarriage. The live birth rate was significantly higher among those who discontinued LMWH treatment than among those who did not (87.2% versus 38.8%; $P < 0.0001$). No difference was found in the live birth rate between patients who continued LMWH after temporary withdrawal and those who received it continuously (16/43 [37.2%]; versus 10/24 [41.7%]).

The median gestational age at the time of miscarriage was 12 [9–16] weeks. The median time elapsed from presenting with threatened abortion to final miscarriage was 3 [1–4] weeks and did not differ between patients who continued or discontinued LMWH (**Table 2**). Pregnancy complications other than miscarriage were not different between patients who continued and discontinued LMWH treatment (**Table 2**). Ten (90.9%) of the 11 patients with APLS experienced live birth: eight of the nine who had continued LMWH, and both of those who discontinued it. Among the 10 women with APLS who experienced live birth, seven were taking aspirin at the occurrence of the threatened abortion; in six of them it was continued.

Demographic characteristics, gestational history, gestational age at presentation, severity of bleeding, inherited thrombophilia, blood counts, aspirin administration, presence of subchorionic haematoma and length of stay were comparable between patients who experienced live birth and miscarriage (**Table 3**). In univariate analysis, APLS ($P = 0.03$) and discontinuation of LMWH treatment after threatened abortion ($P < 0.0001$) were positively associated with live birth rate.

Table 2 – Patient outcomes in relation to the management of low-molecular weight heparin after threatened abortion.[a]

	All patients (n = 114)	Discontinued LMWH (n = 47)	Continued LMWH (n = 67)	P-value
No other bleeding episodes after discharge, n (%)	63 (55.3)	34 (72.3)	29 (43.3)	0.002
Miscarriage, n (%)	47 (41.2)	6 (12.8)	41 (61.3)	<0.0001
Gestational age at miscarriage, weeks	12 [9–16] (12.7)	12 [9–17] (13.1)	11 [9–18] (12.6)	NS
Time elapsed from threatened abortion, weeks	3 [1–4] (2.8)	3 [1–3] (3.4)	3 [1–4] (2.6)	NS
Miscarriage ≥10 weeks of gestation n (%)[b]	32 (68.1)	4 (66.7%)	28 (68.2)	NS
Live birth, n (%)	67 (58.8)	41 (87.2)	26 (38.8)	<0.0001
Gestational age at delivery, weeks	37 [37–38] (37)	38 [37–38] (37.3)	37 [37–38] (36.6)	NS
Birth weight, g	2960 [2500–3200] (2795)	2980 [2502–3240] (2829)	2894 [2424–3174] (2741)	NS
Mode of delivery, n (%)[c]				NS
Vaginal delivery	22 (32.8)	15 (36.6)	7 (26.9)	
Caesarean section	45 (67.2)	26 (63.4)	19 (73.1)	
Pregnancy complications, n (%)[c]				
Preeclampsia	3 (4.5)	2 (4.9)	1 (3.8)	NS
PPROM	4 (6.0)	2 (4.9)	2 (7.7)	NS
Placental abruption	0	0	0	
Intrauterine fetal death	0	0	0	
Small for gestation age (10th percentile)	9 (13.4%)	6 (14.6)	3 (11.5)	NS
Premature delivery[c]	11 (16.4%)	5 (12.2)	6 (23.1)	NS
≥24 to <28 weeks, n	2	1	1	
≥28 to <32 weeks, n	0	0	0	
≥32 to <37 weeks, n	9	4	5	

[a] All continuous variables are expressed as medians [interquartile range] (mean).
[b] Denominator is the number of women who experienced miscarriage.
[c] Denominators are the number of women with live birth.
LMWH, low-molecular weight heparin; NS, not statistically significant; PPROM, preterm premature rupture of membranes.

Table 3 – Factors associated with live birth outcome.[a]

	All patients (n = 114)	Live birth (n = 67)	No live birth (n = 47)
Age at presentation, years	33 [29–37] (33)	34 [30–38] (34)	32 [26–37] (32)
Gestational age at presentation, weeks	10 [7–13] (10.4)	10 [8–13] (10.8)	9 [7–13] (9.8)
Previous live birth, n (%)	80 (70.2)	49 (73.1)	31 (66.0)
Number of previous miscarriages	3 [2–4] (3.4)	3 [2–5] (3.5)	3 [2–4] (3.1)
≥ 3 miscarriages, n (%)	74 (64.9)	46 (68.7)	28 (59.6)
Thrombophilia, n (%)			
Inherited thrombophilia	27 (23.7)	14 (20.9)	13 (27.7)
APLA[b]	11 (9.6)	10 (14.9)	1 (2.1)
Severity of bleeding, n (%)			
Mild	38 (33.3)	26 (38.8)	12 (25.5)
Moderate	56 (49.1)	30 (44.8)	26 (55.3)
Severe	20 (17.5)	11 (16.4)	9 (19.1)
Hemoglobin at admission (g/dl)	12.5 [11.5–13.1] (12.2)	12.6 [11.5–13.3] (12.4)	12.3 [11.5–12.9] (12.0)
Platelet count at admission (X 10^9/l)	244 [192–285] (246)	232 [180–275] (234)	254 [192–304] (264)
Blood transfusion, n (%)	2 (1.8)	1 (1.5)	1 (2.1)
LMWH management,[c] n (%)			
Discontinued	47 (41.2)	41 (61.2)	6 (12.8)
Continued	67 (58.8)	26 (38.8)	41 (87.2)
Aspirin co-therapy at presentation, n (%)	18 (15.8)	12 (17.9)	6 (12.8)
Continued aspirin, n (%)	14 (77.8)	9 (75)	5 (83.3)
Multifetal gestation, n (%)	8 (7.0)	4 (6)	4 (8.5)
Subchorionic hematoma, n (%)	46 (40.4)	26 (38.8)	20 (42.6)
Length of hospital stay, days	2 [1–3] (2.7)	2 [1–4] (3.0)	2 [1–3] (2.3)

[a] All continuous variables are expressed as medians [interquartile range] (mean).
[b] $P = 0.03$.
[c] $P < 0.0001$.
APLA, antiphospholipid antibodies; LMWH, Low-molecular weight heparin.

A multivariable logistic regression model for the outcome of live birth rate was created. Discontinuation of LMWH treatment was shown to be the only independent predictor of live birth (OR 95% CI 10.78; 4.01 to 28.93; $P < 0.0001$). After controlling for thrombophilia and severity of bleeding, the association was even more robust (OR 95% CI 13.71; 4.74 to 39.66; $P < 0.0001$).

Discussion

In this retrospective, observational study, the discontinuation of prophylactic-dose LMWH treatment after threatened abortion was significantly associated with a higher live birth rate in women who had experieced recurrent early pregnancy loss. To the best of our knowledge, this is the first study published to date that has evaluated the outcomes of threatened abortion in patients treated with LMWH for RPL.

We addressed a key question in a large and vulnerable group of patients. Despite the lack of benefit of LMWH in preventing future pregnancy loss, as concluded by a recent meta-analysis of randomized trials (Skeith et al., 2016), LMWH is commonly prescribed in many centres for women with unexplained pregnancy loss (Rodger *et al*, 2014a, 2014b, 2016; Pasquier et al., 2015; Schleussner *et al*, 2015) Use of LMWH, however, is not without risks; among them is an increased bleeding rate (Lindqvist and Dahlbäck, 2000; McLintock et al., 2009; Choosing Wisely Canada, 2014). An important review by Greer and Nelson-Piercy (2005) showed that antepartum bleeding events are significantly more common among patients treated with antepartum LMWH treatment. Nevertheless, a study that evaluated the safety and efficacy of LMWH in the prevention of future pregnancy loss reported surprisingly low rates of bleeding events (Brenner et al., 2005). None of the above mentioned studies reported rates of threatened abortion. Since, by definition, threatened abortion manifests with bleeding, we believe it should be referred to as a bleeding complication that challenges the continuation of LMWH. The lower live birth rate in association with continuation of LMWH treatment, as reported herein, suggests that antepartum anticoagulant prophylaxis should be withdrawn once threatened abortion has occurred in women with a history of RPL. Moreover, our data, coupled with results from the aforementioned studies that showed no benefit of LMWH in the prevention of RPL, support a recommendation against the use of LMWH in this setting.

Pregnancy outcomes in women with a threatened abortion and without a prior history of pregnancy loss have been shown to be favourable, with a live birth rate reaching up to 95% after the documentation of a fetal heart rate (Sotiriadis et al., 2004). Although fetal cardiac activity was demonstrated in all patients included in our study, the overall live birth rate (58.8%) was much lower. The live birth rate we observed among patients who discontinued LMWH treatment (87.2%) was substantially lower than reported by Sotiriadis et al. (2004). Nonetheless, our finding concurs with a study that demonstrated a higher abortion rate after threatened abortion in patients with prior pregnancy loss (Brigham et al., 1999). The rate of premature delivery in our series was relatively high (16.4%). This supports the association of threatened abortion with preterm delivery, which has been reported by others (Weiss *et al*, 2004; Yang et al., 2004; Saraswat et al., 2010). In addition, in agreement with a recent observational study (Kling et al., 2016), patients' prior history of pregnancy loss and the inclusion of multifetal pregnancies probably accounts for the high rate of preterm delivery we observed.

In the present study, the presence of inherited thrombophilia was not found to affect the live birth rate. Indeed, cumulative evidence regarding the association between inherited thrombophilia and pregnancy loss suggests a weak association at best (Lykke et al., 2012; Rodger et al., 2010, 2014b). However, among our patients with APLS, LMWH was mostly continued, and the live birth rate was relatively high (90.9%). This is in accordance with prior studies in which antithrombotic treatment was more strongly associated with a beneficial effect in the prevention of pregnancy loss among patients with APLS than among those with inherited thrombophilia (de Jong et al., 2013; Ismail et al., 2016). It is worth noting that previous studies of the effect of LMWH in the prevention of RPL did not always include patients with APLS (Laskin et al., 2009; Skeith et al., 2016). Although our number of APLS patients was small, we believe that, among this subgroup of patients, antithrombotic treatment should not be withdrawn after the occurrence of threatened abortion.

We report that the presence of subchorionic haematoma was not associated with adverse pregnancy outcome. This concurs with a prospective series and with other studies that failed to demonstrate any effect of the presence of subchorionic haematoma on miscarriage rate (Falco et al., 1996, 2003; Pedersen and Mantoni, 1990). In contrast to other studies that demonstrated an inverse association between the severity of bleeding and live birth rate (Weiss *et al*, 2004; Gracia et al., 2005), we did not find such a correlation. In our cohort, the severity of bleeding did not differ between patients who continued or discontinued LMWH treatment. Moreover, after discharge, a complete cessation of bleeding was observed in a significantly higher proportion of patients who discontinued anticoagulation treatment. Importantly, subjective assessment of blood loss is often erroneous and inaccurate.

The role of aspirin in the prevention of recurrent miscarriage is unproven (de Jong et al., 2014; Schisterman et al., 2014). On the basis of mice models, aspirin was postulated to have a potential effect in the prevention of pregnancy loss, through inhibition of protease activated receptor-mediated maternal platelet activation (de Jong et al., 2014). In contrast, a recent meta-analysis showed that aspirin may even have a negative effect on the prevention of RPL. This suggests that its inhibition of prostaglandin synthesis may hamper the process of embryo implantation (Zhang et al., 2015). In our cohort, a minority of patients received aspirin in addition to enoxaparin; most of them were patients with APLS. As this study was not designed to assess the effect of aspirin on pregnancy outcomes, however, we believe this matter should be directly addressed in larger studies.

Some questions are left unanswered. Unaccounted for factors, including genetic or thrombophilic factors, could have affected pregnancy and live-birth outcomes (Aracic et al., 2016; Rogenhofer et al., 2017). The identification of such potential confounders may help in the future to individualize management strategies among patients with RPL.

Strengths and limitations

The retrospective design of the present study raises the possibility of biases inherent to such investigations. In addition, because of the small sample size, we acknowledge that subgroup analyses (e.g. according to thrombophilia subtypes) could not be conducted. Moreover, the potential for treatment bias in relation to the presence of thrombophilia remains possible, despite the adjustment for such in the multivariate analysis. Finally, we used a broad definition of RPL (≥2 consecutive early losses), which is in line with the current definitions used by the American College of Obstetricians and Gynecologists

and the American Society of Reproductive Medicine (ACOG, 2002; ASRM, 2013). Despite these limitations, the characteristics of our patients were similar to those of other cohorts, with 65% of patients after three or more consecutive early losses (Clark et al., 2010; Kaandorp et al., 2010; Pasquier et al., 2015). A major strength of our study is the generalizability attained by the homogenous characteristics of the study group in terms of baseline characteristics and the agent and dose of LMWH used.

To the best of our knowledge, this is the first study to date documenting the outcome of patients who experienced threatened abortion while taking anticoagulation treatment for the prevention of RPL. Our data show that continuation of LMWH treatment was negatively associated with live birth rates. Accordingly, we support discontinuation of LMWH treatment in this setting. The potentially deleterious effect of LMWH on pregnancy outcome is worrisome in light of the widely adopted practice of prescribing LMWH to women with a history of unexplained RPL, despite lack of evidence of benefit. Clinicians should be aware of the risk for adverse outcomes associated with continuation of LMWH following threatened abortion in patients with RPL. Since, among APLS patients, LMWH continuation resulted in a relatively high live birth rate, we advocate against its withdrawal in the setting of threatened abortion.

In conclusion, for women with threatened abortions, continuation of LMWH indicated to prevent RPL was negatively associated with live birth rates. Large prospective studies are warranted to further evaluate the optimal management of LMWH treatment in the setting of threatened abortion in women with a history of RPL, and to better delineate the risk-to-benefit ratio.

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REFERENCES

ACOG, 2002. ACOG practice bulletin. Management of recurrent pregnancy loss. Number 24, February 2001. (Replaces Technical Bulletin Number 212, September 1995). American College of Obstetricians and Gynecologists. Int. J. Gynaecol. Obstet. 78, 179–190.

Aracic, N., Roje, D., Jakus, I.A., Bakotin, M., Stefanovic, V., 2016. The impact of inherited thrombophilia types and low molecular weight heparin treatment on pregnancy complications in women with previous adverse outcome. Yonsei Med. J. 57, 1230–1235.

ASRM, 2013. Practice Committee. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil. Steril. 99, 63.

Branch, D.W., Gibson, M., Silver, R.M., 2010. Clinical practice. Recurrent miscarriage. N. Engl. J. Med. 363, 1740–1747.

Brenner, B., Hoffman, R., Carp, H., Dulitsky, M., Younis, J., Investigators, L.I.V.E.-E.N.O.X., 2005. Efficacy and safety of two doses of enoxaparin in women with thrombophilia and recurrent pregnancy loss: the LIVE-ENOX study. J. Thromb. Haemost. 3, 227–229.

Brigham, S.A., Conlon, C., Farquharson, R.G., 1999. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. Hum. Reprod. 14, 2868–2871.

Choosing Wisely Canada. Hematology: five things physicians and patients should question, 2014. http://www.choosingwiselycanada.org/recommendations/hematology/. (Accessed 18 November 2016).

Clark, P., Walker, I.D., Langhorne, P., Crichton, L., Thomson, A., Greaves, M., Whyte, S., Greer, I.A., 2010. Scottish Pregnancy Intervention Study (SPIN) collaborators, 2010. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. Blood 115, 4162–4167.

de Jong, P.G., Goddijn, M., Middeldorp, S., 2013. Antithrombotic therapy for pregnancy loss. Hum. Reprod. Update 19, 656–673.

de Jong, P.G., Kaandorp, S., Di Nisio, M., Goddijn, M., Middeldorp, S., 2014. Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia. In: de Jong, P.G. (Ed.), Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd, Chichester, UK.

Dolitzky, M., Inbal, A., Segal, Y., Weiss, A., Brenner, B., Carp, H., 2006. A randomized study of thromboprophylaxis in women with unexplained consecutive recurrent miscarriages. Fertil. Steril. 86, 362–366.

Everett, C., 1997. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. BMJ 315, 32–34.

Falco, P., Milano, V., Pilu, G., David, C., Grisolia, G., Rizzo, N., Bovicelli, L., 1996. Sonography of pregnancies with first-trimester bleeding and a viable embryo: a study of prognostic indicators by logistic regression analysis. Ultrasound Obstet. Gynecol. 7, 165–169.

Falco, P., Zagonari, S., Gabrielli, S., Bevini, M., Pilu, G., Bovicelli, L., 2003. Sonography of pregnancies with first-trimester bleeding and a small intrauterine gestational sac without a demonstrable embryo. Ultrasound Obstet. Gynecol. 21, 62–65.

Fawzy, M., Shokeir, T., El-Tatongy, M., Warda, O., El-Refaiey, A.A., Mosbah, A., 2008. Treatment options and pregnancy outcome in women with idiopathic recurrent miscarriage: a randomized placebo-controlled study. Arch. Gynecol. Obstet. 278, 33–38.

Gracia, C.R., Sammel, M.D., Chittams, J., Hummel, A.C., Shaunik, A., Barnhart, K.T., 2005. Risk factors for spontaneous abortion in early symptomatic first-trimester pregnancies. Obstet. Gynecol. 106, 993–999.

Grandone, E., Brancaccio, V., Colaizzo, D., Sciannamé, N., Pavone, G., Di Minno, G., Margaglione, M., 2002. Preventing adverse obstetric outcomes in women with genetic thrombophilia. Fertil. Steril. 78, 371–375.

Greer, I.A., Nelson-Piercy, C., 2005. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood 106, 401–407.

Gris, J.-C., Mercier, E., Quéré, I., Lavigne-Lissalde, G., Cochery-Nouvellon, E., Hoffet, M., Ripart-Neveu, S., Tailland, M.-L., Dauzat, M., Marès, P., 2004. Low-molecular-weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder. Blood 103, 3695–3699.

Ismail, A.M., Hamed, A.H., Saso, S., Abu-Elhasan, A.M., Abu-Elghar, M.M., Abdelmeged, A.N., 2016. Randomized controlled study of pre-conception thromboprophylaxis among patients with recurrent spontaneous abortion related to antiphospholipid syndrome. Int. J. Gynaecol. Obstet. 132, 219–223.

Kaandorp, S.P., Goddijn, M., van der Post, J.A.M., Hutten, B.A., Verhoeve, H.R., Hamulyák, K., Mol, B.W., Folkeringa, N., Nahuis, M., Papatsonis, D.N.M., Büller, H.R., van der Veen, F., Middeldorp, S., 2010. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. N. Engl. J. Med. 362, 1586–1596.

Kling, C., Magez, J., Hedderich, J., von Otte, S., Kabelitz, D., 2016. Two-year outcome after recurrent first trimester miscarriages: prognostic value of the past obstetric history. Arch. Gynecol. Obstet. 293, 1113–1123.

Kupferminc, M., Fait, G., Many, A., Lessing, J., Yair, D., Bar-Am, A., Eldor, A., 2001. Low-molecular-weight heparin for the prevention of obstetric complications in women with thrombophilias. Hypertens. Pregnancy 20, 35–44.

Kwak-Kim, J., Yang, K.M., Gilman-Sachs, A., 2009. Recurrent pregnancy loss: a disease of inflammation and coagulation. J. Obstet. Gynaecol. Res. 35, 609–622.

Laskin, C.A., Spitzer, K.A., Clark, C.A., Crowther, M.R., Ginsberg, J.S., Hawker, G.A., Kingdom, J.C., Barrett, J., Gent, M., 2009. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial. J. Rheumatol. 36, 279–287.

Lindqvist, P.G., Dahlbäck, B., 2000. Bleeding complications associated with low molecular weight heparin prophylaxis during pregnancy. Thromb. Haemost. 84, 140–141.

Lykke, J.A., Bare, L.A., Olsen, J., Lagier, R., Arellano, A.R., Tong, C., Paidas, M.J., Langhoff-Roos, J., 2012. Thrombophilias and adverse pregnancy outcomes: results from the Danish National Birth Cohort. J. Thromb. Haemost. 10, 1320–1325.

McLintock, C., McCowan, L., North, R., 2009. Maternal complications and pregnancy outcome in women with mechanical prosthetic heart valves treated with enoxaparin. BJOG 116, 1585–1592.

Miyakis, S., Lockshin, M.D., Atsumi, T., Branch, D.W., Brey, R.L., Cervera, R., Derksen, R.H.W.M., DE Groot, P.G., Koike, T., Meroni, P.L., Reber, G., Shoenfeld, Y., Tincani, A., Vlachoyiannopoulos, P.G., Krilis, S.A., 2006. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J. Thromb. Haemost. 4, 295–306.

Pasquier, E., de Saint Martin, L., Bohec, C., Chauleur, C., Bretelle, F., Marhic, G., Le Gal, G., Debarge, V., Lecomte, F., Denoual-Ziad, C., Lejeune-Saada, V., Douvier, S., Heisert, M., Mottier, D., 2015. Enoxaparin for prevention of unexplained recurrent miscarriage: a multicenter randomized double-blind placebo-controlled trial. Blood 125, 2200–2205.

Pedersen, J.F., Mantoni, M., 1990. Prevalence and significance of subchorionic hemorrhage in threatened abortion: a sonographic study. AJR Am. J. Roentgenol. 154, 535–537.

Rai, R., Regan, L., 2006. Recurrent miscarriage. Lancet 368, 601–611.

Rodger, M.A., Betancourt, M.T., Clark, P., Lindqvist, P.G., Dizon-Townson, D., Said, J., Seligsohn, U., Carrier, M., Salomon, O., Greer, I.A., 2010. The association of factor V leiden and prothrombin gene mutation and placenta-mediated pregnancy complications: a systematic review and meta-analysis of prospective cohort studies. PLoS Med. 7, e1000292.

Rodger, M.A., Hague, W.M., Kingdom, J., Kahn, S.R., Karovitch, A., Sermer, M., Clement, A.M., Coat, S., Chan, W.S., Said, J., Rey, E., Robinson, S., Khurana, R., Demers, C., Kovacs, M.J., Solymoss, S., Hinshaw, K., Dwyer, J., Smith, G., McDonald, S., Newstead-Angel, J., McLeod, A., Khandelwal, M., Silver, R.M., Le Gal, G., Greer, I.A., Keely, E., Rosene-Montella, K., Walker, M., Wells, P.S., TIPPS Investigators, 2014a. Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial. Lancet 384, 1673–1683.

Rodger, M.A., Walker, M.C., Smith, G.N., Wells, P.S., Ramsay, T., Langlois, N.J., Carson, N., Carrier, M., Rennicks White, R., Shachkina, S., Wen, S.W., 2014b. Is thrombophilia associated with placenta-mediated pregnancy complications? A prospective cohort study. J. Thromb. Haemost. 12, 469–478.

Rodger, M.A., Gris, J.-C., de Vries, J.I.P., Martinelli, I., Rey, É., Schleussner, E., Middeldorp, S., Kaaja, R., Langlois, N.J., Ramsay, T., Mallick, R., Bates, S.M., Abheiden, C.N.H., Perna, A., Petroff, D., de Jong, P., van Hoorn, M.E., Bezemer, P.D., Mayhew, A.D., Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications Study Group, 2016. Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials. Lancet 388, 2629–2641.

Rogenhofer, N., Markoff, A., Wagner, A., Klein, H.-G., Petroff, D., Schleussner, E., EThIG, I.I., Group, C.J., Thaler, C.J., 2017. Lessons from the EThIGII trial: proper putative benefit assessment of low-molecular-weight heparin treatment in M2/ANXA5 haplotype carriers. Clin. Appl. Thromb. Hemost 23, 27–33.

Saraswat, L., Bhattacharya, S., Maheshwari, A., Bhattacharya, S., 2010. Maternal and perinatal outcome in women with threatened miscarriage in the first trimester: a systematic review. BJOG 117, 245–257.

Schisterman, E.F., Silver, R.M., Lesher, L.L., Faraggi, D., Wactawski-Wende, J., Townsend, J.M., Lynch, A.M., Perkins, N.J., Mumford, S.L., Galai, N., 2014. Preconception low-dose aspirin and pregnancy outcomes: results from the EAGeR randomised trial. Lancet 384, 29–36.

Schleussner, E., Kamin, G., Seliger, G., Rogenhofer, N., Ebner, S., Toth, B., Schenk, M., Henes, M., Bohlmann, M.K., Fischer, T., Brosteanu, O., Bauersachs, R., Petroff, D., ETHIG II group, 2015. Low-molecular-weight heparin for women with unexplained recurrent pregnancy loss: a multicenter trial with a minimization randomization scheme. Ann. Intern. Med. 162, 601–609.

Skeith, L., Carrier, M., Kaaja, R., Martinelli, I., Petroff, D., Schleußner, E., Laskin, C.A., Rodger, M.A., 2016. A meta-analysis of low-molecular-weight heparin to prevent pregnancy loss in women with inherited thrombophilia. Blood 127, 1650–1655.

Sotiriadis, A., Papatheodorou, S., Makrydimas, G., 2004. Threatened miscarriage: evaluation and management. BMJ 329, 152–155.

Tulppala, M., Palosuo, T., Ramsay, T., Miettinen, A., Salonen, R., Ylikorkala, O., 1993. A prospective study of 63 couples with a history of recurrent spontaneous abortion: contributing factors and outcome of subsequent pregnancies. Hum. Reprod. 8, 764–770.

Weiss, J.L., Malone, F.D., Vidaver, J., Ball, R.H., Nyberg, D.A., Comstock, C.H., Hankins, G.D., Berkowitz, R.L., Gross, S.J., Dugoff, L., Timor-Tritsch, I.E., D'Alton, M.E., FASTER Consortium, 2004. Threatened abortion: a risk factor for poor pregnancy outcome, a population-based screening study. Am. J. Obstet. Gynecol. 190, 745–750.

Yang, J., Hartmann, K.E., Savitz, D.A., Herring, A.H., Dole, N., Olshan, A.F., Thorp, J.M., 2004. Vaginal bleeding during pregnancy and preterm birth. Am. J. Epidemiol. 160, 118–125.

Zhang, T., Ye, X., Zhu, T., Xiao, X., Liu, Y., Wei, X., Liu, Y., Wu, C., Guan, R., Li, X., Guo, X., Hu, H., He, J., 2015. Antithrombotic treatment for recurrent miscarriage: Bayesian network meta-analysis and systematic review. Medicine (Baltimore) 94, 1–12.