



The effect of rupture of membranes and labour on the risk of hepatitis B vertical transmission: Prospective multicentre observational study

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ABSTRACT

Objective: To evaluate the effect of rupture of membranes and labour on the risk of hepatitis B virus (HBV) vertical transmission.

Study design: A prospective multicentre observational study was carried out in Hong Kong between 2014–2016. Pregnant HBV carriers were recruited. The duration of rupture of membranes, labour and mode of delivery were collected prospectively. HBV DNA was examined at 28–30 weeks of gestation. All newborns received standard HBV vaccination and immunoglobulin. Hepatitis B surface antigen of infants was tested at 9–12 months of age.

Results: 641 pregnancies were recruited and analyzed. No statistically significant difference was found in gravida, parity, gestational age at delivery, mode of delivery, duration of rupture of membranes, duration of labour, preterm delivery, preterm rupture of membranes or birth weight ($p > 0.05$). Subgroup analysis in viral load $> 7\log_{10}\text{IU/ml}$ and $8\log_{10}\text{IU/ml}$ also did not find a significant association between duration of rupture of membranes and labour with immunoprophylaxis failure.

Conclusions: Duration of rupture of membranes and labour would not affect the risk of HBV vertical transmission in infants following standard HBV vaccination and hepatitis B immunoglobulin administration.

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Introduction

Hepatitis B virus (HBV) infection remains the commonest form of chronic hepatitis with approximately 257 million people living with HBV infection and 887,000 HBV related death in 2015 [1]. The risk of acquiring chronic HBV infection is highest during the perinatal period as 90% of newborns and less than 5% of adults will become chronic carriers after HBV exposure [2]. A course of HBV vaccine and hepatitis B immunoglobulin (HBIG) at birth can prevent the majority of vertical transmission [3]. Vertical transmission still occurs in around 1–4% in newborns of HBV carriers despite optimal immunization [4–9]. While maternal viral load is a determining factor for immunoprophylaxis failure (IF),

obstetric factors as a potential cause for vertical transmission are rarely examined.

Human immunodeficiency virus (HIV) and herpes simplex virus (HSV) are two common viral infections that can be transmitted from the mother to the newborn during pregnancy [10,11]. Prolonged rupture of membranes (ROM) and vaginal delivery are associated with a higher risk of vertical transmission by the exposure of these viruses to the newborns in the lower genital tract. Induction of labour or Caesarean delivery after ROM may be required to expedite the delivery and reduce the risk of viral transmission [12,13]. In a systematic review, Caesarean delivery was associated with a lower risk of HBV vertical transmission [14]. No data is available for the effect of duration of ROM and preterm ROM on HBV vertical transmission. HBV DNA quantification during pregnancy is recommended to assess the risk of IF [15,16]. However, the obstetric management in preterm ROM, term ROM and the mode of delivery in HBV women with different viral load levels remains unclear. Therefore, a prospective multicentre

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observational study was carried out to evaluate the effect of viral load and obstetric factors on the risk of HBV vertical transmission. The effect of viral load was previously reported [9]. The objective of this study is to evaluate obstetric factors on the risk of HBV vertical transmission.

Methods

During January 2014 to December 2016, pregnant women who were found to be hepatitis B surface antigen (HBsAg) positive at their first antenatal visit were recruited from five public regional hospitals in Hong Kong. Women were excluded if they were receiving antiviral treatment or had miscarriage/ termination of pregnancy/ stillbirth. All women gave a written informed consent and were enrolled under protocols approved by the Institutional Review Board of each hospital.

Blood samples were collected from each subject at recruitment and 28–30 weeks. Maternal hepatitis B e antigen (HBeAg) status was examined. HBV DNA was measured using the sample obtained at 28–30 weeks by COBAS TaqMan HBV Monitor Test coupled with the COBAS Ampliprep extraction system (Roche Diagnostics, Branchburg, NJ). The DNA load lower limit of detection is 17 IU/ml, and the upper limit is ~170,000,000 IU/ml. Both pregnant women and their obstetricians were blinded to HBeAg and HBV DNA results, which would not affect the obstetric management of the recruited women. The management of the recruited women was similar to other pregnant women. They were followed up every 4–6 weeks before 30 weeks then 1–2 weeks until delivery. Management of preterm and term ROM followed standard departmental protocols. Breastfeeding was not restricted.

All newborns received 10 µg HBV vaccines (EngerixTM-B, GlaxoSmithKline, Belgium) and 110 IU HBIG (HyperHEP® B, Grifols, USA) within 12 h after birth. They received same dose of HBV vaccine at one month and six months. IF was defined as infant's HBsAg status positive at 9–12 months.

Women with missing data were excluded from final analysis. Preterm delivery was defined as delivery before 37 weeks of gestational age. Preterm ROM was defined as ROM before 37 weeks of gestation. Low birth weight was defined as birth weight ≤ 2500 g. Duration of labour was defined as cervical dilatation more than 3 cm to delivery of the fetus. The sample size was calculated in our previous study, based on comparing the proportions of IF in infants between high and low maternal

viral load during pregnancy [9]. Results were presented as mean [standard deviation (SD)] or median [interquartile range (IQR)] or n (%). The difference of continuous variables between IF and non-IF was explored by Mann-Whitney's test. The risk factors of IF were investigated by Fisher's exact test. P values of less than 0.05 were considered to indicate statistical significance. All data were analyzed with SAS software, version 9.2 (SAS Institute Inc. Cary, NC).

Result

750 women were recruited in the study. 109 pregnancies were excluded due to no maternal HBV DNA testing (n=42), use of antiviral treatment (n=16), withdrew consent (n=8), miscarriage/ termination of pregnancy (n=4), stillbirth (n=1) and defaulted infants HBsAg testing (n=38). A total 641 pregnancies were available for analysis and Table 1 summarized the basic demographics of the women. 68% of women delivered vaginally and 69% of women had ROM less than 4 h. Labour duration was less than 4 h in 74% of women.

Obstetric factors for IF were shown in Table 2. No significant differences were found in gravida, parity, gestational age at delivery, mode of delivery, duration of ROM, duration of labour, preterm delivery, preterm ROM or birth weight. There was no case of preterm ROM in the IF group.

As IF only occurred in high viremic women, we further evaluated the effect of duration of ROM and labour in these women (Table 3). Again, no statistically significant difference was found in duration of ROM, duration of labour and preterm ROM.

Discussion

We found that no obstetric factors, including duration of ROM and labour, increased the risk of IF in infants after standard HBV vaccination. To date, this is the first study examining the effect of obstetric factors on the risk of HBV vertical transmission with reference to the maternal HBV viral load. The prospective design of this study using sensitive HBV DNA assay, timely birth dose and strict compliance to the immunization schedule, and postnatal infants' HBsAg testing at 9–12 months ensured accurate data collection and analysis.

HBV viral load is a critical factor to assess the risk of the persistent vertical transmission despite adequate immunization.

Table 1
Demographic and obstetric characteristics.

	N = 641 Mean (SD)/ Median (IQR)/ n (%)
Age (mean, years)	32.8 (4.5)
Gravida (median)	2.0 (2.0)
Parity (median)	0 (1.0)
Gestational age at delivery (mean, weeks)	39.0 (1.6)
Nulliparity	352 (54.9%)
Delivery mode	
- Elective Caesarean section	107 (16.7%)
- Emergency Caesarean section	95 (14.8%)
- Forceps	9 (1.4%)
- Spontaneous vaginal delivery	396 (61.8%)
- Vacuum extraction	34 (5.3%)
Duration of rupture of membranes (median, minutes)	90 (347.5)
Duration of labour (median, minutes)	90 (250.5)
Preterm delivery	19 (2.9%)
Preterm rupture of membranes	20 (3.1%)
Birth weight (mean, grams)	3122.8 (49.0)
Breast feeding	600 (94.5%)
Immunoprophylaxis failure	7 (1.1%)

SD, standard deviation; IQR, interquartile range.

Table 2
Obstetric factor to predict immunoprophylaxis failure.

	IF N = 7 Median (IQR)/ n (%)	Non- IF N = 634 Median (IQR)/ n (%)	p value
Age (years)	29.0 (10.0)	33.0 (6.0)	0.218
Gravida	2.4 (1.0)	2.1 (1.2)	0.284
Nulliparity	1 (14.3%)	351 (55.4%)	0.050
In vitro fertilization			1.000
- No	7 (100%)	615 (97.0%)	
- Yes	0 (0%)	19 (3.0%)	
Gestational age at delivery (weeks)	39.14 (2.29)	39.29 (1.71)	0.995
Delivery mode			0.407
- Caesarean delivery	1 (14.3%)	201 (31.7%)	
- Normal spontaneous delivery	6 (85.7%)	390 (61.5%)	
- Instrumental delivery	0 (0%)	43 (6.78%)	
Preterm delivery	0 (0%)	19 (3%)	1.000
Preterm rupture of membranes	0 (0%)	20 (3.2%)	1.000
Birth weight (grams)	3200 (840)	3120 (490)	0.871
Median (IQR) duration of rupture of membranes	51.0 (340.0)	100.0 (350.3)	0.602
Duration of rupture of membranes			0.806
- ≤4 hours	5 (71.4%)	438 (69.1%)	
- 4.1 – 8 hours	1 (14.3%)	87 (13.7%)	
- 8.1 – 12 hours	1 (14.3%)	51 (8.0%)	
- >12 hours	0 (0%)	58 (9.15%)	
Median (IQR) duration of labour	88.0 (112.0)	90.0 (251.3)	0.827
Duration of labour			0.850
- ≤4 hours	6 (85.7%)	468 (73.8%)	
- 4.1 – 8 hours	1 (14.3%)	109 (17.2%)	
- 8.1 – 12 hours	0 (0%)	33 (5.2%)	
- >12 hours	0 (0%)	24 (3.8%)	
Breast feeding			0.326
- No	1 (14.3%)	34 (5.4%)	
- Yes	6 (85.7%)	600 (94.6%)	

IF, immunoprophylaxis failure; IQR, interquartile range.

Table 3
Preterm rupture of membranes, duration of rupture of membranes and labour in HBV women with high viral load.

	IF n (%)	Non- IF n (%)	p value
Viral load > 7 log ₁₀ IU/ml	N = 7	N = 118	
- Median (IQR) duration of rupture of membranes (minustes)	51.0 (340.0)	100.0 (366.3)	0.505
> 4 hours of ROM	2 (28.6%)	42 (35.6%)	1.000
- Median (IQR) duration of labour (minustes)	88.0 (122.0)	120.0 (257.8)	0.571
> 4 hours duration of labour	1 (14.3%)	37 (31.4%)	0.674
- Preterm rupture of membranes	0 (0%)	3 (2.5%)	1.000
Viral load > 8 log ₁₀ IU/ml	N = 6	N = 86	
- Median (IQR) duration of rupture of membranes (minustes)	25.5 (401.0)	103.5 (391.8)	0.347
> 4 hours of ROM	2 (33.3%)	33 (38.4%)	1.000
- Median (IQR) duration of labour (minustes)	93.5 (168.8)	130.0 (255.0)	0.495
> 4 hours duration of labour	1 (16.7%)	28 (32.5%)	0.661
- Preterm rupture of membranes	0 (0%)	2 (2.3%)	1.000

IF, immunoprophylaxis failure.

Highly viremic women may harbour significant amount of HBV in the lower genital tract and exposure of HBV to the newborns during vaginal delivery can theoretically increase the risk of vertical transmission, in particular for increased exposure in prolonged ROM and labour. The condition is seen in women with HIV. The risk of HIV vertical transmission is increased by 2% for every hour of ROM (adjusted odds ratio, 1.02; 95% CI, 1.01–1.04) [17] but the association is not found in women when the viral load is adequately suppressed by combined antiretroviral therapy [18,19]. Therefore, the risk of vertical transmission likely depends on the total amount of viral exposure by the maternal viral load, the duration of ROM and vaginal delivery. However, we showed that the intrapartum factor was unlikely to cause significant effect on the rate of IF, even in women with high viral load by our subgroup analysis. One of the possible reasons is the HBV

vaccination and HBIG at birth could adequately neutralize the acute transient exposure to HBV in the lower genital tract during ROM and vaginal delivery. In addition, the timing of HBV vaccination at birth is also crucial in women with high viral load. A randomized controlled trial showed no vertical transmission in newborns of highly viremic women after HBIG and HBV vaccine given at a median time of 1.3 h and 1.2 h after delivery [20]. All our newborns received vaccination as soon as possible and within 12 h of birth. The other possible reason is the HBV infection could have already occurred in-utero [21] and therefore modifying intrapartum factors could not alter the risk of vertical transmission. One of our vertical transmission occurred despite Caesarean section without onset of labour or ROM. We also studied the effect of preterm ROM. In fact, in-utero HBV exposure is common and does not predict the risk of IF [22]. The exact

mechanism of in-utero infection and subsequent vertical transmission remains largely unknown.

We expect there will be more HBV women with viral load quantified during pregnancy according to international recommendations [15,16]. In the absence of strong evidence, the mode of delivery in HBV women should be based on obstetric indications. Although the data from systematic review suggests the possible beneficial effect from Caesarean section in reducing vertical transmission, the significant heterogeneity in the use of antenatal maternal HBIG and postnatal HBIG to infants, and the definition of vertical transmission among the included studies hinder proper interpretation [14]. Our observation is also consistent with other studies that preterm ROM is not associated with vertical transmission [23,24].

There are several limitations in our study. Because of the effective immunization programme in Hong Kong, the rate of vertical transmission in this cohort is 1%. The small number of IF in the subgroup analysis may not be sufficiently powered to detect small differences. Secondly, the HBV DNA was not examined during the onset of labour or ROM, but we believe the effect of gestational age on viral load quantification should be minimal, as HBV DNA could remain static throughout the course of the pregnancy [25]. Finally, the design of the study cannot determine the optimal mode of delivery and management of ROM. However, the double blinded HBV DNA result to the obstetrician and the HBV infected women would avoid bias in obstetric management, such as immediate induction after ROM or lower threshold for Caesarean delivery after prolonged ROM. In this multicentre study with analysis based on different viral load levels, our results could be generalized to other population.

Conclusion

After standard immunization to newborn, prolonged duration of ROM and labour would not affect the rate of vertical transmission even in HBV women with high viral load.

Disclosure

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Author contributions

K.W.C. prepared the manuscript. W.W. performed statistical analysis. All authors contributed to the conception and design of the study and were involved in subject's recruitment, data analysis, amendment and approval of the final manuscript.

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