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Low-molecular-weight heparin in patients with preeclampsia – does the sword cut both ways? : Three case report and review of literature

Shan D *et al.* LMWH in patients with preeclampsia

Dan Shan, Tao Li, Xi Tan, Ya-Yi Hu

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Abstract

BACKGROUND

Low-molecular-weight heparins (LMWH) are the most commonly used anticoagulants during pregnancy. It is considered to be the drug of choice due to its safety in not crossing placenta. Considering the beneficial effect in the improvement of microcirculation, prophylactic application of LMWH in patients with preeclampsia became a trend. However, the bleeding risk related with LMWH in preeclampsia patients has seldomly been evaluated. This current study aimed to identify the potential risks regarding LMWH application in patients with preeclampsia.

CASE SUMMARY

Herein we present a case series of three pregnant women diagnosed with preeclampsia on LMWH therapy during pregnancy. All the cases experienced catastrophic hemorrhagic events. After reviewing the twenty-one meta-analyses, the bleeding risk related with LMWH seems ignorable. Only one study analyzed the bleeding risk of LMWH and found a significantly higher risk of developing PPH in women receiving LMWH. Other studies reported minor bleeding risks, none of these were serious enough to stop LMWH treatment. Possibilities of bleeding either from uterus or from

intrabdominal organs in preeclampsia patients on LMWH therapy should not be ignored. Intensive management of blood pressure even after delivery and homeostasis suture in surgery are crucial.

CONCLUSION

Consideration should be given to the balance between benefits and risks of LMWH in patients with preeclampsia.

Key Words: Pregnancy; Preeclampsia; Low-molecular-weight heparin; Hemorrhage; Case report

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Core Tip: Benefits and risks of low molecular weight heparins in pregnant patients diagnosed with preeclampsia should be carefully assessed. Strict control of blood pressure is needed to prevent further bleeding events.

INTRODUCTION

Due to its safety in not crossing the placental-fetal barrier, low-molecular-weight heparin (LMWH) is widely used in several placenta-mediated complications^[1-4]. Many randomized controlled trials (RCTs) and meta-analyses regarding the improving function in placental micro-circulation of LMWH were conducted. However, heterogeneities in participant recruitment and difference in underlying physiopathological mechanisms of these placenta-mediated pregnancy complications contributed to controversial results. Most studies reported that LMWH is the anticoagulant of choice in pregnancy because of its favorable maternal safety profiles^[5]. The safety parameters in long-term application of LMWH during pregnancy still needs

to be considered. The safety parameters of LMWH including bleeding risk, allergy, heparin-induced thrombocytopenia, or heparin-induced osteoporosis were seldomly summarized. Especially the bleeding risk associated with LMWH, which might be seriously underestimated. The bleeding risk in pregnant women using LMWH is still a subject of debate.

Most studies on LMWH application in pregnant women reported ignorable bleeding risks^[6-9]. However, in patients with preeclampsia, a population with high risk of postpartum hemorrhage, the information on bleeding risk related with LMWH was insufficiently evaluated. In spite, previous studies implied LMWH was an ideal treatment by indicating the efficacy of LMWH in preventing the development of preeclampsia and improving pregnancy outcomes. To illustrate the bleeding risk related with LMWH therapy in patients with preeclampsia, herein, we report three cases and review the literature.

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CASE PRESENTATION

Chief complaints

Case 1: Case 1 was a 34-year-old pregnant woman with a singleton fetus.

Case 2:

Case 3:

Chief complaint and history of present illness: Case 2 was a 36-year-old woman with preeclampsia. She had regular antenatal care and was admitted to our hospital at 28 gestational weeks. Her blood pressure was controlled but she was still presented with severe proteinuria and elevated liver enzymes. The antinuclear antibodies, anti-nucleosome antibodies, anti-SSA antibodies, anti-Ro52 antibodies and anti-β2-glycoprotein antibodies were positive. Suspicion of obstetric antiphospholipid syndrome (OAPS) and Sjogren's syndrome were made after consultation by rheumatologic doctors.

1

History of past illness, personal and family history, physical examination, laboratory examinations, and imaging examinations: Not special.

Final diagnosis : severe preeclampsia, pregnancy complicated with immune disorders: obstetric antiphospholipid syndrome (OAPS) and Sjogren's syndrome

Treatment and outcome follow-up: Antihypertensive therapy, hepatoprotective treatments, immune regulation and LMWH were given as the rheumatologic doctor suggested. At 32 gestational weeks, she had upper abdominal pain and vomiting after an unhygienic diet. Acute gastroenteritis was first suspected. Symptomatic and supportive treatment was given but the symptoms were not relieved. She had uncontrolled vomiting and the upper abdominal pain was aggressive. Abdominal ultrasound revealed large amount of ascites which emerged in short time. Emergent CS was performed. A female fetus with an Apgar score 3-6-8-9 was born. Large amounts of blood clots accumulated in the pelvic cavity, spleen and liver area. A small rupture with bleeding with a diameter of approximately 1cm was found in the Glisson's capsule behind the gall bladder, which was repaired meticulously by a hepatobiliary surgeon during surgery. The patient recovered well and was discharged on day eight after delivery.

Case 3

Chief complaint and history of present illness: Case 3 was a 38-year-old woman with preeclampsia. She was transferred to our hospital five days after CS because of uncontrolled blood pressure and huge hematoma formation in the abdominal wall. She had irregular antenatal care at a local hospital and emergency CS was performed by the local hospital at 36th gestational week due to the presentation of severe headache and uncontrolled blood pressure. Antihypertensive drugs and LWMH was prescribed after CS in the local hospital. She was discharged three days after CS, but she presented with aggressive abdominal pain one day before she was transferred to our hospital. The blood pressure was as high as 180/100 mmHg at admission. Huge hematoma formation was found in the anterior abdominal wall (14.1cm x 3.4 cm x 10.4 cm).

1

History of past illness, personal and family history, physical examination, laboratory examinations, and imaging examinations: Not special.

Final diagnosis : severe preeclampsia, hematoma in abdominal wall.

Treatment and outcome follow-up: Intensive antihypertensive therapy was immediately administered. Intravenous antihypertensive medications were converted to oral antihypertensive medications progressively for three days after admission. Conservative treatments for hematoma with activating blood circulation herbs were applied after communication with the patients. The hematoma shrank to 10.1 cm x 3.0 cm x 8.9 cm at the 8 days after admission (Figure 1), and was 6.0 cm x 2.0 cm x 3.0 cm two months later (Figure 2).

History of present illness

Case 1: She was diagnosed with preeclampsia at 28th gestational week at local hospital and was admitted to our hospital due to poorly controlled blood pressure on 29th gestational week. She was also presented with intrauterine growth restriction (IUGR) and elevated umbilical artery flow velocity S/D value.

History of past illness

2

Case 1:

Case 2:

Case 3:

Personal and family history

Case 1:

Case 2:

Case 3:

Physical examination

2

Case 1:

Case 2:

Case 3:

Laboratory examinations

Case 1:

Case 2:

Case 3:

Imaging examinations

Case 1:

Case 2:

Case 3:

FINAL DIAGNOSIS

Case 1: Severe preeclampsia, intrauterine growth restriction.

Case 2:

Case 3:

TREATMENT

Case 1: Magnesium sulfate, antihypertensive therapy and LMWH were prescribed. At 31 gestational weeks, emergent CS was performed due to repeated non-response non-stress tests on fetal monitoring. The CS was successful with a baby of Apgar score 8-9-9 was born. However, hours after CS, her blood pressure declined progressively and the vital signs were not stable. Blood tests implied significantly decreased hemoglobin and abdominal paracentesis revealed hemoperitoneum. An emergent relaparotomy was performed. Large amount of fresh blood with clots were found in the abdomen (uncoagulable blood 1660 mL, blood clots 670g). Bleeding was found in a small mesenteric artery. After evacuation of blood clots and hemostasis suture, the patient was transferred to the intensive care unit and then the general ward. The patient recovered well and was discharged on day seven after CS.

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Case 2:

Case 3:

OUTCOME AND FOLLOW-UP

Case 1:

Case 2:

Case 3:

DISCUSSION

Low-molecular-weight heparin thromboprophylaxis recommendations differ across clinical practice guidelines for patients with preeclampsia^[2-4,10,11]. Application of LMWH was not a common treatment option for patients at high risk for preeclampsia in the past decades in China. However, as the maternal mortality rate caused by pulmonary

embolism increased, more attention was given to the LMWH prophylaxis and treatment in pregnant women in recent years. Lack of experience in LMWH usage sometimes put the obstetricians in a dilemma in balancing the benefits and risks. Here we reported three severe bleeding events in patients with preeclampsia receiving LMWH.

The hemorrhagic event caused by mesenteric artery was a rare event in case one. During pregnancy, the physiological changes of abdominal vessels during pregnancy included increased blood supply and hypostasis resulting from an enlarged uterus. Suspicion of spontaneous rupture in mesenteric artery is a possible and reasonable cause considering the uncontrolled blood pressure in this patient. Common tocolytic applications is an effective method for uterine bleeding, but functioned less in controlling bleeding from the mesenteric arteries. High blood pressure and LMWH significantly increased the possibility for aggressive intrabdominal bleeding. Case two of our report was diagnosed as acute gastroenteritis, with an initial history of unhygienic diet at first. Possibility of intrabdominal bleeding was considered due to the continuous presentation of vomiting with abdominal pain and large amount of ascites which emerged in a short time detected by ultrasound. Preeclampsia and sudden increased abdominal pressure during vomiting might lead to small rupture in Glisson's capsule. With the application of LMWH, subsequent severe hemorrhage from liver, of which the blood supplementation significantly increased compared with that in non-pregnancies, put the patient in hypovolemic shock immediately. Although being a rare event in pregnant women, spontaneous bleeding from abdominal organ and large vessels was reported in pregnant women in the literature, especially in patients with preeclampsia^[12-14]. It was reported that sub-capsular liver hematoma occurred in 1%–2% of patients with HELLP syndrome^[13,14]. The presentation of hematoma might be nonspecific. Possible complaints of patients might be nausea and right upper quadrant discomfort. But in pregnant women, none of these symptoms are typical, this certainly would lead to the possibility of misdiagnosis. Huge hematoma formation in case 3 indicated the urgent needs for strict control of blood pressure even after delivery. Management of blood pressure is still crucial in postpartum patients. The uncontrolled

blood pressure after the CS together with LMWH led to hematoma formation in the pregnant woman's uncompacted abdominal wall in case three.

Due to its pharmacological properties in improving microcirculation, the efficacy of LMWH has been evaluated in several pregnancy related complications in recent decades. The review on LMWH application in patients with preeclampsia patients were not identified by searching Pubmed and Embase databases. However, we found several meta-analyses regarding the preventive and treatment effect of LMWH on antiphospholipid syndrome (APS), recurrent pregnancy loss (RPL), venous thromboembolism (VTE), preeclampsia, intrauterine growth restriction (IUGR) and small for gestational age (SGA). A total of 21 studies were summarized (Table 1)^[6-9,15-31]. However, by analyzing these researches, we found limited information on bleeding risk either antenatally or postnatally. Only one study by Sirico *et al*^[28] analysed thromboprophylaxis with LMWH in women during the third trimester of pregnancy. Some studies reported increased risk in minor bleeding^[18,24,25,31]. Majority of the meta-analyses found no significant difference in bleeding events rate in LMWH group compared with LDA or placebo. No studies reported hepatic hematoma or major bleeding events from intrabdominal vessel.

Three meta-analyses focused on patients with preeclampsia^[6,26,29]. These studies reported consistencies of the beneficial effect on reduction of PE rate from LMWH treatment. The reduction on SGA development were testified and neonatal birthweight were also improved. However, only one study reported non-significant difference in bleeding risk of LMWH in patients with preeclampsia^[6]. The bleeding risk of LMWH was not reported in other two studies.

Similar with our reported cases, Sirico *et. al* reported augmented risk of bleeding^[28]. They included eight randomized controlled trails and indicated that women who received LMWH during pregnancy had a significantly higher risk of developing postpartum hemorrhage (PPH). No difference was found in the mean blood loss during delivery or risk for blood transfusion. Except for PPH, serious antenatal bleeding in patients with placenta previa was also reported as an important reason to quite LMWH

treatment^[25]. Despite recognizing this as a small probability event, the safety of LMWH in patients with high risk of antenatal hemorrhage should be evaluated. For minor bleeding events, one study reported increased risk in LMWH group from nine trials. The risk for bruises and epistaxis was 2 times higher in patients in heparin group^[18]. Bloody vaginal discharge, minor vaginal bleeding and subcutaneous hemorrhage from injection point were also reported. However, none of these symptoms were serious. None of these minor bleeding events stopped patients from LMWH treatment.

Notably, the indication of LMWH application in these three patients worth our serious consideration. Due to its advantages in the safety to the fetus and less possibility of causing osteopenia, LMWH is the recommended treatment in pregnant women over unfractionated heparin (UFH)^[32]. In our three cases, both of these patients were treated with a prophylaxis dose of LMWH. However, since LMWH did not have direct antihypertensive function, application of LMWH in PE patients renders more consideration. Despite its benefiting effects in improving microcirculation, LMWH is not included in the treatment strategy of PE patients^[33-35] and patients with IUGR risk factors^[36-39] as suggested by many guidelines. In case 1 and case 3, the LMWH was prescribed in view of improving the microcirculation in preeclampsia patients. In case 2, LMWH was given due to the suspicion of immune disorders. OAPS was suspected in this case although the patient lack other diagnostic criteria. Whether or not LMWH could improve the pregnancy outcomes in patients with PE and IUGR is still in debate. From the meta-analyses we included, it seemed that the beneficial effect of LMWH in improving some key obstetric outcomes in pregnancies including birth live rates, pregnancy loss rates, SGA and IUGR still seemed controversial. The absence of effect of LMWH in these placenta-mediated pregnancy complications might reflect the multifactorial pathophysiology. ³ The safety parameter of LMWH for the fetus has already been assessed, since it does not pass the placental barrier. The safety parameter of LMWH for the mothers was not adequately estimated. The association of anticoagulation with bleeding should still be postulated.

Bearing in mind the benefits and risks of LMWH in the treatment and prevention of preeclampsia, the application of LMWH should be reconsidered. In patients with preeclampsia and IUGR, LMWH was not included in the treatment strategy, but prophylaxis application of LMWH might have beneficial effect for improving microcirculations. However, the overall effect of improving pregnancy outcomes in these patients is still in debate. If prescribed, a planned labour was recommended with enough time interval from last dose of LMWH. In emergency situations, careful check and hemostasis procedures are crucial during CS. Careful management of blood pressure after delivery have key significance in preventing complications after delivery. Obstetricians should be remind of the elevated bleeding risk in patients with preeclampsia taking LMWH.

CONCLUSION

Pending further data to establish a balance between benefits and risks of LMWH in patients with preeclampsia, the cases in our report represented the nonnegligible bleeding risks during LMWH therapy. When patients presented signs suggestive of hemorrhage without vaginal bleeding, the possibility of intraabdominal hemorrhage should be taken into consideration. If conservative management is inadequate, exploratory laparotomy should be implemented.

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