2019 12th Paris Hepatology Conference

Treatment of hepatitis B : the guidelines and real life

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Disclosure Statement of Financial Interest

I currently have, or have had over the last two years, an affiliation or financial interests or interests of any order with a company or I receive compensation or fees or research grants with a commercial company :

Speaker's name : Teerha, PIRATVISUTH, Hat Yai

I have the following potential conflicts of interest to report:

Participation in a company-sponsored speaker's bur: Bayer, Bristol-Myers Squibb, Gilead, MSD

Research Support: Fibrogen, Gilead, Janssen, Roche Diagnostic

Case 1

- A 30-year old Chinese man
- Known HBeAg-positive chronic hepatitis B with persistent normal ALT (<35 IU/L) for 15 years
- His mother died from HBV-related HCC at age of 55-year old
- Unremarkable physical examination
- HBeAg positive antiHBe negative
- HBV DNA 8.6 logs IU/ml, antiHCV negative, HIV negative
- qHBsAg 45,000 IU/ml
- US showed normal liver

How to manage this man ?

Treat or not to treat HBV?

When to treat and how?

Natural history of chronic hepatitis B

APASL EASL	Immune tolerant HBeAg positive Chronic infection	Immune active HBeAg positive Chronic hepatitis	Immune control HBeAg negative Chronic infection	Immune escape HBeAg negative Chronic hepatitis	Occult
HBeAg PEIU/mL	Positive 2000-5000	Positive 100-1000	Negative	Negative	Negative
Anti-HBe					
HBsAg Log IU/mL	4.5-5	4.0-4.5	2.9-3.0	3.3-3.9	Negative
Anti-HBs					
HBV DNA IU/mL	>>>20,000	>20,000	≤2,000	>2,000	<200
Viral diversity Precore/core					
Serum ALT U/L	Normal	Elevated, fluctuating	Normal	Elevated, fluctuating	Normal
Liver histology	Normal	Moderate to severe CH	Normal to cirrhosis	Moderate to severe CH, cirrhosis	Normal to cirrhosis

Modified from Dandri M, Locarnini. Gut 2012

Indication for treatment in HBeAg positive Chronic Infection

EASL 2017	AASLD 2016	APASL 2016
May be treated if they are older than 30 years or with family history of HCC or cirrhosis or having significant liver disease or extrahepatic manifestations	Should be monitored every 3-6 months and should undergo testing to evaluate liver disease severity, especially those > 40 years old. HBV treatment if moderate or severe inflammation or significant fibrosis ≥ F2 is confirmed	Should be monitored every 3 months. They should be assessed for liver disease in those with persistently elevated ALT or age > 35 years old or with family history of HCC or cirrhosis. HBV treatment if moderate or severe inflammation of significant fibrosis is confirmed

ULN of ALT is 35 U/L for male and 25 U/L for female

Terrault N, et al. Hepatology 2018
EASL. J Hepatol 2017
Sarin Sk, et al. Hepatol Int 2016;10:1–98.

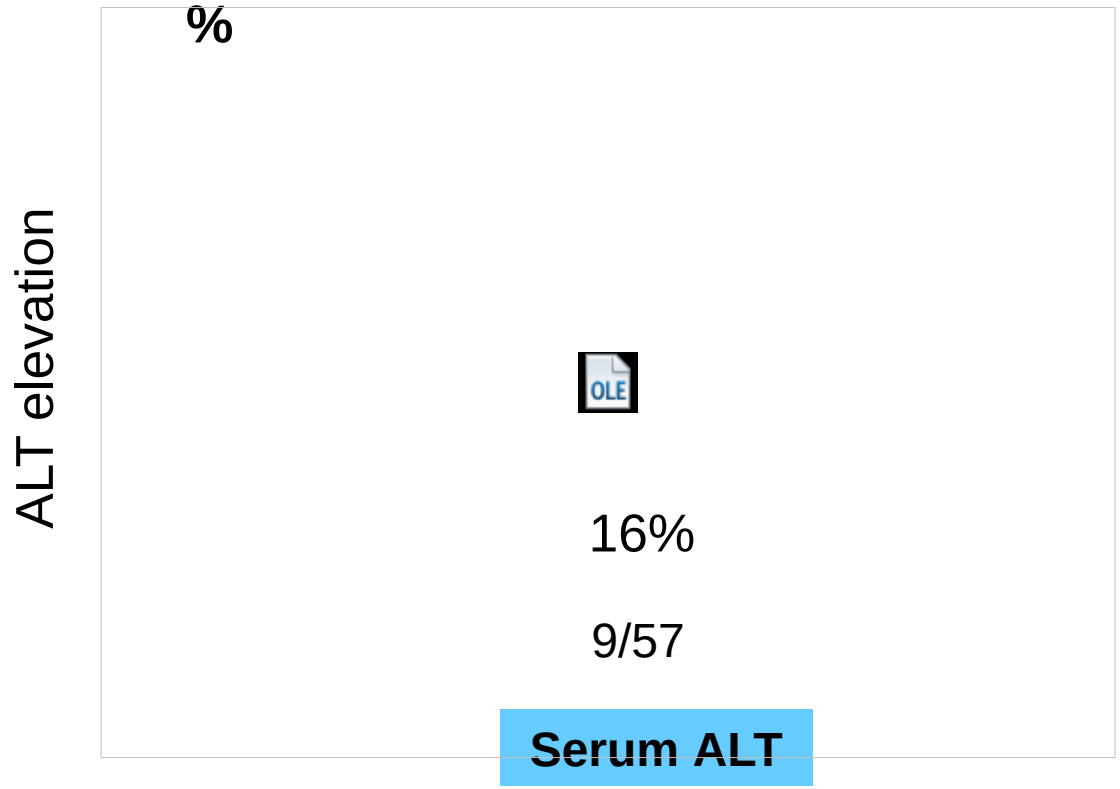
Liver biopsies of the 48 patients who remained in immune tolerant Phase at end of 5- year follow-up

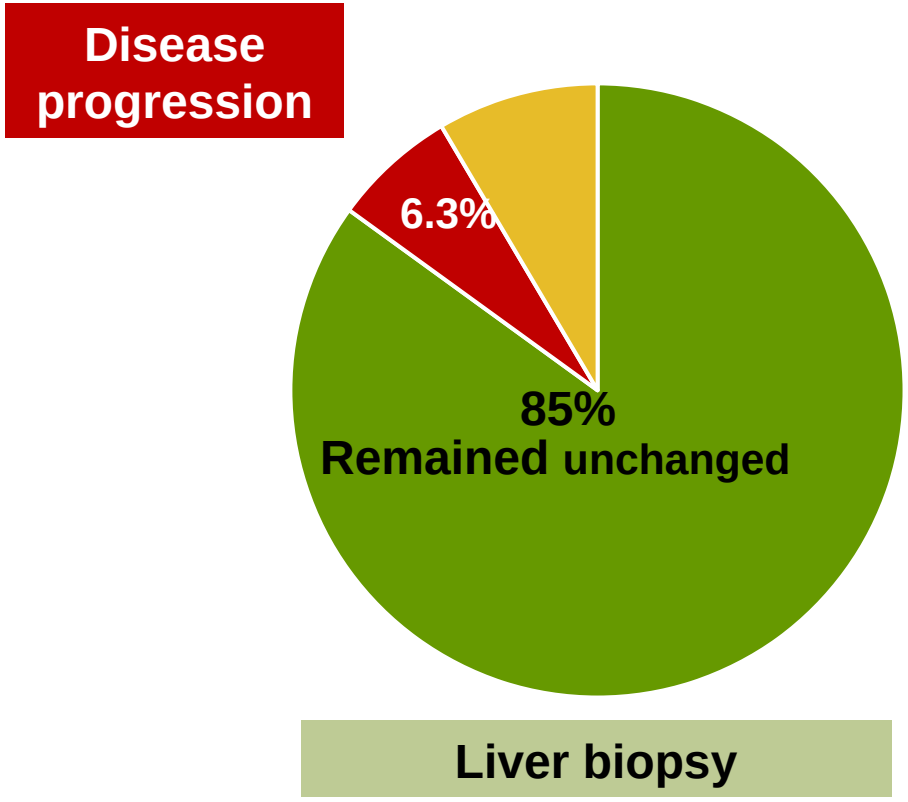
Stage of fibrosis	Initial liver biopsy	Follow-up liver biopsy	P value
F0	15	16	0.58
F1	33	31	
F2	0	1	
Median Modified HAI score	**3(1-6)**	**3(1-5)**	

Hui CK. et al. Hepatology 2007;46:395-401.

The natural history of immune tolerant chronic HBV

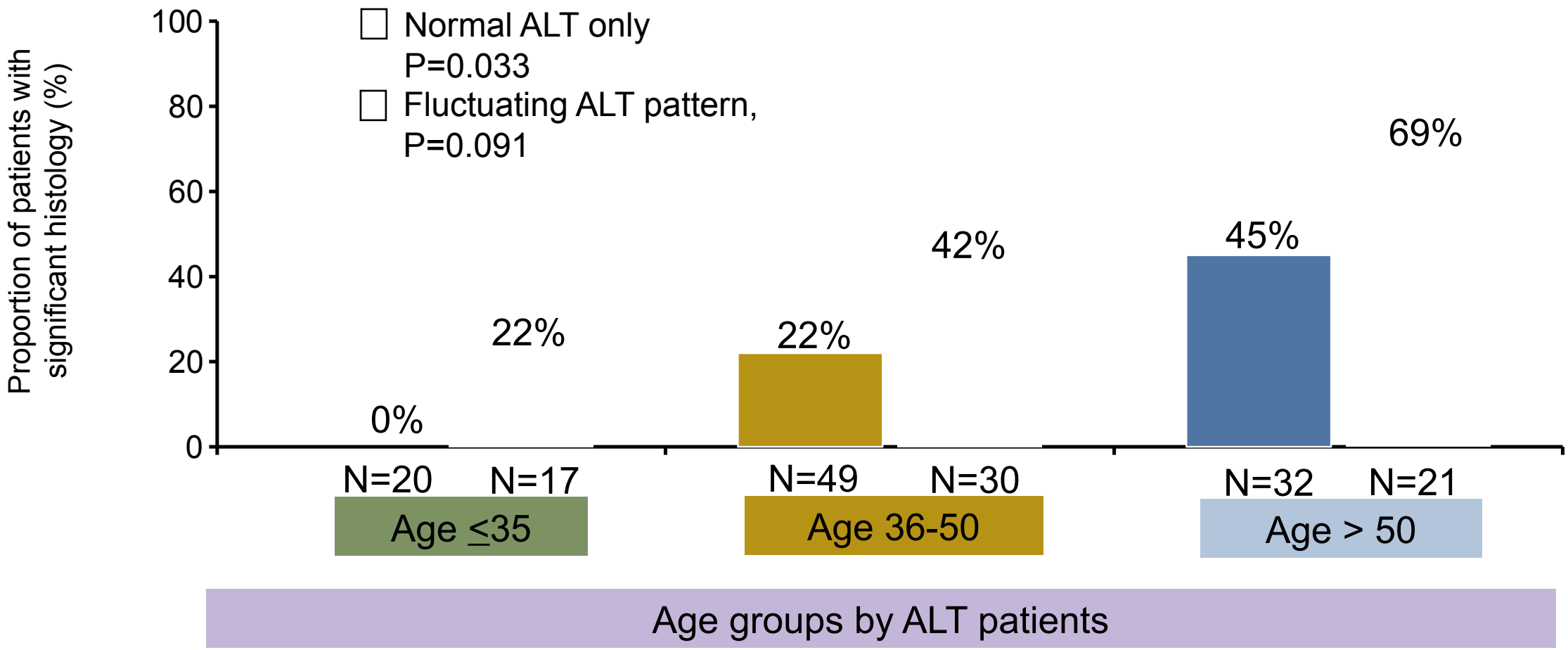
Over period of 5-year follow up





Hui CK. et al. Hepatology 2007; 46: 395-401.

Prevalence of significant histology by age groups and ALT patterns for patients with ALT ≤ 40 U / l at biopsy



Nguyen MH, et al. Am J Gastroenterol. 2009;104_2206–2213.

Predictors of significant fibrosis and inflammation-results of multiple logistic regression analysis

	Odd ratio	95% CI	p-Value
Predictors of significant fibrosis			
Age (year)	1.080	(1.034–1.127)	0.0005
Age (decade)	2.151	(1.397–3.311)	0.0005
Grade	7.403	(3.431–15.975)	<0.0001
ALT Group	1.584	(1.027–2.442)	0.0373
E antigen positive	2.837	(1.018–7.900)	0.0460
Predictors of significant inflammation			
Stage	2.222	(1.479–3.339)	0.0001
ALT	2.012	(1.285–3.151)	0.0022

Benjamin ML, et al. J Hepatol 2007; 760-767.

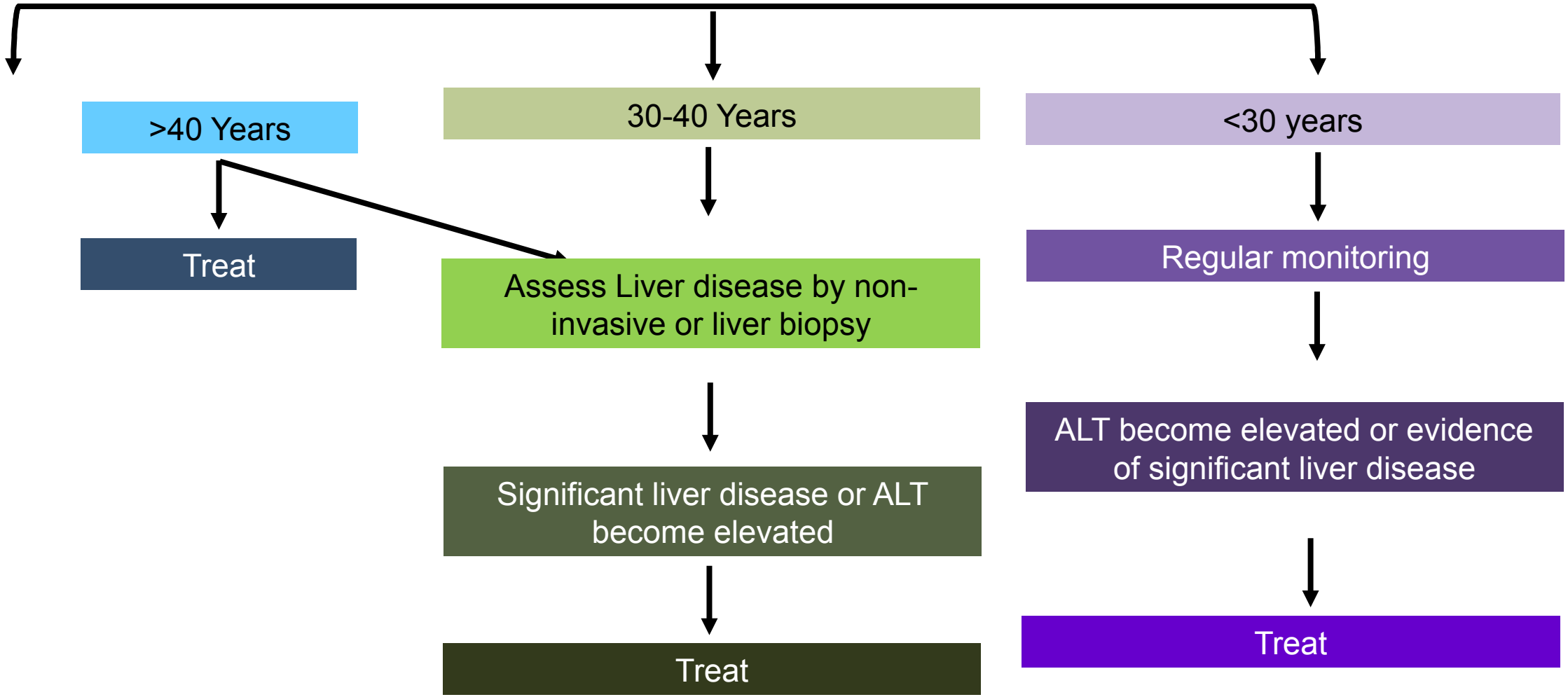
Treatment response of HBeAg-positive patients with normal or mildly elevated ALT levels using different antiviral agents

Treatment	Baseline ALT levels	Drug	Treatment duration	Response rates (HBeAg seroconversion)
Peg-IFN	<1x ULN	Unknown		
	1-2x ULN	PegIFN	1 year	18.5%
NUC	<1x ULN	Tenofovir	4 years	4.8%
		Tenofovir+ emtricitabine	4 years	0%
		Lamivudine	1 year	2%
	1-2x ULN	Entecavir	2 years	8%
		Lamivudine	2 years	5%

ULN, upper limit of normal; PegIFN, pegylated interferon; NUC, nucleos(t)ide analogue.

Tseng TC, et al. J Viral Hepatitis 2015; 22: 77–84.

Management of immunotolerant chronic HBV patients

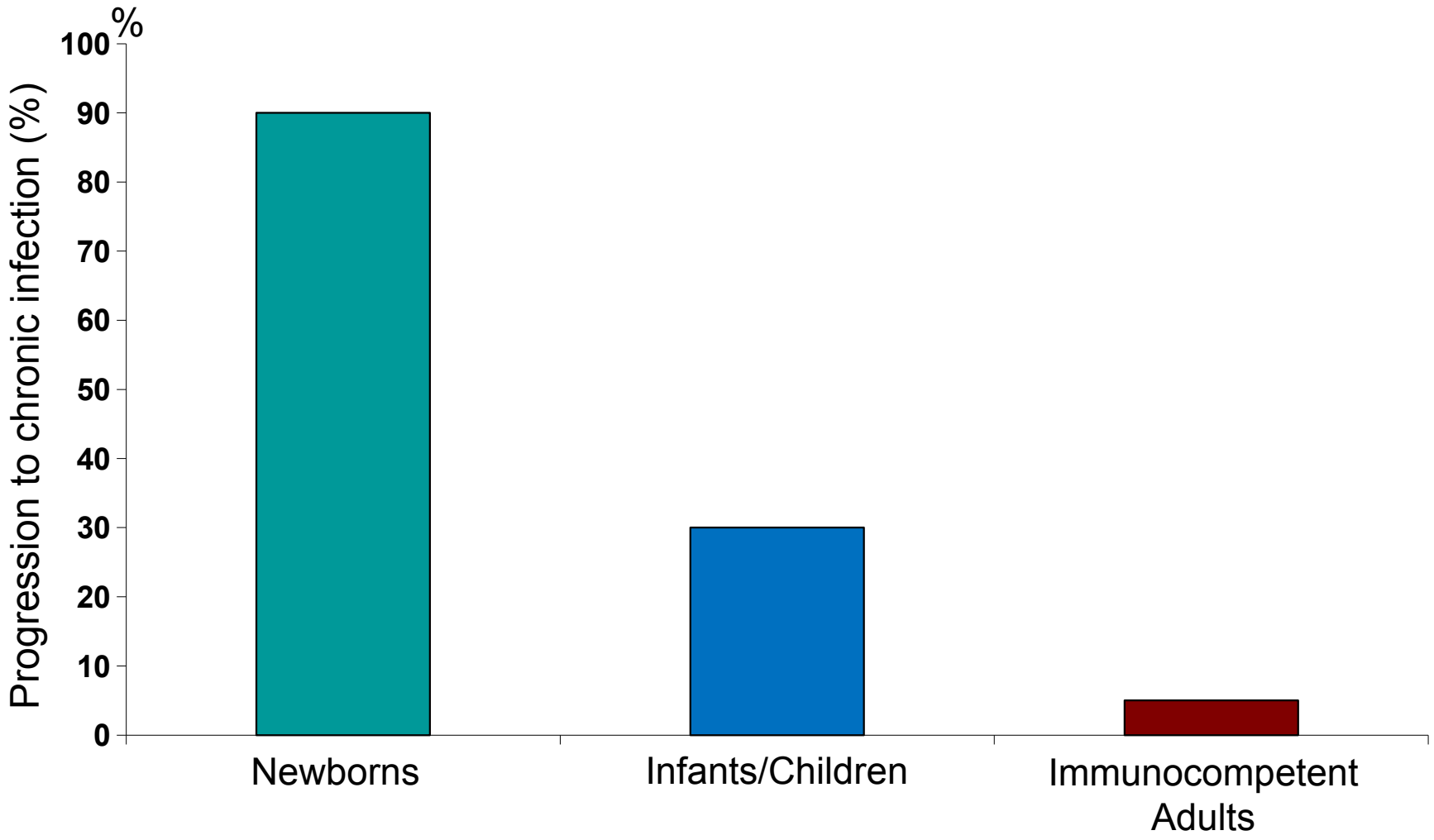


Case 2

- A 27-year old pregnant woman with 16-week gestational age G1P0A0
- HBsAg positive HBeAg positive antiHBe negative
  anti HCV negative HIV: non-reactive
- HBV DNA 8.9 logs IU/ml
- LFTs: WNL
- Unremarkable physical examination

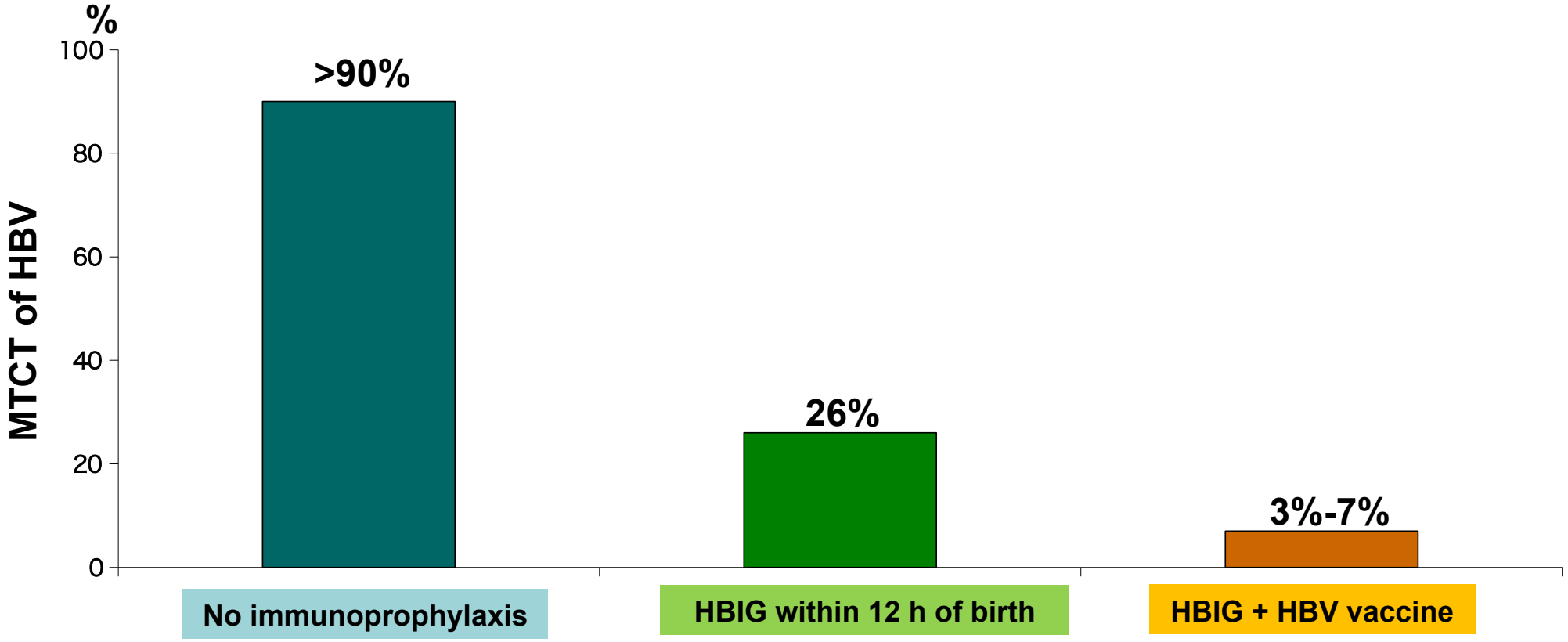
How would you manage this pregnant woman?

Mother-to-Child Transmission of HBV is associated with high rate of progression to chronic HBV infection



Lok AS, et al. Hepatology 2009;50:661-662;
Chen HL, et al. J Infect Dis. 2017;216(suppl_8):S785-S791

Immunoprophylaxis for prevention of MTCT of HBV in infants born to HBeAg-positive Mothers



Beasley RP. et al. Lancet 1981; 2.
Beasley RP. et al. Hepatology 1983; 3
Beasley RP. et al. Lacet 1983; 2
Lee C. et al. BMJ 2006; 332.

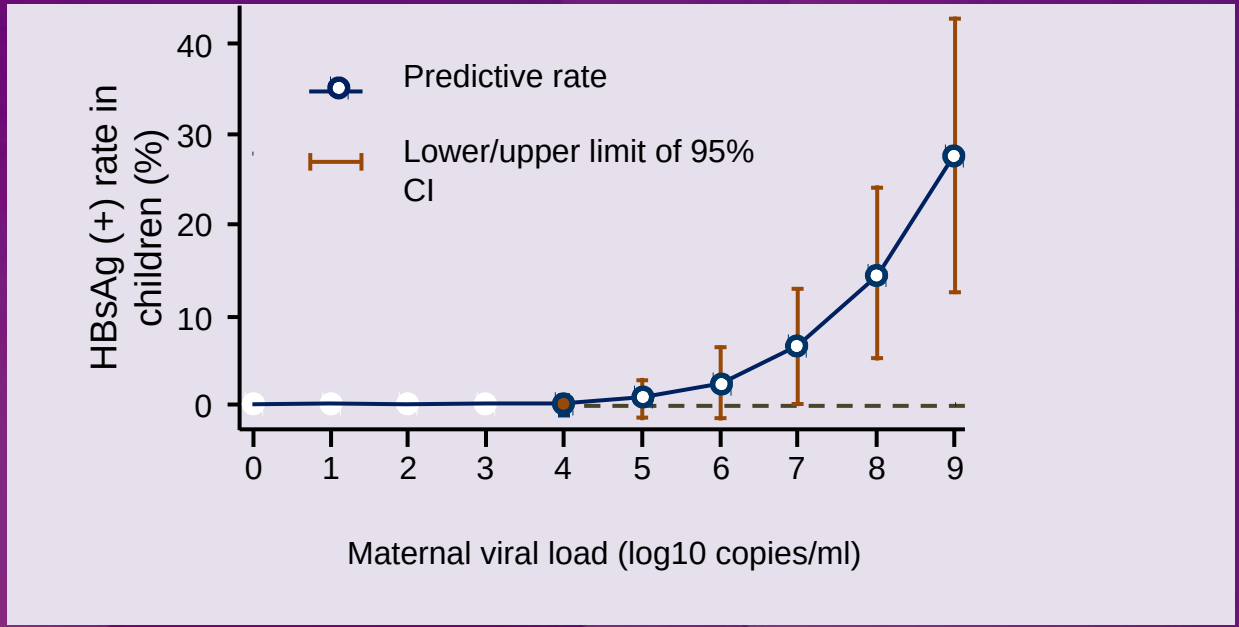
Immunoprophylaxis to prevent MTCT of HBV : meta-analysis

Intervention	Relative Risk of neonatal HBV infection
HBV vaccine VS Placebo	0.28 (95% CI 0.2-0.4)
HBIG +HBV vaccine VS HBV vaccine	0.54 (95% CI, 0.41-0.73)

Lee C. et al. BMJ 2006; 332: 328-36.

High maternal HBV DNA is associated with Immunoprophylaxis failure

HBV DNA (log cp/ml)	Adjusted odds ratio	P value
5	0.9%	0.334
6	2.6%	0.165
7	6.6%	0.033
8	14.6%	0.001
9	27.7%	<0.001

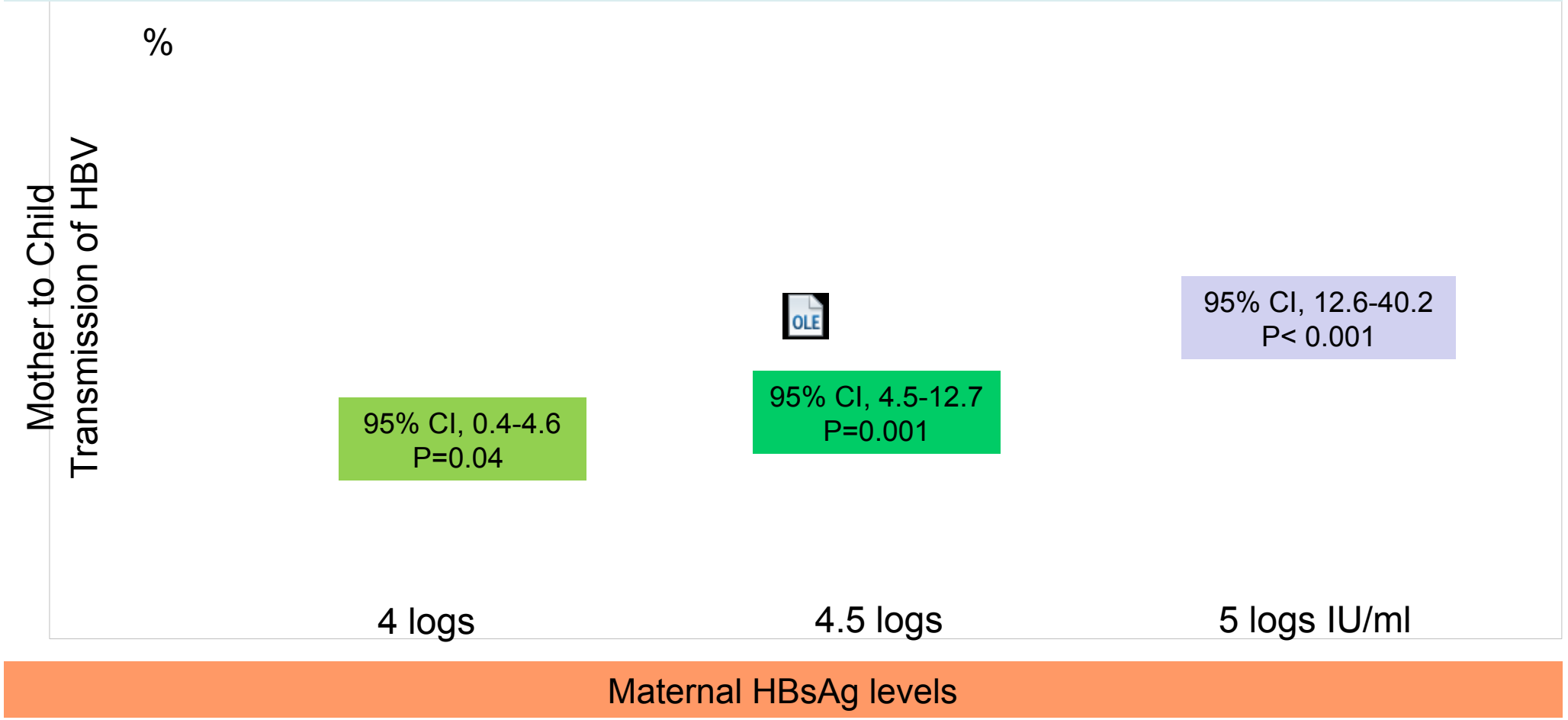


- 10 of 303 babies born to HBV carrier mothers had HBV infection despite HBV vaccination
- All mothers of infected babies had positive HBeAg
- All infected babies had 3 doses of vaccine with HBIG at birth

Wen WH, et al. J Hepatol 2013;59:24–30

Multivariate logistic regression model:Quantitative maternal HBsAg levels predicts immunoprophylaxis failure

All 162 infants with HBeAg-positive mothers and 331 of 364 (90.9%) with HBeAg-negative mothers received HBIG and HBV vaccination (9% of infants with HBeAg-ve mothers received only HBV vaccination)



Wen WH. et al. Hepatology 2016; 64: 1451-1461.

Antiviral therapy (Lamivudine or Telbivudine) can reduce maternal to child transmission of HBV

Study name	RR (95% CI)	Events, Treatment	Events, Control	% Weight
HBsAg seropositivity				
Guo et al. 2008	0.19 (0.07, 0.55)	4/70	12/40	24.08
Guo et al. 2011	0.34 (0.12, 0.93)	4/28	11/26	26.54
Li WF et al. 2006	0.17 (0.02, 1.35)	1/36	7/44	6.48
Xu et al. 2009	0.53 (0.14, 2.01)	3/56	6/59	15.22
Yang et al. 2008	0.26 (0.16, 0.44)	2/20	2/19	7.89
Yao et al. 2011	0.12 (0.01, 2.11)	0/28	4/30	3.28
Zhang and Wang. 2009	0.11 (0.01, 1.92)	0/31	4/30	3.28
Zhang et al. 2010	0.13 (0.02, 0.96)	1/50	8/50	6.53
Zhang et al. 2010	0.09 (0.01, 0.68)	1/60	11/60	6.69
Subtotal (I-squared = 0.0%, p=0.639)	0.31 (0.20, 0.49)	16/379	65/358	100.0
HBV DNA seropositivity				
Guo et al. 2008	0.29 (0.12, 0.70)	6/70	12/40	25.92

NOTE: Weights are from random effects analysis

Brown JJ, RS, et al. Hepatology. 2016;63:319–33

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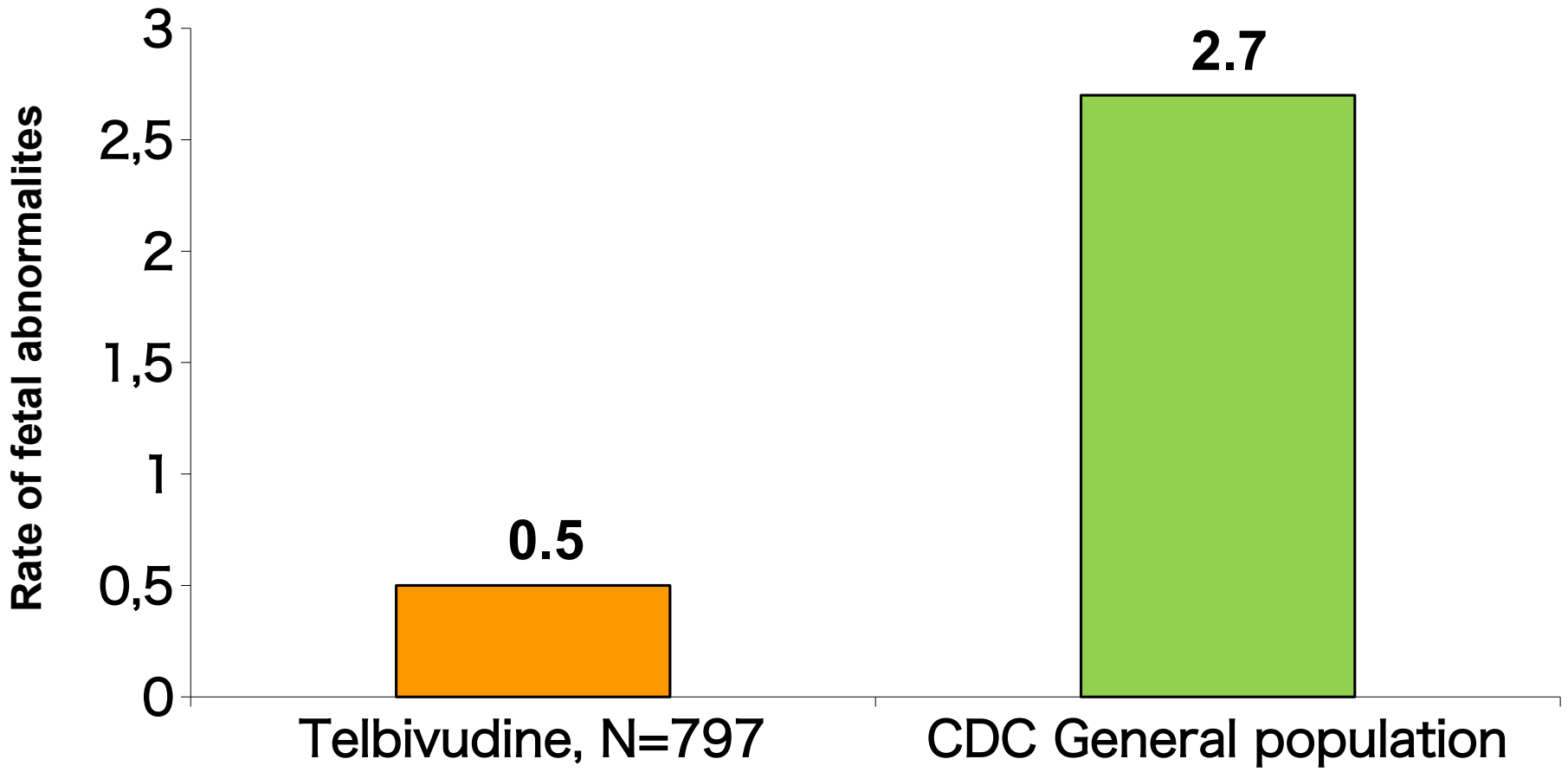
Overall Rate Of Fetal Abnormalities

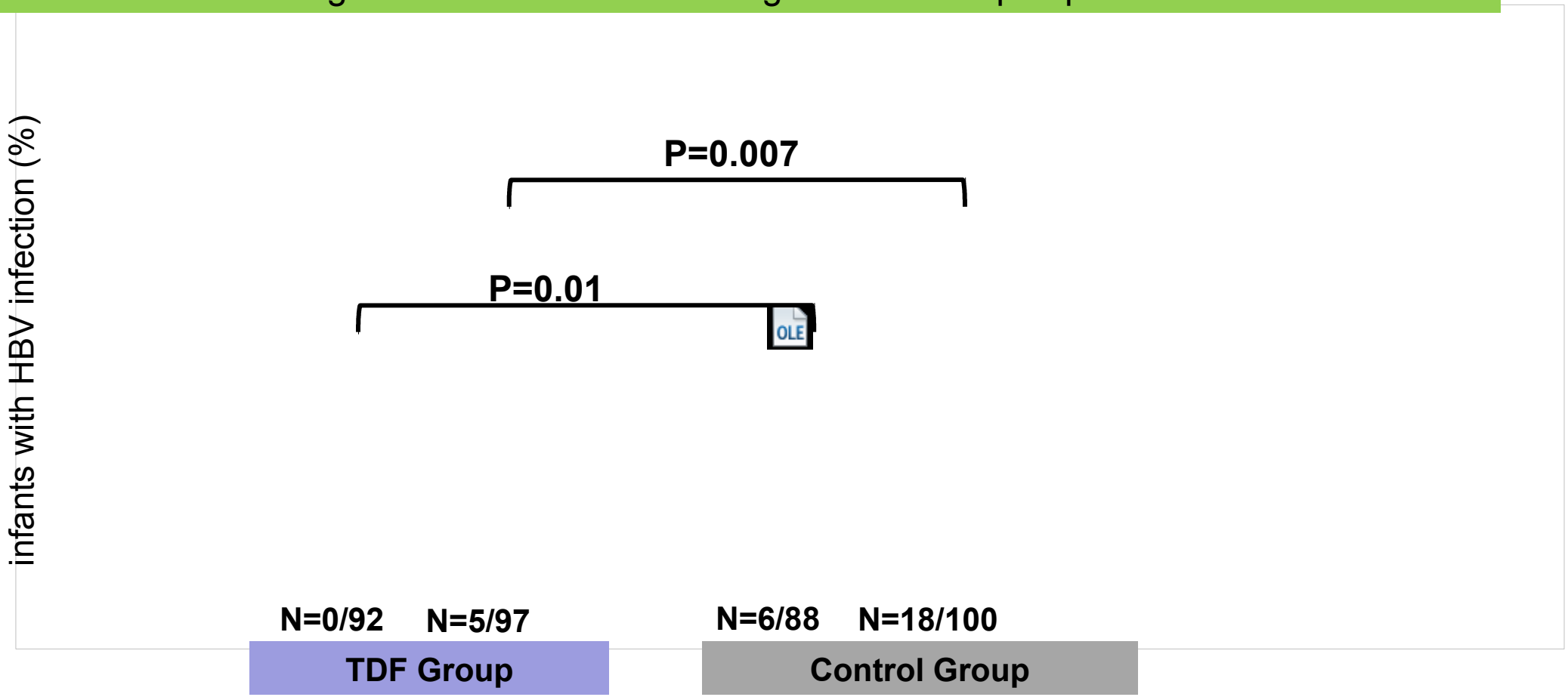


Han GR, et al. Accepted at APASL 2013, Abstract # 388.

Rate of Hepatitis B Virus (HBV) Infection among Infants born to HBsAg positive mothers treated with TDF

Prospective randomized cohort HBeAg-positive mothers withHBV DNA > 200,000 IU/L

TDF was given from 30-32 weeks of gestation until postpartum week 4

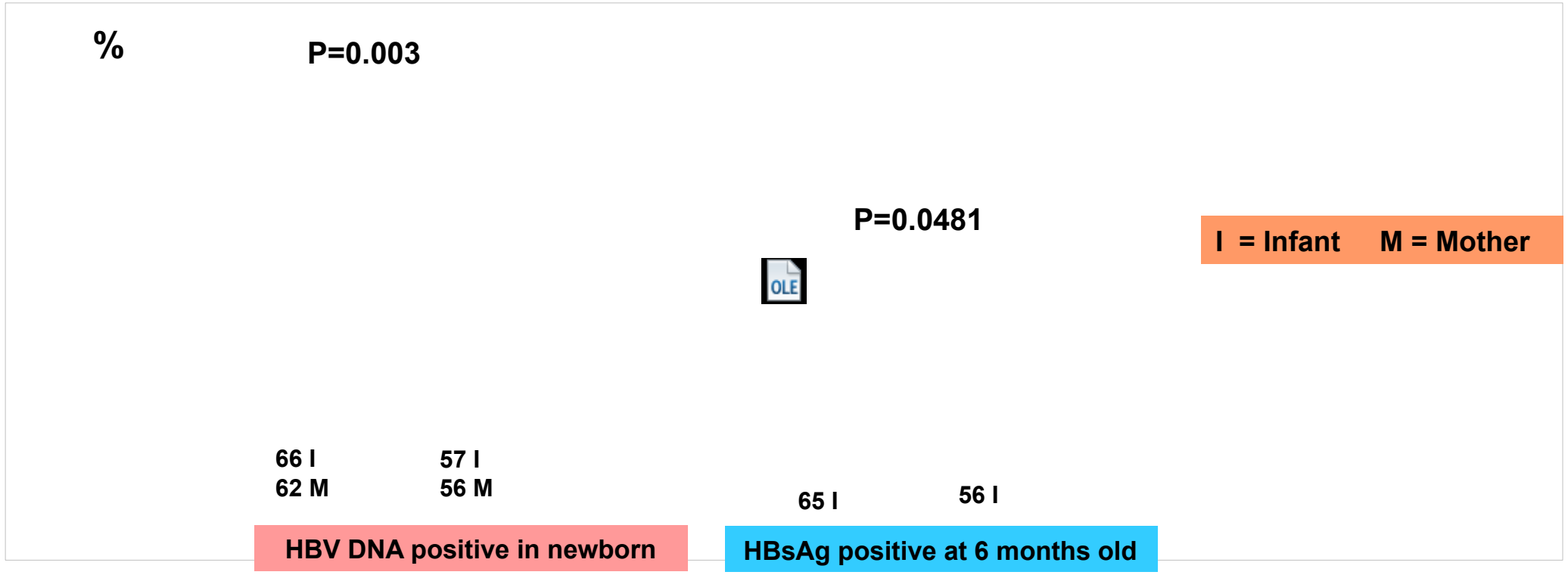


Pan CQ. et al. N Engl J Med. 2016; 374: 2324-34.

Tenofovir Disoproxil Fumarate in HBeAg-positive mothers

HBeAg-positive mothers with HBV DNA ≥ 7.5 log10 IU/ml

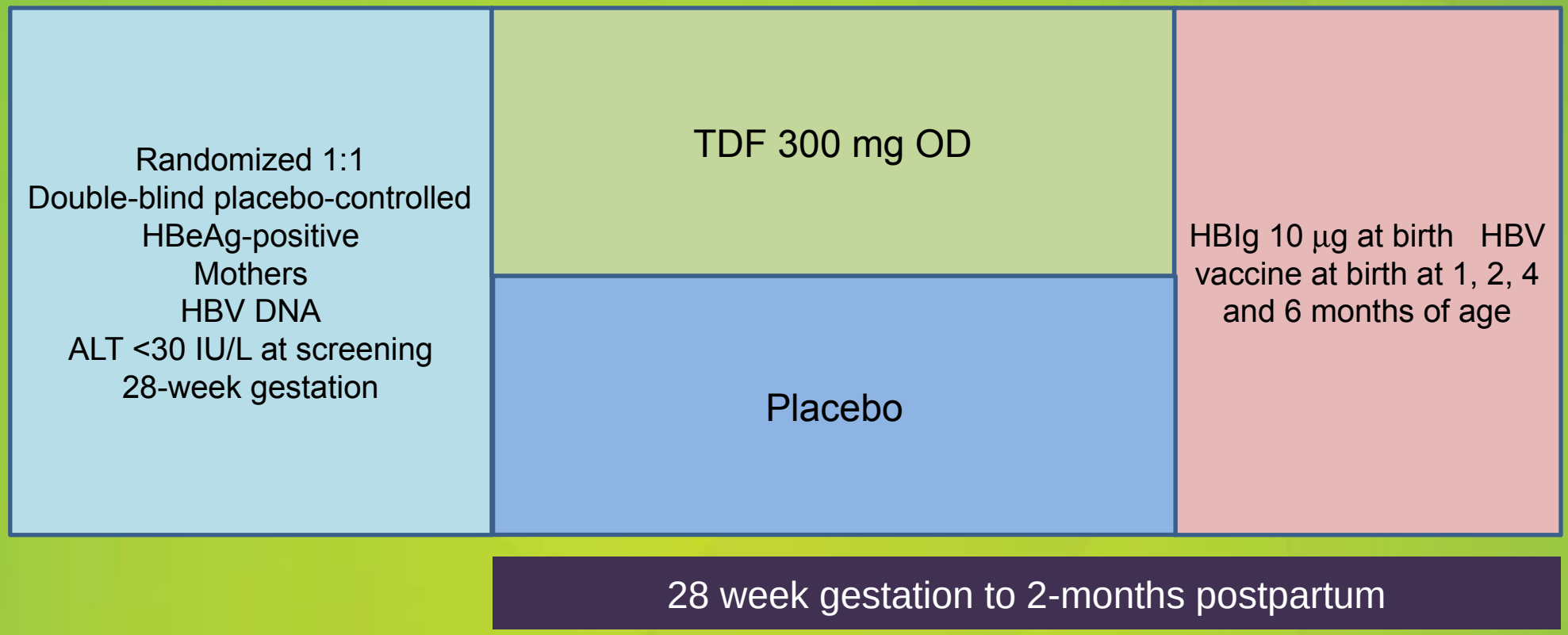
TDF was given from 30-32 weeks of gestation until 1 month postpartum based on their willingness



No different rates of congenital anomaly , premature birth, growth parameters in infants and maternal creatinine

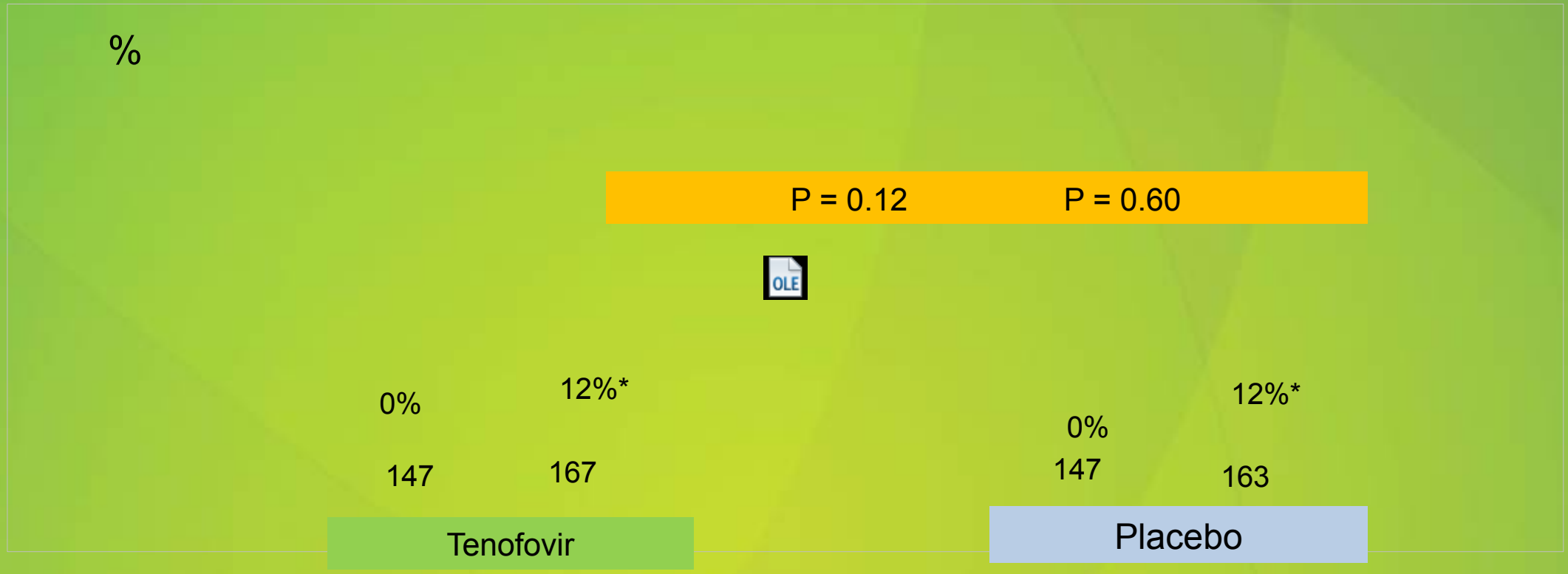
Chen HL. et al. Hepatology. 2015;62: 375-386.

Tenofovir to prevent perinatal transmission of hepatitis



Jourdain G. et al. N Engl J Med 2018;911-23

HBV infection in infants at 6 months



*: Analysis with missing data imputed as infected

The median time from birth to HBIg 1.3 hours

The median time form birth to HBV vaccine 1.2 hours

Jourdain G. et al. N Engl J Med 2018;911-23

Guidelines for antiviral treatment in pregnant women with high viraemia

EASL 2017	AASLD 2016	APASL 2016
In all pregnant women with high HBV DNA levels [**200,000 IU/ml**] or HBsAg levels [**4 log10 IU/ml**], antiviral prophylaxis with TDF should start at week 24–28 of gestation (Level 1, Grade 1).	The AASLD suggests antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive pregnant women with an HBV DNA level **>200,000 IU/ml** (C1)	Short-term maternal NA starting from **28 to 32 weeks** of gestation is recommended using either tenofovir or telbivudine for those mothers with HBV DNA ≥ **6 log10 copies/ml** (B2)

Terrault N, et al. Hepatology 2016;63:261–83;
EASL. J Hepatol 2017;67:370–98;
Sarin S, et al. Hepatol Int 2016;10:1–98.

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Faculty of Medicine
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To stop or not to stop NA after delivery?

Post-partum ALT flare

ALT increase post-partum (ULN = 40 U/L)	TDF (N=97)	Control (N=100)	P
ALT 1.1–5x ULN	56%	32%	0.001
ALT 5.1–10x ULN	5%	6%	NS
ALT >10x ULN	1%	3%	NS
Any time during trial	62%	41%	0.004
Baseline to post-partum wk 4	16%	22%	NS
Post-partum wk 5–28	46%	30%	0.03

Pan CQ, et al. N Engl J Med 2016;374:2324–34

Hepatitis flare after stopping NA

- Hepatitis flare may occur after stopping NA;
  can have ALT elevation to >5 x ULN (6%)
- 17% to 45% of women may experience a hepatitis flare (as compared to 25% in untreated CHB patients)
- Most hepatitis flares resolve spontaneously
- Hepatic decompensation rarely reported

Ter Borg MJ, et al. J Viral Hepat 2008;15:37–41;
Greenup AJ, et al. J Hepatol 2014;61:502–7;
Chen HL, et al. Hepatology 2015;62:375–86;
Kochakaraie GS, et al. J Viral Hepat 2016;23:15–22;
Giles M, et al. Gut 2015;64:1810–5

What if NA is continued till the second pregnancy?

Safety of NUC in first trimester

	Nucleoside analogs		Nucleotide analogs		All antivirals	
	Birth defects/non-live birth	%	Birth defects/non-live birth	%	Birth defects/non-live birth	%
Spontaneous loss	0/287	0	0/109	0	0/306	0
Stillbirth	3/88	3.4	0/32	0	3/97	3.0
Induced abortions	7/353	2.0	3/98	1.3	7/395	1.8
Overall	10/728	1.4	3/239	1.3	10/798	1.3

No increase in birth defects
No data on developmental delay and growth

Brown Jr et al. J Hepatol 2012;57:953

Guidelines for stopping antiviral treatment in pregnant women on antiviral treatment

EASL 2017	AASLD 2016	APASL 2016
May be continued up to 12 weeks after delivery (Level 1, Grade 1)	Antiviral therapy was discontinued at birth to 3 months postpartum in most of the studies. With discontinuation of treatment, women should be monitored for ALT flares every 3 months for 6 months. (C1)	The NAs could be stopped at birth and when breastfeeding starts, if there is no contraindication to stopping NAs (B2)

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Terrault N, et al. Hepatology 2016;63:261–83;
EASL. J Hepatol 2017;67:370–98;
Sarin S, et al. Hepatol Int 2016;10:1–98.

Would you allow breastfeeding?

Safety of breastfeeding in case of chronic hepatitis B virus infection of mothers

Author	No. of infants	Population	Prophylaxis	Infected or failed seroconversion to antiHBs		*P*
				BF (%)	FF (%)	
Beasley et al	147	USA, Taiwan (China)	No	53	60	NS
Tseng et al	170	Hong Kong (China)	HBIG + Vx	7	6	NS
De Martino et al	85	Italy	Vx	4.6	3.2	NS
Hill et al	369	USA	HBIG + Vx	0	3	0.06

BF: Breastfeeding; FF: Formula feeding; HBIG: Hepatitis B immune globulin; NS: Nonsignificant

Petrova M. et al. World J Gastroenterol. 2010; 16(40): 5042-46.

Hepatitis B transmission by feeding and HBeAg status

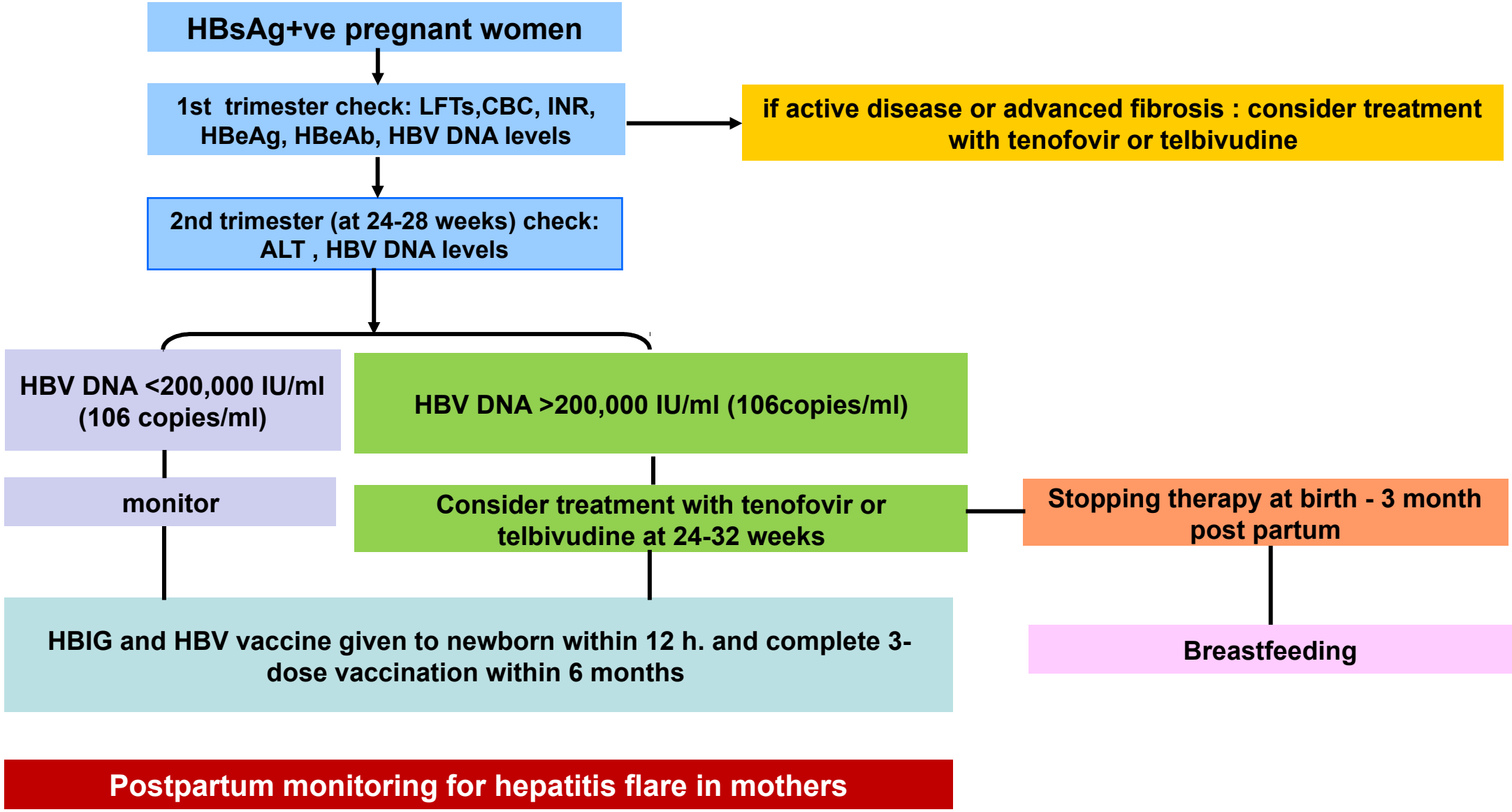
HBeAg	Breast-fed (n = 101)	Formula-fed (n =268)	Total (n=369)
Positive	0/11	5/41	5/52 (9.6%)
Negative	0/40	3/116	3/156*(1.9%)
Not done	0/50	1/111	1/161
Overall	0/101	9/268(3.4%)**	9/369 (2.4%)

***P=.002 compared with HBeAg-positive women (Fisher exact test).**
****P=0.0639 compared with breast-fed**

All infant received immuoprophylaxis with HBIg and HBV vaccine at birth

Beasley RP. et al. Lancet 1975; 2: 740-1.

Management of HBV during pregnancy

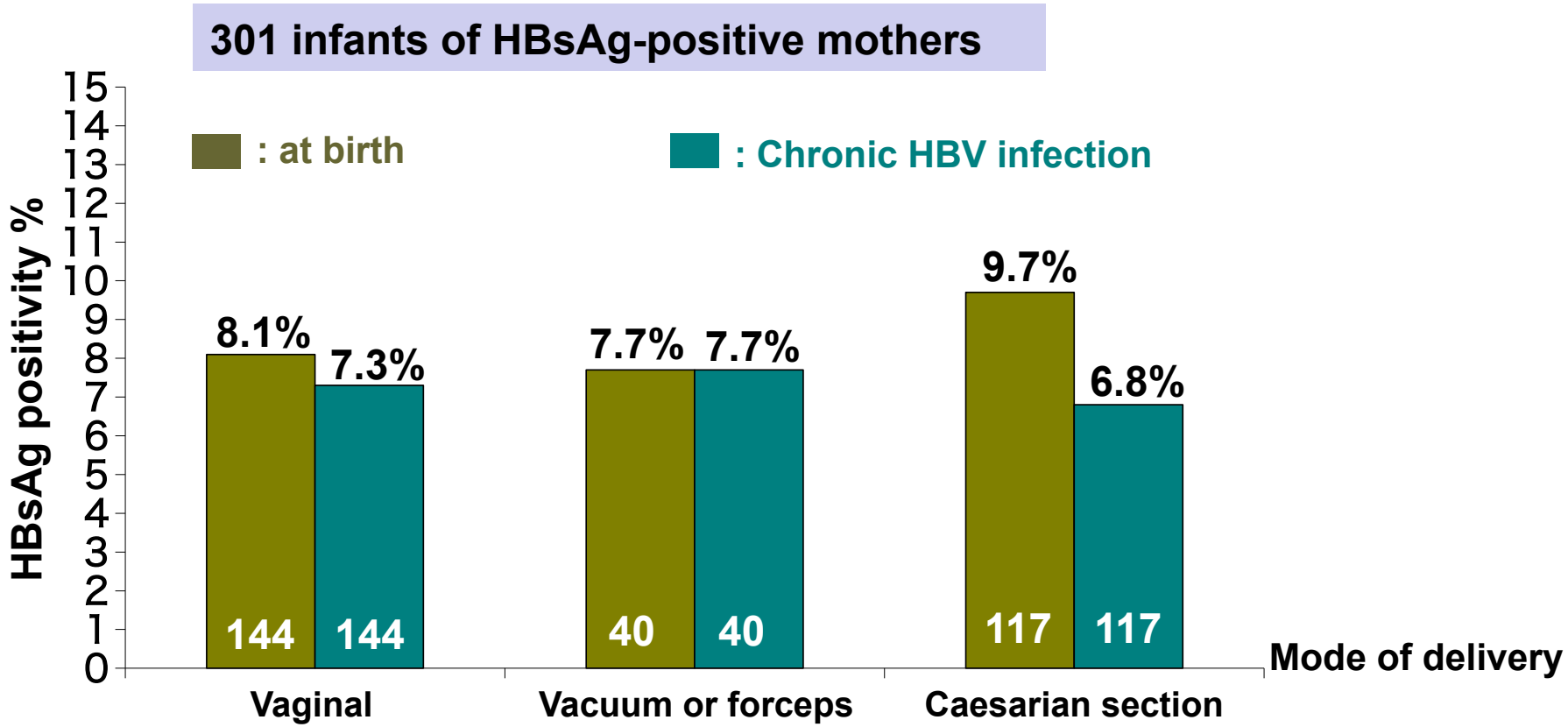


Piratvisuth T. Liver Inter.2013

Chamroonkul N, Piratvisuth T.Paediatr Drugs. 2017 Jun;19(3):173-181


Thank you

Mode of delivery: MTCT of HBV

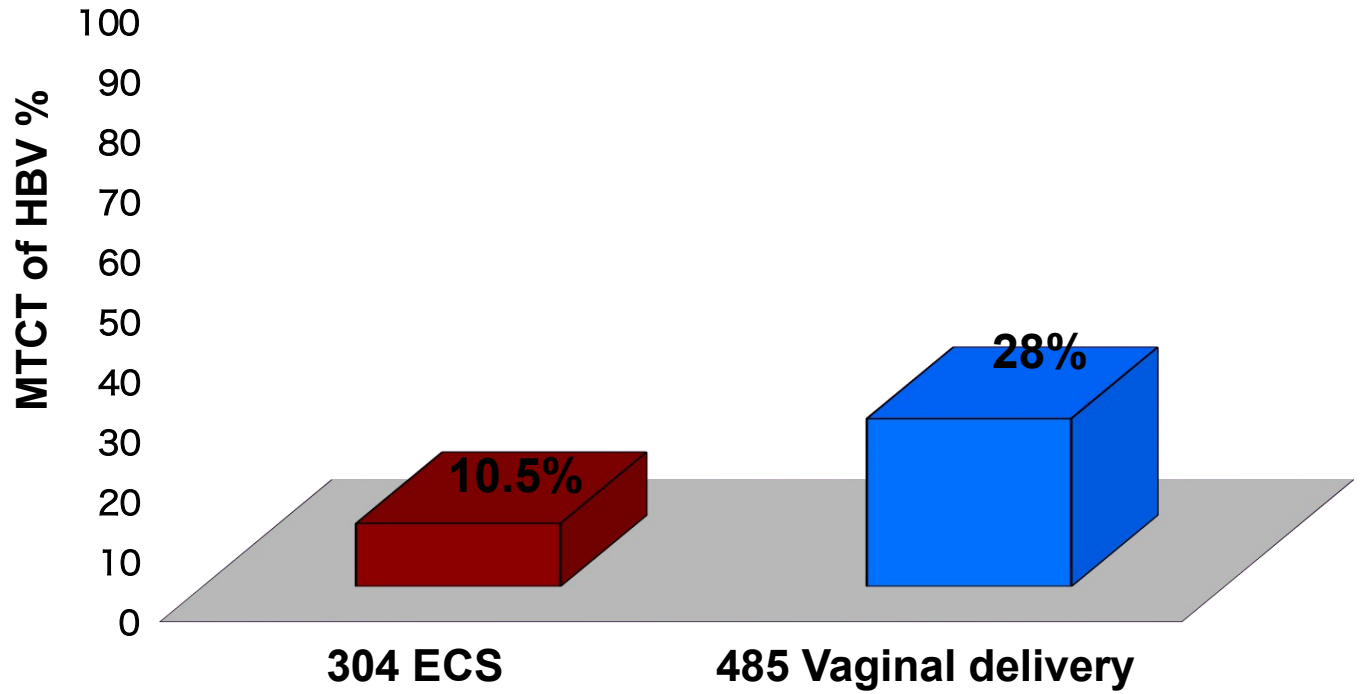


All infants received HBIG and vaccine

Wang J. et al. Clin Med J 2002: 1510-12.

Meta-analysis: Elective cesarean reduces the MTCT of HBV

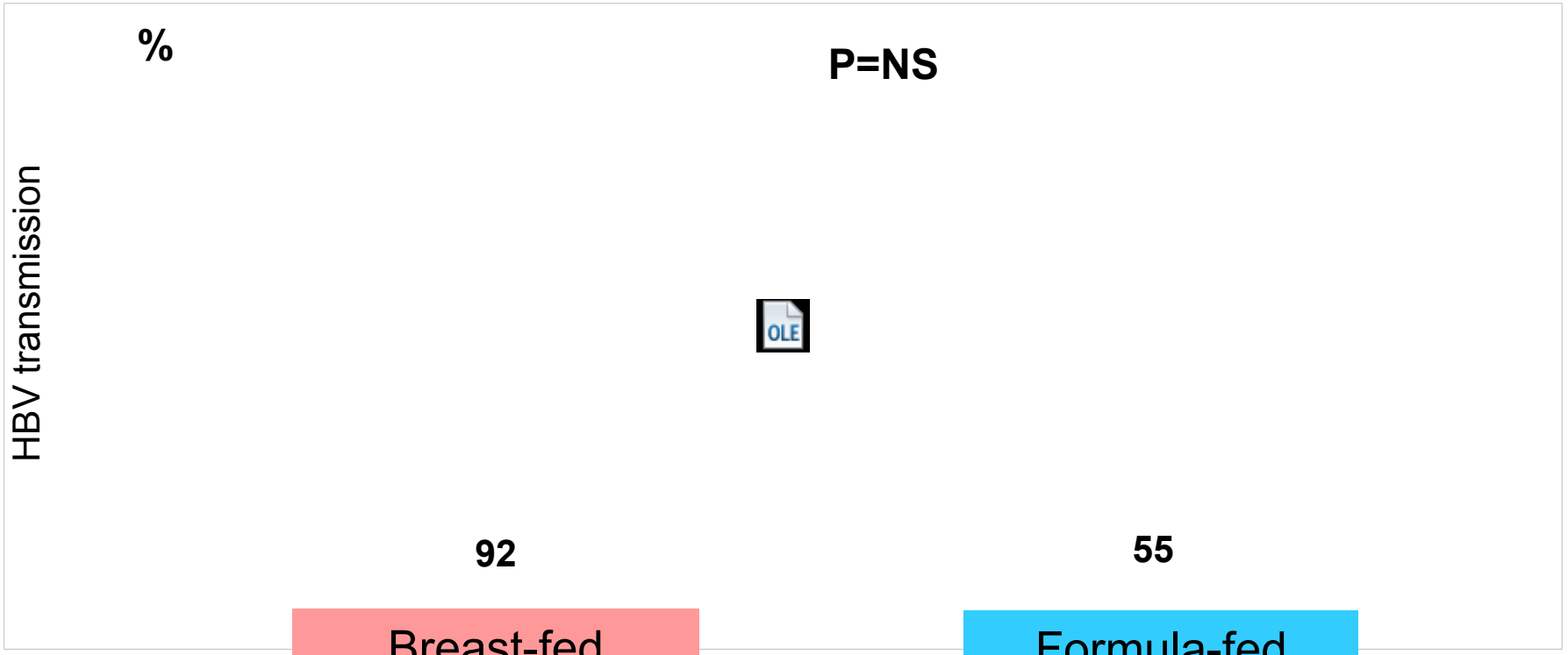
4 RCTs with 789 pregnant mothers



RR 0.41 , 95% CI 0.28 – 0.60

Yang J. etal. Virol J. 2008: 100.

Hepatitis B transmission by feeding in infants not receiving immunophophylaxis



Mean-age at last follow-up of 11 months

Beasley RP. et al. Lancet 1975; 2: 740-1.