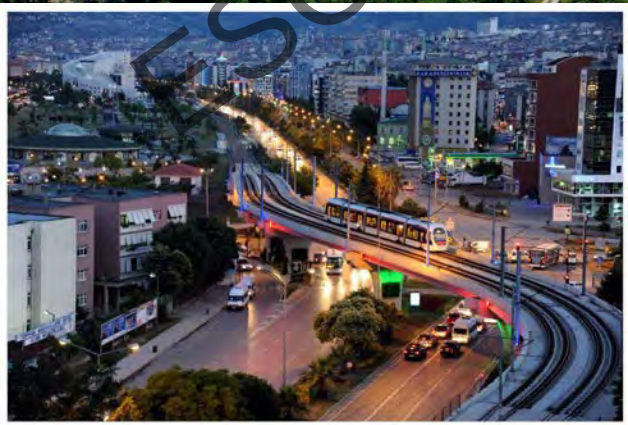
Hepatitis B virus infection and pregnant women



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Hepatitis B virus

- Chronic HBV infection affects 350-400 million people worldwide
- ~50% of them have acquired HBV in the perinatal or neonatal period
- 0.14-6% of mothers are estimated to have chronic HBV infection
- Up to 600.000 die each year from HBV infection
- Cirrhosis and hepatocellular carcinoma are frequent complications

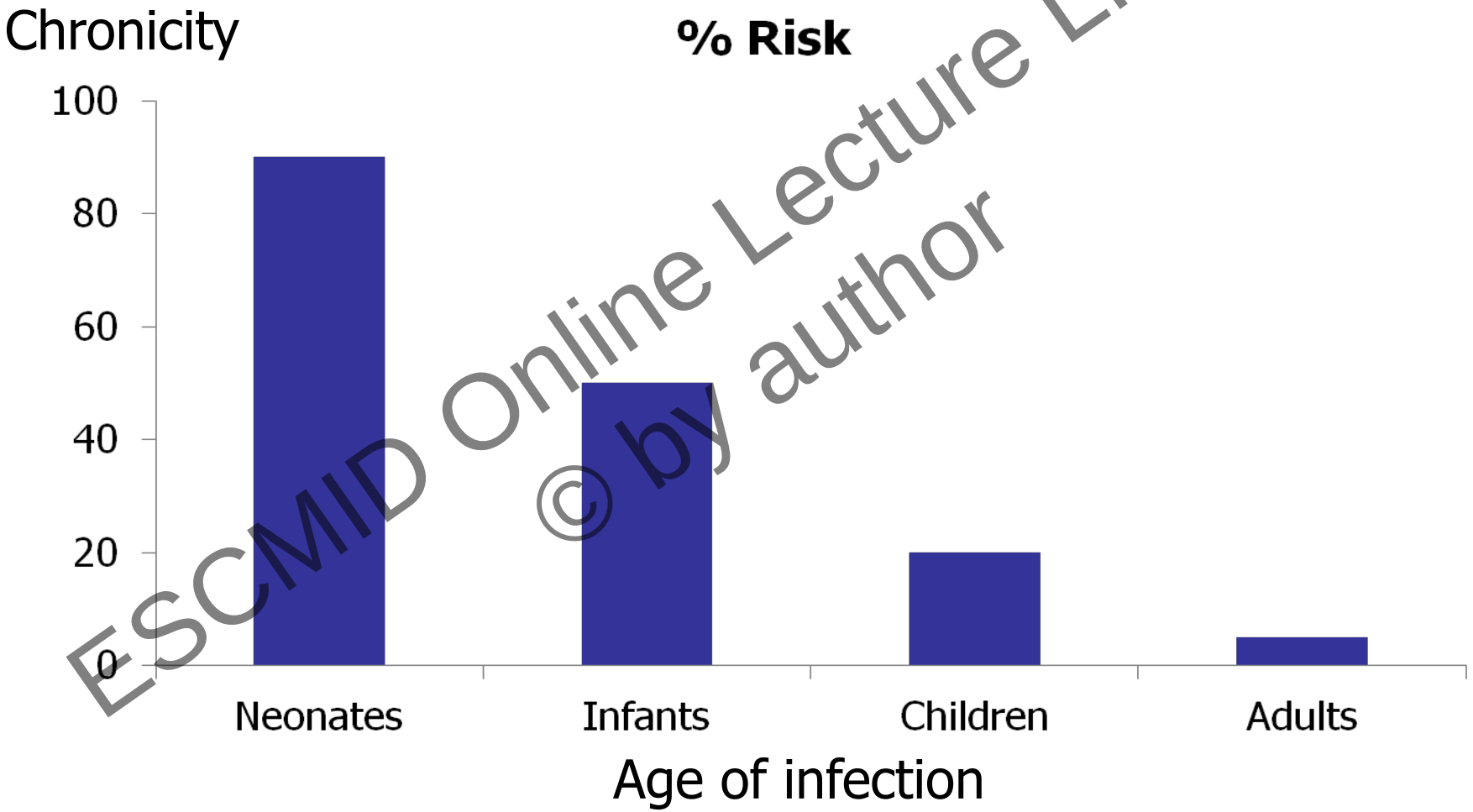
CDC. MMWR. 2001;50:RR-11
Jonas M. Liver Int. 2009;29 (suppl 1):133–139.
Euler GL, et al. Pediatrics 2003;111:1192-7

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

Outcome of HBV Infection by Age of Infection



McMahon al. J Infect Dis 1985;151:599–603
Chang MH. J Gastroenterol Hepatol 2000;15(suppl);E16-E19

Impact of HBV on pregnancy

- Association with gestational diabetes and lower Apgar scores
- Threatened preterm labor
- Antepartum hemorrhage
- 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)

Tse KY et al. J Hepatol. 2005;43(5):771-5
Lao TT et al. Diabetes Care. 2003 Nov;26(11):3011-6
Rasheed SM et al. Int J Gynaecol Obstet 2013 (In press)

Impact of pregnancy on HBV

- No worsening of liver disease in majority of women
- Overall increase in median 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

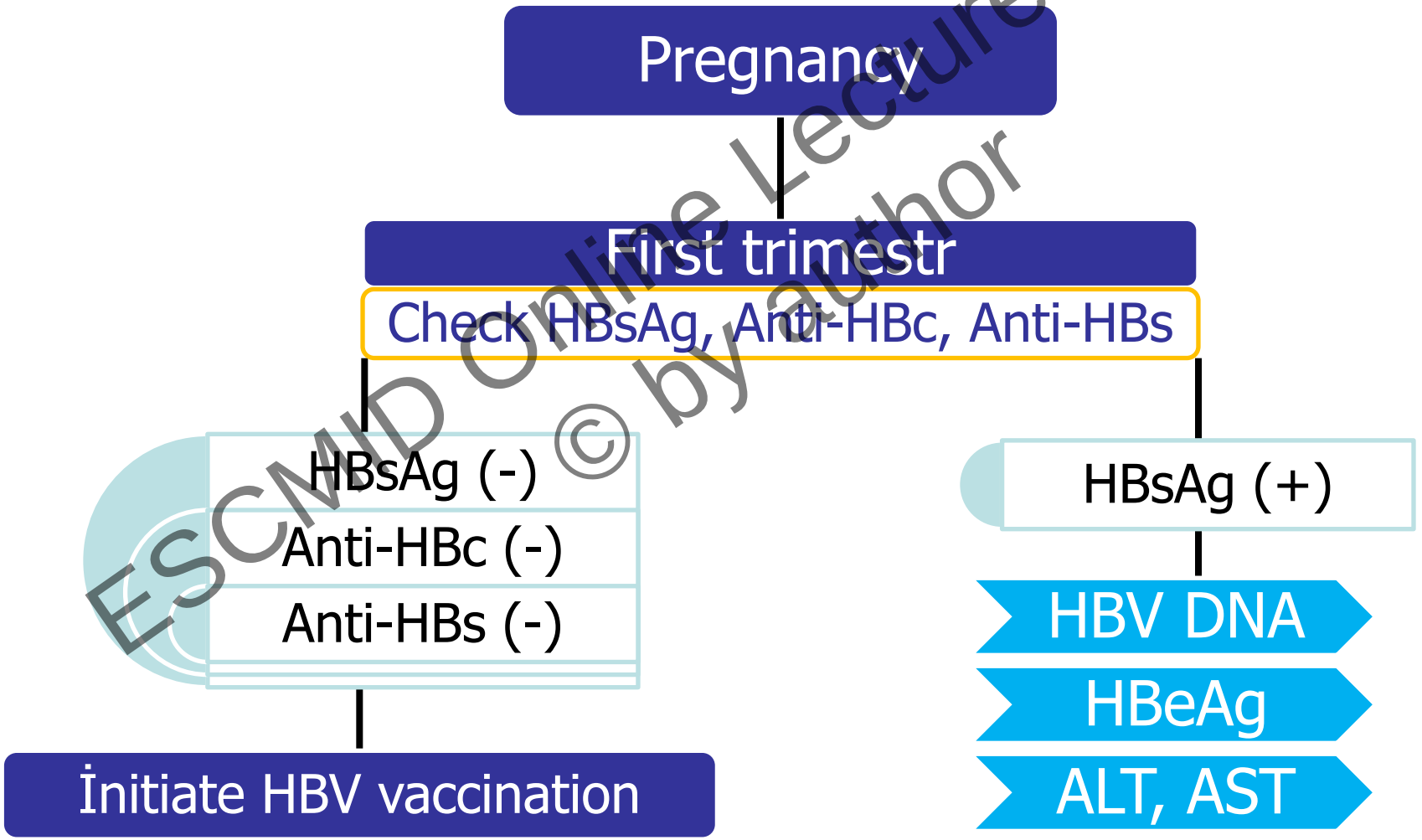
Terrault NA, et al. Semin Liver Dis. 2007;(suppl 1):18-24 2
SoderstromA,etal. Scand J Infect Dis 2003;35:814-819
Borg MJ,etal. J Viral Hep 2008:15;37-41

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 to the hospital or delivery setting
- Appropriate implementation and monitoring of hospital practices are needed to eliminate perinatal HBV transmission

Center for Disease Prevention and Control, 2004
Bayo C, et al. Pediatrics 2010;125:704–711

Management of HBV in pregnancy



Antiviral drugs used to treat CHB

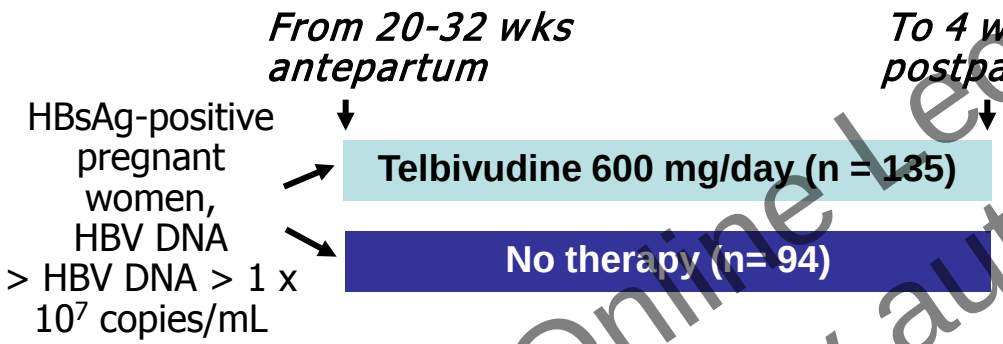
Drug	Pregnancy Category	Comment
IFN alfa	C	Not recommended
PegIFN alfa	C	Not recommended
Adefovir	C	Not recommended
Entecavir	C	Not recommended
Lamivudine	C	Extensive human safety data, risk of antiviral resistance
Telbivudine	B	Positive human safety data; pregnancy class, risk of antiviral resistance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

Antiviral drugs and pregnancy

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

Brown RS, et al. Journal of Hepatology 2012;57:953-9

Telbivudine treatment during pregnancy



- All infants received HBV vaccine series and HBIG (200 IU, single dose)

- Telbivudine was well-tolerated
- No safety concerns in mothers or their infants on short term follow up

Han GR, et al. Journal of Hepatology 2011;55:1215-21

Clinical Scenarios

- Chronic HBV infection in women desire to be pregnant
- Chronic HBV infection in women who are first detected during pregnancy
- Became pregnant while receiving treatment for HBV infection
- Prevention of perinatal HBV transmission

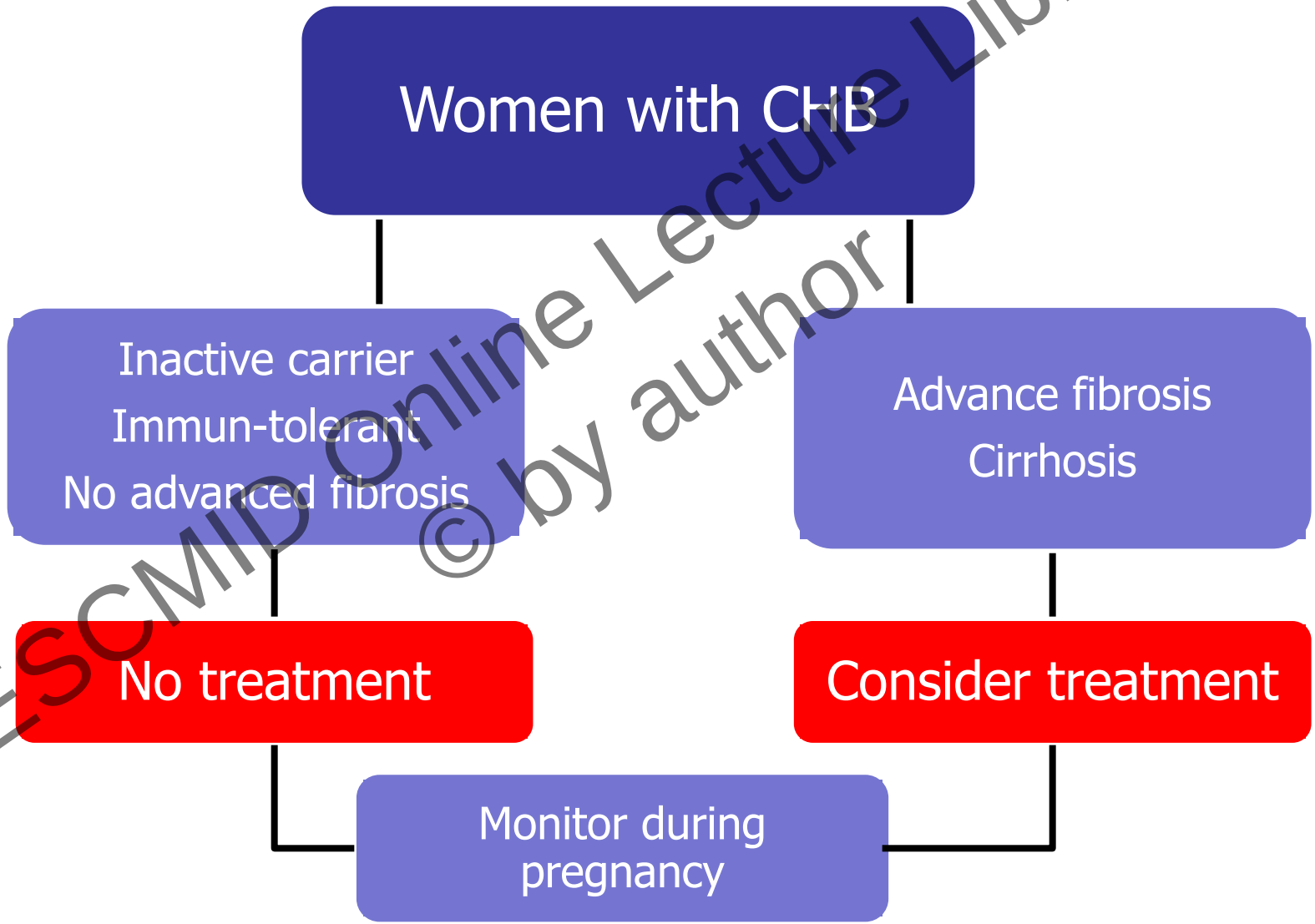
Case 1

- 32 years old woman
- Anti-HBe positive
- HBV DNA = 1.000 IU/ml
- ALT 25 IU/ml
- Diagnosed for HBV five years ago
- Desire to be pregnant

Q1: Choices

- Order liver biopsy
- Treat with antiviral drug
- Treat with pegylated interferon
- Plan pregnancy

Women desire to be pregnant



Kumar M, et al. J Clin Exp Hepatol 2012;2:366-81

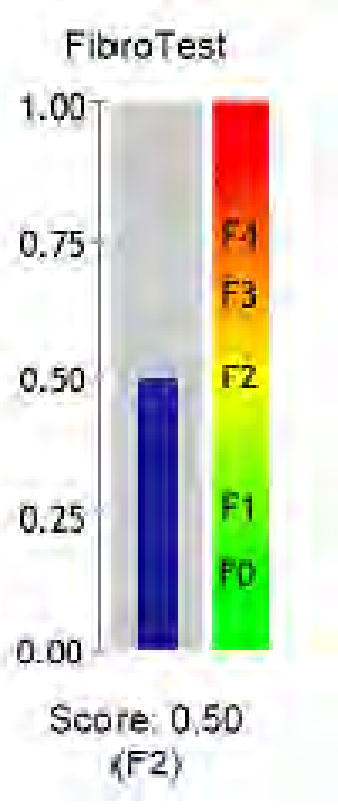
Women desire to be pregnant :Treatment

- Finite course of peginterferon therapy before becoming pregnant
- May defer treatment until after pregnancy if clinical disease is stable
- May treat only in the third trimester of pregnancy to reduce transmission risk
- Treatment with tenofovir and planned pregnancy

Bzowej NH. Curr Hepatitis Rep 2012);11:82-9
www.clinicaloptions.com

Case 2

- Chronic HBV infection in woman who is first detected during pregnancy
- 36 years old woman
- 24 weeks of gestation
- HBeAg positive
- ALT=65 IU/ml
- HBV DNA=400.000 IU/ml ($2x10^6$ cp/ml)
- Ultrasound
  - Intrauterine pregnancy, normal liver



Q2: Choices

- Order liver biopsy
- No treatment, observe patient
- Consider treatment with antivirals

Chronic HBV infection in women who are first detected during pregnancy

- Decision based on:
  - Women
    - Trimester of the pregnancy
    - Severity of underlying liver disease (advanced fibrosis, cirrhosis)
    - Breast feeding
  - Drug
    - Safety in pregnancy
    - Efficacy
    - Barrier to resistance
    - Length of therapy

Start treatment with category B drugs if there is advanced fibrosis or cirrhosis

Kumar M, et al. J Clin Exp Hepatol 2012;2:366-81

Case 3

- Chronic HBV infection in woman who become pregnant while taking entecavir for six months
- 33 years old woman
- 8 weeks of gestation
- Anti-HBe positive
- Initial ALT=65 IU/ml, now 25 IU/ml
- Initial HBV DNA=4.000.000 IU/ml ($2x10^7$ cp/ml), now undetectable

Q3: Choices

- Discontinue treatment
- Continue treatment with entecavir
- Change entecavir to lamivudine
- Change entecavir to telbivudine
- Change entecavir to tenofovir

Became pregnant while receiving treatment for HBV infection

- Continue or stop treatment? decision based on:
  - Women
    - Trimester of the pregnancy
    - Severity of underlying liver disease (advanced fibrosis, cirrhosis)
    - Risk of flares when stopping the medications
- Breast feeding
  - Drug
    - Safety in pregnancy
    - Efficacy
    - Barrier to resistance
    - Length of therapy

Continue treatment with category B drugs if there is advanced fibrosis or cirrhosis

Kumar M, et al. J Clin Exp Hepatol 2012;2:366-81

Treatment during pregnancy

- Peginterferon alfa should be discontinued and therapy continued with a nucleos(t)ide analogue
- FDA category C nucleos(t)ide analogues should be replaced with category B agents; tenofovir is preferred

Case 4

- 23 years old pregnant woman
- Known to be HBeAg positive
- ALT=24 IU/ml
- HBV DNA=20.000 IU/ml (10^5 cp/ml) in first trimester
- HBV DNA=2.000.000 IU/ml (10^7 cp/ml) at 28 weeks of pregnancy

Q4: Choices

- No treatment, give HBIG + HBV vaccine series to newborn after delivery
- Cesarean delivery, give HBIG + HBV vaccine series to newborn after delivery
- Consider antiviral therapy and give HBIG + HBV vaccine series to newborn after delivery

Prevention of perinatal HBV transmission

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

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

Failures of prophylaxis

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

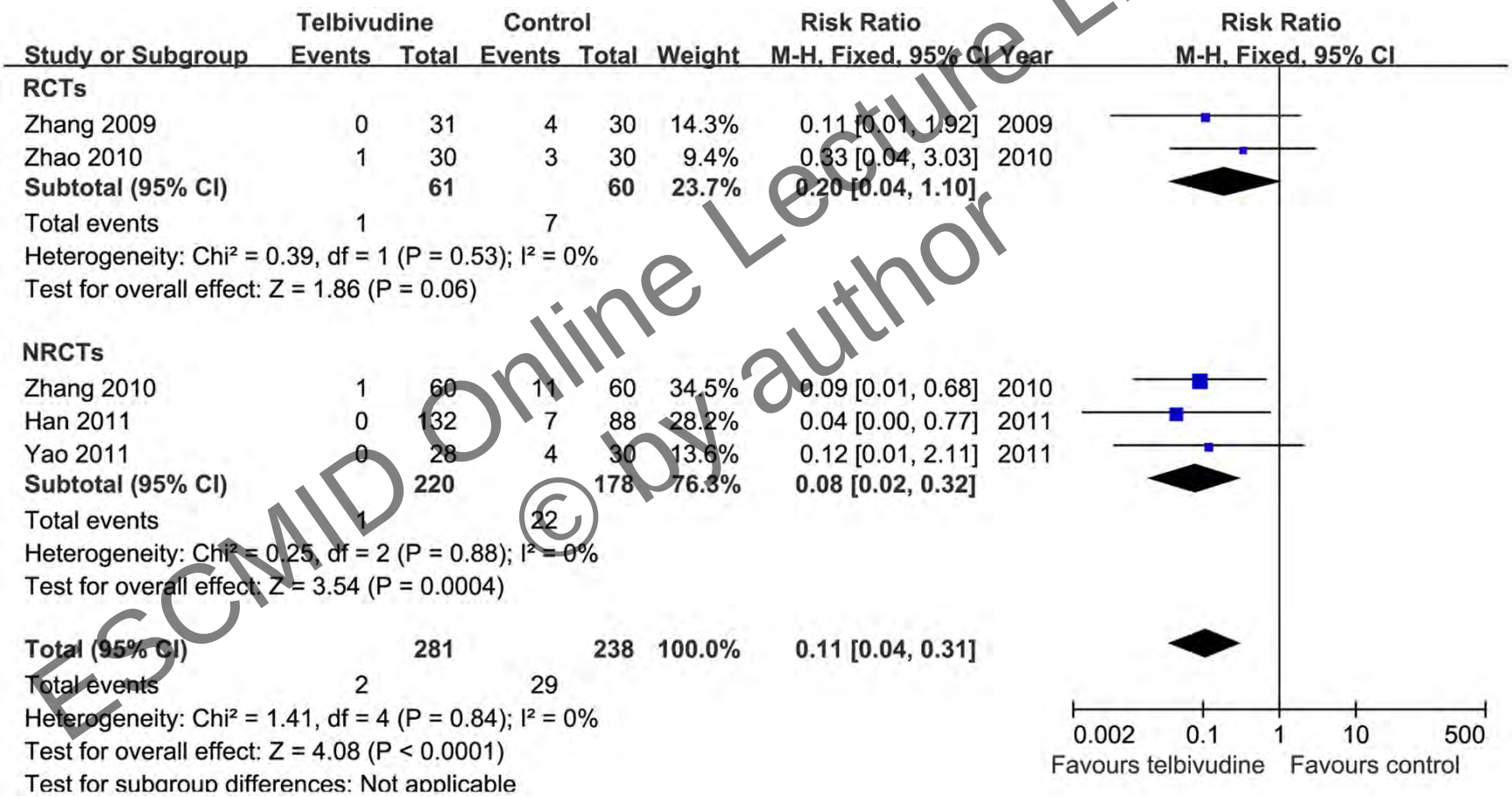
Sa-nguanmoo P,, et al. J Med Virol 201284:1177-1185
Wiseman E, et al. Med J Aust 2009;190:489–92
Song YM, et al. Eur J Pediatr 2007;166:813-18
Zou H, et al. J Viral Hepat 2012;19:e18–25

Lamivudine in late pregnancy to interrupt transmission of HBV

- Two meta-analysis
  - 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 reduced to < 10^6 copies/mL by lamivudine treatment, HBV MTCT can be prevented more efficiently as indicated by newborn serum HBsAg

Shi Z, et al. Obstet Gynecol 2010;116:147-59
Han L, et al. World J Gastroenterol 2011;14;17:4321-33

Telbivudine in late pregnancy to interrupt transmission of HBV



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

576 mothers in total
306 received telbivudine

Deng et al. Virology Journal 2012, 9:185

Vertical transmission of HBV

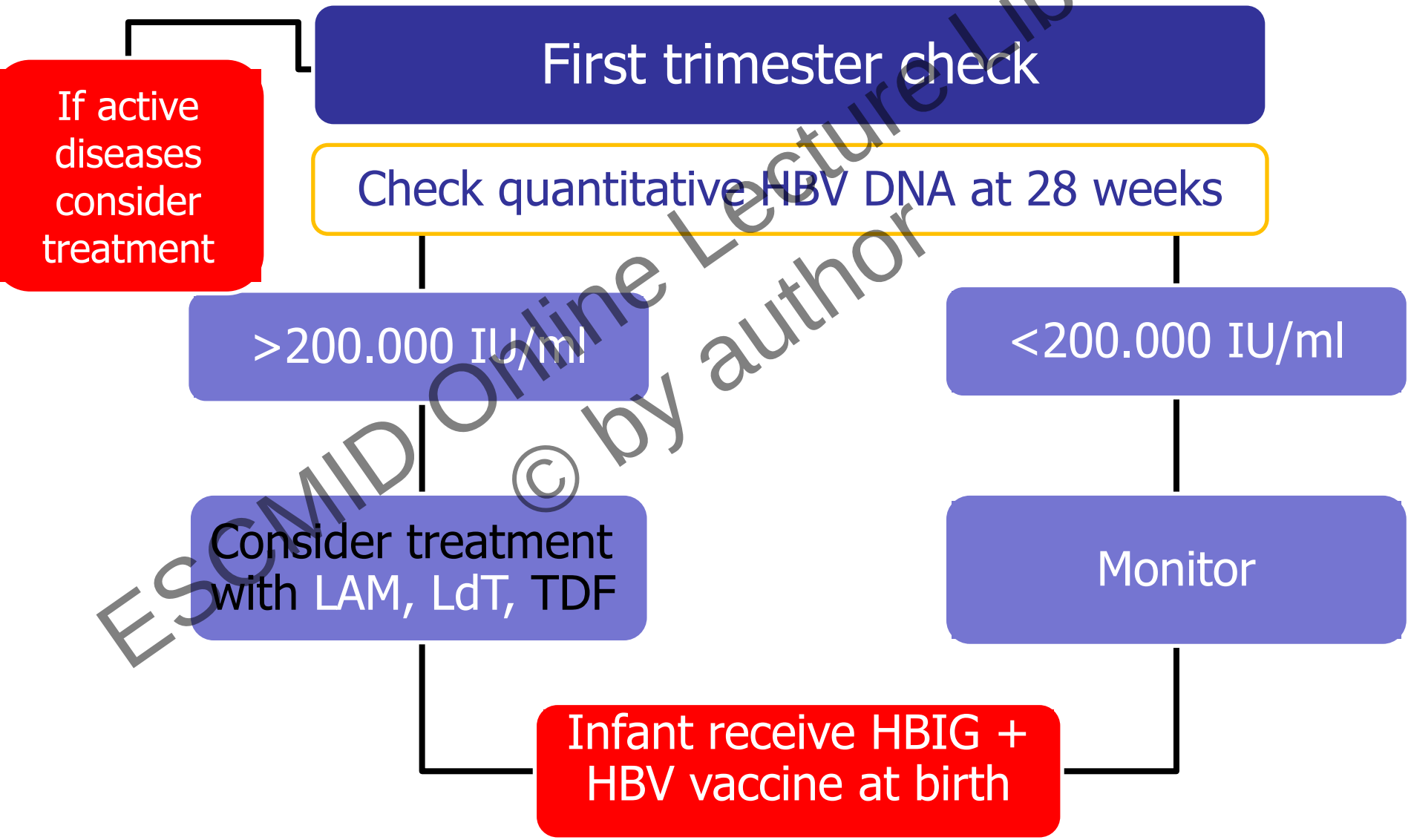
HBV DNA	Transmission
10^6 cp/ml	3%
10^7 cp/ml	5.5%
10^8 cp/ml	9.6%

Consider to begin antiviral therapy at 2./3. trimester

with >200.000 IU/ml (10^6 cp/ml) HBV-DNA

Han GR, et al. Journal of Hepatology 2011;55:1215-21
Petersen J. J Hepatol 2011;55:1171-3

Management of HBV in pregnancy



Adapted from Bzowej NH. Curr Hepatitis Rep 2012);11:82-9

Duration of treatment

- Discontinue treatment after birth to 1 month post delivery
- Treatment up to 6 months post-partum
- After delivery, monitoring possible postpartum exacerbation at least 6 months
  - ALT and HBV DNA

Shi Z, et al. Obstet Gynecol 2010;116:147-59

Breastfeeding

- It does not increase the risk of HBV infection in the infant
- HBIG and HBV vaccine are protective
- Breastfeeding is not contraindicated for treatment-naive mothers
- For mothers on antiviral therapy, breastfeeding is not recommended

Gartner LM, et al. American Academy of Pediatrics. Pediatrics 2005;115:496-506
Zhongjie S, et al. Arch Pediatr Adolesc Med 2011;165(9):837-846

Take home messages

- Screening of pregnant women for HBsAg during pregnancy
- Management of HBsAg-positive mothers and their infants
- Immunoprophylaxis for infants born to infected mothers
- Routine vaccination of all infants with the Hepatitis B vaccine series

ESCMID Observership Program Collaborative Center

Thank you for your attention

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