Pre-term delivery in women taking protease inhibitors: **a class effect or due to individual agents?**

Helen Parker[1], Sarah Allstaff[2], Janet Wilson[1]

[1]Centre for Sexual Health, Leeds General Infirmary, [2]Tayside Sexual and Reproductive Health Service, Ninewells Hospital and Medical School, Dundee

The Leeds Teaching Hospitals NHS Trust

BACKGROUND

An association between highly active antiretroviral therapy (HAART) and preterm delivery (PTD) was first reported in 1998 by the Swiss Cohort[1 2] and has subsequently been reported in several analyses of the European Collaborative Study.[3 4 5] Although this association has not been found in two large American studies[6 7] it remains a significant concern and a number of studies have looked for an association between PTD and specific drug classes.

Protease Inhibitors (PIs) are recommended as part of combination anti-retroviral therapy (ART) for the prevention of mother-to-child-transmission for HIV infected women in whom the use of nevirapine (NVP) is contraindicated. However, there are conflicting data regarding their association with PTD. Whilst two studies reported that the association between ART and PTD only exists if a PI formed part of the treatment regime[8 9] both a 2007 US meta-analysis[10] and an ART Pregnancy Register analysis[11] including data from over 10.000 women between 1989 and 2010 found no association between PIs and PTD. Although the NSHPC UK and Ireland data showed an association between HAART and PTD there was no significant difference between PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) containing regimes.[12] Further evidence is awaited to guide decision making regarding the best choice of third drug use in pregnant HIV-infected women.

METHODS

A pregnancy database has been maintained within the Leeds Centre for Sexual Health (LCSH) since 2006. Data recorded on a Microsoft Excel™ Spreadsheet include demographics, HIV history, obstetric history, anti-retroviral treatment, delivery data and maternal and neonatal outcomes. Delivery data were analysed retrospectively for all women completing their pregnancies under the care of the LCSH in relation to ART, mean gestation at delivery and mean CD4 at diagnosis of pregnancy. Statistical analysis was undertaken using the Mann-Whitney U Test.

RESULTS

Data for 101 pregnancies in 97 patients occurring between July 2006 and April 2009 were available. The cohort was predominately of black African origin with a mean age of 30.4 years (see baseline characteristics). Of the 101 pregnancies two were terminated and there were three first trimester miscarriages. Those patients whose outcomes were unknown due to transfer, dispersal or emigration were excluded as was a patient who refused treatment. A further patient was also excluded as she took both saquinavir (SQV/r) and lopinavir (LPV/r) during the course of her pregnancy. The remaining 93 pregnancies were then analysed according to antirerovirals taken in pregnancy. All patients also took a nucleoside reverse transcriptase inhibitor backbone. Two patients who took atzanavir/ritonavir had a mean gestation of 35.5 weeks at delivery but were excluded from further analysis due to the small numbers.

The mean gestation at delivery for women on SQV/r was 39.2 weeks with no PTDs (defined as gestation below 37 completed weeks). In contrast the mean gestation at delivery for women on LPV/r was 37.4 weeks with eight PTDs of which three were before 34 weeks' gestation. The mean gestation with NVP was 38.4 weeks with four PTDs three of which were pre-34 weeks.

Whilst no significant difference was found between the mean gestation in those taking LPV/r versus NVP and SQV/r versus NVP, the mean gestation at delivery was significantly lower with LPV/r compared with SQV/r (Mann-Whitney U test $p = 0.005$).

The mean CD4 of the NVP group at diagnosis of pregnancy was significantly lower than that of the SQV/r group (Mann-Whitney U test $p=0.0057$) but there was no significant difference between the mean CD4 of the NVP group and the LPV/r group or between LPV/r and SQV/r. Those with an early preterm delivery were more likely to have a lower CD4 compared to those with a gestation of 37 or more completed weeks (Mann-Whitney U test $p=0.026$) however these deliveries were evenly split between the NVP and LPV/r groups.

NEVIRAPINE

23 PREGNANCIES — 38.4 WEEKS MEAN GESTATION AT DELIVERY

4 PRETERM DELIVERIES <37 COMPLETED WEEKS

3 PRETERM DELIVERIES <34 COMPLETED WEEKS

CD4 — 321 MEAN CD4 AT DIAGNOSIS OF PREGNANCY
CD4 RANGE 9-859

SAQUINAVIR/r

38 PREGNANCIES — 39.2 WEEKS MEAN GESTATION AT DELIVERY

0 PRETERM DELIVERIES <37 COMPLETED WEEKS

0 PRETERM DELIVERIES <34 COMPLETED WEEKS

CD4 — 468 MEAN CD4 AT DIAGNOSIS OF PREGNANCY
CD4 RANGE 192-1380

LOPINAVIR/r

27 PREGNANCIES — 37.4 WEEKS MEAN GESTATION AT DELIVERY

8 PRETERM DELIVERIES <37 COMPLETED WEEKS

3 PRETERM DELIVERIES <34 COMPLETED WEEKS

CD4 — 406 MEAN CD4 AT DIAGNOSIS OF PREGNANCY
CD4 RANGE 120-882

BASELINE CHARACTERISTICS

Total pregnancies	101
Total patients	97
Exclusions	10
Miscarriage	3
Termination	2
Transferred care out of LCSH	1
Dispersal	1
Loss to follow up	1
Treatment refusal	1
Received both LPV and SQV	1
Total pregnancies included	93
Ethnicity	
Black African	79 (85%)
Black British	1 (1%)
White	9 (10%)
Other	4 (4%)
Age mean (range)	30.4 (20-41)
CD4 mean (range)	409 (9-1380)
Diagnosed in this pregnancy	32 (34%)
Conceived on HAART	32 (34%)

CONCLUSIONS

These findings suggest that PTD may not be associated with PIs as a class of drug but with individual PIs. In this study LPV/r was significantly associated with a shorter gestation at delivery compared with saquinavir. Although our cohort was reasonably sized there were few pre-term deliveries and although there was no significant difference between CD4 in women taking LPV/r and SQV/r the women on LPV/r did have a slightly lower mean CD4 count at pregnancy diagnosis. Clearly though a lower CD4 count is not the whole answer between the significantly shorter gestation with LPV/r compared with SQV/r, as women taking NVP did have a significantly lower CD4 count (as would be expected in view of the prescribing cautions with NVP) but no significantly shorter gestation at delivery was seen in these women. There are other known confounding variables such as previous PTD, smoking or the presence of sexually transmitted infections which have not been adjusted for in this study. The LCSH pregnancy database continues to collate data and these questions can be addressed in future analyses. As SQV/r is no longer used as a first-line PI in pregnant women in our clinic, further research is required to establish if increased rates of PTD are associated with newer PIs which we are now currently favouring.

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