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IMPACTS OF LAMIVUDINE AND TENOFOVIR ON THE TRANSMISSION OF HEPATITIS B VIRUS FROM MOTHERS TO CHILDREN AND SOME RELATED FACTORS IN HAI DUONG

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SUMMARY OF DOCTORAL THESIS

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At …… hour …… date …… month …… year 2020

The thesis can be found at:

INTRODUCTION

Hepatitis B is a worldwide burden of health with high prevalence and severe consequences as cirrhosis and liver cancer. So far, the worldwide general trend is to focus on prevention of HBV transmission, with the primary goal of preventing mother-to-child transmission in areas with high prevalence of hepatitis B, including Vietnam. Many advanced and effective preventive measures have been applied such as vaccination and HBIG for children born to mothers infected with HBV, most recently, anti-viral treatment for pregnant women with high HBV DNA load around last 3 months of pregnancy. In Vietnam, since 2014 the Ministry of Health has issued the guideline for treatment of antiviral drugs to prevent mother-to-child transmission of HBV. At pressence, this guideline has been gradually applied at different levels in each locality. In Hai Duong province however, up to the time of our research, it has not been applied yet. Therefore, we conducted this study with two goals:

1. To evaluate the efficacy of LAM and TDF in late pregnancy in interrupting mother-to-child transmission of hepatitis B virus in chronic HBV infected pregnant women with high viral load from March 2015 to January 2019 in Hai Duong.

2. To identify some factors related to mother-to-child transmission of hepatitis B virus in chronic HBV infected pregnant women with high viral load in Hai Duong.

NEW CONTRIBUTIONS OF THE THESIS

This was the first longitudinal follow-up study at provincial level, evaluating the efficacy of lamivudine and tenofovir from 28th week of pregnancy in interrupting mother-to-child transmission of hepatitis B virus, allowing to confirm the feasibility of Decision No. 5448/QD-BYT of the Ministry of Health at the provincial level.

This was the first study in Vietnam investigating the impact of breast milk and delivery methods (vaginal delivery, caesarean section) on mother-to-child transmission of hepatitis B virus.

STRUCTURE OF THE THESIS

The main body of the thesis contains 121 pages, including the following sections: introduction (3 pages), overview (35 pages), methods (22 pages), results (32 pages), discussion (27 pages) conclusion (1 pages) and recommendation (1 page). The thesis cited 107 references, including 15 in Vietnamese and 92 in English. The thesis contains 31 tables, 21 pictures with 6 appendices.

Chapter 1. OVERVIEW

1.2 Epidemiology of hepatitis B virus infection: HBV infection rates vary widely among regions of the world, most concentrated in Africa, in the Western Pacific and in developing countries with large population. In Vietnam, the prevalence in the community is about 10-15%; among pregnant women this rate varies between 9.5% and 13.03%.

1.3 Mother-to-child transmission of HBV is an important mode of transmission in areas with high rates of HBV infection, including Vietnam. Some factors presumed as related to mother-to-child transmission of HBV are on debate:

+ *Presence of HBeAg (+) and high load of HBV DNA* ($\geq 10^6$ *copies/ml or >200.000 IU/mL*) in regnant women were considered as high risk factor for mother-to-child- transmission of HBV.

+ *Method of delivery:* Up todate, however, many contradictory points of view existed, so no recommendation on either vaginal delivery or caesarean section to prevent the transmission of HBV from mother to child had been issued.

+ *Breastfeeding:* many findings from recent studies such as from Shi (2011), Chen (2013), Zhang (2014) showed that breastfeeding is not a risk factor for mother to child transmission of HBV, even breast-feeding with HBV positive breast milk.

1.4 Prevention of perinatal transmission of HBV

1.4.4 Treatment of antiviral drugs during pregnancy

1.4.4.1 Scientific basis is the "vaccine breakthrough" phenomenon of HBV might happen, in case too high load of maternal HBV DNA, beyond the protection of the placental barrier which is the basic cause of this phenomenon. Therefore, intervention studies on antiviral drugs for pregnant women have been conducted to rapidly reduce viral load, thereby preventing mother to child transmission of HBV.

Based on several previous studies and to ensure consistency in treatment, prestigious hepatology associations around the world, such as AASLD, EASL and Ministry of Health of Vietnam have issued guidelines for the treatment of antiviral drugs for preventing HBV transmission from mother to child.

Table 1.5 Antiviral therapy guidelines for prevention of mother-to-child transmission of HBV

Associations	Year of issue	Treatment threshold for HBV DNA in pregnant women (copies/ml)	Drugs	Start of treatment	End of treatment
Ministry of Health of Vietnam	2014	10^6	TDF LAM	from the last 3 months of gestation	3 months postpartum
EASL	2017	10^6	TDF	24^{th} – 28^{th} week of gestation	12 weeks postpartum
AASLD	2018	10^6	TDF* LAM telbivudine	28^{th} – 32^{th} week of gestation	3 months postpartum

1.4.4.3 Efficacy of LAM and TDF treatment for preventing mother-to-child transmission of HBV

+ For LAM: there are many studies confirming the effectiveness of lamivudine in preventing HBV transmission to offspring, in addition, the reported side effects were minimal and there were no serious events with mothers and their babies.

Table 1.6 Some meta- analyses for studies about effectiveness of lamivudine used during pregnancy in prevention of mother-to-child HBV transmission *(by Han et al, 2011)*

Author/year	HBV infection rate in children (n/N)		RR (95% CI)
	LAM treatment group	Control group	
Han (2005)	0/43	5/35	0.07 (0.00 – 1.30)
Li (2006)	1/36	7/44	0.17 (0.02 – 1.35)
Feng (2007)	7/48	16/42	0.38 (0.17 – 0.84)
Guo (2008)	4/70	12/40	0.19 (0.07 – 0.55)
Xu (2009)	10/56	23/59	0.46 (0.24 – 0.87)
Zhang (2010)	1/50	8/50	0.13 (0.02 – 0.96)
Total	23/303	71/270	0.33 (0.21 – 0.50)

+ For TDF

Table 1.7 Some meta- analyses of TDF used during pregnancy in preventing mother-to-child HBV transmission *(by Chen et al, 2017)*

Author/year	HBV infection rate in children (n/N)		OR (95% CI)
	TDF treatment group	Control group	
Samadi (2016)	0/24	1/146	1.98 (0.08 – 50.0)
Pan (2016)	0/92	6/88	0.07 (0.00 – 1.24)
Chen (2015)	2/66	6/57	0.27 (0.05 – 1.37)
Greenup (2014)	1/58	2/20	0.16 (0.01 – 1.84)
Celen (2013)	0/211	2/23	0.20 (0.01 – 4.42)
Total	3/261	17/334	0.21 (0.07 – 0.61)

The results of many studies show that TDF is effective in reducing mother-to-child transmission of HBV. More over, the side effects in pregnant women were moderate and there was no difference in the incidence of congenital malformation in children between the TDF group and the control group.

1.4.4.4 About the adverse effects of TDF treatment during pregnancy on children: The researchs of Viganò (2011) and Salvadori (2018) have showed that no adverse effects on the physical development and bone mineral density in babies born to mothers treated with TDF in pregnancy period.

1.4.4.5 Breastfeeding and using antiviral drugs LAM, TDF in mothers

Many researchs have shown that the LAM and TDF concentration that children received through breast milk was much lower than the therapeutic dose, so it might not adversely affect children. Most recently, the 2018 recommendations of AASLD on breastfeeding clearly stated: breastfeeding is not contraindicated for mothers infected with HBV, including those receiving antiviral therapy (LAM, TDF). However, there is not enough long-term safety data for infants when mothers take antiviral drugs from pregnancy and lactation, and subsequent studies are therefore it is necessary to carry out further studies with high confidence to further clarify this issue.

CHAPTER 2. MATERIALS AND METHODS

2.1 Subjects, time and location of study

2.1.1 Research subjects

+ Selection criteria

- Pregnant women with chronic HBV infection having a HBV DNA load $> 10^6$ copies/mL

- Children of the above-mentionned women born during the study
- Voluntary to participate in the research

+ *Exclusion criteria*

- Pregnant women co-infected with HIV or hepatitis C
- Pregnant women have clinical manifestations and tests showing liver, kidney, blood disease, pregnancy toxicity, gestational diabetes.
- Pregnant women with abnormal test: AST, ALT ≥ 2 times the upper normal limit, blood creatinine> 150 µmol/l, Haemoglobin <80 g/l.
- Pregnant women who had previously been treated with antiviral drugs
- Pregnant women having results of antenatal ultrasound and/or check-ups that suspected fetal underdevelopment or have morphological abnormalities (congenital malformations).

+ ***Evidence of vertical transmission of the HBV virus from mother to child:*** the final conclusions on mother-to-child HBV transmission are based on the results of a venous blood test at 6 to 12 months of age, with HBsAg(+) and/or HBV DNA(+) and the test results confirm chronic infection with total HbcAb(+)/HBcAb IgM(-).

+ Criteria for determining gestational age:

Gestational age is calculated from the first day of the last period. In the event that the woman does not remember this information, the ultrasound test is used to calculate gestational age. Pregnancy to the 7th month is when the gestational age is 28 weeks (196 days).

2.1.2 Research timelime: Conducting intervention study on antiviral treatment (LAM or TDF) for pregnant women from March 2015 to March 2018. Monitoring HBV infection status in the offspring of these pregnant women until January 2019.

2.1.3 Research location: Hai Duong Hospital of Obstetrics and Gynecology and Hai Duong Medical Technical University Hospital, Hai Duong Province.

2.2 Research Methods

2.2.1 Research design

2.2.1.1 Research design for the first goal

- Clinical intervention study by randomizing research subjects assigned to 2 treated groups LAM and TDF. Pregnant women and babies born were followed up to comparing the efficacy of TDF (new FDA approved drug for pregnant women) and LAM (approved drug for pregnant women before) in interrupting mother-to-child transmission of hepatitis B virus.

- Random grouping method: the women were randomly selected to receive treatment by lottery.

- Intervention isues:

+ *Interventions by antiviral treatment for pregnant women:* according to the content of Decision No. 5448/QD-BYT dated December 30, 2014 of the Ministry of Health on promulgating the Guidelines for diagnosis and treatment of HBV:

Drug: LAM or TDF. Dose: lamivudine 100mg: 1 capsule daily, tenofovir disoproxil fumarate (TDF) 300mg: 1 capsule daily. Duration of treatment: from the 28th week of pregnancy and continue to maintain the drug until 3 months after birth.

+ *Vaccin Hepatitis B and HBIG in children*

Vaccination against hepatitis B: 4 doses given: 0 - 2 - 3 and 4 months old, applied under the Expanded Program of Immunization in Vietnam approved by the Ministry of Health since 2010. HBIG injection: Inject

1ml (Immuno-HBs 180IU/ml) x 01 time within the first 24 hours after birth.

2.2.1.2 Research design for the second goal

"Case series" study to assess the relationship between some factors that are likely to be relate to HBV infection in children by comparing the frequency of occurrence of these factors in both HBV infected and uninfected groups.

2.2.2 Study sample size

The sample size of the study was calculated using the following theoretical sample size formula for the intervention study below:

$$n_1 = n_2 = \frac{\left[Z_{1-\alpha/2}\sqrt{2P(1-P)} + Z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\right]^2}{(P_1-P_2)^2}$$

After calculation, the minimum theoretical sample size for each intervention group was 39 women.

2.2.3 Research content and method of implementation

2.2.3.3 Materials and techniques applied in research

+ *Clinical examination*: Pregnant women were clinically examined by doctors at Hai Duong Obstetric Hospital at 28 weeks of gestation, 1 month after antiviral therapy, at birth, 1-3 months after birth. The offspring of pregnant women in the study were weighed, examined to detect congenital malformations, pathologies immediately after birth and at the following time: 1 month, 6 - 12 months of age.

+ *Labo tests:* All tests are performed at the Laboratory Department of Hai Duong Medical Technical University Hospital according to the approved testing technical procedures. Tests are checked daily and monthly checked with the Testing Center of Hanoi Medical University:

- HBV DNA loading was measured using Realtime PCR gene amplification biotechnology. The test was performed on Eppendorf's Realplex 4 machine (Federal Republic of Germany), using ^{iVA}HBV qPCR Mix kit for realtime PCR reaction of Viet A Technology Joint Stock Company with a detection threshold of 3×10^2 copies / ml.
- HBsAg test: SD BIOLINE HBsAg test kit, manufacturer of Standard Diagnostics, Inc. (Korea); sensitivity 98.9% and specificity 100%.
- HBeAg test: SERO-CHECK test kit of the US, distributed by MITpharmaceutical Co., Ltd; sensitivity 98.2%; specificity 98.2%.

2.3 Data processing: Use SPSS 20.0 medical statistics software. In addition, the study used the conversion of HBV DNA to $\log_{10}$HBV DNA, (lg HBV DNA) (copies / ml). The $\log_{10}$ HBV DNA values obtained after conversion will be rounded according to rule 5.

2.4 Ethical issues in the research: The research was approved by the Scientific Council of Hai Phong University of Medicine and Pharmacy. The pregnant women were recieved free drugs and tests in the Science and Technology project of Hai Duong Department of Science and Technology, code: YD.14.ĐHKTYT.15.

Chapter 3. RESULTS

3.1 Distribution of research samples and characteristics of research subjects

3.1.1 Distribution of research samples*:* In the period from March 2015 to March 2018, we conducted intervention studies and data analysis on 80 pregnant women with HBV DNA level > 10^6 copies / ml and eligible for research, in which 39 women received LAM and 41 women treated with TDF. The newborns were monitored at the time right after birth (n = 68), 1 month of age (n = 58), 6 - 12 months of age (n = 47).

3.1.2 Characteristics of research subjects

3.1.2.1 Characteristics of pregnant women

At the 28th week of gestation:

- Pregnant women in the two groups treated under LAM or TDF did not have differences in age, occupation, geography, number of births and number of people infected with HBV in the household (p> 0.05).
- The average duration of treatment in LAM group was 74.13 ± 12.07 days, not different from TDF group of 73.59 ± 14.29 days (p = 0.855)
- The mean load $\log_{10}$ copies/ml HBV DNA in LAM group was 6.98 ± 0.49 (6.08 - 8.36), in TDF group was 7.16 ± 0.69 (6.02 - 9.07), the difference was not statistically significant (p = 0.192).

3.1.2.2 Characteristics of the children

In this study, 80 babies were born from 80 women. All of them did not have to interfere with postpartum support and did not detect congenital malformations. There were similarities in the characteristics of birth weight, gestational age, hepatitis B vaccination, HBIG status and breastfeeding status of two children groups whose mothers under LAM, TDF treatment.

3.2 Impact of LAM and TDF in late pregnancy in interrupting mother to child transmission of HBV

Table 3.5 HBV infection in children over time

HBV infection in children	Right after birth	1 month of age	6 - 12 months of age
Yes (n,%)	7 (10.3)	**0 (0)**	**3 (6.4)**
No (n,%)	61 (89.7)	58 (100)	44 (93.6)
Total (n,%)	68 (100)	58 (100)	47 (100)

At the time of birth, there were 7/68 babies (10.3%) had HBsAg (+). At 6 - 12 months of age only 3/47 children were infected with HBV, in which

1 child with acute HBV infection and 2 children with chronic HBV infection with high HBV DNA load >10^7 copies/ml.

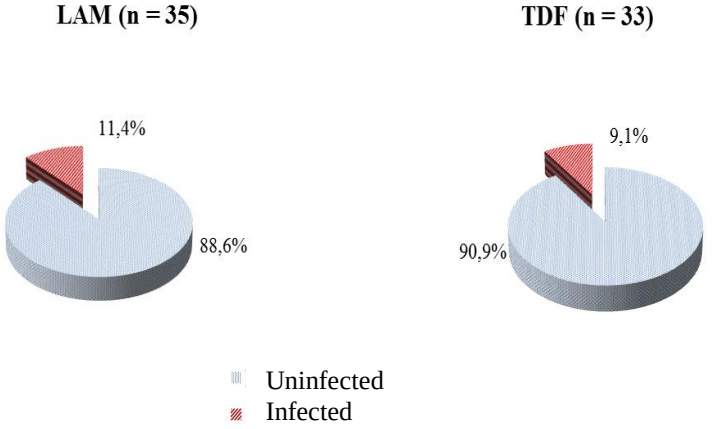

Figure 3.7 Umbilical cord HBV infection in two babies groups whose mothers under LAM, TDF treatment

Among children whose mothers were treated with LAM, 11.4% (4/35) had an umbilical cord HBV infection, and among children of mothers treated with TDF, this prevalence was 9.1% (3/33). This difference was not statistically significant (p = 1.000).

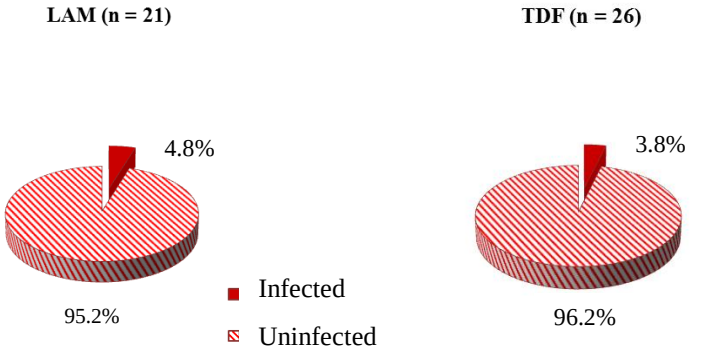

Figure 3.8 The status of chronic HBV infection in two children groups whose mothers under LAM, TDF treatment

In the children group whose mothers under LAM treatment, 4.8% (01/21) children were chronically infected with HBV. The prevalence of chronic HBV infection in children whose mothers treated with TDF was 3.8% (01/26), the difference was not statistically significant (p = 1.000).

3.3 Impact of LAM and TDF in late pregnancy on pregnant women

3.3.1 Efficacy of reducing HBV DNA viral load after treatment

Average HBV DNA viral load of pregnant women after LAM treatment is 4.7 ± 1.3 (0 - 6.9), higher than after TDF treatment with 3.1 ± 1.7 (0 - 6.2) log_{10} copies/ml, this difference was statistically significant with p <0.001.

Table 3.8 Efficacy of reducing HBV DNA load before and after treatment in LAM and TDF groups (log_{10} copies/ml)

Reduction in HBV DNA (log_{10} copies/ml)	Treatment group		*p*
	LAM n (%)	TDF n (%)	
≤ 2.4 log_{10}	**25 (64.1)**	9 (22.0)	*0.006*
2.5 - 3.4 log_{10}	8 (20.5)	3 (7.3)	*0.132*
3.5 - 4.4 log_{10}	3 (7.7)	**14 (34.1)**	*0.008*
≥ 4.5 log_{10}	3 (7.7)	**15 (36.6)**	*0.005*
Total	39 (100)	41 (100)	

In TDF-treated pregnant women, the HBV DNA load after treatment was reduced by ≥ 3.5 log_{10} copies/ml. In the LAM-treated pregnant women, the HBV DNA load after treatment decreased at a lower level by ≤ 2.4 log_{10} copies/ml, this difference was statistically significant (p <0.05).

3.3.2 Effects of antiviral drugs on some functions of organs

After LAM treatment, ALT value increased by an average of 1.2 times, of which only one case saw the highest increase of 5.4 times before treatment and reached to 115.5 U/l. The creatinine index increased by an average of 1.2 times compared to before treatment.

After TDF treatment, ALT value increased by an average of 1.4 times, in one case the highest value was 115 U/l and AST value was 90 U/l. The creatinine index increased by an average of 1.2 times compared to before treatment, of which the highest value was 94 µmol/l.

3.3.3. Side effects in two groups of pregnant women treated under LAM and TDF

Side effects have occurred in 6.3% (5/80), including 1 case in the LAM - treated group and 4 cases in the TDF-treated group.

The side effects noted in this study were mainly gastrointestinal manifestations (anorexia, nausea, vomiting, diarrhea); other symptoms included: fatigue, dizziness, erythema and skin.

3.4 Some factors related to the perinatal transmission of HBV *3.4.1 Relationship between HBeAg status of pregnant woman at labor with HBV infection in their children*

In the HBeAg(+) pregnant women, the rate of HBV infected umbilical cord was 11.5% (7/61) and 4.9% (2/41) children were infected with HBV at 6 - 12 month of age.

In the HBeAg (-) pregnant women, there was no case of HBV infected umbilical cord and none of the children had been infected with HBV at 6 - 12 month of age.

3.4.2 Relationship between HBV DNA viral load of pregnant women at labor with HBV infection status in their children

The possibility of being infected HBV umbilical cord in pregnant women group with HBV DNA load at labor $>10^4$ copies/ml was 2.58 times higher than HBV DNA $\leq 10^4$ copies/ml group. However, this difference was not statistically significant, OR (95% CI): 2.58 (0.47 - 14.35).

The possibility of HBV mother-to-child transmission in pregnant women group with HBV DNA load at labor $>10^4$ copies/ml was 1.045 times higher than HBV DNA $\leq 10^4$ copies/ml group. However, this difference was not statistically significant, OR (95% CI): 1.045 (0.06 - 17.77).

3.4.3 Relationship between delivery methods (vaginal/cesarean delivery) with HBV infection status in their children

The possibility of being HBV infected umbilical cord in vaginal delivery group was 2.1 times higher than that in cesarean section group. However, this difference was not statistically significant with OR (95% CI): 2.1 (0.4 - 11.8)

The possibility of HBV mother-to-child transmission in the caesarean section group was 1.5 times higher than that in vaginal delivery group. However, this difference was not statistically significant with OR (95% CI): 1.5 (0.09 - 25.6).

3.4.5 Relationship between breastfeeding and mother-to-child transmission of HBV

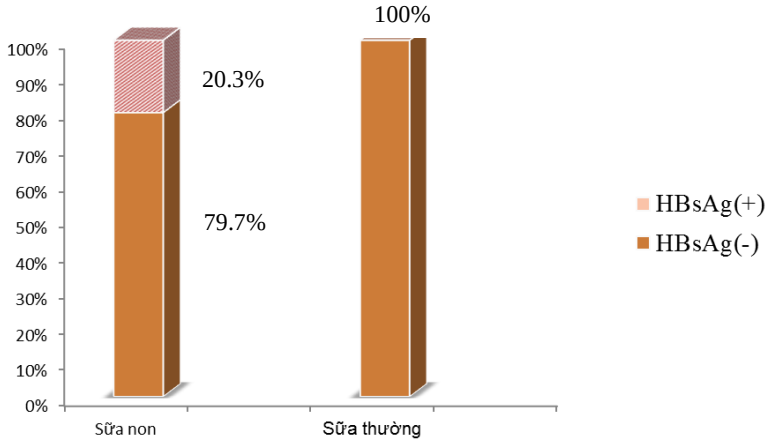

Figure 3.13 Occurrence of HBsAg in breast milk (colostrum and milk)

The rate of infected HBsAg colostrum samples was 20.3% (16/79) and 100% (79/79) milk samples were negative for HBsAg.

Among mothers with HBsAg(+) in colostrum, none of the children had been infected with HBV. There were 2 children with chronic HBV infection due to perinatal transmission. Both of them were breastfed and the mother's colostrum sample were negative for HBsAg.

Chapter 4. DISCUSSION

In this study we intervened to use antiviral drugs for pregnant women with HBV DNA> 10^6 copies/ml and from the 28th week of gestation with the aim of preventing mother-to-child transmission of HBV. Thus, the earlier treatment time and lower treatment threshold

compared to the pioneering research in this field by Nguyen Van Bang et al (2014), this is completely consistent with the general trend of the world according to EASL (2017) and AASLD (2018).

4.2 Impact of LAM and TDF in late pregnancy in interrupting mother to child transmission of HBV

4.2.1 HBV infection of umbilical cord

The presence of HBV in umbilical cord blood indicates the transmission of HBV from maternal blood to the baby from intrauterine period and during labor. For mothers infected with HBV, the prevalence of cord blood HBV infection was also high at 35.6% (Chu Thi Thu Ha *et al.*).

In contrast, after antiviral therapy is used in pregnant women in our study, the rate of umbilical cord HBV infection is greatly reduced. Other studies of Nguyen Van Bang, Chen et al also showed similar results.

On the other hand, umbilical cord HBV infection also suggests later HBV infection in the child. The study results of Chen et al (2015) showed that children infected with HBV in cord blood were likely to be infected at 6 months of age with OR (95% CI) = 6.20 (1.35 – 28.47). In our study, because HBV infection was not assessed in all cord blood samples, the number of samples analyzed was not large enough. Therefore, the research results have not shown this relationship.

4.2.2 HBV infection at 6 - 12 months of age

Our results show that tenofovir and lamivudine administered in late pregnancy showed the efficacy in preventing mother-to-child HBV transmission. The rate of HBV transmission from mother to child after

LAM and TDF intervention in our study was very low, similar to many studies in this field in the world and in Vietnam:

A controlled clinical trial of Zhang et al. (2014) was conducted on women with chronic HBV infection with HBV DNA> 10^6copies/ml who were receiving lamivudine (n = 53) or telbivudine (n = 257) starting at 28^{th} – 30^{th} week of gestation. The results showed that the intervention effectiveness was very good, no children were infected with HBV at 52^{nd} week of age, while the rate of children infected with HBV in the control group (n = 363) was 2.84%. Chen et al (2015) studied intervention of tenofovir 300mg/day for 62 women from 30^{th} - 32^{th} week of pregnancy and 56 untreated women in the control group. Comparison of the effectiveness of preventing mother-to-child transmission of HBV from the two groups showed that: in the tenofovir treated group, the rate of HBV transmission from mother to child was 1.54%, much lower than the control group with the rate of 10.71% with p = 0.0481.

In Vietnam, the first study in this field by Nguyen Van Bang et al (2014) on pregnant women with chronic HBV infection with HBV DNA load > 10^7copies/ml, who received intervention with lamivudine (n = 33) and tenofovir (n = 49) at 32^{nd} week of pregnancy and 4 weeks postpartum. The results showed that both lamivudine and tenofovir proved effective in reducing HBV transmission from mother to child with the rate of HBV infection in children at 52 weeks of age was only 2.4%, of which the percentage in the group of mother treated with lamivudine was 3% and the group with the mother receiving tenofovir was 2%.

Thus, in our study, LAM and TDF in late pregnancy showed efficacy and safety in preventing mother-to-child transmission of HBV.

4.2.3 Infant's abnormal symptoms immediately after delivery

The results of this study provided scientific evidence for the safety of LAM and TDF in last 3 months of pregnancy in infant.

4.3 Impact of LAM and TDF in late pregnancy on pregnant women

4.3.1 Efficacy in reducing HBV DNA viral load after treatment

The reduction of HBV DNA levels in mothers under tenofovir group was significantly higher than lamivudine group.

Our results was similar to many studies in the world and in Vietnam.

Han et al. (2011) showed that the HBV DNA load reduction after LAM treatment, until the time of labor, was only about 2-3 lg copies/ml. Samadi Kochaksaraei et al. (2016) found that the HBV DNA load of pregnant women decreased by an average of 5.49 lg after TDF treatment in the last 3 months of pregnancy.

4.3.2 Effects of antiviral drugs on some functions of organs

Our research results are similar to other studies in the world: Pan and colleagues' research showed that ALT levels increased from 1.1 to 5 times and creatinine increased from 1.3 to 3 times of average values after TDF treatment; Zhang et al. (2014) also reported an increase in ALT of 1.3 to 4.5 times after LAM treatment for pregnant women and no case of "flare" was seen.

4.3.3 Side-effects of antiviral drugs

Our results are similar to those of Xu, Han, Chen et al. The side effects after LAM and TDF treatment for pregnant women were mainly gastrointestinal symptoms. In addition, Pan et al recorded other events after TDF treatment such as cough, headache, insomnia, dizziness,

itching, erythema. Zhang et al (2014) have noted additional side effects after LAM treatment for pregnant women including: myalgia, arthralgia.

4.4 Some factors related to the perinatal transmission of HBV

4.4.1 Relationship between HBeAg status of pregnant woman at labor with HBV infection in their children

Many studies in the world have also confirmed that pregnant women with HBeAg (+) is one of the factors that increase the transmission of HBV from mother to child during the perinatal period. Research of Yin et al. (2013) showed that the rate of mother- to- child HBV transmission among HBsAg(+)/HBeAg(+) pregnant women was 4.4%, while in the HBeAg (-) pregnant women, no infants were infected with HBV from mother ($p < 0.05$). Research of Phi Duc Long and colleagues showed that: the risk of HBV infection at 12 months of age in children born to HBeAg (+) mothers was 12 times higher than that of HBeAg (-) mothers. Thus our research results are similar to previous studies.

4.4.2 Relationship between HBV DNA viral load of pregnant women at labor with HBV infection status in their children

Research of Zou et al (2012) has shown a close relationship between HBV DNA load of pregnant women and HBV infection to the offspring, particularly when prenatal HBV DNA levels of mothers have been stratified according to the level: under 6; 6 – 6.99; 7 – 7.99 and $\geq$ 8 $\log_{10}$copies/ml, the proportion of children infected with HBV infection from mother was 0%; 3.2%; 6.7% and 7.6% with $p < 0.001$. Research of Yin et al (2013) have

shown that perinatal HBV infection only occurs when the HBV DNA load of mothers is > 10^3 copies/ml.

Our study does not indicate a relationship between HBV DNA viral load of pregnant women at labor and HBV infected children.

4.4.3 Relationship between delivery methods (vaginal/cesarean delivery) with HBV infection status in their children

In this study, we have not yet shown the relationship between the delivery method (vaginal/cesarean delivery) and the mother-to-child transmission of HBV. This result is similar to the study of Hu et al. That there is no difference in the rate of HBV infection in the two groups of infants whose mothers had active cesarean delivery and vaginal delivery which were 2.5% (7/285) and 2.3% (6/261), respectively, p = 0.944.

In contrast, results of Pan et al. (2013) showed that ECS helped reduce the rate of HBV transmission from mother to child ($p < 0.05$). The conflicting results between the studies show that this issue is still unclear. However, according to a survey of Guo et al. on HBV-infected pregnant women showed that the rate of caesarean section was quite high at 82.3% and 28.5% of these were aimed at preventing mother-to-child transmission of HBV. This suggests that more scientific studies are needed to clarify this issue.

4.4.5 Relationship between breastfeeding and mother-to-child transmission of HBV

4.4.5.1 The presence of HBV markers in breast milk

Until now, this is the first study in Vietnam to investigate the presence of HBV markers in breast milk. Research results show that the rate of HBsAg (+) in colostrum was 20.3% (16/79).

Other studies have shown a higher rate of HBV infection in breastmilk: 71% according to Lee's study and 42.6% according to Yang's study. The reason may be that pregnant women infected with HBV in our study were treated with LAM or TDF right from the 28th week of pregnancy, so the rate of detection of HBsAg in breast milk may be affected by antiviral drugs, while other studies were conducted on women who did not interfere with antiviral treatment.

4.4.5.2 Breastfeeding and the risk of mother-to-child transmission of HBV

Our results also have not shown the relationship between the presence of HBsAg in colostrum and the mother-to-child transmission of HBV. However, this is the first study in Vietnam in this field, the sample size is not large enough, there is no control group to compare, so there is not enough scientific evidence to make suitable recommendations about breastfeeding and the transmission of HBV. While other studies in the world such as Hill, Wang, Zheng, Shi all draw conclusions that breastfeeding does not increase the risk of mother-to-child transmission of HBV. Most recently, according to the AASLD 2018 recommendation, breastfeeding is not contraindicated in HBV-infected mothers. However, in fact, the rate of breastfeeding among HBV-infected mothers was 39.2%, lower than the HBV-uninfected group at 47.6%, $p < 0.001$, according to Leung et al (2012).

CONCLUSIONS

1. Efficacy of LAM and TDF in late pregnancy in interrupting mother to child transmission of HBV

The reduction of HBV DNA levels of tenofovir was significantly higher than lamivudine.

Both tenofovir and lamivudine administered in late pregnancy showed the same efficacy in interrupting mother to child transmission of HBV.

2. Some factors related to the perinatal transmission of HBV

Among studied factors that are likely to relate mother-to-child transmission of HBV (including HBeAg (+) status of pregnant women at labor; HBV DNA viral load of pregnant women at labor $>10^4$ copies/ml; the delivery methods and the presence of HBsAg in colostrum) none was found significantly related to perinatal transmission of hepatitis B virus.

RECOMMENDATIONS

TDF should be the preferred treatment for preventing mother-to-child transmission of HBV for pregnant women with high HBV DNA $>10^6$ copies/ml from the 28th week of pregnancy.

Further researchs are needed to find out factors that increase the risk of mother-to-child transmission of HBV, in which breastfeeding and delivery methods should be considered.

LIST OF SCIENTIFIC PUBLICATIONS RELATED TO THE THESIS

Order	Name of the scientific article	Name of the journal	Publishing year	Pages	Oder of author
1	Đánh giá hiệu quả điều trị phòng lây truyền virus viêm gan B từ mẹ sang con ở các thai phụ có tải lượng virus máu cao bằng thuốc lamivudine và tenofovir tại Bệnh viện phụ sản tỉnh Hải Dương	Tạp chí Y học thực hành số 1047 - 2017	2017	160 - 165	43
2	Đặc điểm thai phụ nhiễm virus VGB mạn tính có tải lượng HBV DNA máu cao tại Hải Dương	Tạp chí Y học thực hành số 11(1063) - 2017	2017	63 - 65	21
3	Kết quả nghiên cứu điều trị dự phòng lây truyền virus viêm gan B từ mẹ sang con	Tạp chí Khoa học và công nghệ Hải Dương Số 2* 4/2017	2017	24 - 26	8
4	Một số yếu tố liên quan đến lây truyền vi rút viêm gan B sang con từ các thai phụ HBsAg mạn tính có tải lượng vi rút máu cao	Tạp chí Y học Việt Nam, tháng 11/2019 - số đặc biệt, tập 484	2019	549 - 555	82