Viral Hepatitis and Pregnancy A to E

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Disclosure Slide

- Received a Grant from Gilead Sciences for setting up a “Viral Hepatitis in sub-Saharan Africa” ECHO program
Viral Hepatitis and Pregnancy

Need to consider

• **Type of viral hepatitis - acute or chronic hepatitis**
  o Different risks to pregnant woman and her foetus/newborn
  o Risks of vertical transmission may be higher with acute hepatitis

• **Impact of viral hepatitis on pregnancy outcomes**

• **Risk of vertical transmission**
  o Intrauterine
  o Intrapartum
  o Postnatal

• **Differential diagnosis**
  o Liver diseases of pregnancy: PET, HELLP, acute fatty liver of pregnancy
  o Drugs/Toxin induced liver injury
  o Autoimmune hepatitis

• **Acute viral hepatitis is most common cause of jaundice in pregnancy**
Global Distribution of Hepatitis A

WHO 2016: Globally
- 1.4 M new cases
- 7,134 deaths in 2016
Hepatitis A

• Unlike HEV, Hepatitis A infection during pregnancy is not usually associated with serious maternal or foetal outcomes

• Hepatitis A in second and third trimester: Gestational complications
  - Increased risk of placental abruption, premature rupture of membranes and preterm labour

• Vertical HAV transmission during pregnancy or puerperium is rare
  - anti-HAV IgG antibodies present during initial stages of HAV infection cross the placenta and provide protection to the infant after delivery

• Rare cases of intrauterine infection reported - first trimester infection
  - Foetal ascites, meconium peritonitis, neonatal icteric HAV infection, and distal ileum perforation
  - No teratogenicity reported

Hepatitis A

Prevention

• Vaccine safe in pregnancy
  o Vaccinate pregnant women traveling to endemic areas

• Administer immune globulin to pregnant women who had contact with persons with acute hepatitis A

• Third trimester infection: Immunoglobulin to newborn within 48 hours of birth

• Management is supportive, no indication for termination

• Vaginal delivery and breastfeeding not contraindicated

• Isolate infected mother and neonate - Nosocomial spread can occur in Maternity Units and Neonatal ICUs

Estimates for countries with data and a model, or for which data were extrapolated from countries in the same GBD region with available data (all ages)

- HBsAg prevalence 6.1% (95% UI 4.6-8.5) in SSA
Hepatitis B

Global HBeAg prevalence: 20-50% in women of childbearing age

- 50 M new cases of hepatitis B diagnosed each year, most due to mother-to-child transmission (MTCT)

Systematic Review and Meta-analysis: Pregnant women in Africa

145 studies : 258 251 participants

- HBV prevalence in pregnant women: 6.8% (95% CI: 6.1-7.6; 113 studies)
  - 104 983 participants
  - 18.9% (95% CI: 14.4-23.9) were HBeAg positive

- Overall HBV prevalence in pregnant women in different regions
  - Central Africa: 9.7% (95% CI: 6.2-13.9)
  - Western Africa: 8.3% (95% CI: 7.1-9.5)
  - Eastern Africa: 5.5% (95% CI: 4.4-6.7)
  - Southern Africa: 3.8% (95% CI: 2.0-6.0)
  - Northern Africa: 2.8% (95% CI: 2.0-3.7)

Hepatitis B

Systematic Review and Meta-analysis: Pregnant women in Africa
145 studies: 258,251 participants

- HBV infection prevalence significantly higher in rural areas (12.2%) compared to urban areas (6.0%); P < 0.0001

Multivariable meta-regression analysis: HBV prevalence significantly increased with:
- Decreasing gender development index \( R^2 = 6.8\% \)
- Decreasing males’ level of education \( R^2 = 0.1\% \)
- Decreasing females’ expected years of schooling \( R^2 = 19.7\% \)
- Increasing gender inequality index \( R^2 = 30.6\% \)

Prevalence highest in rural Western and Central Africa (\( R^2 = 13.8\% \))
- Higher risk behaviours
- Weaker Health systems
- Weakest HIV infection control indicators

Prevalence in pregnant women similar to general population in WHO Africa (6.1%)
Hepatitis B

HBsAg screening of pregnant women is essential

- During first trimester of each pregnancy
- Pregnant women not immune to HBV and with risk factors for infection should be vaccinated against HBV – **VACCINE SAFE IN PREGNANCY**
- Ongoing high-risk behavior during pregnancy and HBsAg status unknown
  - Test for HBsAg at admission for delivery
- HBsAg positive women must be referred for additional testing, counseling and medical management: HBeAg, HBV DNA and LFTs
  - Partners, siblings and children should be screened
- Most women of childbearing age (20’s and 30’s) are likely to be in the immune tolerant or immune control phase and are not candidates for HBV treatment
- **Risk of mother-to-child transmission (MTCT) needs to be considered in pregnant women with high HBV viral loads (HBV DNA >200 000 IU/ml) in both HBeAg positive and negative pregnant women**

Hepatitis B

Acute Hepatitis B

• Usually benign, not associated with increased mortality
• Monitor closely (LFTs, INR) & treat conservatively
• Risk of MTCT increases with gestation
  o Only 10% risk early in pregnancy
  o 60% risk in 3\textsuperscript{rd} trimester close to delivery
• **Antivirals are generally not recommended**, unless evidence of ALF
  o Antivirals (TDF) to prevent MTCT if HBV DNA>200 000 IU/L
• **Newborn**
  o Increased risk of low birth weight and prematurity
  o No teratogenicity
  o HBIG and HB Birth dose vaccine: Mother remains HBsAg positive or has detectable HBV DNA
• **Not an indication for termination of pregnancy**

  Ann Hepatol 2006;5:231; Liver International 2009;29 (Suppl 1):133
Hepatitis B

Impact of pregnancy on Hepatitis B

Chronic Hepatitis B

- Does not usually affect pregnancy outcomes in absence of cirrhosis
- Acute HBV flares can occur during pregnancy and postpartum (25%)
  - Postpartum flares may be related to immune reconstitution
  - HBeAg positive pregnant women more likely to have flares
  - Maybe associated with spontaneous HBeAg clearance (12-17%)
  - HBeAg seroconversion unrelated to age, parity or PC/BCP mutations
- HBV DNA levels may increase, but usually remain stable

Hepatitis B

Impact of pregnancy on chronic Hepatitis B

- Immunologic, metabolic & haemodynamic changes can unmask cirrhosis

Chronic HBV cirrhosis and portal hypertension

- Increased risk of decompensation, variceal bleed and death: 2nd trimester
  - Decompensation risk increased with MELD score $\geq 10$: 83% sensitivity and specificity for pre-conception prediction

- Screen for varices in 2nd trimester
  - 25% risk of variceal bleed with pre-existent varices
  - Band as necessary and start B-Blocker

Impact of chronic hepatitis B cirrhosis on pregnancy

- Less likely to become pregnant – anovulation, amenorrhoea, infertility

  **Maternal complications:** GPH, placental abruptio, peripartum haemorrhage, premature labour and spontaneous abortion

- **Infants:** Intrauterine growth restriction, prematurity & stillbirths (5.2 vs 2.1%)
Hepatitis B

Treatment in pregnancy

Indications for treatment are the same as for non-pregnant women

Women requiring HBV treatment and considering pregnancy

• Tenofovir disoproxil fumarate is the treatment of choice for HBV viral suppression prior to pregnancy

• HBV suppression preconception decreases risk of MTCT

Pregnant whilst on HBV treatment

• Tenofovir disoproxil fumarate is preferred NUC to maintain HBV suppression

• Review type of treatment: Entecavir should be switched to Tenofovir disoproxil fumarate

Tenofovir has an excellent safety record in pregnancy in HIV-infected women with no increase in birth defects compared to the general population (i.e. 2%)

Hepatitis B

Mother-to-child Transmission

Intrauterine (transplacental) transmission (<5%)

- Responsible for minority of infections not prevented by prompt immunization

Associated with breach of placental barrier

- HBV in villous capillary endothelial cells and trophoblasts of placenta
- Mixing of maternal and fetal blood
  - Preterm labour
  - Spontaneous abortion
- Risk factor: High HBV DNA levels

Hepatitis B

Mother-to-child transmission

Perinatal transmission: Risk factors
• HBeAg positive
• HBV DNA >200 000 IU/ml
• Mothers <25yrs – often immune tolerant

Impact of HIV/HBV co-infection
• Pregnant women 3x more likely to test positive for HBV DNA, higher HBV DNA
• Twice as likely to test positive for HBeAg
• Increased risk of HBV MTCT by 2.5 fold

Perinatal infection: 90% risk of chronicity

Impact of Perinatal Infection

90% risk of chronic infection

Systematic review:
Earlier age at infection associated with:
• Increasing probability of chronic HBV infection
• Worse liver outcomes

Shimakawa et al; PlosOne 2013; 8(7): e69430

Longitudinal study in The Gambia: HBV MTCT was a risk factor for:
• Persistent high viral replication
• Significant fibrosis
• HCC

Shimakawa et al; Gut 2016;65(12):2007
Hepatitis B Epidemiology: SSA

Median HBeAg prevalence in HBsAg positive pregnant women

- **West Africa:** Nigeria 28.5%  Burkina Faso 21.2%  Cote d’Ivoire 14.5%  Benin 11.4%
- **Central Africa:** Cameroon 12.1%  Gabon 10.1%
- **Eastern & Southern Africa:** Zimbabwe 3.3%  Kenya 8.8%  Tanzania 12%  Ethiopia 12.5%  Uganda 14.9%  Zambia 16.1%  South Africa 17.1%
- **Most SSA countries (70%):** Implemented Universal HBV vaccine into EPI schedule: 6,10,14 weeks
  - Low risk of perinatal transmission from HBeAg negative women

Perinatal transmission from HBeAg positive women in SSA

- **Asia:** 70-90% vs 5-30% HBeAg negative women
- **SSA:** Lower rate at 38.3% : ? Related to HBV viral load, Genotype

*References:*
MTCT of HBV and HIV in SSA

Estimated no of infants perinatally infected each year in SSA

11 African countries: 15 articles were included

- HBeAg-positive women: Pooled risk 38.3% (95% CI: 7.0–74.4%) without prophylaxis - significantly lower than 70–90% risk in literature (P = 0.007)
- HBeAg-negative women: Pooled risk 4.8% (95% CI: 0.1–13.3%) without prophylaxis - within the lower range of 5–30% risk in Asia

Perinatal transmission: 90% risk of chronic infection

Keane et al; Aliment Pharmacol Ther 2016; 44: 1005
Hepatitis B

Prevention of MTCT of HBV

• Antenatal HBsAg screening
  o Not routine policy in many SSA countries vs HIV screening

HBsAg positive: Test for HBeAg and HBV DNA levels

• Tenofovir in 3rd trimester pregnancy (HBV DNA >200 000 IU/ml)
  o Measure HBV DNA at 26-28 weeks if low in 1st trimester
  o Continue TDF up to 4-12 weeks post delivery, monitor after stopping TDF

• Birth dose HBV vaccine within 24 hours of delivery

• IMI HBIG at time of delivery
  o Expensive and not readily available

• Combination of HBIG and vaccination given within 12 h of birth
  o Reduces rate of perinatal transmission to <10%

• Universal HBV vaccination - complete 3 vaccine doses

Hepatology 2016;63:319
Hepatitis B

Preventing MTCT of Hepatitis B

Amniocentesis
- Risk of HBV transmission is low esp HBeAg negative with low HBV DNA

Invasive monitoring
- Chorionic villous sampling, invasive fetal monitoring: risk unknown

Preterm premature rupture of membranes
- Conflicting data on risk of MTCT; manage as usual

Mode of delivery
- Caesarean section is NOT indicated to prevent HBV MTCT

Breastfeeding not contraindicated
- HBsAg-positive untreated women in absence of cracked or bleeding nipples
  - Infants received HBlG passive prophylaxis and HBV Birth dose vaccine
- HBsAg positive women virally suppressed on Tenofovir-based treatment or prophylaxis
  - TDF excreted in milk but low concentrations

Global distribution of Hepatitis C

2015 Global HCV prevalence was 1·0% (95% UI 0·8–1·1)
- 71·1 million (95% UI 62·5–79·4) viraemic HCV individuals

Hepatitis C

Worldwide, estimated that 8% pregnant women are HCV-infected

Systematic Review and Meta-analysis: Pregnant women in Africa

145 studies : 258 251 participants

- HCV prevalence in pregnant women: 3.4% (95% CI: 2.6–4.4, 58 studies)
  - 62.3% (95% CI: 51.6–72.5) were viraemic
- HCV prevalence varied between and within countries
  - 0.4% in Ethiopia to 7.4% in Benin
  - Egypt: 0.7% (2017) to 19% (2000)
- Overall HCV prevalence in pregnant women in different regions
  - Northern Africa: 4.6% (95% CI: 2.3-7.7)
  - Western Africa: 3.3% (95% CI: 2.6-4.1)
  - Central Africa: 2.8% (95% CI: 1.7-4.1)
  - Eastern Africa: 2.1% (95% CI: 1.0-3.6)

Infectious Diseases of Poverty 2019;8:16
Hepatitis C

Systematic Review and Meta-analysis: Pregnant women in Africa

145 studies: 258,251 participants

- HCV prevalence in this study higher than in general population (1%; 95% UI 0.7–1.6)
  - Exposure of pregnant women to unsafe medical or traditional procedures

- No difference between rural and urban areas

- HCV prevalence increased with decreasing proportion of seats held by women in parliament

Infectious Diseases of Poverty 2019;8:16
Hepatitis C

Who should be screened? ACOG, CDC, AASLD/IDSA Guidelines

- anti-HCV at first prenatal visit: pregnant women at increased risk
- Repeat during pregnancy if negative and ongoing or new risk
- HCV PCR, if anti-HCV negative and potential exposure within last 6 mnths

Impact of pregnancy on chronic hepatitis C

Down-regulation of maternal immune response

- ALT levels tend to decrease in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester of HCV-infected pregnant women and return to baseline after delivery
- HCV RNA levels may increase in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester
- Conflicting data on fibrosis progression during pregnancy

Hepatitis C

Post delivery changes in chronic hepatitis C

- Reported cases of sharp decreases in HCV viraemia 1-3 months post delivery
  - Broader HCV-specific T cell IFN-gamma-producing responses
- Clearance of HCV postpartum reported

Impact of pregnancy on acute Hepatitis C

- Jaundice present in majority of reported cases of pregnant women
  - ? Diagnostic bias
  - Asymptomatic acute HCV difficult to diagnose in pregnancy unless there is a clear exposure risk
- Immunomodulation may favour viral persistence
- Unknown whether acute HCV increases risk of MTCT or is associated more adverse pregnancy outcomes

Hepatitis C

Impact of chronic hepatitis C on pregnancy outcomes

HCV-infected women of childbearing age undergo premature ovarian senescence (*J Hepatol* 2018;68:33)

- Menopausal levels of anti-Müllerian hormone, an accurate marker of ovarian reserve
- Greater risk of infertility
  - Fertility rate 0.7 vs 1.37 in HCV-negative women
- Higher rates of gestational diabetes, pre-eclampsia and miscarriage
- Preterm labour; fetal growth restriction; lower birth weight; fewer live births

Early successful HCV treatment reduces these adverse outcomes including miscarriage rate
Hepatitis C

Pregnant HCV-infected women: Intrahepatic cholestasis of pregnancy

Systematic review and Meta-analysis: Screen for HCV in ICP

• Pooled OR of ICP in HCV-infected pregnant women was 20.40 (95%CI 9.39-44.33) compared to non-HCV pregnant women
• Pooled OR of later HCV infection among ICP patients was 4.08 (95% CI 3.13-5.31)

Mechanisms unclear: Potential role of bile acid transporters

• Downregulation of ABC transporter multidrug-resistance-protein 2 (MRP2)
• Altered regulation of Na+-taurocholate co-transporting polypeptide (NTCP)
• Common ABCB11 transporter genotype associated with increased bile acid levels is present in 40% HCV-infected patients
  o ABCB11 polymorphism present in ICP
  o May explain association between ICP and HCV before & after pregnancy

Hepatitis C

Mother-to-child transmission: Viral and Obstetric factors

• Commonest HCV transmission route in children
  o 6% risk in newborns from HCV mono-infected mothers
  o 11% risk in HIV/HCV co-infected mothers
  o 4-8.5% risk if on ART

• Higher viral loads increases risk, but no association with genotype
  o No HCV cut-off level for increased transmission risk

• Vertical transfer could potentially occur during pregnancy, during delivery or in the neonatal period

• Infection before delivery occurs in as many as 33% of patients

• Transfer of HCV infection to female infants may be twice as high as transfer to male infants (OR 2.07; 95% CI 1.23-3.48)
Hepatitis C

Mother-to-child transmission: Viral and Obstetric factors

Invasive prenatal diagnostic testing: Limited data on impact of viral load
- Amniocentesis recommended over chorionic villous sampling

Mode of delivery

2013 Systematic review: 14 observational studies
- No association between mode of delivery and vertical transmission
  - Did not distinguish between elective & emergency Caesarean
  - Most studies did not assess HCV viral load at time of delivery

Labour management: Increased risk of vertical transmission
- Internal fetal monitoring
- Prolonged rupture of membranes >6 hours
- Episiotomy

Caesarean delivery based on viral load is not advocated

Hepatitis C

Mother-to-child transmission: Viral and Obstetric factors

Breast-feeding

Systematic review: 14 cohort studies

• Breast-feeding does NOT affect risk of HCV MTCT in mono-infection
• CDC recommends that women abstain from breast-feeding if nipples are bleeding or cracked

Transmission during breastfeeding more common in HIV/HCV coinfection

Infants born to HCV-infected mothers: Screen

• HCV RNA positive on 2 occasions in infants \( \geq 1 \) month of age \ OR
• Anti-HCV \( >18 \) months of age
• Infected infants tend to do well, and severe hepatitis is rare
• FDA just approved SOF/Ledipasvir (oral pellets) for children \( >3 \) years

Society Maternal-Fetal Medicine Consult Series 43; Nov 2017
Hepatitis C

DAAs in pregnancy

- No published data on the safety or efficacy of DAAs in pregnancy
- Treatment is delayed until after delivery
- Recent phase 1 study data demonstrated no adverse events in women treated with sofosbuvir-ledipasvir in third trimester

Identify potentially HCV-infected women of child-bearing age

- Screen and treat prior to pregnancy to decrease the risk of adverse pregnancy outcomes
- Screen for other sexually transmitted diseases: HIV, syphilis, gonorrhea, chlamydia and HBV
Hepatitis E: Global Distribution

WHO: 20 million HEV infections (GT1 & 2) worldwide
- 3.4 million symptomatic HEV cases
- 70,000 deaths
- 3,000 stillbirths

Outbreaks or Confirmed Infection in >25% Sporadic Non-ABC Hepatitis

HEV IgG seroprevalence in Africa

North Africa: 50.01 (95% CI 4.43–95.58)
East Africa: 35.0 (95% CI 21.74–48.26)
West Africa: 16.40 (95% CI 11.39–21.41)
Central Africa: 10.45 (95%, CI 3.02–17.88)
Hepatitis E

Hepatitis E in pregnant women in Africa: Systematic review and meta-analysis: 22 studies: 12 African studies: 8008 pregnant women in North, West, Central and East Africa

• Pooled HEV IgG seroprevalence among pregnant women in Africa was 29.13% (95% CI 14.63–43.63)
  o Highest seroprevalence: 84.3% in Egypt
  o Lowest seroprevalence: 6.6% in Gabon

• HEV seroprevalence varies between countries and within countries
  o Egypt: 45-84.3%
  o Ethiopia: 31.1-58%
  o Sudan: 12.5-61.2%

• Decreasing seroprevalence trend over time in pregnant women

HEV Outbreaks in Africa

• Reported in Ethiopia, Somalia, Uganda, DRC, Sudan, South Sudan, Kenya, Uganda, Algeria, Tunisia, Morocco, Egypt and Somalia

BMC Infect Dis. 2014;14:308
Hepatitis E in Africa

Figure 2 Map of Africa. Colored areas represent countries where HEV is endemic at least for some subpopulations or sporadic HEV cases or outbreaks have been detected. Circles indicate HEV outbreaks with centers and areas indicating the location and outbreak size, respectively. Different colors represent different genotypes. White areas indicate countries where no data is available.
Hepatitis E

Hepatitis E virus infection during pregnancy can have severe consequences for both mother and child

Systematic review: 23 observational studies: 1338 cases
Hospital based; majority from India

- Median maternal mortality: 26% (IQR 17%-41%)
- Median foetal mortality: 33% (IQR 19%-37%)
- Median neonatal case-fatality: 8% (IQR 3%-20%)
- Median prevalence of fulminant hepatic failure was 45.3% (9.1% to 70%)
- Fulminant hepatic failure associated with highest case-fatality rates

HEV infection thought to be responsible for 2400 to 3000 stillbirths each year in developing countries, with many additional foetal deaths linked to antenatal maternal deaths

J Viral Hepatol 2019 May 16
Hepatitis E

Systematic review: 23 observational studies: 1338 cases
Hospital based; Majority from India

- Preterm labour: Median prevalence 51.9%; range 2.22%–90.4%
- Premature rupture of membranes: Prevalence estimates bet 9.1 & 11.1%
- Postpartum haemorrhage: Prevalence ranged from 13.6% to 30%
- Low birth weight ranged from 57.4% to 86.7%
- Vertical transmission ranged from 27.9% to 78.9%

Increasing severity with gestational age, maximum 3rd trimester (GT 1/2)
  - Elevated HEV viral load and prolonged viremia

Maternal mortality

- ALF, hypertensive and renal complications

J Viral Hepatol 2019 May 16
Hepatitis E

Vertical transmission

44 HEV-infected pregnant women

- 14.63% (6/41) pregnant women with ALF died before delivery
- **Vertical transmission (HEV-RNA positive) in 46.09% (59/128) of HEV-IgM-positive mothers**
  - 23.80% (10/42) newborns in acute viral hepatitis group
  - 29.41% (5/17) in ALF group
- **Maternal viral load: Only independent predictor of vertical transmission**
  - **Cut-off >13 266 copies/mL**: sensitivity 98.31%, specificity 84.71%
- **Predictive score based on viral load and adjusted for Hb and folate**

J Viral Hep 2017;24(11):1067
Hepatitis E

Prevention and Management

• HEV vaccine not commercially available outside China
  o Safety of vaccine in pregnancy not known
• No Immunoglobulin available
• Management is supportive
• Ribavirin contraindicated due to teratogenicity
• Liver transplantation for fulminant liver failure
• Breastfeeding safe in asymptomatic women but advised against in symptomatic acute hepatitis

Viral Hepatitis in Pregnancy

• Pregnancy is generally considered an immunosuppressed state

• Impact of pregnancy on mothers with viral hepatitis and the impact of viral hepatitis on the foetus/newborn is variable

• Need to consider the risk of vertical transmission and implement appropriate preventative measures

• In general, MTCT risk is not increased with amniocentesis and vaginal delivery

• Caesarean section should not be recommended to prevent MTCT

• Breastfeeding is considered safe for women with chronic hepatitis B and chronic hepatitis C - unless they have cracked or bleeding nipples

• Hepatitis A and B vaccines; and Immunoglobulins are safe in pregnancy