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Prophylaxis with Low Molecular Weight Heparin for Prevention of Placenta-related Recurrent Adverse Pregnancy Outcomes

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Authors' contributions

This work was carried out in collaboration between all authors. Author JHK collected the data for the study and presented it at the Society for Gynecologic Investigation meeting in 2012. Author AG designed the study, wrote the protocol, and wrote the manuscript. Author JCP performed the statistical analysis. Author SHP supervised the data collection and contributed to the draft of the manuscript. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: To determine whether antenatal administration of low-molecular-weight-heparin (LMWH) reduces the recurrence of adverse pregnancy outcomes (APO).
Study Design: Retrospective cohort study.
Place and Duration of the Study: Inova Alexandria Hospital, Alexandria, VA and Georgetown University Medical Center, Washington, DC during the period of January 1, 2006 and December 31, 2009.
Methodology: All pregnant women with history of APOs, including preeclampsia or abruption at <35 weeks, birth weight <5th centile, fetal loss at ≥20 weeks, or ≥2 spontaneous losses between 12 and 20 weeks, were administered LMWH or not at the discretion of the managing physician. Excluded were cases with antiphospholipid

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syndrome. The independent effect of LMWH on recurrence was assessed using logistic regression analysis with odds ratios (OR) having 95% confidence interval (CI) not inclusive of the unity considered significant.

Results: Of the 140 women in the cohort, 44 (31%) received LMWH during the subsequent pregnancy and the remainder did not. APO recurred in 23.6% (33/140). Logistic regression analysis demonstrated that LMWH significantly and independently lowered the risk of recurrent APO (adjusted OR=0.08, 95% CI 0.01-0.45), whereas history of fetal growth restriction (OR=3.88, 95% CI 1.51-9.99) and positive results for inherited thrombophilias (OR=6.96, 95% CI 1.58-30.67) increased the risk.

Conclusion: In patients with rigorously defined history of severe APO, prophylaxis with LMWH is associated with a significant reduction in recurrence of severe APO.

Keywords: Low molecular weight heparin; pregnancy complication; preeclampsia; fetal growth restriction; abruption; fetal death; recurrence.

1. INTRODUCTION

Several obstetric complications, including preterm preeclampsia or placental abruption, severe and preterm fetal growth restriction (FGR), and fetal death after 10 weeks, are adverse pregnancy outcomes (APO) often characterized by defective placentation eliciting inadequate uteroplacental blood perfusion and ischemia [1]. Normal placentation comprises trophoblast cell invasion of the spiral arteries, which results in reversible changes in the normal arterial wall architecture [2]. Physiological trophoblastic invasion of the spiral arteries develops from 8 weeks' gestation and is mostly completed in the majority of cases by 20 to 22 weeks of gestation [1,3,4]. Inadequate perfusion and placental ischemia evoke endothelial dysfunction, with platelet and clotting system activation [5,6]. Disturbed placentation is thought to account for 8%-10% of all APO [7], and it has high risk of recurrence in subsequent pregnancies [8,9]. The risk increases with the number of complicated pregnancies: in a published trial of low dose aspirin for prevention of recurrent APO, control patients with prior poor outcome defined as FGR, fetal demise or placental abruption, had a recurrence risk of 26% with one prior complication and 46% with 2 or more prior APOs, without regard to thrombophilia [10]. Recurrences can manifest clinically with different APOs from one pregnancy to the next: a large Swedish study found that severe FGR in a woman's first pregnancy is associated with a two-fold higher risk of fetal death in the next pregnancy [11]. Similarly, a large retrospective cohort study found that women with preeclampsia, FGR, and placental abruption in their first pregnancy are at substantially increased risk of recurrence of any or all these conditions in their second pregnancy [12]. Finally, the earlier in pregnancy APOs occur, the higher the risk of recurrence [13].

In the 1990s, case-control studies suggested an association between risk of placental implantation-related APOs and inherited thrombophilias [14-17]. Such studies gave impetus to preventative studies exploring the benefit of anticoagulants for the prevention of APO recurrences. Case-control studies of women with inherited thrombophilias showed that low molecular weight heparin (LMWH) reduced the risk of recurrence of fetal death, preterm preeclampsia, preterm FGR, or placental abruption [18-23]. Similar results were reported in the multicenter prospective randomized LIVE-ENOX trial [24].

Although cohort studies failed to confirm an association between inherited thrombophilias and APO [25-28], evidence emerged suggesting that the benefit of LMWH for prevention of APO may be independent of inherited thrombophilic status. A Cochrane meta-analysis of

randomized clinical trials of thromboprophylaxis for APO related to placental insufficiency concluded that treatment with heparin appeared promising, with a reduction in preeclampsia, eclampsia and infant birth weight <10th centile [29]. The issue is however far from settled: for women with a history of recurrent or late pregnancy loss, a meta-analysis concluded that there is insufficient evidence to support the routine use of LMWH to improve pregnancy outcome [30].

We decided to undertake this retrospective study to determine whether LMWH reduces the recurrence of placenta-mediated APO.

2. MATERIALS AND METHOD

We conducted a retrospective cohort study of all multiparous women referred for maternal-fetal medicine consultation before conception or in early pregnancy because of previous history of FGR, preeclampsia, abruption or fetal death. All patients were managed and delivered at Inova Alexandria Hospital, Alexandria, VA, or Georgetown University Medical Center, Washington, DC during the period of January 1, 2006 and December 31, 2009.

Index pregnancy was defined as the pregnancy which qualified for inclusion in the study. Inclusion criteria were: severe preeclampsia resulting in delivery at <35 weeks gestation, complicated or not with HELLP syndrome; abruption resulting in preterm birth at <35 weeks; birth weight <5th centile [31], unexplained fetal death (i.e. in the absence of major congenital malformations, aneuploidy, or acute infection) at 20.0 weeks or greater; or 2 unexplained fetal deaths between 12.0 and 19.6 weeks' gestation. Severe preeclampsia was defined according to the criteria of the National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy [32]. Abruption was defined based on clinical diagnosis of premature separation of the placenta presenting with vaginal bleeding and uterine contractions leading to delivery.

All patients underwent laboratory screening for acquired thrombophilic conditions, including lupus anticoagulant, IgG and IgM anticardiolipin antibodies, and beta 2 glycoprotein I antibodies. Screening for inherited thrombophilias (Factor V Leiden mutation, prothrombin gene mutation G20210A, and deficiencies of the natural anticoagulants antithrombin III, Proteins S and Protein C) was left at the discretion of the managing Maternal-Fetal Medicine specialist. Excluded from the study were women with positive results for acquired thrombophilias; multiple gestations; cases requiring LMWH prophylaxis for medical indications (e.g. history of thromboembolism), use of tobacco, alcohol or illegal drugs; as well as any of the following in the index pregnancy: Clinical record of true knot in umbilical cord; presence of fetal chromosomal anomalies; or any underlying maternal metabolic disease (i.e. diabetes mellitus, renal disease or thyroid dysfunction). Positive results for inherited thrombophilias were retained in the analysis to allow multivariate statistical analysis to dissect their effect on the risk of recurrence of placenta-mediated APO.

Due to the absence of a standardized protocol for the management of patients with prior APOs, patients were allocated to receive LMWH (Lovenox40mg subcutaneous injection daily) or not based on physician preference. When chosen, prophylaxis was started in the 1st trimester. The duration of prophylaxis varied with the practitioner, ranging from 36 weeks to term, but always it was stopped before labor. All patients received folate supplementation (800mcg or 1000mcg daily). Patients were managed according to established high–risk pregnancy protocols at the managing institutions, which usually included serial ultrasonographic assessment of fetal growth, and fetal testing with non-stress test or

biophysical profile in the presence of FGR, preeclampsia, and always from 32 weeks onward with history of fetal death after 20 weeks. Low dose aspirin was prescribed at the discretion of the managing physician. Pregnancy outcome information was retrieved by chart review.

Data analysis and statistical evaluation were performed by an investigator (JCP) not involved in the clinical care of these patients. Main outcome variable was recurrence of APO, defined as any one of the following: severe preeclampsia or placental abruption leading to delivery at <35 weeks, birth weight <5th centile adjusted for gestational age and gender; and fetal death at 20 weeks or later. Unadjusted associations between recurrence of APO and potential predictive variables, including inherited thrombophilia status, type of APO in the index pregnancy, and type of prophylaxis, if any, were assessed using Fisher's exact test or Chi square for categorical variables or Student t-test for continuous variables. Adjusted odds ratios and 95% confidence intervals were calculated from logistic regression models.

3. RESULT

A total of 140 women fulfilled the study inclusion and exclusion criteria. Among the study patients, 44 (31%) received LMWH during pregnancy and 96 (69%) did not. Demographic data and delivery outcomes based on whether LMWH was administered are shown in Table 1.

Table 1. Characteristics of study population in relation to prophylaxis with Low Molecular Weight Heparin (LMWH)

	LMWH (n=44)	No LMWH (n=96)	*P*-value
Maternal age (years)	34.8±4.9	32.8±5.7	.04
Body mass index	24.7±6.8	26.2±7.7	.27
African American ethnicity	11 (25%)	35 (36%)	.18
APO in index pregnancy:			
Fetal Growth Restriction	4 (9%)	38 (40%)	<.001
Fetal death ≥20 weeks	20 (45%)	20 (21%)	.003
Severe preterm preeclampsia	8 (18%)	39 (40%)	.009
Preterm placental abruptio	1 (2%)	9 (9%)	.13
>2 fetal losses at 12-20 weeks	18 (41%)	11 (11%)	<.001
Positive results for inherited thrombophilias	30 (68%)	10 (11.6%)	<.001
Low dose aspirin	17 (39%)	30 (31%)	.39
Induction of labor	20 (45%)	11 (11%)	.01
Cesarean Section	16 (36%)	66 (69%)	.01
Gestational age at delivery (weeks)	37.6±1.4	36.3±4.1	.03
Male gender	22 (50%)	53 (55%)	.70
Birth weight (grams)	3112±507	2768±970	.03

APO, adverse pregnancy outcome

Overall, laboratory work-up for inherited thrombophilia yielded positive results in 40 women (29%) and negative results in 46 (33%); the remaining 54 patients were not tested. Women treated with LMWH were slightly older, had more frequently a history of fetal death at ≥20 weeks or recurrent fetal deaths before 20 weeks, and positive results at inherited thrombophilia screen than untreated women. The latter group had higher rates of history of FGR or preterm preeclampsia than treated women Table 1. None of the patients treated with LMWH developed complications during pregnancy or delivery.

A recurrence of any severe placenta-related APO was observed in 33/140 women (23.6%) and it was significantly more frequent among women not treated with LMWH Table 2. Recurrence of APO was also significantly related to African American ethnicity and history of FGR, but not to use of LDA or inherited thrombophilia status Table 2.

Table 2. Characteristics of study population in relation to recurrence of APO

	Recurrence yes (n=33)	Recurrence no (n=107)	*P*-value
Maternal age (years)	32.3±5.5	33.7±5.5	.20
Multiparity	31 (94%)	96 (90%)	.33
Body mass index	26.3±6.3	25.5±7.8	.57
African American ethnicity	16 (48%)	30 (28%)	.02
APO in index pregnancy			
Fetal growth restriction	18 (54%)	24 (22%)	<.001
Fetal death ≥20 weeks	11 (33%)	29 (27%)	.80
Severe preterm preeclampsia	14 (42%)	33 (31%)	.22
Preterm placental abruptio	2 (6%)	8 (7%)	.78
>2 fetal losses at 12-20 weeks	3 (%)	26 (24%)	.07
Positive results for inherited thrombophilias	9 (27%)	31 (28%)	.93
LMWH	3 (9%)	41 (38%)	.004
Low dose aspirin	7 (21%)	40 (37%)	.09
Induction of labor	9 (27%)	23 (21%)	.49
Cesarean Section	20(61%)	62 (58%)	.79
Male gender	21(64%)	54 (50%)	.19
Gestational Age (weeks)	33.3±5.1	37.7±1.9	<.001
Birth weight (grams)	1938±991	3166±571	<.001
5-minute Apgar score <7	5*	0	.001
NICU admit	17/29 (59%)	11 (10%)	<.001

*Legend: LMWH, low molecular weight heparin; NICU, neonatal intensive care unit admission; * includes 4 stillbirths and 1 neonatal death*

Table 3. Adjusted odds ratios for recurrence of adverse pregnancy outcome (APO) at stepwise logistic regression analysis

	P value	Adjusted Odds Ratio* (95% CI)
Low molecular weight heparin	0.004	0.08 (0.01-0.45)
History of FGR in index pregnancy	0.005	3.88 (1.51-9.99)
Positive results for inherited thrombophilias	0.01	6.96 (1.58-30.67)
Low dose aspirin	0.06	0.38 (0.13-1.06)

*Legend: FGR, fetal growth restriction (birth weight <5th centile); * Odds ratios were adjusted for maternal age, parity, body mass index, ethnicity, history of FGR, history of fetal death ≥20 weeks, history of recurrent fetal deaths <20 weeks, history of abruption, positive results for inherited thrombophililas, use of low molecular weight heparin or low dose aspirin.*

There were 14 (42%) women in the "Recurrence Yes" group and 12 (11%) in the "Recurrence No" group who had multiple adverse pregnancy outcomes (APO) (*P*<.001). Of the 3/44 patients who received LMWH and had recurrence of APO, 2 were positive for inherited thrombophilias and 1 was negative. Of the 30 patients who did not receive LMWH and developed recurrence, 7 were positive for inherited thrombophilia, 11 were negative and 12 were not tested for thrombophilias. Of the 9/40 patients with inherited thrombophilia who

had recurrence, 2 received LMWH.

Logistic regression analysis Table 3 demonstrated that LMWH was independently associated with significantly reduced risk of recurrent APO (OR=0.08, 95% CI 0.01-0.45), whereas positive thrombophilia status (OR=6.96, 95% CI: 1.58-30.67), and history of severe FGR (OR 3.88, 95% CI 1.51-9.99) significantly increased the risk of recurrent APO. Low dose aspirin did not significantly improve outcome (OR =0.38, 95% CI 0.13-1.06).

We calculated that 4.1 women (95% CI=3.2 to 11.6) would need to be treated with LMWH to prevent 1 recurrence of severe APO.

4. DISCUSSION

We have found that administration of LMWH significantly and independently reduces by over 90% the risk of recurrence of APOs commonly attributed to abnormal placental function. In a population similar to the one we studied, which was at high risk for recurrence of an APO, only 4 women would need to be treated to prevent 1 case of recurrence of severe APO. Such ratio compares favorably with other obstetric conditions, such as history of prematurity, for which prophylaxis with progesterone is recommended, with a number needed to treat of 12. Our findings are in line with other studies on the subject, though ours is the only one to employ multivariate analysis to control for possible confounders [18,20,33-38].

The beneficial effect of LMWH was independent of the presence of inherited thrombophilias. A limitation of the study is that not all women were tested for inherited thrombophilias: 38.6% of women had not been tested. For the purpose of multivariate analysis, such women were considered as thrombophilia negative, as indeed studies have shown that rate of positive thrombophilias in women with APO is <20% [37,38]. The beneficial effect of LMWH would remain unchanged if the variable thrombophilia were removed from the analysis. However, also in other published studies the benefit of LMWH was independent from thrombophilia status [29,36]. Although presence of inherited thrombophilias in our study had an independent adverse effect on risk of recurrence of APO, increasing such risk nearly 7-fold, our results militate against routine evaluation for inherited thrombophilias, since the laboratory results would not affect the benefit of administration of LMWH. More studies are needed to establish the optimal dosage of LMWH in different subsets of women with history of APO. Testing for inherited thrombophilias should still be considered in the setting of a personal history of venous thromboembolism associated with a nonrecurrent risk factor or a first-degree relative with a history of high-risk thrombophilia or venous thromboembolism before age 50 years [39].

Limitations of our study include its retrospective design, the absence of placenta pathology examinations in the index or the current pregnancy, the lack of placebo controls, and the unblinded study design, which may introduce biases, as demonstrated by the higher rate of inherited thrombophilia in the treated than in the untreated group, as well as the uneven distribution of qualifying criteria for APO in the treated vs untreated group.

However, our study also had several strengths. The number of women enrolled was large, making our study one of the largest to date on the subject. Moreover, our entry criteria were quite strict: by limiting inclusion only to women with preeclampsia or abruption resulting in preterm delivery at <35 weeks, or fetal growth restriction <5th centile, we increased the odds that the severe APO considered was indeed placenta-related and at high risk for recurrence [13]. Another strength of our study is that both LDA and positive thrombophilia screen were

unevenly present in the study population, which allowed us to perform logistic regression analysis to evaluate the independent effect of each variable on the outcome of interest.

5. CONCLUSION

Our results are encouraging, and suggest that in selected cases of severe and preterm APO, LMWH may provide patients with the option of decreasing risk of recurrence in subsequent pregnancies. Future large randomized clinical trials are needed to confirm whether LMWH is more efficacious than LDA started before 16 weeks in women with a history of APO to prevent recurrences.

CONSENT

No consent was required given the retrospective nature of the study and the de-identification of study patients.

ETHICAL APPROVAL

The study was approved by Ethics Board from Georgetown University and Inova Health System.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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