Low Molecular Weight Heparin as Thromboprophylaxis in Pregnancy

A Retrospective Analysis from 14 European Clinics

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Sir,

Low molecular weight (LMW) heparins are gradually replacing heparin in the main thromboprophylaxis indication of medium- and high-risk surgery for prevention of thromboembolism. However, since these products have been on the market for only the last years, there exist limited data as to the safety of these drugs in long-term use.

Controlled studies with heparin for thromboprophylaxis in pregnancy are practically nonexistent, however, due to the fact that heparin does not cross the placental barrier, it is preferred to oral anticoagulants. Not only with anticoagulants but also with heparin significant malformation rates could occur [1]. This might be related to the general high-risk profile in pregnant women with a thrombotic disposition. Heparin is also associated with osteoporosis [2]. Since heparin has to be injected at least twice daily and should continuously be monitored by coagulation assays during the later stages of pregnancy, there is a need of more convenient and safe antithrombotic drugs.

A possible candidate would be LMW heparins because they do not cross the placental barrier [3] and could have a lower risk of osteoporosis than heparin [4].

Before planning controlled studies with LMW heparin, we made a retrospective analysis comprising 184 pregnant women obtaining the LMW heparin Fragmin (Dalteparin, Kabi Pharmacia) for thromboprophylaxis in 14 European obstetric clinics. The primary objective was to obtain a crude estimation of the safety/efficacy profile in comparison with heparin. We used a specially designed questionnaire where demographic data and medical history, focused on thrombosis risk, were asked for. The LMW heparin dosages and existing anti-FXa measurements, both in patients and newborn children were noted, together with thromboembolic, bleeding, and other adverse events as well as obstetric complications.

Fragmin was used in a low dose, 2,500 IU, in 65% of the given treatments. 5,000 IU was used in 27% of the medication periods and higher dosages (7,200-16,000 IU) were only given in 8% of all Fragmin treatments. The median thromboprophylactic period was

42.5 days (range 1-476). Only in 36 patients, assessments of anti-FXa were made and only 24 patients had their dosages changed (19 were increased and 5 decreased). The criteria for dose adjustments were not possible to estimate in this study. No placental passage of anti-FXa was found (9 patients investigated). One child, but no mother died. The malformation rate was 3.3%, which would not be abnormal in pregnant patients, needing thromboprophylaxis [5]. Four

bleedings (2.2%) without sequelae occurred. Four deep vein thromboses (DVT) were found (2.2%). One patient had clinically diagnosed nonfatal PE and 4 patients had thrombophlebitis. The daily subcutaneous (mostly single) injections were well tolerated with 6.5% local reactions at injection sites.

This retrospective study indicates that LMW heparins have been used in a relatively low dose, with few dose adjustments, based on anti-FXa measurements in comparison with heparin. The benefit/risk ratio should be assessed in prospective comparative randomized clinical studies, with various risk groups for developing throm-

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boembolic complications during pregnancy. The dose requirement and need of monitoring the anticoagulant effect should be related to assessments of DVT with noninvasive methods and bleeding complications. The Fragmin dose used in most patients in this study was 2,500 IU. According to clinical experience, this dose would correspond to a standard heparin regimen of 5,000 IU b.i.d. for thromboprophylaxis in surgery with a moderate risk of DVT [6]. This relationship indicates that higher dosages of Fragmin might be needed in pregnancy, especially in women with an expected high risk of thrombosis, for whom the current therapy today is increased heparin dosages, especially in later stages of the pregnancies.

Appendix

Study sites. The following 14 clinics participated in the study

France CHU Caen (Dr. A. Derlon) CHG Aries (Dr. B. Barriot) CHU Rouen (Dr. J.Y. Borg) Hôpital Bel-Air, Metz, Thionville (Dr. A. Kadour, Dr. P. Dellinger, Dr. E. Welter) Hôpital Sainte-Croix, Metz (Dr. J.M. Bouschbacher) CH Dieppe (Dr. M. Cingotti) CH Haguenau (Dr. D. Le Lanne) CHRU Angers (Dr. C. Monrigan) CH Chambéry (Dr. D. Henriquet)
Denmark Herning Centralsykehus (Dr. I. Rasmussen)
United Kingdom The Women's Hospital, Liverpool (Dr. R.G. Farquharson) U.C.M. London (Dr. S.J. Macmin)
Germany Frauenklinik der Universität Göttingen (Dr. Dittmer) St. Katharinen, Frechen (Dr. M. Hövel)

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