Viral Hepatitis in Pregnancy

Dr Eleni Nastouli
Consultant in Virology and Paediatric Infectious Diseases
UCLH and Great Ormond Street Hospital NHS Trust
Chronic hepatitis B: Mother-to-child-transmission (MTCT)

- Vertical transmission remains most common route of infection worldwide
- Women of childbearing age the reservoir in endemic areas where >20% of women have CHB
- Risk of transmission without immunoprophylaxis is 70-90%
- 90% of infected infants progress to chronicity

10% - 15% risk of transmission despite vaccine and HBIG when mother is high risk
  - HBV DNA > $10^8$ c/mL or $2 \times 10^7$ IU/mL
  - HBeAg +

Canho Vaccine 1997
Singh J Virol 2011
The woman with a new diagnosis: the patient’s perspective

Offer optimal care

1. Screening- discuss results
2. Referral to Liver Specialist
3. See a Liver Specialist
4. Work up for CHB and transmission risk
5. When high risk have a clear plan..
6. FU baby with vaccination/testing
7. Have an uninfected baby
8. Boosters..

and receive optimal care

? specialist midwife
? referral
? social issues
? local protocols
? that I understand
? Who/where/when
? result
? when ? GP aware
NCL Audit: Referrals to Hepatology

H1 68% (48/70) *Specialist Midwife*
H2 49% (44/68) as 20 women transferred care and 1 miscarried
H3 86% (55/64) and
H4 51% (101/200)

NCL Audit: Testing for bloodborne viruses

Testing for *Laboratory systems*

HIV 99%
HCV 53%
HDV 31%

One woman had an HDV superinfection in pregnancy
NCL Audit: HBV DNA quantitation in pregnancy (n=295/401)
Clinical pathway

Antenatal clinic
Booking bloods after verbal consent

Virology
HBsAg+, confirmed, viral markers, viral load

Antenatal Team
Email, letter posted
Advice: HBIG, vaccine in birth plan

Pharmacy or ANC
Arrange HBIG supply from HPA/Cfl

Refer to Hepatology
Inform GP
Assess liver disease, advise about transmission risk

Neonatology
Letter of referral

Vaccinate +/- HBIG to the baby, FU 1 year
Refer to GP
UCLH: HBV Hepatology review within 6 weeks of diagnosis

Hep B: Specialist review within 6 weeks

- Jan-March: 30%
- Apr-June: 50%
- July-Sept: 72.70%
- Oct-Dec: 92.30%
Breastfeeding
Length of treatment
When to start
When to stop
Flares

Treatment decision making

Treat the mother?
Treat for MTCT?

Efficacy
Safety
Barrier to resistance
Antiviral treatment: safety in pregnancy

Immunomodulators

IFNa
PegIFN

Antivirals

Lamivudine
Adefovir
Entecavir
Telbivudine
Tenofovir

Contraindicated

B: Animal studies no evidence of harm to the fetus—no adequate studies in pregnant women

or Animal studies have shown adverse effect but data in humans shown no risk

C: Animal data have shown adverse effects—no adequate data in women

or No animal studies conducted and no human data
Treatment for MTCT
Lamivudine (LAM)

141 women with HBV DNA > 10^9 c/mL

- 56 women had LAM
  - Infants had vaccine and HBIG
  - 10 infants (18%) with CHB

- 59 women had placebo
  - Infants had vaccine and HBIG
  - 23 (39%) with CHB

Xu J Viral Hep 2009
Short duration of lamivudine for the prevention of hepatitis B virus transmission in pregnancy: lack of potency and selection of resistance mutations

- ↑ quasispecies “complexity”
- ↑ LAM-related mutations
- ↓ HBsAg escape

26 women
HBV DNA >10^7 IU/ml
median 53 days LAM

Ayres A et al, Journal of Viral Hepatitis  Oct 2013
Treatment for MTCT
Telbivudine (LdT)

229 women with HBV DNA > 10^7 c/mL

450 women >10^6 IU/mL

135 women had TBV
Infants had vaccine and HBIG

94 women had placebo
Infants had vaccine and HBIG

279 women had LdT

0/132 infants (0%) with CHB

171 women placebo

7/88 (8%) with CHB

0% infants with CHB

14.7% infants with CHB

Han GR et al J Hep 2011

Wu Q Clin Gastro Hepatol, June 2015
Treatment for MTCT
LAM vs LdT

700 eligible mothers enrolled, eight withdrew consent prior to the baseline

263 enrolled to LdT treatment. Six withdrew consent prior to delivery (one had grade II AE and five returned to local hospital).

55 enrolled to LAM treatment. Two mothers withdrew consent and returned to local hospital before delivery.

374 enrolled to controls, and 11 mothers withdrew consent and returned to local hospital before delivery.

252/257 mothers and 257/262 infants completed study.

51/53 mothers and 52/54 infants completed study.

345/363 mothers and 352/370 infants completed study.

HBV DNA >6 log\textsubscript{10} copies/ml

Zhang H et al, Hepatology 2014
Treatment for MTCT
LAM vs LdT

Women with HBV DNA $>6 \log_{10}$ copies/ml

- Significant reduction in MTCT rate

- Comparable safety and efficacy

Zhang H et al, Hepatology 2014
Treatment for MTCT
Tenofovir (TDF)

11 Asian women received TDF median gestational age 29/40

Median duration of TDF use before delivery was 10 (7-12) weeks.

- significant reduction in serum HBV-DNA
  mean 5.25 ± 1.79 vs. 8.87 ± 0.45 log_{10} copies/mL

- 3/11 had serum ALT >1.5 times ULN; 2/11 normalized before delivery

- 11 infants were born with no obstetric complication or birth defects

- 5/11 infants were breastfed

- 11/11 infants were hepatitis B surface antigen negative 28-36 weeks after birth

Pan CQ et al Dig Dis Sci 2012
Treatment for MTCT
Tenofovir (TDF)

HBV DNA $> 7 \log_{10}$ IU/ml

Total pregnancies

<table>
<thead>
<tr>
<th>TDF pregnancies</th>
<th>Lamivudine pregnancies</th>
<th>Untreated pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n = 58$</td>
<td>$n = 52^*$</td>
<td>$n = 20$</td>
</tr>
</tbody>
</table>

- Perinatal transmission assessed $n = 44$
- Virological response assessed $n = 54$
- Perinatal transmission assessed $n = 43$ (one set of twins)
- Virological response assessed $n = 21$ (Ayres et al., 2013)
- Perinatal transmission assessed $n = 10$
- Virological response assessed $n = 5$ (Ayres et al., 2013)

Greenup AJ, J Hepatology 2014
Virological efficacy

A: Mean birth viral load >7 log_{10}
LAM n=21, TDF n=54 18% vs 3%

B: Mean reduction of viral load (baseline to birth)
LAM n=21, TDF n=42

Transmission outcomes

TDF case
? early in utero transmission
4.4 log_{10} at delivery

Greenup AJ, J Hepatology 2014
Tenofovir: APR data

606 women in first trimester and
336 in second trimester

rate of birth defects associated with tenofovir

2.3% (first-trimester use) to
1.5% (second-trimester use)

similar to the background rate

Source: APR
Lamivudine and Telbivudine appear safe and effective for prevention of mother-to-child transmission;

Tenofovir might be preferred especially if long-term treatment is anticipated.
Offer optimal care

1. OPD appointment
1. Management at childbearing age
1. On antivirals when pregnant
1. FU baby with vaccination/testing
1. Have an uninfected baby
1. Boosters..

Receive optimal care

? start or defer treatment
? discontinue
? who/where/when
? testing
? when ? GP aware
Treatment at childbearing age

- Advanced Fibrosis
  - Yes: Consider PEG –IFN before pregnancy
  - No: Defer treatment

- Initiate nucleoside analogue if not successful

EASL Guidelines 2012
Pregnant and already on treatment

• **Stop** if on Peg-IFN

• If on nucleoside analogues **consider discontinuation carefully**; think of the severity of liver disease, the gestational age, the risk of flares

• If decision is to treat **replace FDA category C antivirals with category B**

• **Discuss**
  - breastfeeding
  - unknown toxicity
Of the 18 women with VL > 10^7 IU/ml, HBeAg + and eligible for antiviral therapy

4 were treated with lamivudine / tenofovir

13 were not offered antivirals

1 had a miscarriage,

A further 9 women with VL between 10^6 to 10^7 IU/ml, HBeAg + were also treated
UK NSC National Hepatitis B in Pregnancy Audit

Hep B Audit 2014

Chronic hepatitis B infection is a major cause of liver disease worldwide and can be transmitted vertically from mother to baby. An estimated 0.4% of pregnant women in England have hepatitis B (1% in London). Routine screening for hepatitis B has been part of the Infectious Diseases in Pregnancy Screening (IDPS) programme in the UK since 2000, with around 3000 babies born to women with HBV each year. Uptake of screening is high, around 97%.

The UK National Screening Committee (UK NSC) has commissioned the first national audit of practice regarding management of hepatitis B in pregnancy. The aim is to undertake a national clinical audit of the management of pregnant women with hepatitis B infection booked to receive antenatal care over a 12 month period.

The audit will measure current practice against the IDPS Programme Standards. It will highlight aspects of service provision requiring improvement, in order to optimise current strategies for prevention of vertically-acquired hepatitis B and to inform future service planning.

Project Briefs and Newsflashes

We will keep you updated with progress in regular Project Briefs (see bottom of this page) and audit Newsflashes.

June 2014 - A huge thanks to all those who have submitted notification data for the audit so far. We received over 700 notifications by the end of May, and so are making excellent progress.

Hepatitis B in Pregnancy - 2014 and beyond: this meeting is specifically for all specialist clinical teams. We have responded to requests from clinicians to have as much notice as possible. As such we are rearranging this event from Thursday 10th July 2014 to a date early in September. Invitations will be sent out shortly.

Questions to the audit team?

The audit team will post questions and answers as they are received to further inform you on the audit. If you cannot find what you need please contact them on hep-b.audit@nhs.net

What kind of approval does this audit have?

The audit has approval from the Secretary of State Confidentiality Advisory Group (reference CAG 5-07(b)/2013) for use of patient identifiable information without consent. This approval is subject to strict conditions around the secure handling of the personal data (including the web-based system for submissions). Although eligible women are not required to give consent for their data to be used, they must be informed that the audit is taking place and given the opportunity to opt out.

We already inform all patients receiving care at our Trust that their data may be used for audit purposes. Do we need to inform eligible women separately about the Hepatitis B in Pregnancy Audit?

Yes – it is a condition of approval for this audit that eligible women are informed that this specific audit is taking place and given the opportunity to opt out. The audit patient information leaflet should be distributed to eligible women by the screening coordinator or midwife for this purpose.
Data collection

Previously diagnosed & screen positive

Booking

Delivery

12 months

Maternity services

Notification Referral Outcome of pregnancy, HBIG and vaccine at delivery

Liver Specialist

Survey on high risk pregnancies; modifications to treatment, stop dates

Collaboration with PHE Immunisation, Hepatitis and Blood Safety:

infant vaccines at 1, 2, 12 months and infant serology
Progress so far

Previously diagnosed & screen positive

Booking

Delivery

12 months

Maternity services

- 2700 notifications
- 850 referral forms

Liver Specialist

Detailed data on management of high risk women
HBV: gaps in our service delivery

• 14 mo old baby HBsAg positive  
  Maternal history: Bulgarian lives with her mum in the UK, limited English. HBeAg + and HBV DNA $10^8$ IU/mL  
  Was started on TDF at 28/40 but stopped 2 weeks into treatment due to nausea.

• 22 yr old Chinese woman  
  HBeAg+ and HBV DNA $10^9$ IU/mL, ALT 17 U/L.  
  TDF started at 24 weeks after 4 consultations with an interpreter.  
  Patient not responding to calls 4 weeks into treatment…
HBV: gaps in our knowledge..

- 34 yr old American of Taiwanese origin
  Known HBV under FU
  HBeAg– HBeAb+ HBV DNA 100,000 IU/mL, ALT 40-50 u/L.
  Previous results from US as above in last 8 years,
  No imaging, no biopsy. Thoughts?

- 36 yr old Chinese woman
  Flare for 8 months and anti-HBe seroconversion. Becomes pregnant.
  Anti- HBe positive and very low HBV DNA at booking
  When would you repeat?
  24/40  HBV DNA $10^3$ IU/mL
  36/40  HBV DNA $10^5$ IU/ml, HBeAg+ and anti- HBe +
Hepatitis C in pregnancy

MTCT rate: 5-7% 15% in HIV co-infection

MTCT and level of viraemia

No evidence that caesarean section reduces the risk

Obstetric management and breastfeeding
Is antenatal screening for hepatitis C virus cost effective?
A decade’s experience at a London centre
Nowlan Selvapatt, Thomas Ward, Heather Bailey, Hayley Bennett, Claire Thorne, Lay-May See, Gareth Tudor-Williams, Mark Thursz, Phil McEwan, Ashley Brown
Journal of Hepatology May 26, 2015
The way forward..

Treat HBV for MTCT

Safety TDF data

Tailor HBIG management

HCV screening

HCV treatment
UCLH Antenatal Viral Hepatitis Clinic
Flora Wilson
Hillary Hewitt
Mark Sellwood
Melissa Whitten
Judith Meek

NCL Audit
Gauri Godbole
Marina Basarab
Andrew Millar
Mike Jacobs
Geoff Dusheiko
Dianne Irish
Tabitha Mahungu
Deepak Suri
Claire Thorne
William Rosenberg

NSC National Audit
Claire Thorne
Sharon Webb
Heather Bailey
Catherine Peckham

UCL Hospitals
Biomedical Research Centre

Antenatal and Newborn Screening Programmes

University College London Hospitals
NHS Foundation Trust
## Antivirals in pregnancy

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>FDA classification</th>
<th>Birth defects /live births</th>
<th>Birth defects /live births</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Exposure in 1\textsuperscript{st} trimester</td>
<td>Exposure in 2\textsuperscript{nd} /3\textsuperscript{rd} trimester</td>
<td></td>
</tr>
<tr>
<td>Adefovir</td>
<td>C</td>
<td>0 / (0/42)</td>
<td>0/ (0/0)</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Entecavir</td>
<td>C</td>
<td>4 (1/25)</td>
<td>0 (0/2)</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>C</td>
<td>3.1(118/3864)</td>
<td>2.7(169/6230)</td>
<td>Extensively used Antiviral resistance</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>B</td>
<td>0 (0/7)</td>
<td>0 (0/8)</td>
<td>Positive human safety data; Not preferred first-line</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>B</td>
<td>2.4 (26/1092)</td>
<td>3.0 (13/639)</td>
<td>Positive human safety data.</td>
</tr>
</tbody>
</table>