Pregnancy and Hepatitis B

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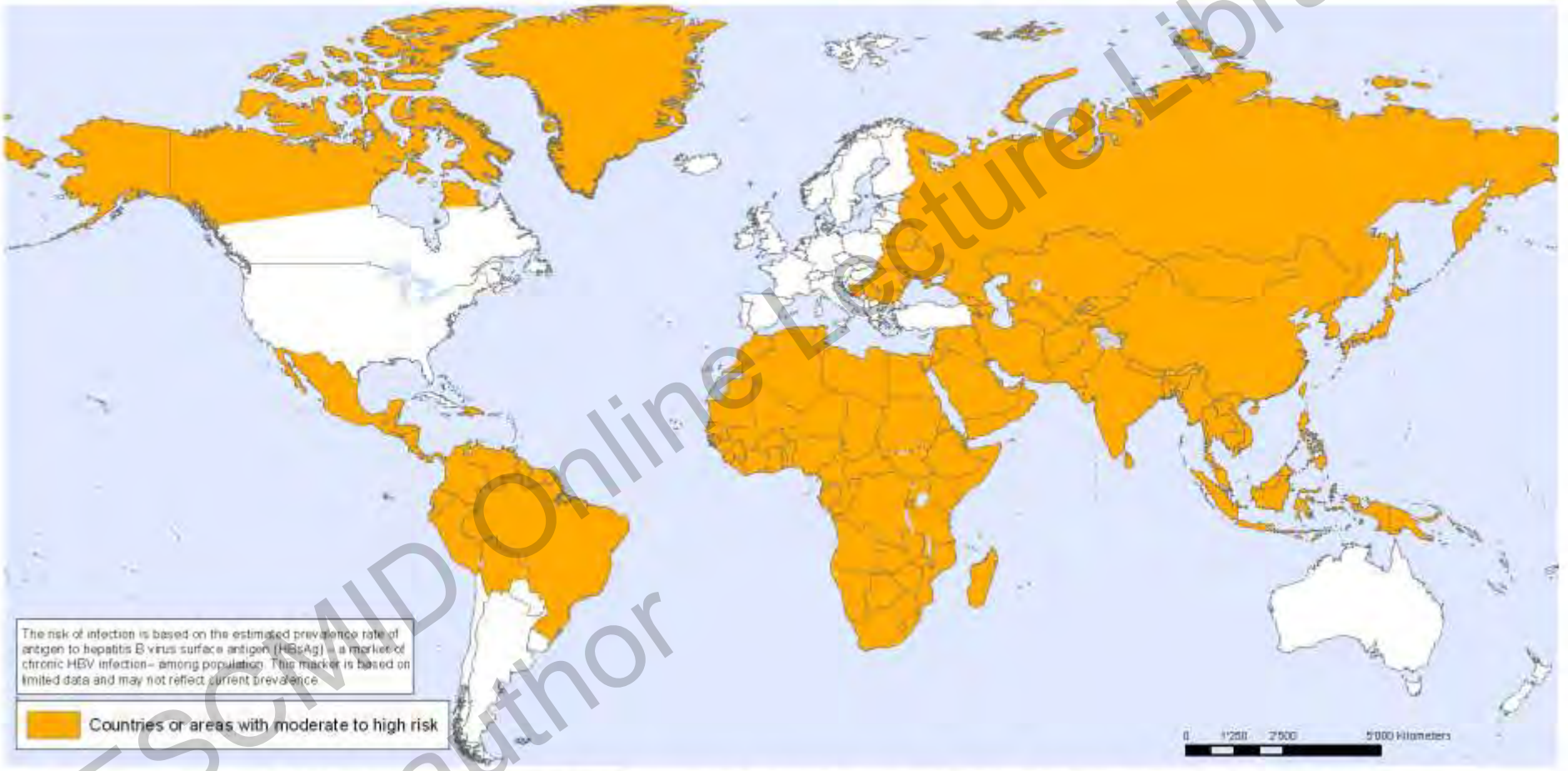
Hepatitis B, countries or areas at risk



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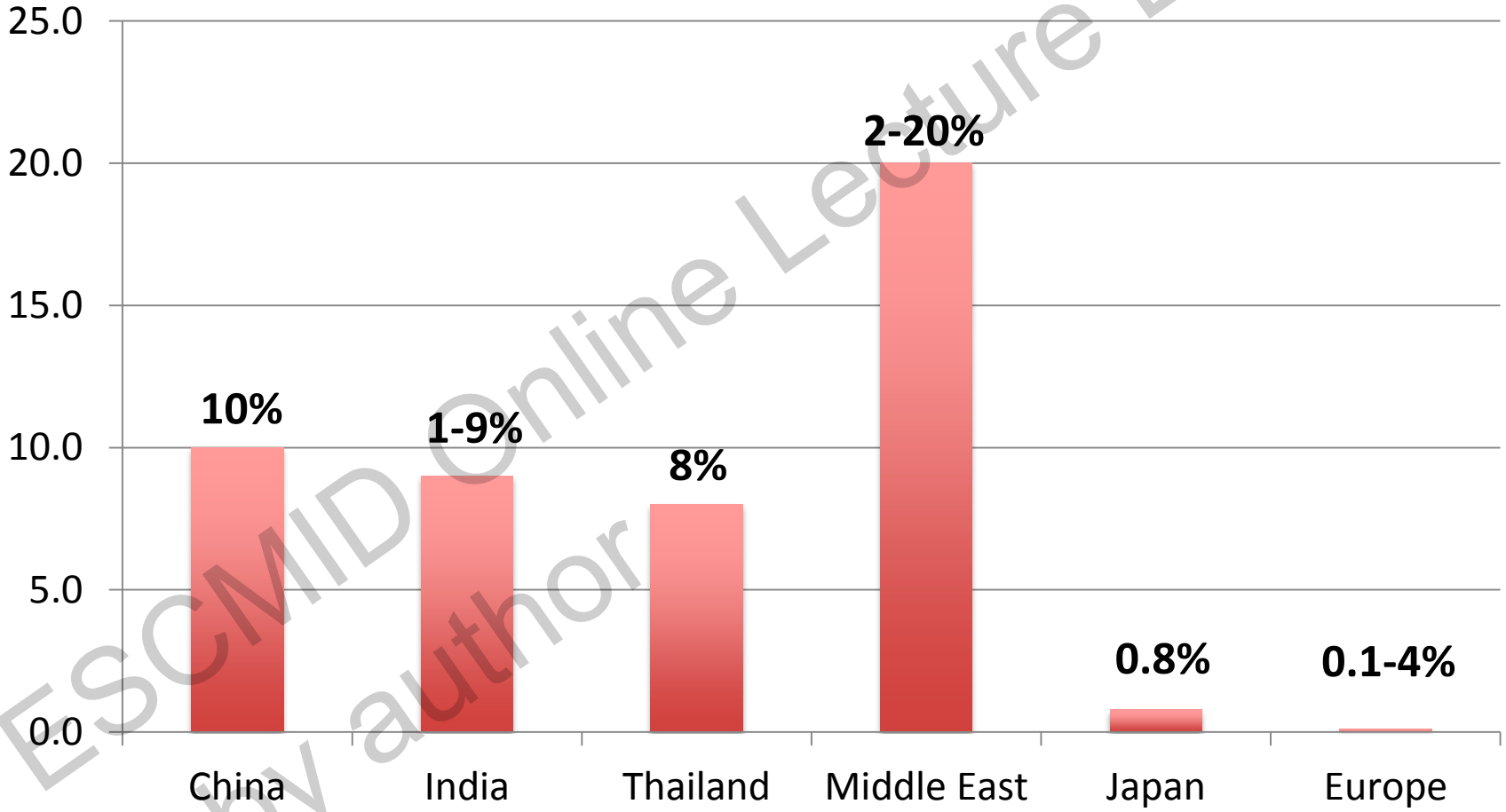
Data Source: World Health Organization/CDC
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

HBV Prevalence in Pregnant Women



Sinha et al. Hepatol Res. 2010;40(1):31

Presentation Plan

- Acute HBV
  - Impact of acute HBV on pregnancy
  - Impact of pregnancy on acute HBV
- **Chronic HBV**
  - **Impact of HBV on pregnancy**
  - **Impact of pregnancy on HBV**
  - **Main issues of HBV, pregnancy, and transmission**
  - **Breastfeeding**
  - **Clinical scenarios**

Impact of Acute HBV on Pregnancy

Acute HBV during pregnancy

- Not severe, not associated with increased mortality or teratogenicity
- Not an indication of termination of pregnancy
- But may increase the rates of complications in the infant
  - Reports of increased incidence of low birth weight and prematurity

Sookian et al. Ann Hepatol 2006;5:231
Hieber et al. J Pediatr 1977;91:545

Impact of Acute HBV on Pregnancy

- Transmission rate
  - 10% in early pregnancy
  - Up to 60% at or near to the time of delivery

Sookian et al. Ann Hepatol 2006;5:231
Jonas et al. Liver Int 2009;29 Supp 1:133

Impact of Pregnancy on Acute HBV

- Usually not severe
  - Biochemistry and prothrombin time are monitored
  - Supportive treatment
  - Antivirals are not needed
- Severe protracted hepatitis, acute liver failure
  - Antivirals: lamivudine, tenofovir, telbivudine

Liver Transplantation During Pregnancy for HBV in the Literature

Publication	GW at Transplant.	Maternal outcome	Delivery mode, GW	Fetal outcome
Fair et al. [1]	22	Survived, Retransplant.	Cesarean, 30 GW	Survived, intrauterine growth restriction
Hamilton et al. [2]	21	Survived	Spontaneous, 22GW	Intrauterine fetal death
Laifer et al. [3]	26	Survived, Retransplant.	Cesarean, 28 GW	Neonatal death
Kimmich et al. [4]	22	Survived	Cesarean, 36 GW	Survived, 2700 g (42 percentile)

1.Transplantation, 1990;50(3):534
2.Transplant Proceed 1993;25(5):2967.
3.Obstetrics Gynecol 1990;76(6):1083
4. Case Rep Obstet Gynecol 2013:356560

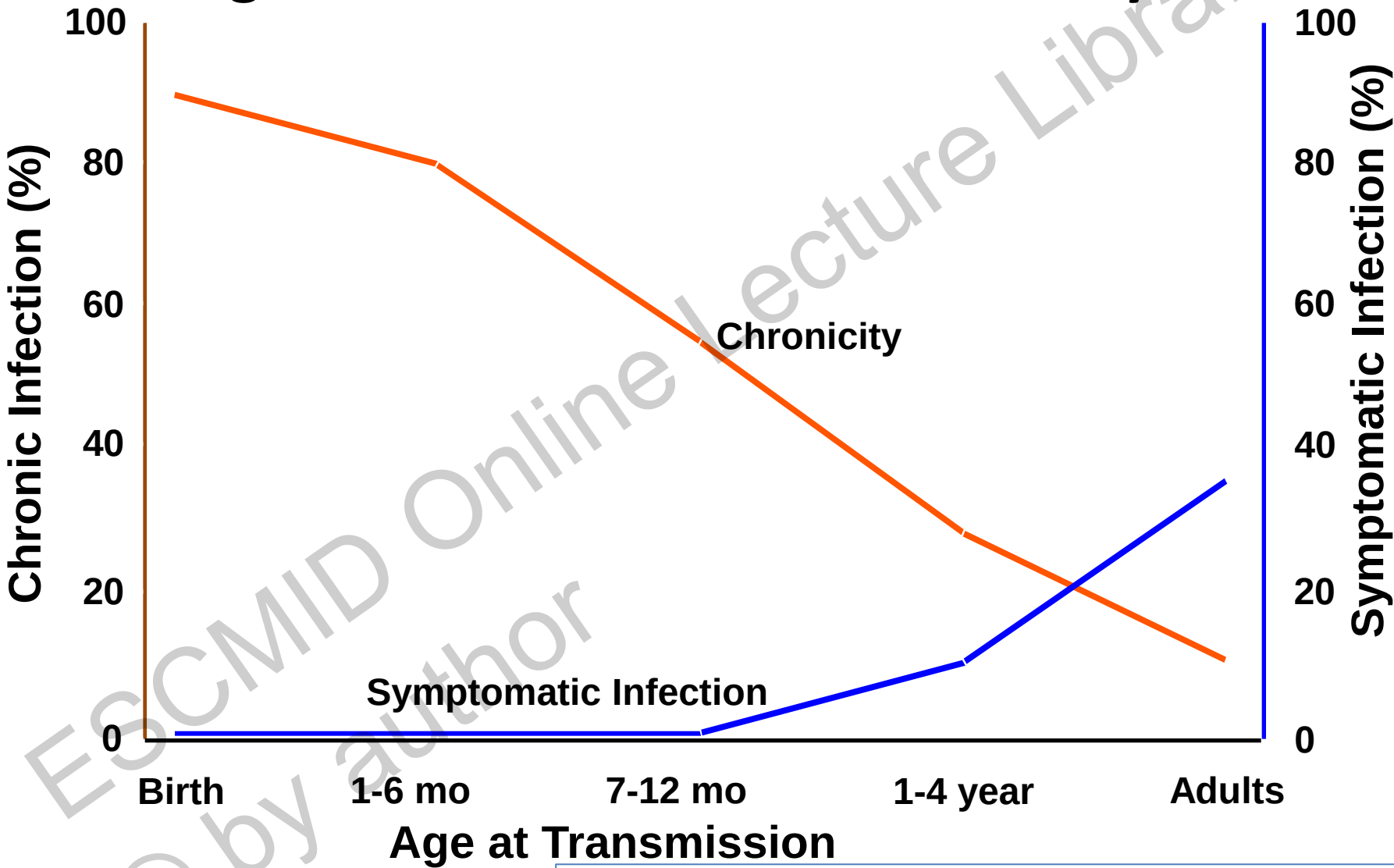
Chronic Hepatitis B and Pregnancy

HBV Transmission

- In utero (<10%)
- **At the time of delivery**
  - **HBeAg-positive mothers: 85%**
  - **HBeAg-negative mothers: 31%**
- After birth
  - Breastfeeding is not associated with transmission
  - May be related to scarification, other parenteral exposures

Gambarin-Gelwan M. Clinics in Liver Disease 2007;11(4):945-963
Beasley Rp et al. Lancet 1975; ii: 740-743

Age at Transmission and Chronicity



McMahon et al. J Infect Dis 1985;151:599

Chang MH. J Gastroenterol Hepatol 2000;15(suppl);E16

Impact of HBV on Pregnancy

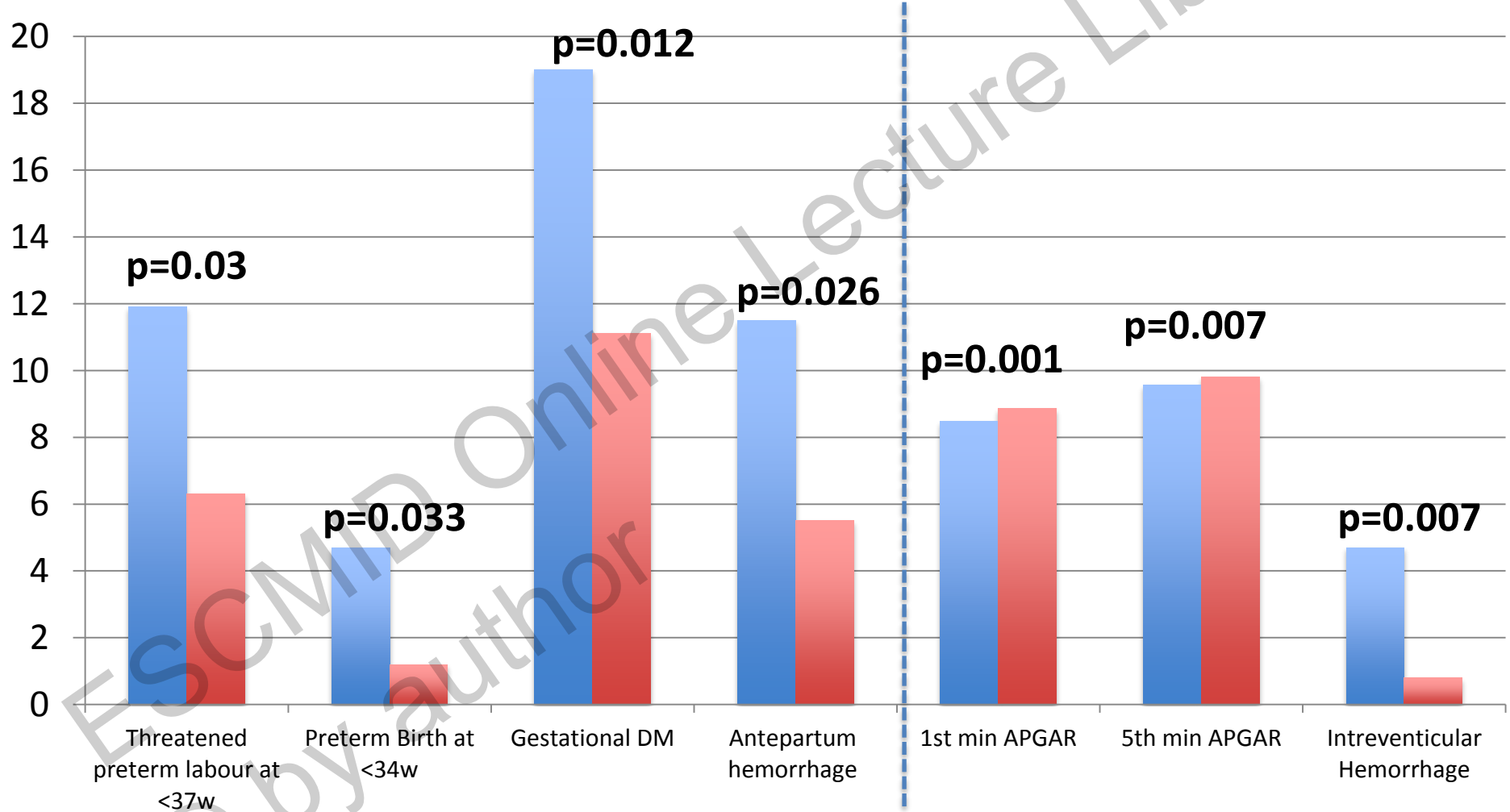
- Association with gestational diabetes
- Threatened preterm labor
- Antepartum hemorrhage

- Low Apgar scores
- High rates of intaventricular hemorrhage

Tse et al. J Hepatol 2005;43(5):771-5
Lao et al. Diabetes Care 2003 Nov;26(11):3011-6

A Case-Control Study

253 HBV(+) Pregnant Women vs. **Age-, Parity-, and Year of Delivery-Matched Controls**



Tse et al. J Hepatol. 2005;43(5):771

Impact of Pregnancy on HBV

- No worsening of liver disease in majority
- Overall increase in HBV DNA levels during pregnancy
- Median ALT levels decreased during pregnancy
- Increase in ALT (3x lowest ALT) within 6 mos after delivery
- Case reports of postpartum hepatic exacerbations
- Liver cirrhosis (LC and pregnant vs LC and non-pregnant)
  - Increase risk of hepatic decompensation
    - (63.6% vs 13.6%; p=0.001)
  - Higher maternal mortality
    - (7.8% vs 2.5%; p=0.001)

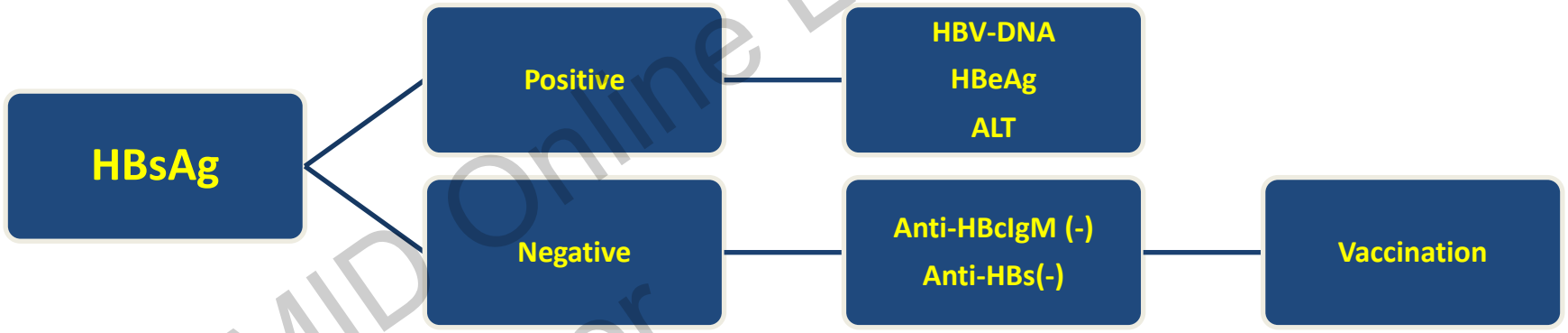
Terrault et al. Semin Liver Dis. 2007;(suppl 1):18
Soderstrom et al. Scand J Infect Dis 2003;35:814
Borg et al. J Viral Hep 2008:15;37
Rasheed et al. Int J Gynaecol Obstet 2013;121(3):247

Main issues of HBV, Pregnancy, and Transmission
Screening

- The goal is prevention of perinatal transmission
- All pregnant women should be routinely tested for hepatitis B surface antigen (HBsAg)
  - At the first trimester
  - At the time of the admission
- Appropriate implementation and monitoring of hospital practices are needed to eliminate perinatal HBV transmission

Center for Disease Prevention and Control, 2004
Bayo et al. Pediatrics 2010;125:704

HBV Screening in Pregnancy



Antiviral Drugs Used to Treat CHB

Drug	Pregnancy Category	Comment
IFN alfa	C	Not recommended
PegIFN alfa	C	Not recommended
Adefovir	C	Not recommended
Entecavir	C	Not recommended
Lamivudine	C	Extensive human safety data, risk of antiviral resistance
Telbivudine	B	Positive human safety data; pregnancy class, risk of antiviral resistance
Tenofovir	B	Extensive human safety data, pregnancy class, First line drug

Antiviral Drugs and Pregnancy

	Defects in 1st trimester	Defects in 3rd trimestr
Lamivudine	3.1%	2.7%
Tenofovir	2.4 %	2.0 %
CDC population-based data	2.7%	

Brown RS, et al. J Hepatol 2012;57:953

Prevention of Perinatal HBV transmission

- Infants born to HBsAg positive mothers must receive
  - HBIG and vaccination within 12 hours of birth
  - Two more doses of vaccine must be given 1 and 6 months after the first dose

	Without HBIG and HBV vaccine series	With HBIG and HBV vaccine series
HBeAg positive	70-90%	5-10%
HBeAg negative	10-40%	<5%

Vertical transmission of HBV

HBV DNA	Transmission
10^6 cp/ml	3%
10^7 cp/ml	5.5%
10^8 cp/ml	9.6%

HBIG+Vaccine series may fail if the viral load is ≥200.000 IU/ml (10^6 cp/ml); consider antiviral therapy at 2nd-3rd trimester

Han et al. J Hepatol 2011;55:1215
Petersen J. J Hepatol 2011;55:1171

- Tenofovir or telbivudine (or lamivudine)
  - For treatment
  - For minimizing mother-to-child transmission

Failures of Prophylaxis

- In utero infection
- HBeAg seropositivity / high maternal viral load e.g. >200.000 IU/ml
- HBsAg mutations (escape mutants)
- Immunocompromised host
- Vaccine-related
  - Poor quality assurance/storage
  - Failure to complete schedule of vaccine

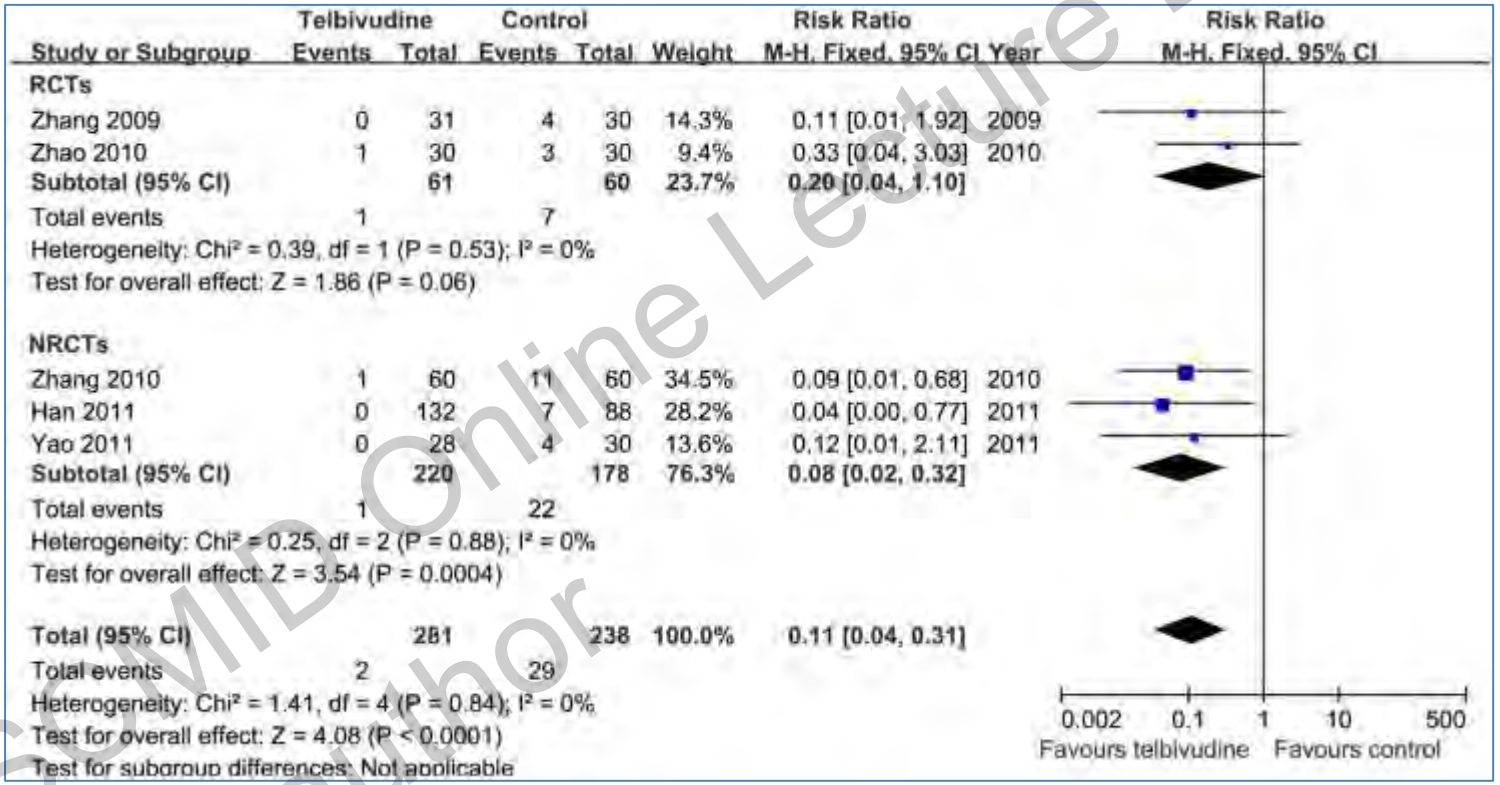
Sa-nguanmoo et al. J Med Virol 201284:1177
Wiseman et al. Med J Aust 2009;190:489
Song et al. Eur J Pediatr 2007;166:813
Zou et al. J Viral Hepat 2012;19:e18

Lamivudine in Late Pregnancy to Interrupt Transmission of HBV

- Three meta-analyses
  - Trials were heterogeneous, small numbers, limited quality
- Lamivudine is safe and more efficient
- Newborns in the lamivudine group had a 10.7–23.7% lower incidence of intrauterine infection
- If maternal viral load is $>10^6$ copies/mL
- **Its effect is moderate: drug-resistant viral variants emerged**

Shi et al. Obstet Gynecol 2010;116:147
Han et al. World J Gastroenterol 2011;14;17:4321
Wong et al. Ann Hepatol. 2014;13(2):187
Ayres et al. J Viral Hepat 2013:Dec11

Telbivudine in Late Pregnancy to Interrupt Transmission of HBV

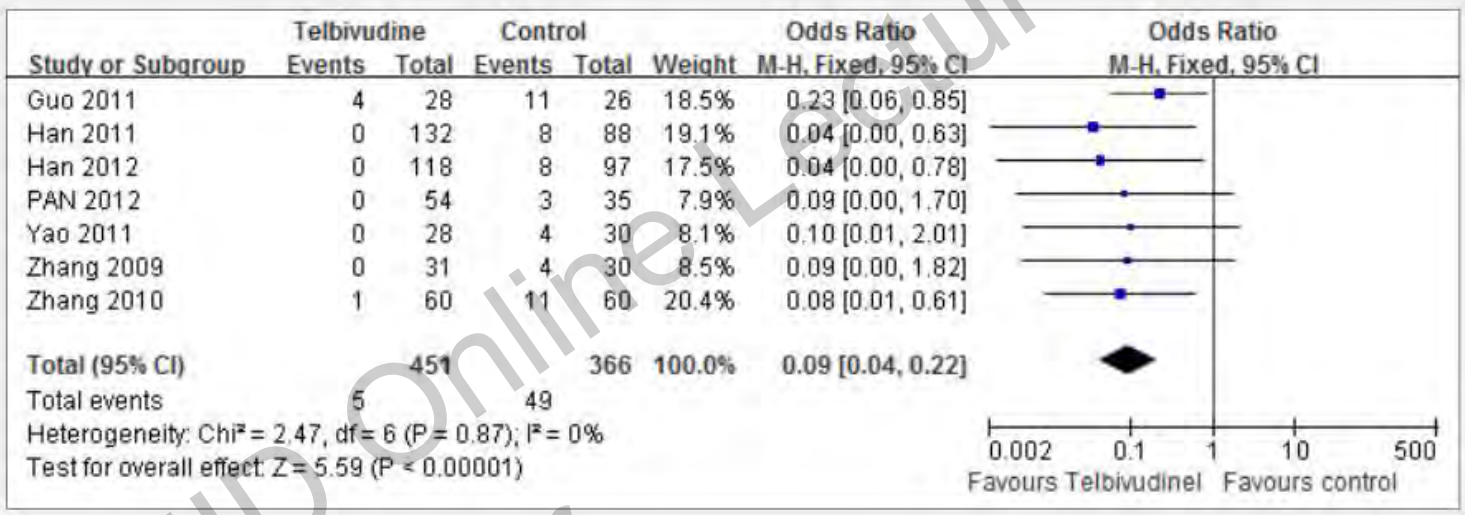


Telbivudine vs. control on infant HBsAg seropositivity at age 6–12 months

Telbivudine: 220
Control: 178

Deng et al. Virol J 2012;9:185

Telbivudine in Late Pregnancy to Interrupt Transmission of HBV



Study or Subgroup	Telbivudine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Guo 2011	4	28	11	26	18.5%	0.23 [0.06, 0.85]
Han 2011	0	132	8	88	19.1%	0.04 [0.00, 0.63]
Han 2012	0	118	8	97	17.5%	0.04 [0.00, 0.78]
PAN 2012	0	54	3	35	7.9%	0.09 [0.00, 1.70]
Yao 2011	0	28	4	30	8.1%	0.10 [0.01, 2.01]
Zhang 2009	0	31	4	30	8.5%	0.09 [0.00, 1.82]
Zhang 2010	1	60	11	60	20.4%	0.08 [0.01, 0.61]
Total (95% CI)		**451**		**366**	**100.0%**	**0.09 [0.04, 0.22]**
Total events	5		49			

Heterogeneity: $Chi^2 = 2.47$, $df = 6$ ($P = 0.87$); $I^2 = 0\%$

Test for overall effect: $Z = 5.59$ ($P < 0.00001$)

Figure 2a. Infant HBsAg seropositivity at 6 - 12 months postpartum.

Telbivudine: 451
Control: 366

Lu et al. Clin Lab. 2014;60(4):571

Tenofovir in Late Pregnancy to Interrupt Transmission of HBV

- A retrospective study
- 45 pregnant women with HBeAg(+) CHB and HBV DNA levels > 10^7 cp/mL
- All infants given HBIG+ vaccine series
- 21 women received TDF 18 to 27 GW
- At week 28,
  - none of the infants of TDF-treated mothers had immunoprophylaxis failure,
  - whereas **2** (8.3 %) of the infants of control mothers had immunoprophylaxis failure (p = 0.022)

Celen et al. World J Gastroenterol 2013;19;(48):9377

Tenofovir in Late Pregnancy to Interrupt Transmission of HBV

- A case series
- 11 Asian, HBeAg(+) women
- All infants given HBIG+ vaccine series
- Received TDF at median GW of 29
- HBV-DNA reduced
  - 8.87 ± 0.45 log(10) cp/mL to 5.25 ± 1.79, $p < 0.01$
- 11 infants with no obstetric complication, no birth defects
- 5 were breastfed
- **All HBsAg(-)** (28-36 weeks after birth)

Pan et al. Dig Dis Sci. 2012;57(9):2423

Evaluation of Antiviral Treatment Efficacy and Risk of Perinatal Transmission

- 108 HBsAg (+) pregnant women, ¼ HBeAg(+)
- Their older children and infants up to one year registered at 10 referral hospitals were included
- Twenty-one pregnant women received antiviral treatment (Lamivudin, telbivudine, tenofovir)
  - None of their infants were HBsAg positive
- 5 (4.6%) infants were HBsAg (+) despite active and passive immunization
  - 4 mothers had **at least one HBsAg(+) sibling**

Ayşe Batirel, İlker İnanç Balkan, Oğuz Karabay, Hülya Kadriye Kart Yaşar, Fazilet Duygu, İsmail Necati Hakyemez, Rahmet Güner, Aziz Öğütlü, Aygül Doğan Çelik, Mustafa Doğan, Bülent Durdu, Ferhat Arslan, Abdurrahman Kaya, Serdar Ozer, Reşat Özaras will be presented at ECCMID 2014

Caesarian vs. Vaginal Delivery

A meta-analysis

- Infant serum **anti-HBs positivity**
  - **at birth** (RR=1.24, 95 % CI 0.89–1.74, p= 0.2) or
  - **at 6–7 months** (RR=0.98, 95% CI 0.86–1.11, p= 0.73)

  was **not significantly different**
- The incidence of infant CHB infection may have been higher in the vaginal delivery group (RR=2.20, 95 % CI 1.02–4.74, p =0.04).

Xu et al. Dig Dis Sci. 2014;59(2):242

Question 1

Breastfeeding

- HBeAg(+) mothers: Colostra have HBV
  - By PCR 100%
- HBIG and HBV vaccine are protective
- It does not increase the risk of HBV infection in the infant
- Breastfeeding is not contraindicated for mothers not receiving treatment
- For mothers on antiviral therapy, breastfeeding is not recommended

Lin et al. J Pediatr Gastroenterol Nutr 1993;17:207
Gartner et al. Pediatrics 2005;115:496
Zhongjie et al. Arch Pediatr Adolesc Med 2011;165(9):837

Breastfeeding

- HIV+ mothers given 600 mg TDF during delivery
- Breast milk samples were obtained from 25 mothers in cohorts 1 and 2.
  - Tenofovir was detectable in 3 of 4 samples collected within 2 days of delivery, with concentrations ranging from 6.3 to 17.8 ng/mL,
  - 1 of 21 samples collected 4– 6 days after delivery, with a concentration of 15.7 ng/mL.

Mirochnick et al. J Acquir Immune Defic Syndr 2014;65:33–41

Breastfeeding

- HIV+, 16 mothers from Cote d'Ivoire
- Median tenofovir dose 0.03%

Benaboud et al. Antimicrob Agents Chemother 2011;55:1315

When to Screen Infants

- Infants who received HBIG+vaccines should be tested for anti-HBs and HBsAg at 9 to 18 months of age.
- Clinical Studies
  - At birth-4w-28 w

Broderick et al. UpToDate 2014
Han et al. J Hepatol. 2011;55(6):1215
Celen et al. World J Gastroenterol 2013;19;(48):9377

Clinical Scenarios

- In all scenarios
  - Inform patient/couple
  - Apply HBIG+vaccination series to the infant

- Question 2

Scenario 1

- Woman desires to be pregnant
  - She is inactive carrier
    - No treatment
    - Monitor during and after pregnancy

Bzowej NH. Curr Hepatitis Rep 2012;11:82-9
Lee et al. UpToDate 2014

Scenario 2

- Woman desires to be pregnant
  - The disease is not severe, HBV-DNA is “low”
    - Consider and discuss treatment BEFORE pregnancy (interferon)
    - AFTER pregnancy—delivery---breastfeeding
    - If treated
      - Prefer telbivudine or tenofovir
    - Monitor during and after pregnancy

Bzowej NH. Curr Hepatitis Rep 2012;11:82-9
Lee et al. UpToDate 2014

Scenario 3

- Woman desires to be pregnant
  - The disease is not severe, HBV-DNA is “high”, previous child(ren) HBsAg(+)
    - Consider and discuss treatment BEFORE pregnancy (interferon may fail in pts with high viral load)
    - Consider treatment (at least for the last trimester)
      - Prefer telbivudine or tenofovir
    - Consider discontinuing treatment after delivery
    - Don’t discourage breastfeeding
    - Monitor during and after pregnancy

Bzowej NH. Curr Hepatitis Rep 2012;11:82-9
Lee et al. UpToDate 2014

Scenario 4

- Woman desires to be pregnant
  - The disease is severe
    - Severe liver disease and pregnancy: can be life-threatening
    - Consider treatment
      - Tenofovir
    - Monitor closely during and after pregnancy
    - Importance of continuing therapy after pregnancy and lack of safety data of breastfeeding

Scenario 5

- Woman desires to be pregnant
  - She is immunotolerant
    - Consider treatment for the last trimester
      - Tenofovir
    - Discontinue after delivery
    - Don’t discourage breastfeeding

Scenario 6

- Woman is pregnant and under treatment
  - The disease is not severe
    - Discontinuation can be an option
      - HBeAg(-), HBV-DNA undetectable for years
      - Closely monitor for flares
    - Switch to telbivudine or tenofovir

Scenario 7

- Woman is pregnant and under treatment
  - The disease is severe
    - Switch to tenofovir
    - Closely monitor during and after pregnancy
    - Importance of continuing therapy after pregnancy and lack of safety data of breastfeeding

Conclusions

- Pregnant women should be screened for HBsAg
- For infants born to infected mothers should be given HBIG plus HBV vaccine series
- HBsAg(+) pregnant women should be considered for treatment
  - If the liver disease is severe
  - If the viral load is high (for the last trimester)

Special Thanks

- Prof. Hakan Leblebicioglu
- Dr. Ayse Batirel