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: Current recommendations for screening & Immunoprophylaxis

PRESENTER: Dr. V. Rajan, Assistant Professor, Hepatology, ILBS

HBV and Pregnancy

- Mother-to-child transmission (MTCT) is the major route of hepatitis B virus (HBV) transmission, accounting for 40% to 50% of chronic infections worldwide.

Lamberth JR, Reddy SC, Pan JJ, et al. Chronic hepatitis B infection in pregnancy. World J Hepatol 2015;7:1233–1237.

The HBe-antigen and vertical transmission of hepatitis B surface antigen

Mother		Infant
HBsAg	HBeAg	Chronic Infection
+	+	70-90 %
+	-	31 %

Beasley RP, et al. Am J Epidemiol, 105 (1977), 94-98

How you get the Virus !

Mode determines Outcome

- **Horizontal**
  - 95% clear
- **Perinatal : Mother to Child Transmission**
  - 90% Persists Life long
  - Looks Healthy

Hepatitis B Virus Infection in Pregnant Women in India

- September2004 to December 2008 consecutive pregnant women attending the antenatal clinic
- 20,104 pregnant women screened, 224(1.1%) women were HBsAg positive
- Median ALT- 43 (11-153) IU/L, Mean Bilirubin- 0.8 (0.2-2.7) mg%
- HBeAg+ in 42 (19%), anti HBe+ in 120 (54%)

Pande C et al. J Med Virol. 2011 Jun;83(6):962-7

Hepatitis B Virus Infection in Pregnant Women in India

HBV DNA (IU/ml)	All women (n=224)	HBeAg positive (n=42)	HBeAg negative (n=182)
< 10	10, 5%	0, 0%	10, 5%
10-2000	54, 24%	2, 5%	52, 29%
> 2000	160, 71%	40, 95%	120, 66%

Pande C et al. J Med Virol. 2011 Jun;83(6):962-7

Serum markers of Hepatitis B

- Infection — HBsAg, HBV DNA+
- Replication — HBeAg, HBV DNA+++, IgM anti-HBc
- Exposure — Anti HBc IgG, Anti-HBe, Anti-HBs
- Protection — Anti HBs

Screening (APASL Practice Guidelines)

- Antenatal screening for hepatitis B in pregnant females to identify newborns who require prophylaxis against perinatal infection is a well-established, evidence-based standard of practice
- Inexpensive and cost effective
- The HBsAg test is the primary way to definitively diagnose chronic HBV infection.
- Screening should be linked to appropriate counseling and referral for further care

Sarin SK, et al. Hepatol Int (2016) 10:1–98

Recommendations

EASL Guidelines

- *Screening for HBsAg in the first trimester of pregnancy is strongly recommended (Evidence level 1, grade of recommendation 1)*

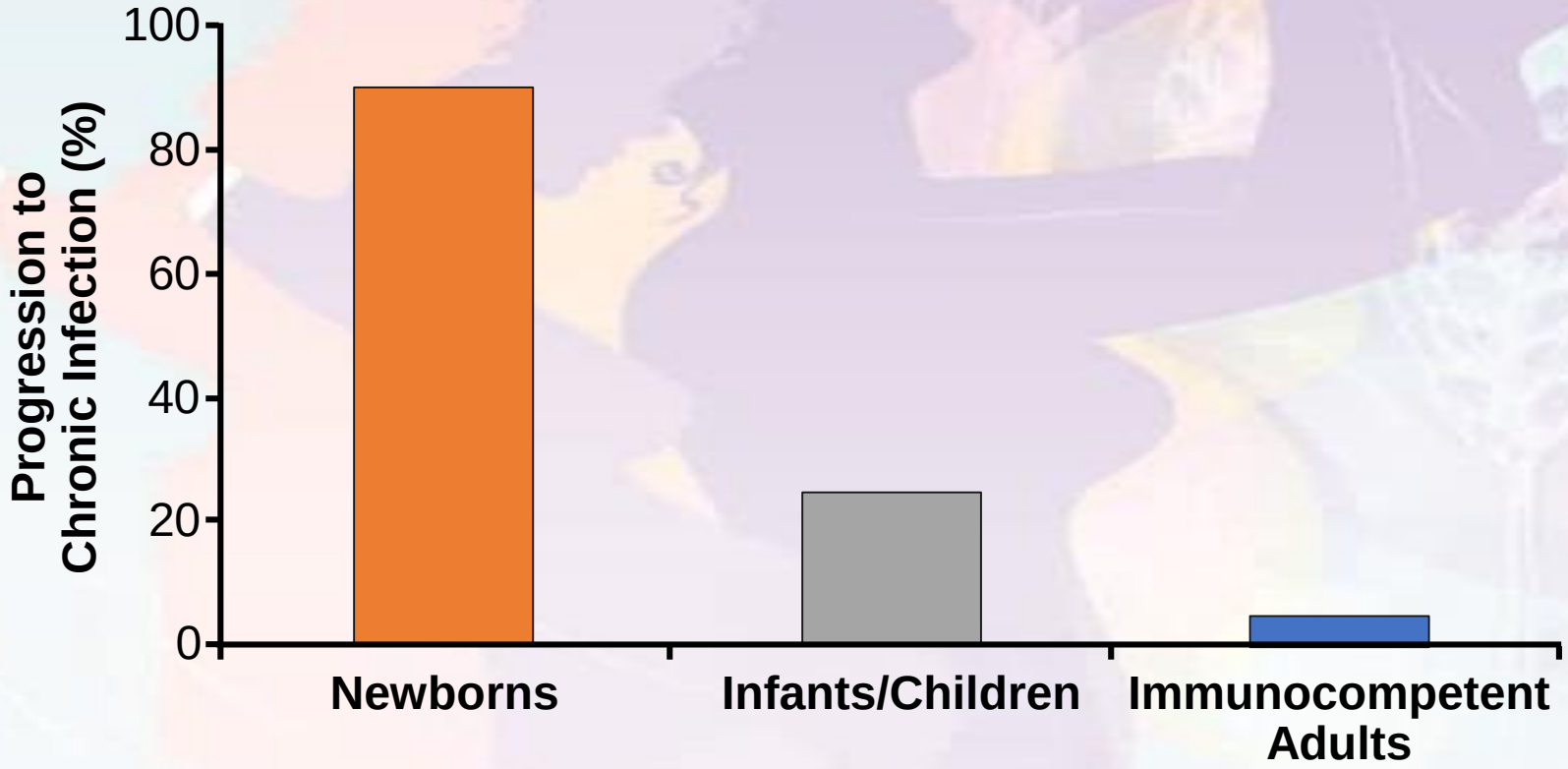
Journal of Hepatology 2017 (67):370–398

AASLD Guidelines

- *The infants of all HBsAg-positive women should receive immunoprophylaxis (HBV vaccination ± hepatitis B immunoglobulin, per WHO/ CDC recommendations).*

Preventing Perinatal HBV Transmission: Why Is It So Important?

- Risk of progression to chronic infection is inversely related to age at infection



Lok AS, et al. Hepatology. 2009;50:661-662.

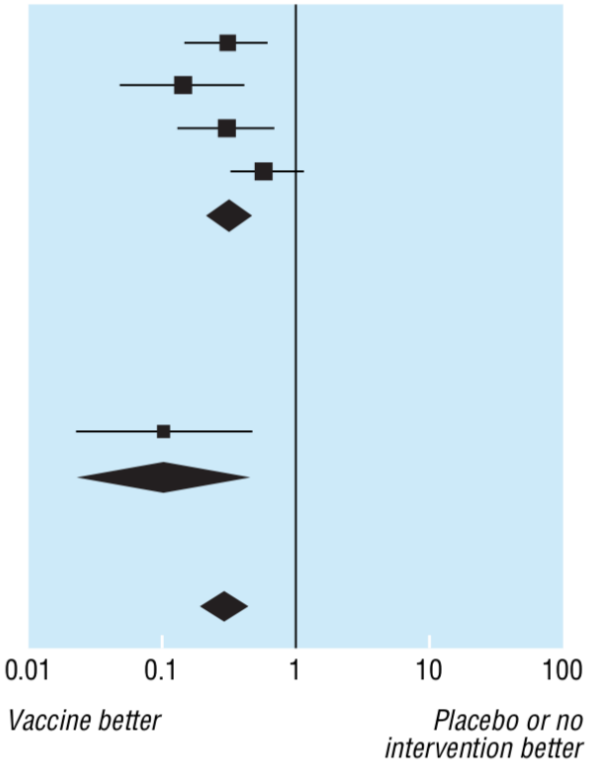
Prevention of Perinatal HBV Transmission

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

Lok AS, et al. Hepatology. 2009;50:661-662. Mast EE, et al. MMWR Recomm Rep. 2005;54(RR-16):1-31.

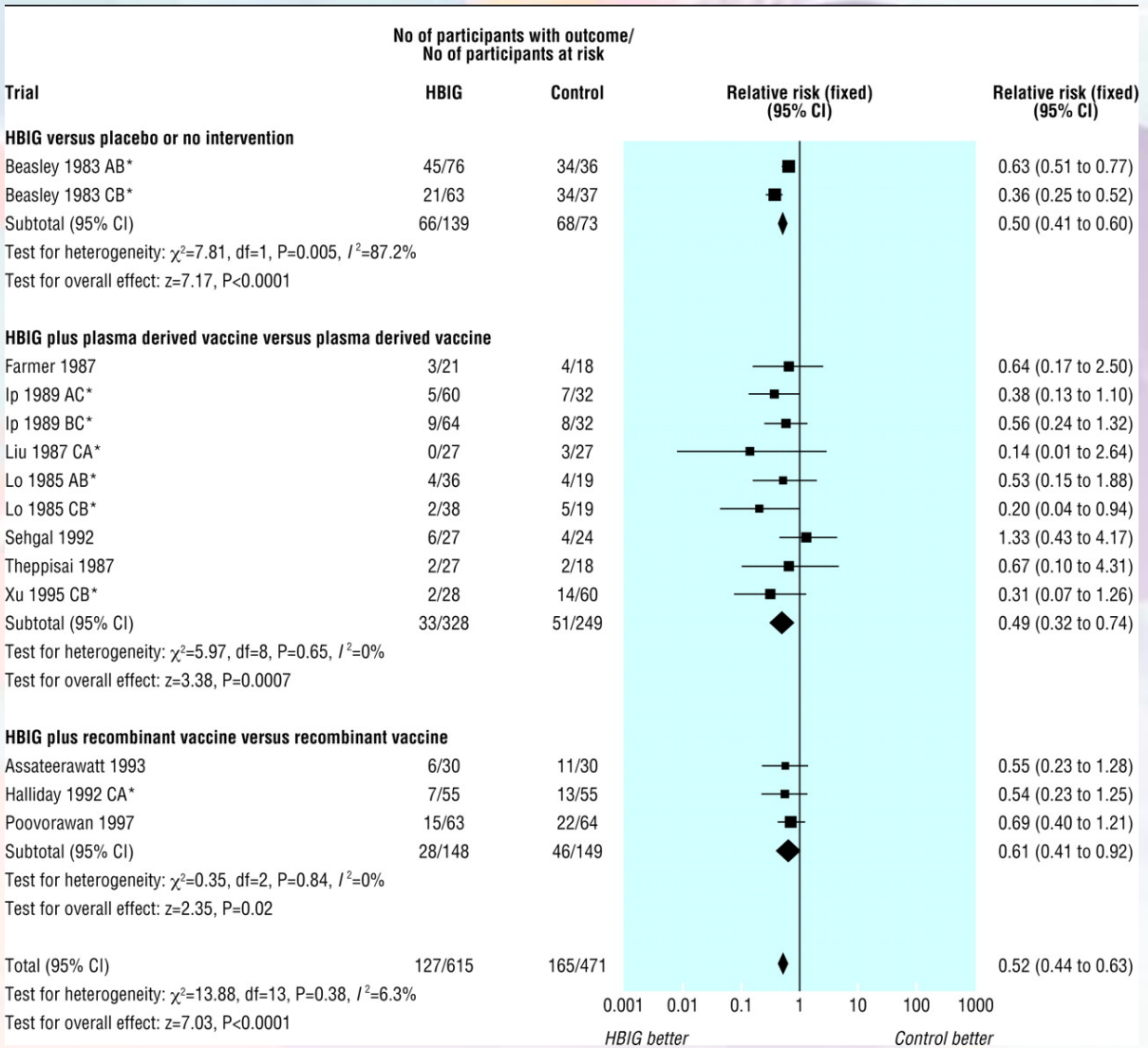
Effect of Hepatitis B Immunisation in Newborn Infants

Trial	Vaccine	Placebo or no intervention	Relative risk (fixed) (95% CI)	Relative risk (fixed) (95% CI)
Plasma derived vaccine versus placebo or no intervention				
Ip 1989 CD*	7/35	23/34		0.30 (0.15 to 0.60)
Liu 1987 AB*	3/27	21/26		0.14 (0.05 to 0.41)
Xu 1995 AD*	7/60	12/30		0.29 (0.13 to 0.66)
Xu 1995 DD*	14/60	12/30		0.58 (0.31 to 1.10)
Subtotal (95% CI)	31/182	68/120		0.31 (0.21 to 0.45)
Test for heterogeneity: χ^2=6.00, df=3, P=0.11, I^2=50.0%				
Test for overall effect: z=6.03, P<0.0001				
Recombinant vaccine versus no intervention				
Khukhlovich 1996	2/70	9/31		0.10 (0.02 to 0.43)
Subtotal (95% CI)	2/70	9/31		0.10 (0.02 to 0.43)
Test for overall effect: z=3.09, P=0.002				
Total (95% CI)	33/252	77/151		0.28 (0.20 to 0.40)
Test for heterogeneity: χ^2=8.74, df=4, P=0.07, I^2=54.2%				
Test for overall effect: z=6.83, P<0.0001				



Chuanfang Lee et al. BMJ 2006;332:328-336

Effect of Hepatitis B Immunisation in Newborn Infants



Trial	No of participants with outcome/ No of participants at risk: HBIG	Control	Relative risk (fixed) (95% CI)	Relative risk (fixed) (95% CI)
HBIG versus placebo or no intervention				
Beasley 1983 AB*	45/76	34/36		0.63 (0.51 to 0.77)
Beasley 1983 CB*	21/63	34/37		0.36 (0.25 to 0.52)
Subtotal (95% CI)	66/139	68/73		0.50 (0.41 to 0.60)
Test for heterogeneity: χ^2=7.81, df=1, P=0.005, I^2=87.2%				
Test for overall effect: z=7.17, P<0.0001				
HBIG plus plasma derived vaccine versus plasma derived vaccine				
Farmer 1987	3/21	4/18		0.64 (0.17 to 2.50)
Ip 1989 AC*	5/60	7/32		0.38 (0.13 to 1.10)
Ip 1989 BC*	9/64	8/32		0.56 (0.24 to 1.32)
Liu 1987 CA*	0/27	3/27		0.14 (0.01 to 2.64)
Lo 1985 AB*	4/36	4/19		0.53 (0.15 to 1.88)
Lo 1985 CB*	2/38	5/19		0.20 (0.04 to 0.94)
Sehgal 1992	6/27	4/24		1.33 (0.43 to 4.17)
Theppisai 1987	2/27	2/18		0.67 (0.10 to 4.31)
Xu 1995 CB*	2/28	14/60		0.31 (0.07 to 1.26)
Subtotal (95% CI)	33/328	51/249		0.49 (0.32 to 0.74)
Test for heterogeneity: χ^2=5.97, df=8, P=0.65, I^2=0%				
Test for overall effect: z=3.38, P=0.0007				
HBIG plus recombinant vaccine versus recombinant vaccine				
Assateerawatt 1993	6/30	11/30		0.55 (0.23 to 1.28)
Halliday 1992 CA*	7/55	13/55		0.54 (0.23 to 1.25)
Poovorawan 1997	15/63	22/64		0.69 (0.40 to 1.21)
Subtotal (95% CI)	28/148	46/149		0.61 (0.41 to 0.92)
Test for heterogeneity: χ^2=0.35, df=2, P=0.84, I^2=0%				
Test for overall effect: z=2.35, P=0.02				
Total (95% CI)	127/615	165/471		0.52 (0.44 to 0.63)
Test for heterogeneity: χ^2=13.88, df=13, P=0.38, I^2=6.3%				
Test for overall effect: z=7.03, P<0.0001				

Chuanfang Lee et al. BMJ 2006;332:328-336

WHO guidelines

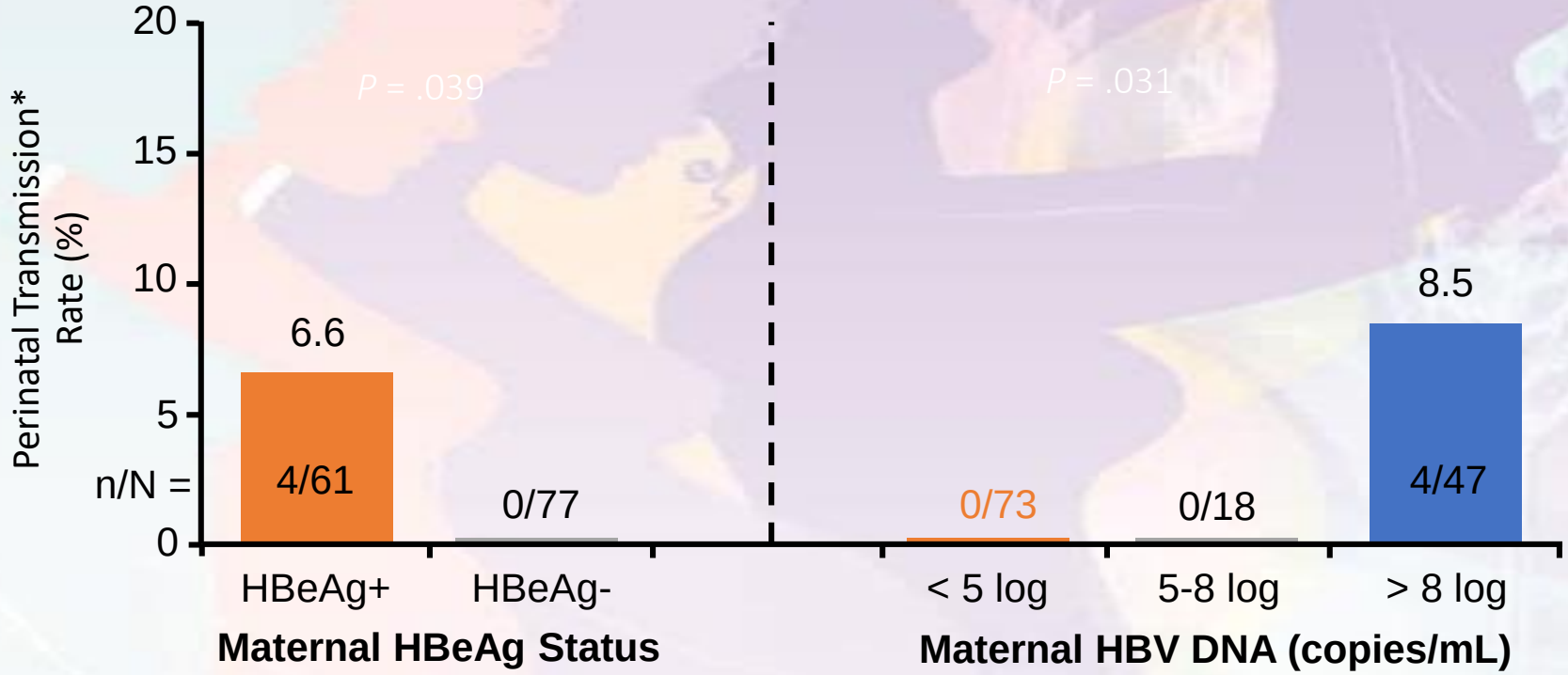
- WHO guidelines stated that HBIG conjunct with vaccination may be of additional benefit for infants from mothers who are **HBsAg+ and HBeAg-positive**

- **More evidences** are needed to warrant on the addition of HBIG to vaccine for infants of HBsAg-positive but HBeAg-negative mothers.

WHO, Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection, Geneva, 2015.

Perinatal HBV Transmission Is Related to Maternal HBV DNA Level

- All infants received HBIG + first dose HBV vaccine within 12 hrs of birth and additional doses of HBV vaccine at 2, 4, and 6 mos



*Perinatal transmission = HBsAg positive at Mo 9.

Wiseman E, et al. Med J Aust. 2009;190:489-492.

MTCT of hepatitis B virus infection: Significance of Maternal viral load and strategies for intervention

- From April 2007 to March 2011, at National Taiwan University Hospital
- 359 deliveries of HBsAg+ women, HBeAg-positive mothers were (n=81/303) **26.7%**
- Higher viral load in HBeAg+ mothers (7.4 ± 1.9 vs. 2.7 ± 1.4 $\log_{10}$copies/ml, $p<0.0001$)

Wen WH et al. Journal of Hepatology2013vol. 59;24–30

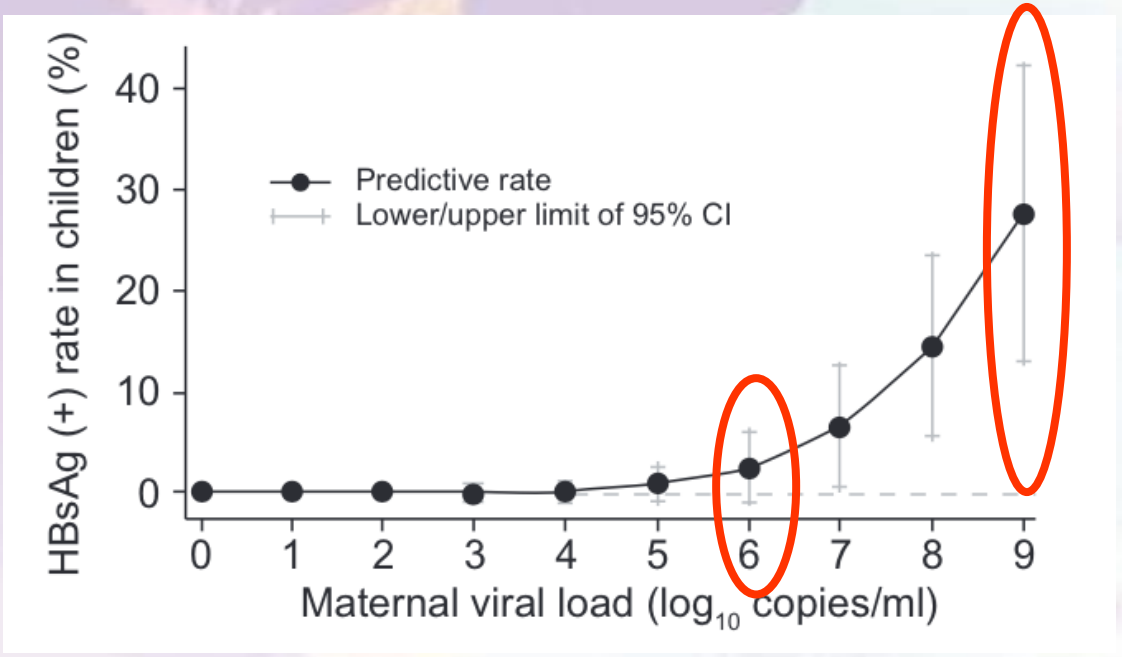
MTCT of hepatitis B virus infection: Significance of Maternal viral load and strategies for intervention

- Factors related to maternally transmitted HBV infection

Factors	OR, 95%CI	p value
Viral load	2.54, 1.42-4.55	0.002
Gestational age (/1-wk increase)	0.69, 0.50-0.94	0.018
Birth weight (/1-kg increase)	0.21, 0.05-0.87	0.031

Factor	OR, 95%CI	p value
Viral load	3.49, 1.63-7.48	0.001

Predictive rates of maternally transmitted HBV infection



Wen WH et al. Journal of Hepatology2013vol. 59;24–30

High prevalence of occult hepatitis B virus infection (OBI) in children born to HBsAg-positive mothers

- Sera of 75 children born to HBsAg-positive mothers at Amol, Iran (Low to intermediate prevalence)
- Previously immunized by HBIG and prophylaxic vaccine regimen
- OBI has received increasing attention in recent years because it appears to accelerate the progression of liver fibrosis and cirrhosis, ultimately leading to HCC
- HBsAg negativity is not sufficient to completely exclude HBV DNA presence.

Journal of Hepatology 2012 vol. 57 ¡515–521

High prevalence of occult hepatitis B virus infection (OBI) in children born to HBsAg-positive mothers

n, N=75	Anti HBc	Anti HBs
n=9, 12%	+	+
n= 55, 73%	-	+
n=11, 15%	-	-

- OBI detected in 21 (28%) of immunized children
- HBV DNA= 77-9240 copies/ml
- OBI seems to be relatively frequent in immunized children born to HBsAg-positive mothers

Hepatitis B vaccine alone or with HBIG in neonates of **HBsAg+/HBeAg-** mothers: A systematic review and meta-analysis

- Nine eligible studies were identified (four randomized controlled trials)

- **No difference** found between occurrence of hepatitis B infection, between neonates who received vaccine only, compared with those who received both vaccine and HBIG (four studies, 3426 patients, OR=0.82, 95%CI= 0.41-1.64)

- This finding was consistent with regards to seroprotection rate (four studies, 1323 patients, OR-1.24, 95% CI- 0.97–1.58).

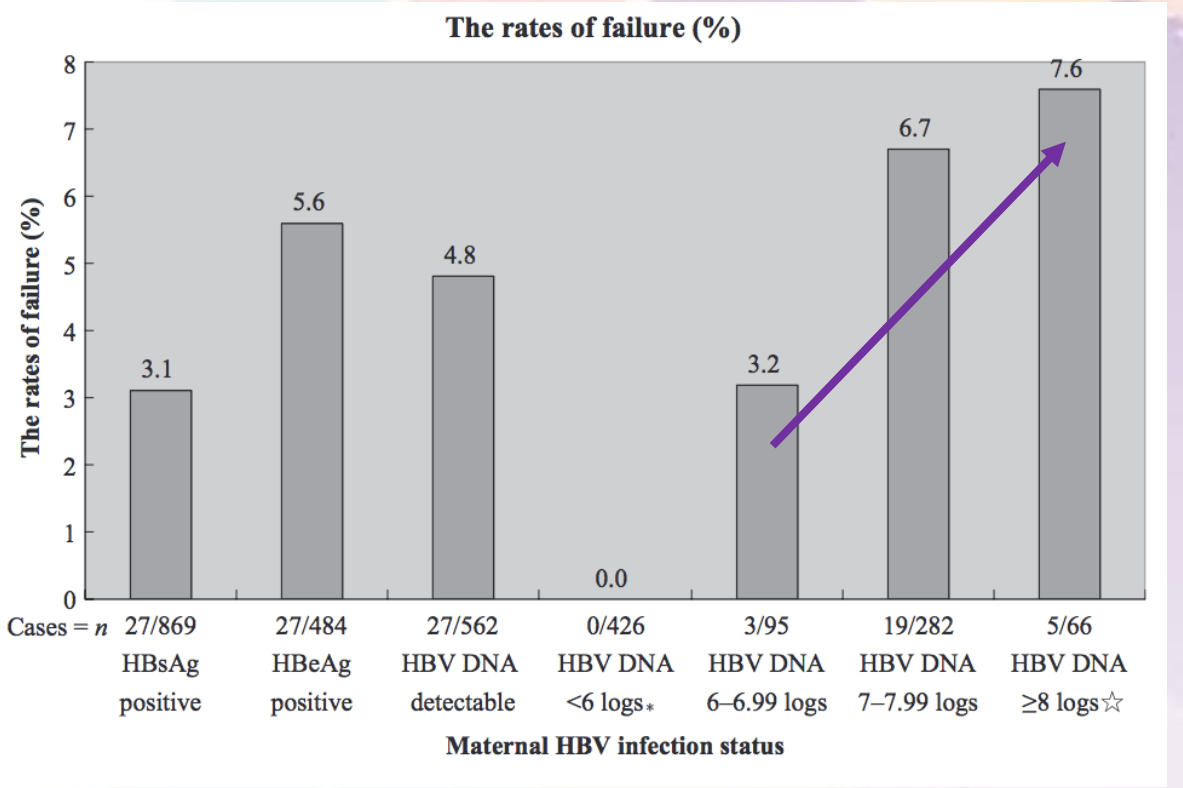
Machaira et al. J Antimicrob Chemother 2015; 70: 396–404

Virologic factors associated with failure to passive-active immunoprophylaxis

- Mother-infant pair- 869 (five sets of twins) eligible
- Of the 864 study mothers, 560 (64.8%) had detectable HBV DNA.
- **Outcome-** HBsAg status at age 7–12 months of the infants evaluated
- The MTCT rate in this cohort was 3.1% (27/869), all mothers were HBeAg+

Zou et al. J Viral Hepat. 2012 Feb;19(2):e18-25

Virologic factors associated with failure to passive–active immunoprophylaxis



Multivariate logistic regression analysis for risk factors associated with immunoprophylaxis failure

Factors	OR	95% CI	p value
HBV detectable in cord blood	39.67	14.22-110.69	<0.0001
Maternal HBV DNA	1.87	1.07-3.30	0.028

Zou et al. J Viral Hepat. 2012 Feb;19(2):e18-25

Hepatitis B virus S gene mutants in infants infected despite immunoprophylaxis

- 106 infants who were born to HBV carrier mothers and failed in HB immunoprophylaxis
- HBV S gene wa

Prevalence of HBV surface mutants is about **30%** in the children failing in HB vaccination

- 93.4% (99/106) of the samples were HBV DNA positive, and 30.3% (30/99) failed to hybridize with at least one of the four probes
- S gene mutation with amino acid (aa) change

Zhu et al. Chin Med J (Engl). 2001 Apr;114(4):352-4.

MTCT risk and anti-HBe levels in Pregnant Women

Maternal blood		HBsAg in followed children		
HBV DNA (IU/ml)	S. anti HBe	Total No.	Positive No.	Rate
≤ 10^6	-	9	0	0
≤ 10^6	+	47	0	0
> 10^6	-	22	5	22.7
> 10^6	+ or weakly +	6	0	0

Presence of maternal anti-Hbe is protective against HBV MTCT, independent of the maternal serum HBV viral load

Lu et al. International Journal of Infectious Diseases 28(2014) 41–44

HBV transmission and mode of delivery

- 1409 infants born to HBsAg-positive mothers from 2007 to 2011, all received appropriate immunoprophylaxis at birth

Mode of delivery (N)	MTCT rate n, (%)
Elective CS (N= 496)	7, (1.4)
Vaginal delivery (N= 673)	23, (3.4)
Urgent CS (N= 240)	10, (4.2)

Pan CQ, et al. Clin Gastroenterol Hepatol. 2013 Oct;11(10):1349-55

HBV transmission and mode of delivery

Variable	OR, 95% CI	p value
HBeAg positivity	1.88, 1.79-1.97	< 0.001
Maternal HBV DNA	1.65, 1.58-1.73	< 0.001
HBV DNA ≥ 6 $\log_{10}$	2.17, 2.05-2.29	< 0.001
Non ECS	4.29, 1.87-9.84	<0.001

Women with HBV DNA levels<1,000,000 copies/mL did not transmit the infection to their infants, regardless of method of delivery

Pan CQ, et al. Clin Gastroenterol Hepatol. 2013 Oct;11(10):1349-55

Effect of elective cesarean section on the risk of mother-to-child transmission of hepatitis B virus

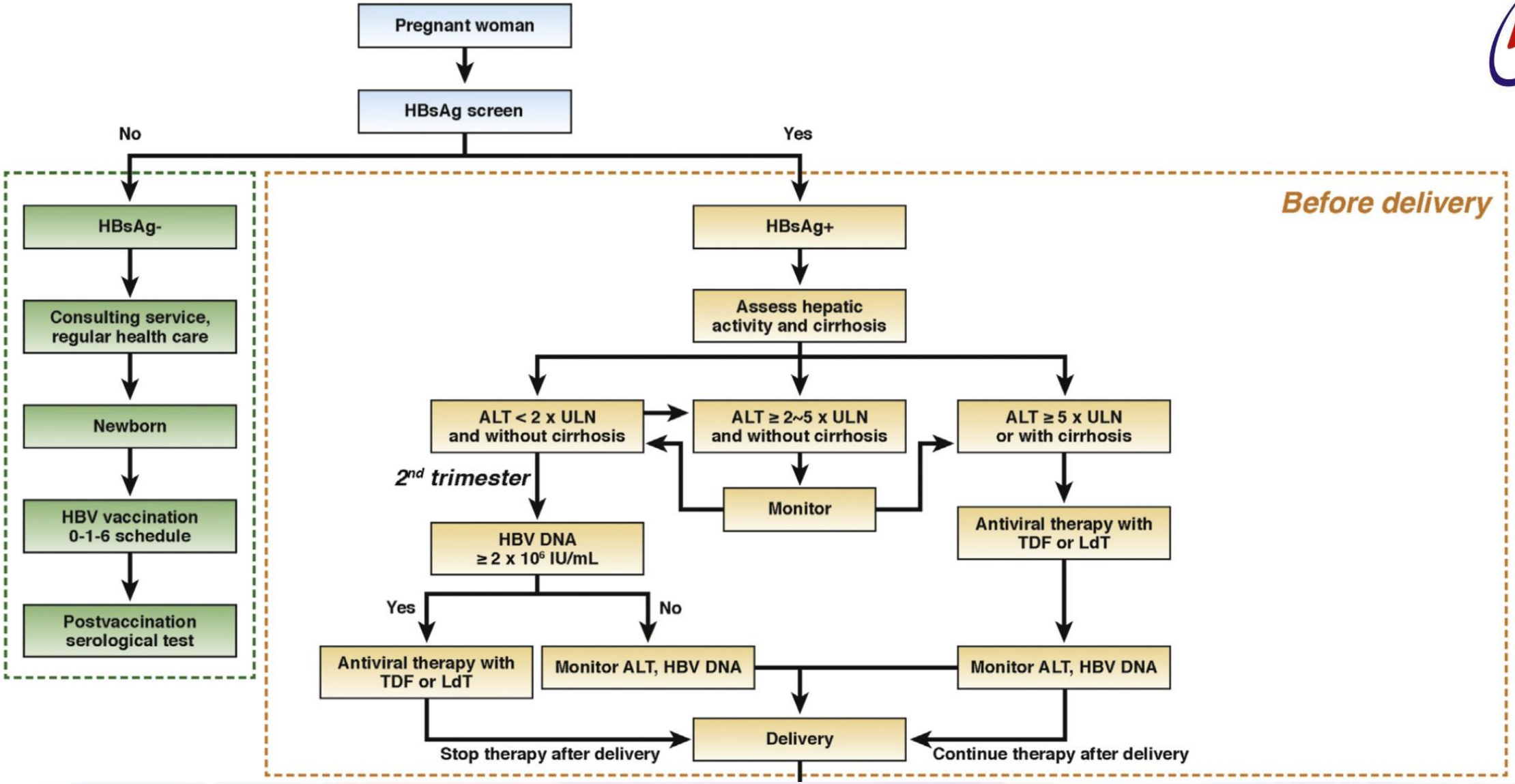
Hu *et al. BMC Pregnancy and Childbirth* 2013, **13**:119

Table 2 HBV serologic markers in 546 children of HBsAg-positive mothers who delivered their infants by ECS and VD

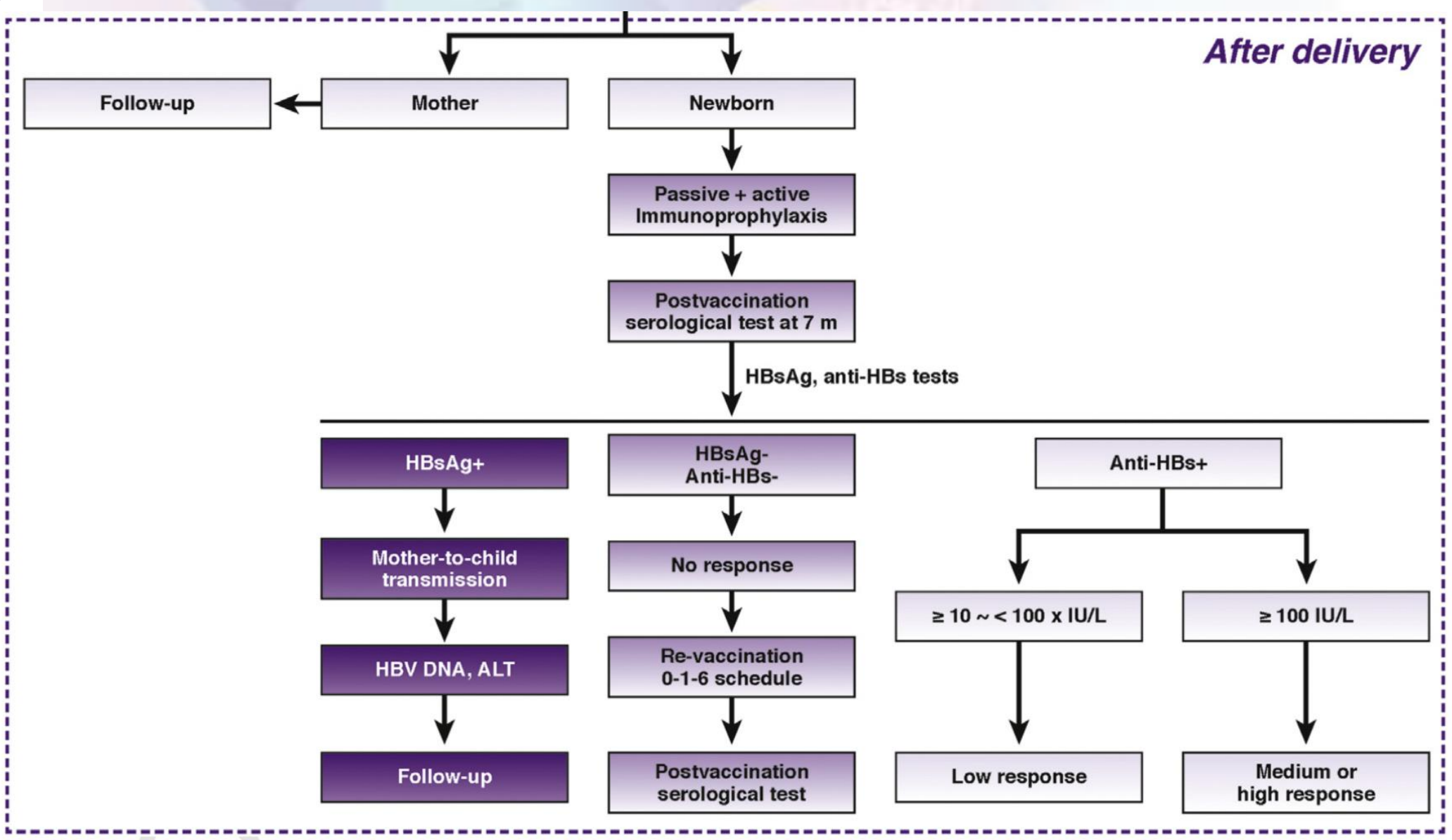
Serologic marker	ECS (n = 285)	VD (n = 261)	p
HBsAg+, n (%)	7 (2.5)	6 (2.3)	0.904
Anti-HBc+/HBsAg−, n (%)	7 (2.5)	10 (3.8)	0.355
Anti-HBs ≥10 mIU/ml, n (%)	206 (72.3)	185 (70.9)	0.717

With the recommended immunoprophylaxis against hepatitis B, ECS does not reduce the risk of mother-to-child transmission of HBV.

Therefore, ECS should not be used in HBsAg-positive pregnant women to prevent mother-to-child transmission of HBV.



Hou J. Clin Gastroenterol Hepatol. 2018



Hou J. Clin Gastroenterol Hepatol. 2018

Antiviral Therapy in Chronic Hepatitis B Viral Infection During Pregnancy: A Systematic Review and Meta-Analysis

- Twenty-six studies that enrolled a total of 3622 pregnant women were included
- Mean HBV DNA= 7.63 $\log_{10}$ IU/ml; ALT- 37.7 IU/L
- Antiviral therapy improves HBV suppression, safe during pregnancy
- Reduces MTCT, defined by infant hepatitis B surface antigen seropositivity (RR=0.3, 95%CI=0.2-0.5) and infant HBV DNA seropositivity (RR=0.3, 95%CI=0.2-0.4) in high viral load women **compared to the use of hepatitis B immunoglobulin and vaccination alone**

Hepatology. Brown RS et al. 2016 Jan;63(1):319-33.

All Women With Newly Diagnosed HBV Infection During Pregnancy

- Register HBV status in record
  - HBIG + first dose of vaccine to baby within 12 hrs of birth
  - Complete full course of vaccine
  - Check baby for HBsAg and anti-HBs at 9-15 mos.
- Counseling on precautions to prevent HBV transmission
- Screening and vaccination of family members

Lok AS, et al. Hepatology. 2009;50:661-662.

All Women With Newly Diagnosed HBV Infection During Pregnancy

- Refer for further evaluation
- Assess HBV replication and liver disease
  - HBeAg/anti-HBe, HBV DNA
  - Blood counts, liver panel ± ultrasound
- Evaluate need for antiviral therapy
  - For control of liver disease in mother
  - For prevention of transmission to baby
- Emphasize importance of long-term follow-up

Pregnancy and HBV

- **Screening for HBsAg** in first trimester is strongly recommended
- Family planning should always be discussed with women of child bearing age
- In a women of child bearing age-
  - Without advanced fibrosis and planning a pregnancy in near future, delay therapy until the child is born
  - With advanced fibrosis, therapy with tenofovir is recommended

Pregnant Women With High HBV DNA and Not Currently on Antiviral Therapy

- 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?


Thank you