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Mini-review

Heparin treatment in pregnancy loss: Potential therapeutic benefits beyond anticoagulation

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Abstract

Interventions with heparin therapies have increased fetal survival in patients with antiphospholipid syndrome (APS). In this review, several physiological and pharmacological effects of heparin are described. These different mechanisms of action could explain the beneficial effects of heparin in the treatment of recurrent pregnancy loss in patients with APS. In addition to direct effects of heparin on the coagulation cascade, heparin might protect pregnancies by reducing the binding of antiphospholipid antibodies, reducing inflammation, facilitating implantation and or inhibiting complement activation.

Keywords: Antiphospholipid syndrome; Pregnancy loss; Heparin

Pregnancy is an acquired hypercoagulable state due to an increase in procoagulants and impaired fibrinolysis. While this setting may prevent bleeding, the likelihood for maternal vascular complications, particularly venous thrombosis, is increased during pregnancy. In addition, it is now thought that fetal loss and possibly recurrent miscarriage are associated with some acquired and inherited thrombophilias. Since 1987, the antiphospholipid syndrome (APS) has been recognized as a major cause of pregnancy loss and growth restriction, whether it is associated with systemic lupus erythematosus or occurs as an independent

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syndrome (primary form). Fetal loss in patients with APS is thought to be associated with thrombosis of placental vessels, often with evidence for placental infarction (Brenner et al., 2000). Treatment with anticoagulant medications, such as heparin, is widely accepted as beneficial for both mother and fetus in pregnancies complicated by APS. Several studies indicate that women with recurrent miscarriage may benefit from heparin administration during pregnancy (Brenner et al., 2000; Carp et al., 2003); however, controlled trials have not yet been published.

The glycosaminoglycan heparin has been used in the clinic as an anticoagulant for more than 50 years. A fully characterized sequence in native heparin is known to be responsible for this activity. However, heparin is a complex polysaccharide, which has an array of properties that are unrelated to its anticoagulant activity. The following sections summarize the potential benefits of heparin with regards to fetal loss.

1. Anticoagulation

Fetal losses in APS, and possibly in association with other thrombophilic conditions, have been attributed to thrombosis of the uteroplacental vasculature and placental infarction. Although thrombosis is observed frequently in the deciduas and placentas of patients with APS, this observation is not universal, nor present in sufficient degree to apparently account for pregnancy loss associated with this syndrome. Not surprisingly, therapy for pregnant women with APS is now focused on preventing thrombosis at the maternal–fetal interface (Levine et al., 2002; Derksen et al., 2004). Heparin and aspirin are the drugs of choice for APS-related miscarriage, although it is not clear whether combination of both drugs is necessary for all women (Ruiz-Irastorza et al., 2002). Low molecular weight heparin, produced by chemical or enzymatic depolymerization of unfractionated heparin, is also used to prevent pregnancy loss and showed to have greater bioavailability and less interaction with platelets than unfractionated heparin (Levine et al., 2002).

Is anticoagulation enough to prevent pregnancy loss? Recent studies in mice demonstrate that the anticoagulants hirudin and fondaparinux sodium do not prevent antiphospholipid antibody-induced fetal loss, despite achieving anticoagulation levels comparable to heparin. These results suggest that anticoagulation may not be sufficient to prevent pregnancy loss in APS (Girardi et al., 2004).

2. Reduction of antiphospholipid antibodies binding

If anticoagulation alone is insufficient to prevent pregnancy loss in APS, the hypothesis that fetal loss is primarily due to a thrombotic mechanism must be questioned. Wagenknecht and McIntyre (1992) suggested there is a direct binding of heparin to antiphospholipid antibodies, and using an ELISA, showed a decrease in antiphospholipid antibody activity with increasing doses of heparin, though the doses used in these studies are several times higher than the therapeutic doses used in women. The effects is not due to an electrostatic interaction, as chondroitin sulfate, which has a negative charge similar to that of heparin, had no effect on antiphospholipid activity in the ELISA. Others have also reported a dose-