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Low–Molecular-Weight Heparin for the Prevention of Placenta-mediated Pregnancy Complications

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Abstract: During the past decade, prophylactic doses of low–molecular-weight heparin (LMWH) have been suggested to decrease the risk of placental-mediated complications. Herein, we review the prospective randomized trials that addressed the usefulness of LMWH in preventing placental-mediated complications in high-risk women. Inclusion criteria and results of these trials are heterogeneous. Unlike older trials (3 of 4 are single center), recent trials (all are multicenter) do not show beneficial effect of LMWH. There is certainly a need of complementary research before stating on the usefulness of LMWH in the prevention of placenta-mediated pregnancy complications in women at high risk.

Key words: low–molecular-weight heparin, prevention, placenta-mediated complications, preeclampsia

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Introduction

Preeclampsia is a multisystem disorder characterized by abnormal vascular response to placentation that is associated with increased systemic vascular resistance, enhanced endothelial-cell dysfunction, platelet aggregation, and activation of the coagulation system.[1]

Preeclampsia is a major cause of maternal mortality and morbidities (acute and long term), perinatal death, preterm birth, and fetal growth restriction.[2] Frequency of the disease is higher in women with previous preeclampsia,[3,4] chronic hypertension,[3,5] pregestational diabetes mellitus,[3] and multifetal gestation.[3,6,7] Particularly, women who have severe preeclampsia before 34 weeks of gestation, are at increased risk of severe maternal and perinatal complications.[8]

Placenta-mediated pregnancy complications such as preeclampsia and eclampsia, small-for-gestational age infant, placental abruption, and perinatal death are thought to be related to impaired placental function. Prevention of placenta-mediated pregnancy complications is likely the best approach to reduce maternal and perinatal mortality and morbidity associated with this condition. The evaluation of preventive treatment has been disappointing. Particularly, low-dose aspirin has modest effects[9] and vitamin C and E supplements do not decrease the risk of preeclampsia.[10,11] As thrombosis in the uteroplacental circulation is frequently observed in placenta-mediated pregnancy complications,[12] anticoagulation represents another preventive option.

During the past decade, prophylactic doses of low–molecular-weight heparin (LMWH) have been suggested to decrease the risk of placental-mediated complications.[13]

Herein, we analyze how heparin might work and review the prospective randomized trials that addressed the prevention of placental-mediated complications in high-risk women.

How Heparin Might Work

Examination of the placenta after birth of women who had preeclampsia or fetal growth restriction may identify the presence of ischemic thrombotic lesions, including infarction or damage to the placental tissue due to clots forming in the placental blood vessels on the maternal side.[12,14,15] Therefore, anticoagulation may avoid these pregnancy complications.

Unfractioned heparin increases endothelial nitric oxide (NO) bioavailability as evidenced by flow-mediated dilation in patients with known coronary artery disease.[16] LMWH causes a dose-dependent relaxation in human internal mammary arteries. The relaxation effects seem to be through endothelium-dependent mechanisms, including generation of NO.[17] In animal models, enoxaparin (a LMWH) had favorable effects on the vascular reactivity in aged-diabetic hamsters, decreased vasoconstriction effect of noradrenaline, and potentiated vasodilatory effects of acetylcholine.[18] In addition, the same team showed that enoxaparin preserved endothelial function through mechanisms that are independent of its anticoagulant activity.[19]

Heparin has also been shown to suppress endothelin-1 mRNA expression from human endothelial cells with a decrease in endothelin-1 peptide release in a dose-dependent manner, while concurrently enhancing the production of NO.[20] In addition, the exposure of glomerular endothelial cells to serum from women with preeclampsia induces an increase in permeability and endothelin-1 mRNA expression that are decreased in the presence of LMWH.[21]

Active systemic inflammation is hypothesized to contribute to endothelial dysfunction in women with preeclampsia,[22,23] including the activation of the complement system that mediates renal injury.[24] In a murine model of antiphospholipid antibody-mediated complement activation heparins exert anti-inflammatory actions along the complement pathway rather than by their anticoagulant effects to prevent fetal loss.[25]

Together, these results suggest that LMWH may have beneficial effects on endothelial function and LMWH has

emerged as a novel therapeutic option to prevent impaired placentation-related complications as it has been shown to be anti-inflammatory and improve vascular functions.[26] As thrombosis in the uteroplacental circulation is frequently observed in placenta-mediated pregnancy complications, anticoagulation represents another preventive option.

The Trials

LMWH has been tested as preventive treatment of placenta-mediated pregnancy complications in several small or nonrandomized trials.[27–29]

Brenner and colleagues evaluated the efficacy and safety of the LMWH enoxaparin in 50 women with inherited or acquired thrombophilia having 61 pregnancies. LMWH enoxaparin was given throughout gestation until 4 weeks after delivery. Enoxaparin dosage was 40 mg/d in women with solitary defect and 80 mg/d in combined defects. In women with antiphospholipid syndrome aspirin (75 mg daily) was given in addition to enoxaparin. The authors found a success rate in live born infants of 75% (46/61) in treated women by enoxaparin compared with only 20% (38/193) in untreated pregnancies in these 50 women before diagnosis of thrombophilia ($P < 0.00001$). The authors conclude that enoxaparin is effective in prevention of pregnancy loss in women with inherited and acquired thrombophilia.[27]

Kupferminc and colleagues aimed to evaluate the benefit of prophylactic dose of LMWH enoxaparin 40 mg/d and aspirin in 33 women with inherited thrombophilia and who had a history of severe obstetric complication (severe preeclampsia, placental abruption, intrauterine growth retardation, or intrauterine fetal death). Patients were homozygotes for the methylene-tetrahydrofolate reductase mutation also received folic acid supplementation throughout their pregnancy. The authors found that only 3 (9.1%) of the women developed pregnancy complications, with a mean delivery gestational age of 37.6 weeks and a mean birth weight at delivery of 2719 g.[28] This uncontrolled trial suggests that patients with previous obstetric complications and an inherited thrombophilia may benefit from treatment with combined LMWH and aspirin in subsequent pregnancies.

Grandone and colleagues aimed to determine whether low fixed dose of heparin [prophylactic fixed doses of unfractioned heparin (5000 IU every 12 h) or LMWH (enoxaparin 4000 IU/d)] (n = 24) or aspirin (n = 7) improve maternal and perinatal outcomes in women with previous obstetric complications and inherited thrombophilia. They found that among the 31 treated pregnant women, 28 (90.3%) compared with 4 of 58 (6.9%) in previous pregnancies had a good obstetric outcome.[29]

On the basis of encouraging pilot studies, 8 prospective randomized trials to prevent placenta-mediated pregnancy complications have been published (7 publications and 1 abstract) in women who had previous adverse pregnancy outcomes. Characteristics and primary outcome results are summarized in Table 1.

Mello and colleagues investigated the effect of LMWH on the pregnancy outcome of 80 nonthrombophilic women with angiotensin-converting enzyme DD homozygote and a previous history of preeclampsia. Women were randomized in 2 groups: 41 treated with dalteparin 5000 IU/d started early at first visit and 39 untreated (control group). LMWH reduced the risk of clinical negative outcomes (74.1% reduction of preeclampsia and 77.5% reduction of fetal growth restriction) and the severity (88.3% reduction of early onset of preeclampsia and 86.4% reduction of early onset of fetal growth restriction). The authors' conclusion was that LMWH reduced the recur-

TABLE 1. Randomized Trials in Women With Previous Placenta-mediated Pregnancy Complications

References	Center	N	Inclusion Criteria	Intervention vs. Control	Primary Outcome	RR (95% CI)
30	Multicenter	249	Previous severe PE < 34 wk (n = 249)	Enoxaparin 4000 IU + ASA vs. ASA	Maternal death, PE, SGA (≤ 10th percentile), perinatal death, or abruption	0.82 (0.59-1.14)
31	Multicenter	289	Inherited or acquired thrombophilia and prior PE (n = 49), or abruption (n = 26), or 3 losses < 10 wk (n = 44), or 2 fetal losses at 10-15 wk (n = 25), or fetal loss > 16 wk (n = 60), or SGA < 10th percentile (n = 45), or thromboembolic events/risk factors (n = 128)	Dalteparin 5000 IU ± ASA vs. no dalteparin ± ASA	Venous thromboembolism, or SGA < 10th percentile, or severe or early onset PE, or pregnancy loss	0.91 (0.55-1.48)
32	Multicenter	139	Inherited thrombophilia and prior HDP < 34 wk [PE (n = 88) and/or HELLP (n = 61) and/or SGA < 10th percentile (n = 94)]	Dalteparin 5000 IU + ASA vs. ASA	PE and/or HELLP and/or eclampsia < 34 wk, and regardless gestational age	0.85 (0.44-1.66)
33	Multicenter	135	Prior PE (n = 40), or HELLP (n = 12), or loss > 15 wk (n = 49), or SGA < 10th percentile (n = 28), or abruption (n = 5) (severe PE: 25 of the 40 PE)	Nadroparin 3800 IU vs. no nadroparin	PE, eclampsia, HELLP, loss > 15 wk, SGA < 10th percentile, or abruption	1.12 (0.55-2.26)
34	Single center	224	Prior severe PE (n = 224)	Enoxaparin 4000 IU + ASA vs. ASA	PE, SB > 20 wk, abruption, or SGA (≤ 5th percentile)	0.36 (0.18-0.70)
35	Single center	160	Prior abruption (n = 160) (of them 70 with PE)	Enoxaparin 4000 IU ± ASA vs. ± ASA	PE, SB > 20 wk, abruption, SGA (≤ 5th percentile)	0.40 (0.21-0.78)
36	Multicenter	114	Prior severe PE < 35 wk (n = 60), or abruption (n = 16), or SGA (< 5th percentile) (n = 21), or uterine death (n = 17)	Dalteparin 5000 IU ± ASA vs. ± ASA	Severe PE, SB, abruption, SGA (≤ 5th percentile)	0.23 (0.07-0.77)
37	Single center	80	Prior PE with ACE DD (n = 80)	Dalteparin 5000 IU vs. no dalteparin	PE, SGA < 10th percentile	0.30 (0.15-0.63)

ACE indicates angiotensin converting enzyme; ASA, acetyl salicylic acid—aspirin; CI, confidence interval; DD, deletion-deletion; HDP, hypertensive disease of pregnancy; HELLP, hemolysis-elevated liver enzyme-low platelet count; PE, preeclampsia; RR, relative risk; SB, stillbirth; SGA, small-for-gestational age.

rence of preeclampsia, and negative outcomes, in angiotensin-converting enzyme DD homozygote women with a previous history of preeclampsia.[37]

Rey and colleagues aimed to investigate the effectiveness of dalteparin, a LMWH, in preventing the recurrence of placenta-mediated pregnancy complications in women without thrombophilia. They included 116 pregnant women at $\leq$16 weeks of gestation randomized to either a prophylactic daily dose of dalteparin 5000 IU (n = 58) or no dalteparin (n = 58). The authors found that dalteparin was associated with a significantly lower rate of the primary outcome [5.5% (n = 3/55) vs. 23.6% (n = 13/55), $P = 0.013$]. In this pilot study, dalteparin was found to be effective in decreasing placental-mediated complications in women without thrombophilia.[36]

Gris and colleagues investigated the effectiveness of LMWH enoxaparin daily in the prevention of placenta-mediated pregnancy complications in women with previous placental abruption and negative for antiphospholipid antibodies. Women were randomized to receive either a prophylactic daily dose of enoxaparin 4000 IU starting from the positive pregnancy test (n = 80), or no enoxaparin (n = 80). Enoxaparin was associated with a lower frequency of primary outcome: 12.5% (n = 10/80) versus 31.3% (25/80), $P = 0.004$. This pilot study showed that enoxaparin given early during pregnancy was associated with a decreased risk of placental vascular complications in women with a previous placental abruption during their first pregnancy.[35]

The same team investigated the effectiveness of LMWH enoxaparin in the prevention of placenta-mediated pregnancy complications in women with a history of severe preeclampsia and negative for antiphospholipid antibodies. Women were randomized to receive either a prophylactic daily dose of enoxaparin 4000 IU starting from the positive pregnancy test (n = 112), or no enoxaparin (n = 112). Here again, enoxaparin was associated with a decreased risk of primary outcome: 8.9% (n = 10/112) versus 25% (28/112), $P = 0.004$.[34]

Martinelli and colleagues aimed to analyze the effectiveness of prophylactic dose of LMWH in the prevention of late pregnancy complications in women with previous history of placenta-mediated pregnancy complications (preeclampsia, hemolysis-elevated liver enzyme-low platelet count syndrome, intrauterine fetal death, fetal growth restriction, or placental abruption) referred at $<$12 weeks of gestation. Women were randomized to nadroparin (3800 IU daily subcutaneous injections) treatment (n = 67) or to medical surveillance alone (n = 68). The study was stopped for futility at the time of the first planned interim analysis. Among the women available for final analyses, 13/63 (21%) randomized to nadroparin compared with 12/65 (18%) on medical surveillance alone progressed to the primary endpoint ($P = 0.76$). In this study, prophylactic dose of LMWH nadroparin did not prevent late-pregnancy complications in women at risk of recurrence.[33]

De Vries and colleagues investigated the usefulness of adding LMWH to aspirin at $<$12 weeks of gestation in reducing the recurrence of hypertensive disease in women with inheritable thrombophilia without antiphospholipid antibodies and previous early onset at $<$34 weeks of gestation of hypertensive disease (preeclampsia, hemolysis-elevated liver enzyme-low platelet count syndrome, and eclampsia) and/or small-for-gestational age infant. Women were randomized to receive either daily LMWH dalteparin (5000 IU, weight adjusted dosage) with aspirin 80 mg or aspirin 80 mg alone. The authors found that adding dalteparin to aspirin reduced recurrent hypertensive disease onset at $<$34 weeks of gestation; however, dalteparin with aspirin did not significantly reduce recurrent hypertensive disease irrespective of gestational age.[32]

TABLE 2. Secondary Outcome Analysis of the Randomized Trials: Rates of Preeclampsia and Small-for-Gestational Age Infants

References	Preeclampsia Intervention vs. Control (%)	*P*	Small-for-Gestational Age (< 10th Percentile) Intervention vs. Control (%)	*P*
30	18 vs. 22.1	NS	19.7 vs. 26.2	NS
31	5.5 vs. 3.5	NS	6.2 vs. 8.4	NS
32	15.7 vs. 21.7	NS	18.2 vs. 28.4	NS
33	7.9 vs. 4.6	NS	7.9 vs. 10.8	NS
34	5.8 vs. 16.7	0.01	5.3 vs. 13.4	0.04
35	7.5 vs. 22.5	< 0.01	7.5 vs. 25	0.002
36	5.4 vs. 20	< 0.04	7.3 vs. 21.8	0.03
37	7.3 vs. 28.2	< 0.01	9.8 vs. 43.6	< 0.001

Recently, Rodger and colleagues published their data on the usefulness of antepartum dalteparin in women with thrombophilia and previous adverse pregnancy outcome or venous thromboembolism in the reduction of placenta-mediated pregnancy complications. Women were randomized to receive either dalteparin (n = 146) or no dalteparin (n = 143). In this trial, dalteparin did not reduce the incidence of the primary composite outcome [dalteparin 25/146 (17.1%) vs. no dalteparin 27/143 (18.9%); $P = 0.70$].[31]

The latest trial was reported by our team. We analyzed in women with a history of severe preeclampsia that occurred at < 34 weeks of gestation and negative for antiphospholipid antibodies the usefulness of antepartum enoxaparin and aspirin compared with aspirin alone in the reduction of placenta-mediated pregnancy complications. Women were randomly assigned to receive either enoxaparin 4000 IU and aspirin 100 mg (n = 130), or aspirin 100 mg alone (n = 127). Outcome data were not available for 13 patients. There were no differences between the groups in either the primary or secondary outcomes (Tables 1 and 2). Therefore in women with previous severe preeclampsia at < 34 weeks of gestation our study did not support the use of antepartum prophylactic enoxaparin added to low dose aspirin for the reduction of placenta-mediated complications as compared with low dose aspirin alone.[30]

A meta-analysis of the published randomized trials[31–37] showed a beneficial effect of LMWH in reducing placenta-mediated composite morbidities (relative risk, 0.57; 95% confidence interval, 0.36-0.91).[31] Five of these trials, however, had multiple inclusion criteria leading to difficulties in the interpretation of the usefulness of LMWH.[31–33,36,37] In addition, the most recent trials (all are multicenter)[31–33] did not show beneficial effect in reducing placenta-mediated composite morbidity compared with the older trials (3 of 4 are single center).[34–37]

Almost all trials analyzed preeclampsia and small-for-gestational age infants as secondary outcomes and therefore data presented in these trials should be considered with caution (Table 2). As for composite outcomes, older trials[34–37] showed statistical effectiveness of LMWH in the reduction of rates of preeclampsia and small-for-gestational age infants whereas more recent trials did not show any benefit.[30–33]

Safety Aspects

Antepartum LMWH is not a benign treatment. Greer and Nelson-Piercy assessed the safety and efficacy of LMWHs for thromboprophylaxis and treatment of venous thromboembolism in pregnancy. They undertook a systematic review of studies to the end of 2003. Data on side

effects were extracted and cumulative incidences of adverse effects calculated in 2777 pregnancies. The indication for LMWH was treatment of acute venous thromboembolism in 174 patients, and thromboprophylaxis or adverse pregnancy outcome in 2603 pregnancies. There were no maternal deaths. Significant bleeding, generally associated with primary obstetric causes, occurred in 1.98%, allergic skin reactions in 1.80%, heparin-induced thrombocytopenia in 0%, and osteoporotic fracture in 0.04%of pregnancies.[38]

Conclusions

In the light of the published data, there is a need of complementary research to confirm or not the effectiveness of LMWH in the prevention of placenta-mediated pregnancy complications in pregnant women at high risk of complications. Until the conclusions of these researches LMWH should not be prescribed as preventive treatment of placenta-mediated pregnancy complications in women at high risk except for antiphospholipid antibody syndrome.

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