

VIRAL HEPATITIS IN PREGNANCY

Unravelling the mystery

SATURDAY, 27TH JULY 2019

(on the occasion of World Hepatitis Day 2019)

**‘National seminar for physicians
in diagnosis and management of viral hepatitis in pregnancy’**

TOPIC: Viral Hepatitis in pregnancy – *An Overview*

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Hepatology, ILBS**

Outline

- Main types of viral hepatitis during pregnancy
- Clinical Presentations of viral hepatitis during pregnancy
- Magnitude of problem
- Risks of viral hepatitis to pregnant women
- Risks of Viral Hepatitis to Fetus/Infant and Preventive Measures
- Specific issues of HBsAg positive pregnant women

Main types of viral hepatitis during pregnancy

- Hepatitis E
- Hepatitis A
- Herpes Simplex Virus

- Hepatitis B
- Hepatitis C

Clinical presentations of viral hepatitis during pregnancy

- Acute viral hepatitis (A/E/B/HSV)
- Fulminant hepatic failure (or ALF) (A/E/B/HSV)
- Incidental detection during prenatal check or during pregnancy (B/C)

Maternal and Fetal Outcomes in Pregnant Women with Acute Hepatitis E Virus Infection

Ann Intern Med. 2007;147:28-33.

Sharda Patra, MS; Ashish Kumar, MD, DM; Shubha Sagar Trivedi, MS; Manju Puri, MS; and Shiv Kumar Sarin, MD, DM

33 385 pregnant women who were admitted at LPMC from January 2003 and July 2005

316 (0.9%) presented with jaundice

Acute viral Hepatitis (single virus):
220/316(69.6%)

Intrahepatic cholestasis of preg:41/316(12.9%)

HELLP syndrome :6/316(1.8%)

Acute fatty liver of pregnancy:3/316(0.94%)

Drug hepatotoxicity:7/316(2.21%)

Hemolytic jaundice :14/316(4.43%)

Choledocholithiasis :6/316(1.8%)

Dual viral infection: 4/316(1.26%)

Unknown cause: 15/316(4.75%)

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Acute viral Hepatitis (single virus): 220

HEV: 132/220(60%)

HBV : 72/220 (32.7%)

HAV:16/220:3/316(7.2%)

Acute viral hepatitis diagnosis:

Serum bilirubin level > 2 mg/dL;
Serum ALT \geq 2.5 x ULN; and

Positivity for : **HBsAg; anti-HCV; IgM-HAV, IgM- HEV**

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Acute viral Hepatitis (single virus): 220

Fulminant hepatic failure/ALF: 91/220 (41.36%)

FHF at admission: 54/91 (60%)

FHF during hospitalization: 37/91 (40%)

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Table 1. Patient Characteristics*

Variable	HEV-Infected Women (n = 132)	Non-HEV-Infected Women (n = 88)	P Value
Mean age (SD), y	22.2 (3.4)	22.5 (3.0)	0.54
Median gravida (range), n	2 (1-6)	2 (1-7)	0.96
Mean gestational age (SD), wk	31 (4.1)	33 (4.4)	0.004
Trimester, n (%)			0.023
Second	44 (33)	17 (19)	
Third	88 (67)	71 (81)	
Socioeconomic status, n (%)†			0.29
Middle	58 (44)	45 (51)	
Low	74 (56)	43 (49)	
Median duration of jaundice before admission (range), d	4 (1-15)	4.5 (2-10)	0.68
Acute viral hepatitis, n (%)			<0.001
With fulminant hepatic failure	73 (55)	18 (20)	
Without fulminant hepatic failure	59 (45)	70 (80)	
Laboratory data			
Mean hemoglobin level (SD), g/L	84 (14)	88 (12)	0.026
Median leukocyte count (range), cells × 10 ⁹ /L	12 (4-33)	9.5 (4-28)	<0.001
Mean platelet count (SD), cells × 10 ⁹ /L	211.3 (59.6)	238.2 (56.4)	0.001
Mean serum bilirubin level (SD)			<0.001
μmol/L	255.0 (90.1)	181.9 (86.7)	
mg/dL	15.0 (5.3)	10.7 (5.1)	
Median alanine aminotransferase level (range), U/L	90.5 (24.8-310.1)	54.5 (10.0-212.2)	0.001
Median prothrombin time (range), s‡	58 (15-150)	19 (15-105)	0.001
Median international normalized ratio (range)	4.0 (1.0-18.6)	1.6 (1.0-7.1)	0.001
Mean serum albumin level (SD), g/L	36 (10)	42 (9)	<0.001



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Fulminant hepatic failure/ALF: 91

Trimester	FHF in HEV (132)	FHF in Non-HEV (88)	P value
3 rd T	46/88 (52%)	11/71 (15%)	<0.001
2 nd T	27/44 (61%)	7/17 (41%)	0.26

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*Table 2. Maternal Mortality and Medical Complications**

Variable	HEV-Infected Women (n = 132), n/n (%)	Non-HEV-Infected Women (n = 88), n/n (%)	Relative Risk (95% CI)	P Value
Maternal mortality rate				
Overall	54/132 (41)	6/88 (7)	6.0 (2.7–13.3)	<0.001
Patients with fulminant hepatic failure	54/73 (74)	6/18 (33)	2.2 (1.1–4.3)	0.001
Second trimester	18/27 (66)	0/7 (0)	–	0.002
Third trimester	36/46 (78)	6/11 (54)	1.4 (0.8–2.5)	0.11
Patients without fulminant hepatic failure	0/59 (0)	0/70 (0)	–	1.00
Medical complications				
Coagulation defect†	104/132 (79)	32/88 (36)	2.2 (1.6–2.9)	<0.001
Nasal or gastrointestinal hemorrhage	25/132 (19)	4/88 (4)	4.2 (1.5–11.6)	0.002
Leukocyte count $\geq 11 \times 10^9$ cells/L	86/132 (65)	31/88 (35)	1.8 (1.4–2.5)	<0.001
Serum creatinine concentration $\geq 34 \mu\text{mol/L}$ ($\geq 2 \text{ mg/dL}$)	39/132 (30)	4/88 (4)	6.5 (2.4–17.5)	<0.001
Ascites	33/132 (25)	5/88 (6)	4.4 (1.8–10.8)	<0.001
Clinical signs of increased intracranial tension	27/132 (20)	1/88 (1)	18.0 (2.5–130.1)	<0.001

* HEV = hepatitis E virus.

Prevalence of Hepatitis B infection in pregnancy

Author [Ref.]	Year	Location	Number of pregnant women screened	Prevalence of HBsAg [%]
Khatri et al. [85]	1980	Mumbai	1,276	0.62
Nayak et al. [86]	1987	Delhi	8,575	3.76
Biswas et al. [87]	1989	Chandigarh	1,000	2.30
Gupta et al. [88]	1992	Chandigarh	2,337	2.48
Mittal et al. [89]	1996	Delhi	850	6.34
Sharma et al. [90]	1996	Aligarh	157	10.19
Prakash et al. [91]	1998	Delhi	1,112	9.53
Abbas et al. [92]	2001	Delhi	6,910	1.01
Sahni et al. [93]	2004	Delhi	987	2.22
Varghese et al. [94]	2004	Delhi	6,341	0.81
Banerjee et al. [95]	2005	Kolkata	400	3.75
Sandesh et al. [77]	2006	Kerala	70,659	0.25
Chatterjee et al. [78]	2009	Multicentric ^a	36,379	0.82
Dwivedi et al. [96]	2011	Allahabad	4,000	0.92
Pande et al. [79]	2011	Delhi	20,104	1.11
	Overall		161,087	0.92

Overall prevalence

HBsAg among Indian pregnant women – approx. 1%

Risks of viral hepatitis to pregnant women

Type of Viral Hepatitis	Potential Risks to Mother	Timing of Pregnancy With Highest Risk
Hepatitis A	Gestational complication; preterm labor	2nd half of pregnancy, especially 3rd trimester
Hepatitis B*	Flares of chronic hepatitis B	Can occur during pregnancy or postpartum period
Hepatitis C*	None	
Hepatitis E	Acute liver failure; eclampsia	2nd and 3rd trimester
HSV hepatitis	Acute liver failure	3rd trimester

*Data based on pregnant women with chronic infection.

Risks of Viral Hepatitis to Fetus/Infant and Preventive Measures-HAV

- There is no evidence that HAV causes birth defects
- Fetal ascites; meconium peritonitis: Rare, mainly if mother is infected during 1st trimester
- There is no evidence of maternal-fetal transmission
- In rare circumstances in which the mother has acute HAV infection at the time of delivery
 - immune serum globulin may be administered to the infant
- Even under these conditions, the risk of transmission to the infant seems very small
- Anti-HAV IgG antibodies is not transmitted from infected mothers to newborn infants

Risks of Viral Hepatitis to Fetus/Infant and Preventive Measures-HEV

- Spontaneous abortion; premature delivery: Risk higher if mother is infected during 3rd trimester
- Transmission occurs intrapartum and peripartum through close contact of mother and neonate.
- Significant vertical transmission among HEV-RNA positive mothers of up to 50%.
- Among women with symptomatic infection the rate of transmission is up to 100%, with significant perinatal morbidity and mortality.

Risks of Viral Hepatitis to Fetus/Infant and Preventive Measures-HCV

- The rate of vertical transmission of hepatitis C is less than 5%
- The risk is higher if the mother is co-infected with (HIV)
 - if she is viremic at the time of delivery
 - if her viral DNA load is greater than 1 million copies/ml
 - if the time from the rupture of membranes to delivery is more than 6 hours.

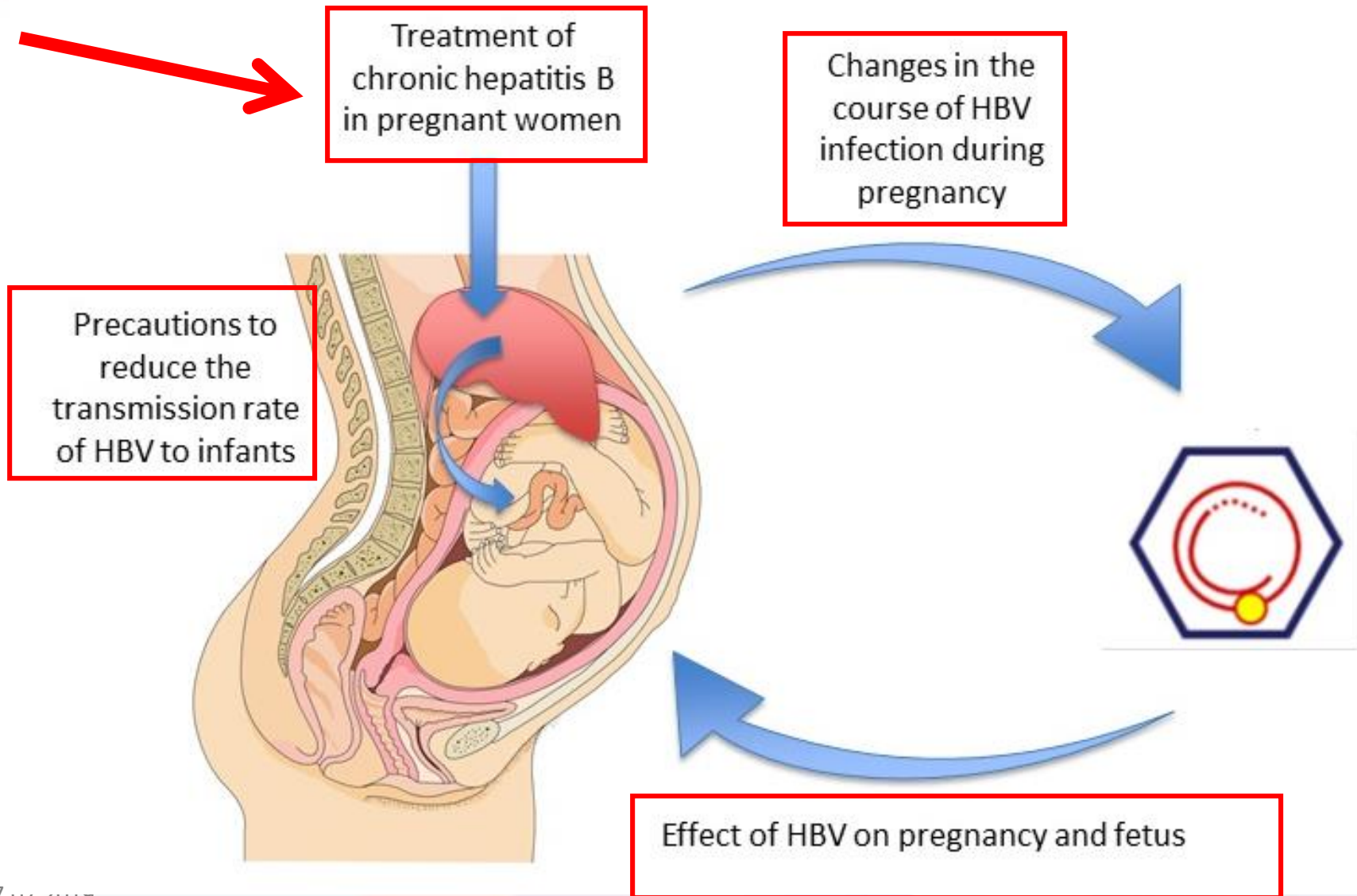
Risks of Viral Hepatitis to Fetus/Infant and Preventive Measures-**HSV**

- Risk of vertical transmission:
 - Primary infection at the time of delivery (40%-44%)
 - First episode of genital nonprimary infection (24%-31%)
 - Recurrent infections (1.3%-3%)
- Intrauterine infection is rare (1 in 250,000).
- 85% infection in perinatal; 10% in postnatal period
- Invasive fetal monitoring, prolonged duration of ruptured membrane, and vaginal delivery increase the risk of vertical transmission

Risks of Viral Hepatitis to Fetus/Infant and Preventive Measures-HSV

- Treat mother with primary or first episode of genital HSV infection with acyclovir
- Consider suppressive therapy for recurrent infections at 36 weeks of pregnancy
- Consider cesarean section delivery if predicted risk of transmission is high

Pregnancy and HBV infection: Key issues



Effect of Hepatitis B on pregnancy outcome

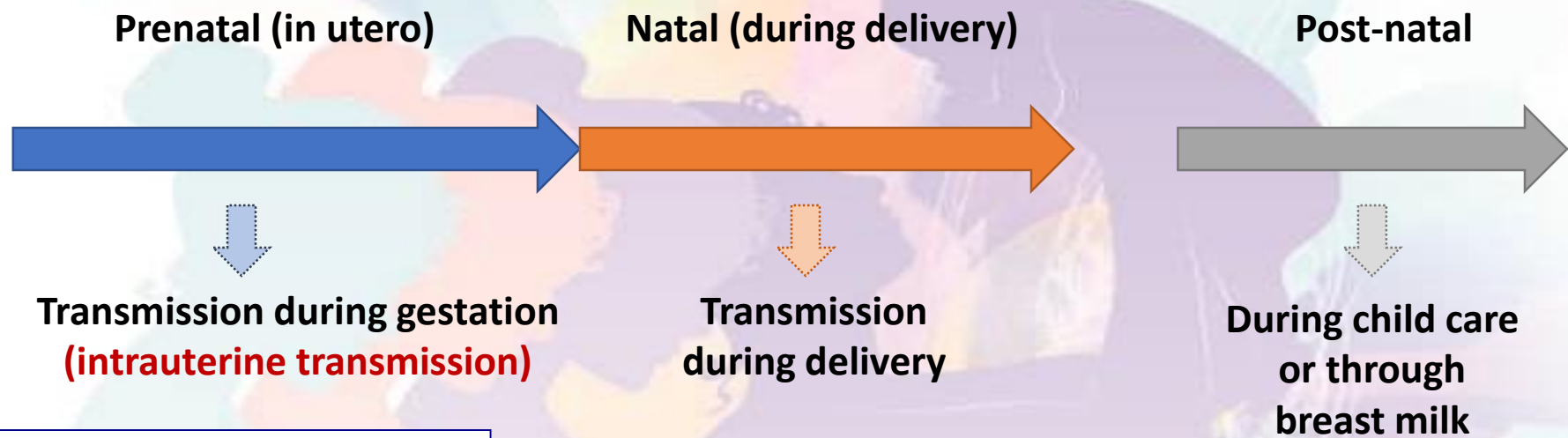
- Acute HBV infection:
 - No increased maternal mortality or teratogenic effects
 - Higher incidence of low birth weight and prematurity have been reported¹
- Chronic HBV infection:
 - Higher incidence of gestational diabetes mellitus?^{2,4,5}
 - Higher risk of prematurity?^{3,4,5}
 - High risk of low birth weight (<2500g)?⁵
 - No association with pre- eclampsia^{4,5}

More adverse outcome if cirrhosis !

Effect of pregnancy on HBV related liver disease

- No worsening of liver disease in majority during pregnancy
- Liver enzymes frequently normalize
- Pregnancy suppress immunity
more TH2 > TH1 and in post partum, TH1 > TH2
- **Post partum flares – 10-30%, more in HBeAg+**
- **Usually asymptomatic and resolve spontaneously**
- Rare decompensation if cirrhosis

Possible routes of transmission of HBV from infected mothers to infants



Intrauterine infection →

13 - 44%

- ◆ Minor laceration of placenta
 - Threatened abortion
 - Threatened preterm labor
 - TORCH infection
- ◆ Placental infection by HBV
- ◆ Infection of peripheral blood leukocytes
- ◆ Oocyte or sperm infection
- ◆ Ascending infection

Perinatal infection → 60 - 80%

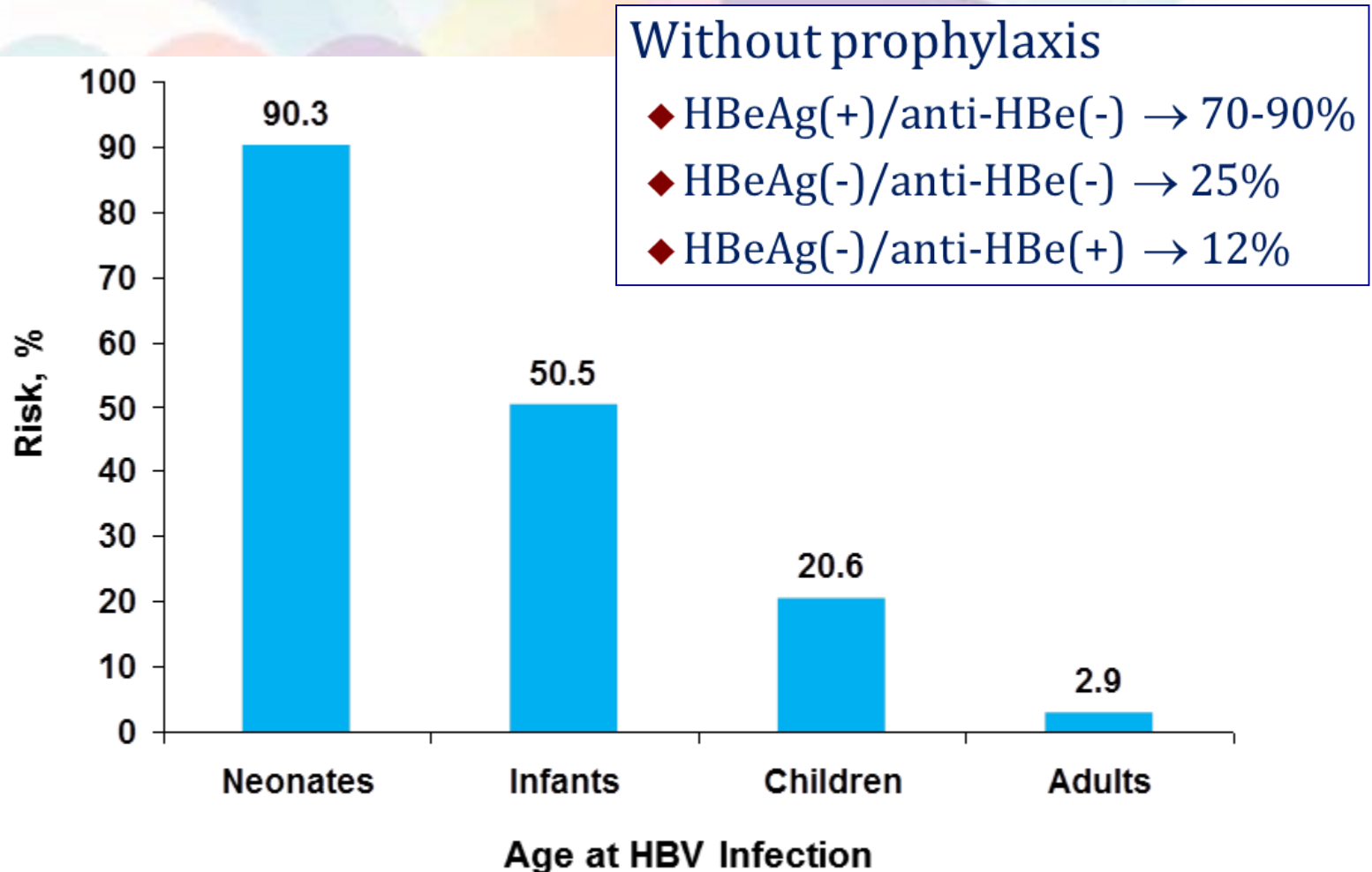
- ◆ maternal-fetal microtransfusion during delivery
 - Threatened preterm labor, instrumentation, placental leakage
- ◆ swallowing of infective fluid.

Postpartum transmission →

5 - 10%

- ◆ Intimate contacts in daily life
- ◆ Exposure to maternal body fluids, milk

HBV transmission rates and risk of chronic HBV infection



Prevention of perinatal HBV transmission

(A) Immunoprophylaxis after delivery

- Cornerstone: HBIG + HBV vaccine

- HBIG + first dose vaccine within 12 hrs of birth, different sites
- Efficacy: ~ 95%

Superior to HBIG or vaccine alone
Hepatitis B vaccine in a 3 or 4 dose schedule

- Reasons for failure

- Delay in administration of HBIG and first dose of vaccine
- Failure to complete vaccine series
- Mother HBeAg positive and/or high HBV DNA

After completion of the vaccine series, HBsAg and anti-HBs should be tested by 9 months of age.

Predictive rates of HBV infection despite immunoprophylaxis

Risk Factor	Exposure rate	P value	Odds ratio	95% CI
Mother HBeAg		0.392	1.9	0.6, 6.6
Positive	13/17 (76%)			
Negative	39/62 (63%)			
Mother Anti-HBe		0.174	2.6	0.8, 8.6
Positive	16/20 (80%)			
Negative	36/59 (61%)			
Mother HBV DNA		0.025	3.2	1.2, 8.5
Detectable	38/50 (76%)			
Undetectable	14/28 (50%)			
Mode of delivery		0.111	2.8	0.8, 9.5
Vaginal	46/65 (71%)			
LSCS	6/13 (46%)			
Gestation		0.528	0.6	0.2, 2.2
Preterm	8/14 (57%)			
Term/post-term	27/40 (68%)			

- Detectable maternal HBV DNA significantly increased the transmission rate ($p=0.025$)

Virologic factors associated with failure to passive–active immunoprophylaxis in infants born to HBsAg-positive mothers

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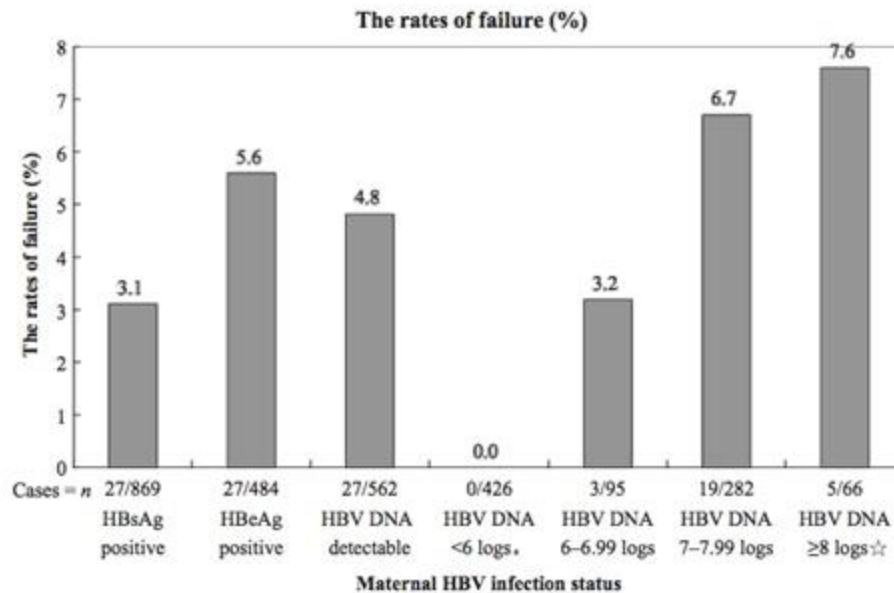


Table 4 Multivariate logistic regression analysis for risk factors associated with immunoprophylaxis failure

Factors	OR	95% CI	P-value
HBV DNA detectable in cord blood	39.670	14.22–110.64	<0.0001
Maternal HBV DNA level	1.878	1.07–3.30	0.028

OR, odds ratio; CI, confidence interval; HBV, hepatitis B virus.



Prevention of Vertical Transmission of Hepatitis B

An Observational Study

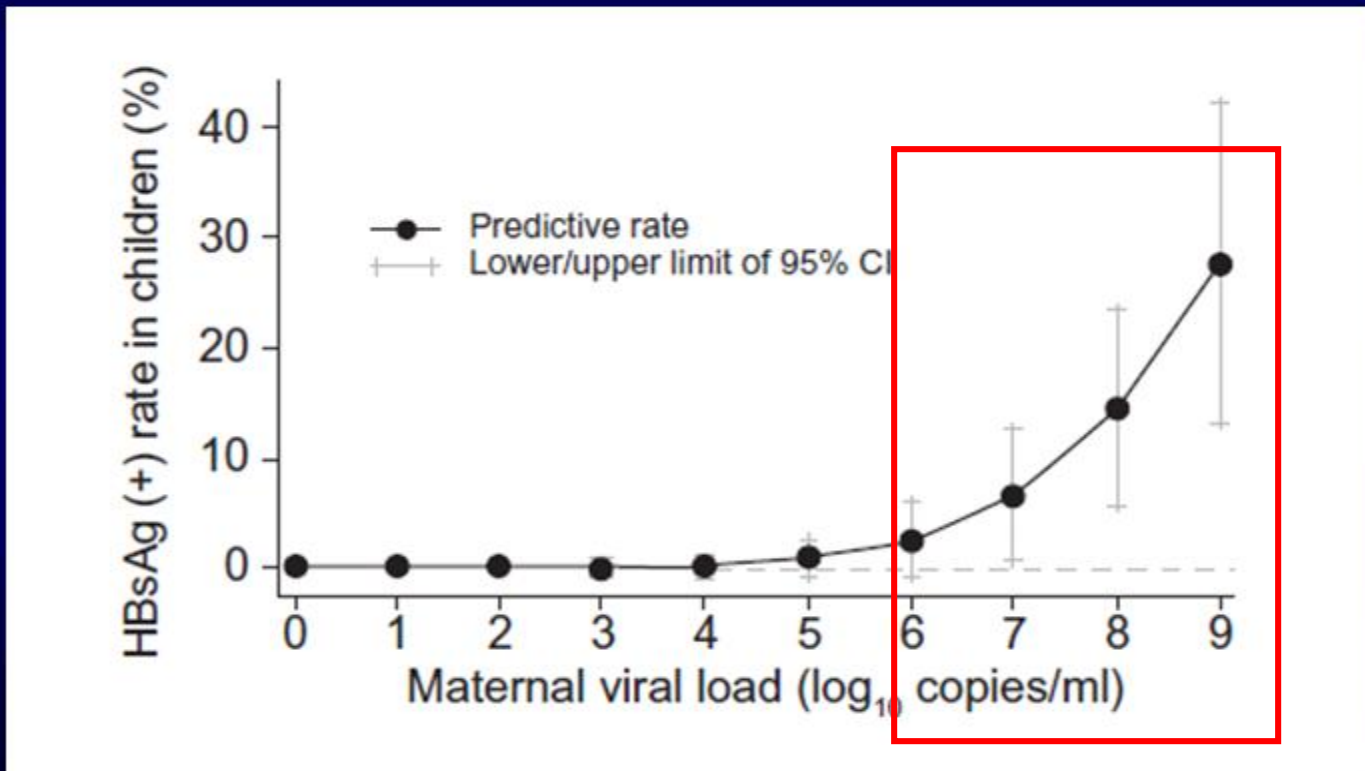
AI Kubo, PhD*; Lyle Shlager, MD*; Amy R. Marks, MPH; Dena Lakritz, RN, MPH; Colette Beaumont, RN, MSN; Kim Gabellini, RN, MS; and Douglas A. Corley, MD, PhD

Variable	Infected/Tested Children, n/N (%)		
	Viral load <5 x 10 ⁷ IU/mL	Viral load ≥5 x 10 ⁷ IU/mL	Total
Mother E Ag(-)	0/671 (0)	0/1 (0)	0/672 (0)
Mother E Ag(+)	0/88 (0)	3/75 (4)	3/163 (1.8)
Total	0/759 (0)	3/76 (3.9)	3/835 (0.4)

A negative e antigen status or a viral load less than 5 x 10⁷ IU/mL (90.9% of women tested) identifies women at extremely low risk for transmission after immunoprophylaxis who are unlikely to benefit from further interventions.

Maternal HBV DNA level and perinatal transmission

302 mother-infant pairs, 26% HBeAg positive



Clinical scenarios in HBV and pregnancy...

- **Pregnant woman is detected to have HBV infection during routine antenatal check up or anytime during pregnancy (with or without symptoms/jaundice)**
- **Woman with HBV infection (with or without liver disease) contemplates pregnancy and seeks opinion**
- **HBV infected women on antivirals- plans pregnancy or gets pregnant**
- **HBV is detected during postpartum period**

Issues in HBsAg(+) Pregnant Women and her baby

- Should antiviral therapy be recommended for liver disease of mother
- Should antiviral therapy be recommended to reduce risk of perinatal transmission?
- What should be the cutoff maternal HBV DNA level for initiation of antiviral therapy?
- When to start?
- Which antiviral drug?
- When to stop?
- What is the risk of posttreatment flares?

Other Issues in HBsAg(+) Pregnant Women and her baby

- Role of caesarian section
- Breast feeding of baby

Conclusions

- Viral hepatitis should be considered in pregnant women presenting with abnormal LFTs or acute hepatic illness or FHF
- Most common cause of jaundice in pregnant women is acute viral hepatitis
- HEV –MC cause of acute viral hepatitis and FHF in pregnant women
- HEV high mortality in pregnant women with FHF

Conclusions

- Some viruses have risk of transmission from mother to infant-
 - HEV esp mother HEV RNA(+)
 - HCV esp if mother HIV(+)
 - HBV (if no immune prophylaxis)
 - HSV
- HBV infection poses some specific issues in pregnant women

Thank you!