

Anexo al informe de la CFT, sobre Tinzaparina para Profilaxis y tratamiento de la Enfermedad Tromboembólica Venosa durante el embarazo presentado en la anterior CFT.

### HBPM EN EMBARAZO: Enoxaparina

Las heparinas de bajo peso molecular son los anticoagulantes de elección en embarazo. La enoxaparina, HBPM disponible en HSLL, se lleva utilizando 20 años en embarazadas con alto riesgo de trombosis y complicaciones de embarazo.

Está **clasificada como Categoría B de la FDA.**

En la siguiente tabal se refleja la información contenida en las fichas técnicas de tinzaparina y enoxaparina respecto al embarazo. (1-2)

Tinzaparina	Enoxaparina
<p>En un número limitado de mujeres embarazadas tratadas con <b>tinzaparina (637)</b>, los datos obtenidos <b>no mostraron un riesgo adicional durante el embarazo, o sobre la salud del feto o del recién-nacido.</b> Hasta la fecha, no se dispone de otros datos epidemiológicos relevantes.</p> <p>En dos estudios clínicos, <b>no se observó el paso de tinzaparina a través de la placenta.</b> Los datos en animales no indican efectos nocivos directos o indirectos sobre el embarazo, el desarrollo embriofetal, el parto o el desarrollo postnatal</p> <p>Debe tenerse precaución a la hora de prescribir tinzaparina a mujeres embarazadas.</p> <p>Mujeres embarazadas con válvulas cardíacas implantadas: Se han comunicado fallos terapéuticos en mujeres embarazadas con válvulas cardíacas implantadas tratadas con dosis anticoagulantes completas de tinzaparina y otras heparinas de bajo peso molecular. <b>No se recomienda la utilización de tinzaparina en mujeres embarazadas con válvulas cardíacas implantadas.</b></p> <p>La <b>anestesia epidural</b> durante el parto en mujeres embarazadas tratadas con dosis profilácticas de heparinas de bajo peso molecular debe ser monitorizada por especialistas</p>	<p>En la mujer embarazada <b>no hay ninguna evidencia de que la enoxaparina atraviese la barrera placentaria durante el segundo y el tercer trimestre de la gestación.</b></p> <p>Por prudencia y por falta de experiencia, se <b>desaconseja la utilización</b> de la enoxaparina durante el <b>primer trimestre del embarazo.</b></p> <p>Si se realiza una <b>anestesia epidural, el tratamiento con enoxaparina debe ser interrumpido.</b></p> <p>En un ensayo clínico en el que se administró enoxaparina sódica a 8 mujeres <b>embarazadas con prótesis valvulares cardíacas</b>, dos de ellas desarrollaron coágulos que bloquearon la válvula, lo que les ocasionó la muerte. *</p>

\* Enoxaparin 40 mg subcutaneously every 12 hours is the prophylactic regimen of choice for pregnant patients who are at high risk for deep venous thrombosis and pulmonary embolism; however, data on efficacy from controlled trials are lacking (Anticoagulation in Prosthetic Valves and Pregnancy Consensus Report Panel and Scientific Roundtable. Anticoagulation and

enoxaparin use in patients with prosthetic heart valves and/or pregnancy. Clinical Cardiology Consensus Reports, American Health Consultants, October 1, 2002)

Las estrategias de mantener la anticoagulación terapéutica evitando el daño materno o fetal debido a agentes antitrombóticos están basadas en gran parte en datos retrospectivos porque por consideraciones éticas y legales hacen que los estudios entre mujeres embarazadas sean difíciles de conducir.

Al igual que con la tinzaparina se han publicado numerosos estudios en donde embarazadas han recibido enoxaparina.

- a) In a review of **57 pregnancies** in 50 women, enoxaparin appeared to be useful for thromboprophylaxis in those patients who may be at risk, without an increase in hemorrhagic adverse events. A small, controlled, prospective study (n=46) suggested that **enoxaparin 40 milligrams mg/day in combination with aspirin 100 mg/day was safe and effective in all trimesters of pregnancy in women with a history of thromboembolism or with evidence of acquired or congenital thrombophilia**. No significant differences were noted between patients treated with enoxaparin-plus-aspirin and patients treated with aspirin only in the incidence of congenital malformations, abortions, intrauterine growth restriction, preterm deliveries, or birth weight. The one case of bilateral post axial polydactyl of the hands occurred in a neonate with a familial history of this condition (3)
  
- b) In a **retrospective** community based study, **bleeding complications during delivery in pregnant women treated with prophylactic low molecular-weight heparin (LMWH)** occurred more often in the LMWH group. Patients received dalteparin 5000 IU daily (n of 33) or enoxaparin 40 mg daily (n of 1) and compared to 1,697 non-heparin treated pregnant women. LMWH treatment resulted in significantly more blood loss during delivery and more postpartum anemia (4). Of the 34 women in the LMWH group, 14 were treated only during the third trimester, 15 during the second and third trimesters, and the remaining 5 received treatment during all three trimesters. All women received 500 milliliters (mL) Dextran 70 before and after delivery. LMWH prophylaxis was continued postpartum in 12 women and 22 switched to warfarin. Profuse hemorrhage (greater than 600 mL during delivery) was experienced in 9 of 34 (26%) LMWH patients compared to 126 of 1697 (7%) controls (p equal to 0.001). Postpartum anemia defined as hemoglobin less than 100 grams per liter (g/L) on the second day after delivery, was experienced by 10 of 34 (29%) LMWH patients compared to 139 of 1697 (8%) control patients (p less than 0.001). **LMWH therapy was**

**associated with significantly more loss of blood during delivery (mean: 473 mL) and a longer mean time of hospitalization (4.5 days) compared to the control group (365 mL and 2.8 days, respectively; p less than or equal to 0.02).**

c)

In a study in which **enoxaparin** was used to **treat 61 pregnant women (69 pregnancies)**, there were five miscarriages early in pregnancy, four fetal losses in the second trimester, and seven infants delivered preterm (5). This, the largest study to date of low-molecular-weight heparin use in pregnancy, confirms previous reports that it is a safe and effective alternative to unfractionated heparin for obstetric thromboprophylaxis in high-risk women. Effects on bone demineralization require further investigation. The authors question whether these adverse **outcomes were due to enoxaparin or to the antiphospholipid syndrome which necessitated treatment with the drug.**

d) **57 pregnancies** in 50 women over six years. **Retrospective review of casenotes of women who received enoxaparin during pregnancy for thromboprophylaxis or treatment of venous thromboembolism.** There were no incidences of heparin-induced thrombocytopenia. Twenty-two women had spinal or epidural anaesthesia and no complications were encountered. There was one instance of antepartum haemorrhage following attempted amniotomy in a woman with previously unknown vasa praevia. Appears effective in preventing venous thromboembolism (6)

e)

In a case-control study, **rates of bleeding complications, including postpartum hemorrhage (PPH) or RBC transfusions, were not increased in patients treated either prophylactically or therapeutically with low molecular weight heparin (n=49) compared to controls (controls to cases ratio, 2:1) matched for delivery route (cesarean vs vaginal).** With the exception of 1 patient who received twice daily dalteparin for a prosthetic mitral valve, cases received twice daily enoxaparin and delivered a total of 55 infants. Prepregnancy obesity occurred in a higher number of cases than controls (odds ratio (OR), 3.91; 95% confidence interval (CI), 1.7-9.09). The rate of PPH (primary endpoint) was defined as an estimated blood loss (EBL) of more than 500 cubic centimeter (cm<sup>3</sup>) for a vaginal delivery and more 1000 cm<sup>3</sup> for a cesarean delivery, or a return to the operating room for postpartum bleeding complications within 14 days of delivery. The rates of PPH were 11% (n=6/55) and 8.2% (n=9/110) for cases and controls, respectively (OR, 1.37; 95% CI, 0.16-11.5). Postpartum RBC transfusions occurred in 5.4% and 3.6% of cases and controls, respectively (OR, 1.5; 95% CI, 0.3-7.48). The EBL was similar between cases and

controls for vaginal (296 vs 307 cm(3), respectively;  $p=0.62$ ) or cesarean delivery (688 vs 765 cm(3), respectively;  $p=0.34$ ). Notably, the study was not adequately powered to detect differences in either PPH or RBC transfusions. Cases were more likely to have a labor induction (45% vs 26%;  $p=0.01$ ) and gestational age was lower in cases versus controls (37.4 vs 38.3 weeks;  $p=0.03$ ). There were no fetal demises or complications from regional anesthesia in either group. Birth weights and length of neonatal hospital stay were similar between the cases and controls, rates of neonatal mortality were not statistically different between cases (3.6%) and controls (0.9%;  $p=0.26$ ) (7)

f)

In a review of **41 pregnancies, enoxaparin treatment was safe and effective**. A total of 34 women were treated with enoxaparin for acute thromboembolic events, history of thromboembolic event, antiphospholipid syndrome, and active lupus disease. The majority of women received a single daily enoxaparin dose of 40 mg administered subcutaneously. No bleeding disorders occurred during therapy, despite continued therapy during surgical procedures including cesarean deliveries. Nine patients received epidural anesthesia with no noted complications. Relative safety and efficacy of low-molecular-weight heparin **therapy in pregnancy and delivery** (8).

g)

For **pregnant patients with prosthetic heart valves**, oral anticoagulants appear to be more efficacious than either unfractionated heparin or low-molecular-weight heparin (LMWH) for preventing thromboembolism. However, oral agents have potential to harm the fetus; inadequate anticoagulation, on the other hand, increases maternal risks. Recent guidelines suggest three possible approaches to using heparin products to manage pregnant patients with mechanical valves: 1) aggressive adjusted-dose heparin throughout pregnancy with target APTT at least 2 times the control or anti-Xa heparin level of 0.35 to 0.70 IU/mL, 2) adjusted-dose LMWH throughout pregnancy with a target 4-hour post-injection anti-Xa heparin level of 1.0 IU/mL, or 3) either of the aforementioned agents until the 13th week of gestation, followed by routine warfarin administration until 2 weeks prior to delivery at which time heparin or LMWH treatment is resumed (9-10). The use of low-dose (e.g. 5000 IU subcutaneously every 12 hours) is considered inadequate in this population. **More information is needed to clarify the optimal dose and/or target therapeutic range of both unfractionated and low-molecular-weight heparins in this patient group.**

h)

There may be a **higher risk for thromboembolism in pregnant women with**

**mechanical prosthetic heart valves.** There are postmarketing reports of both successful use and thromboprophylaxis failure in pregnant women with prosthetic heart valves who received enoxaparin; these latter events have resulted in maternal and fetal death or surgical interventions (11). Based on published case reports and their own investigation, the likelihood of a thromboembolic event was estimated to be 1 event in 66 months of LMWH use; 1 event in 20 months of unfractionated heparin use; and 1 complication in 294 months of warfarin exposure (12). This latter study investigated the frequency of events and successful pregnancy outcome in women who either used LMWH throughout a pregnancy or to use LMWH in early and late pregnancy with warfarin use in the 2nd trimester. Of 14 pregnancies, there were 9 live healthy births, 2 miscarriages and 1 medical termination in patients on enoxaparin; there were no reports of hemorrhagic complications, enoxaparin-induced thrombocytopenia or osteoporotic fractures.

- i) To assess the maternal, fetal and neonatal safety of enoxaparin in pregnant women who require antithrombotic therapy. Data from 624 pregnancies in 604 women between 1988 and 1997. Serious maternal haemorrhage occurred in 11 cases during pregnancy (1.8%), one being reasonably related to enoxaparin, and in nine cases at delivery (1.4%), all unrelated to enoxaparin. Maternal thrombocytopenia was reported in 10 cases (1.6%). two being serious but unrelated to enoxaparin. Eight pregnancies ended in stillbirth (1.1%). Among the 693 live births, 17 major congenital abnormalities (2.5%) and 10 serious neonatal haemorrhages (1.4%) were reported. None of the fetal or neonatal adverse events was related to enoxaparin. Eight venous thromboembolic events (1.3%) were reported. **CONCLUSIONS:** The incidence of adverse events reported could be explained by the high risk profile of the study population. Overall, this retrospective study suggests enoxaparin is well tolerated during pregnancy (13)

#### BILBIOGRAFÍA:

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