Obstetric Outcome with Low Molecular Weight Heparin Therapy during Pregnancy

Abstract:

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This was a prospective study of women attending a combined haematology/obstetric antenatal clinic in the National Maternity Hospital (2002-2008). Obstetric outcome in mothers treated with low molecular weight heparin (LMWH) was compared to the general obstetric population of 2006. There were 133 pregnancies in 105 women. 85 (63.9%) received prophylactic LMWH and 38 (28.6%) received therapeutic LMWH in pregnancy. Ten (7.5%) received postpartum prophylaxis only. The perinatal mortality rate was 7.6/1000 births. 14 (11.3%) women delivered preterm which is significantly higher than the hospital population rate (5.7%, p<0.05). Despite significantly higher labour induction rates (50% vs 29.2%, p<0.01), there was no difference in CS rates compared to the general hospital population (15.4% vs 19.6%, NS). If carefully managed, these high-risk women can achieve similar vaginal delivery rates as the general obstetric population.

Introduction

Venous thromboembolism remains the leading cause of morbidity and mortality amongst pregnant women in developed world. Effective primary prevention and acute management is therefore vital to reduce morbidity and mortality. Over the last 15 years management of VTE in pregnancy has been revolutionized with the introduction of low molecular weight heparin (LMWH) as a treatment option in pregnancy. LMWH has replaced unfractionated heparin (UFH) as agent of choice for prevention and treatment of VTE in pregnancy. The efficacy and safety of LMWHs have been demonstrated by a number of systematic reviews. Their conclusions have been endorsed by international guidelines, including the Royal College of Obstetricians and Gynaecologists and the American Academy of Chest Physicians. Despite this, LMWH still remains unlicensed for use in pregnancy.

Compared to unfractionated heparin, LMWH has many advantages; the pharmacokinetics of LMWHs are stable and predictable with increased clearance compared to unfractionated heparin. LMWHs can be administered subcutaneously; the need for regular laboratory monitoring is reduced significantly. Subcutaneous administration allows for ease of use. LMWHs demonstrate less binding to platelet factor 4, substantially reducing the risk of heparin induced thrombocytopenia (HIT) and osteoporotic fractures.

In the obstetric setting, one of the main advantages of LMWHs over UFH is the potential reduced risk of bleeding, as severe obstetric haemorrhage remains a leading cause of severe obstetric morbidity.

Much of the literature to date has focused on the essential objective of establishing the safety to fetus and mother of LMWH. There is less information available on the effect of LMWH on labour outcomes and complications. High risk pregnancy status is automatically conferred to women who are prescribed LMWH. It is reassuring to note that there does not appear to be an increased risk of massive obstetric haemorrhage >1,500mls, compared to women managed without LMWH. Prematurity has been postulated as a possible complication of LMWH, but the evidence for this is weak, with most studies showing that perinatal mortality to be iatrogenic rather than spontaneous preterm delivery.

Recent work has suggested an association between LMWH and shortened labour length at term without increased operative intervention in women prescribed prophylactic LMWH. The use of LMWH in pregnancy for reasons other than prevention of VTE is controversial, with a wealth of literature both supporting and refuting its use. Our aim was to observe the obstetric outcome in mothers treated with low molecular weight heparin (LMWH) during pregnancy and to compare their obstetric outcome with the general obstetric population.

Methods

The National Maternity Hospital is one of three tertiary level units serving the city of Dublin and its surrounding areas. It has an annual delivery rate of approximately 9,200. All women who require ongoing therapeutic or prophylactic treatment with low molecular weight heparin during pregnancy attend a dedicated multidisciplinary clinic staffed by an obstetrician, haematologist and midwives trained in teaching administration of LMWH. Delivery of antenatal care for these high-risk women in a multidisciplinary clinic is a cornerstone of their management.

Women attending the combined haematology obstetric antenatal clinic are entered prospectively into a database. Cases receiving LMWH were identified by reviewing the database into which the name, diagnosis and date of delivery of all women attending the high-risk clinic are entered. To ensure completeness of data, additional information on patients was obtained from chart review and extraction of information from the electronic Patient Administration System (PAS). Indications for treatment with LMWH included a history of venous thromboembolism (VTE) in a current or previous pregnancy; cardiac valve replacement; the presence of thrombophilia (including factor V Leiden homozygote and protein S and C deficiencies, and antithrombin deficiency); recurrent miscarriage or previous intrauterine death. The prophylactic and therapeutic dosages were calculated by maternal weight. Tinzaparin was administered at a dose of 75IU/Kg for prophylaxis and at 175 IU/Kg for treatment. Enoxaparin was administered depending on maternal anti Xa levels. The decision to use one LMWH over the other was a clinical decision on the part of the treating clinician.

Data was entered into a database for analysis and included age, parity, gestation at delivery, indication for induction/delivery, mode of delivery. For comparison of obstetric outcomes, data from the general hospital population was obtained from the National Maternity Hospital Annual Clinical Report, 2006. Chi-square and Student t test were used for univariable two-group comparisons. Spearman correlations were used to evaluate the association between continuous measures. Statistical computations were performed using SPSS (version 12) software. Two-tailed p values less than 0.05 were judged statistically significant.

Results

Low molecular weight heparin use was identified in 133 pregnancies in 105 women during the period 2004 to 2008. Fifty eight women were multiparous (43.6%) and 75 were multiparous (56.4%). Eighty five (63.9%) women received prophylactic LMWH and 38 (28.6%) received therapeutic LMWH in pregnancy. Ten (7.5%) received postpartum prophylaxis only so these women were not included in the obstetric analysis. Tinzaparin was administered in 98 cases and enoxaparin was administered in 35 cases. The indications for treatment with LMWH included venous thromboembolism in current or previous pregnancy, and the other indications and reasons for thromboprophylaxis are shown in Table 1.
Two women had early second trimester losses. One of these women was on prophylactic LMWH as she had a history of DVT in the past. The other woman was on therapeutic LMWH. She had a history of antiphospholipid syndrome with three previous midtrimester losses and renal impairment. One woman had a stillbirth at 25 weeks, therefore the perinatal mortality rate was 7.6/1000 births. She had a diagnosis of antiphospholipid syndrome and was receiving prophylactic LMWH. One woman on prophylactic LMWH had an abruption at 36 weeks resulting in a live birth. No congenital defects were recorded.

There was no significant difference in age (30.4, 31.7 years; p=0.64), spontaneous vaginal delivery rates (65.9%, 63.2%; p=0.67), emergency Caesarean section (CS) rates (8.2%, 7.9%; p=0.73), admission to neonatal intensive care unit (8.2%, 5.3%; p=0.40), epidural usage (28.2%, 18.4%; p=0.17) or mean estimated blood loss (359ml, 361mls; p=0.86) between women taking prophylactic or therapeutic LMWH. Details of this are shown in Table 2. There was no massive obstetric haemorrhage of greater than 1500mls recorded immediately post partum.

Fourteen (11.3%) women who were receiving LMWH delivered preterm (< 37 weeks) which is significantly higher than the hospital population rate of 5.7% (p<0.05). Nine of the premature deliveries were as a result of spontaneous preterm labour. Seven of these were cephalic spontaneous vaginal deliveries (range 25-36 weeks gestation), one was a spontaneous vaginal breech delivery at 33 weeks, one was a forceps delivery at 36 weeks gestation. One woman was induced at 36 weeks gestation, 3 were elective caesarean sections between 34 to 36 weeks gestation and 1 was a planned emergency caesarean section at 36 weeks gestation.

Overall the CS rate in all women receiving LMWH was 15.4% (19/123) which was similar to that of the entire general obstetric population which had a rate of 19.9% (1508/7985)(p=0.3). The overall CS rate in nulliparous women at any gestation who received LMWH was 16% (8/50). This was not significantly different to the general nulliparous obstetric population who had a 21.4% CS rate (765/3577)(p=0.48). There was a significantly higher rate (p=0.01) of induction in single cephalic nulliparas e37 weeks gestation who received LMWH (50.0%22/44) compared to the single cephalic nulliparas e37 weeks gestation in the general obstetric population (924/3159, 29.2%), (p= 0.05). Interestingly, despite the significantly higher induction rate in women on LMWH, there was no difference in the CS rate in induced single cephalic nulliparas e37 weeks on LMWH (22.7% 5/22%) and induced nulliparas in the general obstetric population (272/924, 29.4%) (p=0.17).
**Discussion**

Women receiving low molecular weight heparin experienced a higher preterm delivery rate than that of the general obstetric population. The majority of these deliveries were as a result of spontaneous preterm labour rather than iatrogenic deliveries. This was a surprising finding. Due to the high-risk nature of the population, prematurity relating to iatrogenic intervention would perhaps be expected. While thrombophilia has been associated with recurrent miscarriage and late pregnancy loss, it has not been associated with prematurity, thus ruling this out as a potential confounder. Previous work has reported an increased risk of preterm birth in women receiving LMWH during pregnancy. However, this elevation was non-significant.

The overall CS rate in nulliparas was similar to the general obstetric population. Heparin has been shown to have immunomodulatory properties which may have an effect on modifying inflammatory pathways involved in the onset or progress of labour. Eckman-Ordeberg et al have demonstrated that LMWH stimulates myometrial contractility and cervical remodeling in vitro. This may be a potential explanation for our findings of increased rates of spontaneous preterm labour and a relatively low CS rate in induced nulliparas. Further work in this area is warranted.

In conclusion LMWH appears to be safe in pregnancy. If carefully managed during pregnancy and labour, our cohort shows that high risk women receiving LMWH can achieve similar high vaginal delivery rate as the general obstetric population.

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**References**