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PHẠM TRẦN DIỆU HIỀN

EPIDEMIOLOGICAL CHARACTERISTICS AND RISK FACTORS OF POSTPARTUM ACTIVE HEPATITIS IN PREGNANT WOMEN WITH CHRONIC HBV INFECTION AT THE HOSPITAL FOR TROPICAL DISEASES

Field: Epidemiology
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SUMMARY OF PhD THESIS

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The thesis will be found at the following libraries:

- Vietnam National Library
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1. Introduction the thesis:

a. Reasons and necessity of the research

Hepatitis B is a global health issue, leading to cirrhosis and liver cancer.

The immune activity of a woman's body changes during pregnancy to prevent fetal rejection, and postpartum immune recovery can lead to **active hepatitis** (**AH**: ALT > 2 ULN, upper limit of normal) or **hepatitis flare** (**HF**: ALT > 5 ULN). Postpartum AH, if not promptly detected, monitored, and appropriately treated, can severely impact maternal health, especially in cases of HF.

The results of global studies are inconsistent. In Vietnam, only one study (2015–2017) monitored mothers with chronic HBV infection up to 2 months postpartum, reporting a hepatitis flare (HF) rate of 12.7% (77/603). Currently, in our country, there is no research have followed postpartum women for a longer period to evaluate the incidence rate and identify risk factors for AH in mothers with chronic HBV infection. The national program has yet to prioritize monitoring the progression of hepatitis in mothers with chronic HBV infection after childbirth. This study aims to elucidate the postpartum course of AH in mothers with chronic HBV infection during the postpartum period, providing clinicians with evidence-based management strategies, contributing to the development of national guidelines, and improving the monitoring and care of maternal health.

b. Research Objectives

1. Describe the epidemiological characteristics and virological markers of pregnant women with chronic HBV

infection at the Hospital for Tropical Diseases, from 2019 to 2022.

2. Determine the incidence rate of postpartum active hepatitis of pregnant women with chronic HBV infection at the Hospital for Tropical Diseases, from 2019 to 2022.

3. Identify risk factors for postpartum active hepatitis of pregnant women with chronic HBV infection at the Hospital for Tropical Diseases, from 2019 to 2022.

c. Participants and research methods

- Design: Retrospective and prospective cohort study.
- Participants: Pregnant women with chronic HBV infection.
- Location and Duration: Hepatology Unit, Hospital for Tropical Diseases, from November 2019 to November 2022.

d. New contributions of the research in terms of theory and in clinical practice

The study on postpartum active hepatitis (AH) in pregnant women with chronic HBV infection is a novel topic in Vietnam. It provides findings on the incidence rates of AH in postpartum women at 3, 6, 9, and 12 months postpartum and identifies risk factors for postpartum AH, including HBeAg positivity, HBV DNA >200,000 IU/mL, and qHBsAg $>10^4$ IU/mL. Additionally, the study offers insights into the epidemiological characteristics and viral markers of pregnant women with chronic HBV infection, as well as the proportion of women requiring TDF (tenofovir disoproxil fumarate) therapy in the third trimester to prevent mother-to-child transmission (MTCT) of HBV and/or treat chronic HBV in the mother.

The findings contribute valuable scientific information,

potentially supporting the inclusion of additional content in national guidelines for monitoring and managing pregnant women with chronic HBV infection during pregnancy and the postpartum period.

e. Thesis structure

The thesis consists of 95 pages (excluding cover pages, table of contents, lists, references, and appendices), comprising: Introduction: 3 pages; Chapter 1: 31 pages; Chapter 2: 14 pages; Chapter 3: 21 pages; Chapter 4: 23 pages; Conclusion: 2 pages; Recommendations: 1 page. The theisis includes 15 tables, 6 figures, 3 diagrams, and 8 charts. References: 120 sources (Vietnamese: 14; English: 106).

2. Literature review

2.1. HBV infection in pregnant women

The prevalence of HBV infection in pregnant women varies by region and generally aligns with HBV prevalence in the general population. In Vietnam, the prevalence ranges from 10-11% across studies.

2.2. HBV transmission

2.2.1. HBV transmission through blood and body fluids

HBV spreads via contaminated needles, tattoos, or contact with infected blood or fluids through non-intact skin or mucosa. Sexual transmission is also significant, particularly among individuals with multiple partners or same-sex partners.

2.2.2. Mother-to-child HBV transmission

MTCT (vertical transmission) is the primary route of HBV spread in high-prevalence regions. Children can also acquire HBV through exposure to blood or bodily fluids after birth (horizontal transmission), especially within the first five years of

life. Up to 90–95% of HBV infections occurring at birth or during early childhood progress to chronic infection.

2.3. Natural progression of chronic HBV during pregnancy

2.3.1. Natural progression of chronic HBV infection in women of reproductive age

Women with chronic HBV infection in reproductive age or during pregnancy may still be in the immune tolerance phase or may have transitioned to the immune clearance phase. During pregnancy, the mother may require antiviral therapy to prevent MTCT of HBV and/or for the specific treatment of chronic hepatitis B (CHB) in the mother.

2.3.2. Immunological changes during pregnancy

Immunological changes during pregnancy partially explain the slight postpartum increase in ALT levels. Cortisol levels in pregnant women peak at the end of pregnancy and during delivery. The abrupt postpartum drop in cortisol levels mimics the effects of corticosteroid withdrawal and can potentially lead to HBV reactivation.

2.3.3. Postpartum active hepatitis and hepatitis flare

In clinical practice, patients with chronic HBV infection and ALT > 2 ULN are diagnosed with active hepatitis (AH), while those with ALT > 5 ULN require monitoring for hepatitis flare (HF). AH and HF are defined based on ALT elevation as follows for research purposes:

- Active hepatitis: ALT > 2 ULN.
- Hepatitis flare: ALT > 5 ULN.

2.4. Risk factors of postpartum active hepatitis in pregnant woman with chronic HBV infection

Risk factors for postpartum AH in pregnant women with chronic HBV infection have been identified in several studies, including age, gravidity, gestational diabetes, HBeAg status, and HBV DNA levels.

2.5. Guidelines for the treatment of chronic hepatitis B in pregnant women and the prevention of mother-to-child transmission of HBV

2.5.1. Treatment of chronic hepatitis B in pregnant women

The indications for treating CHB in pregnant women are similar to those for adults with CHB, with TDF being the preferred choice. Current guidelines do not provide detailed recommendations for managing postpartum AH and HF.

2.5.2. Prevention of mother-to-child transmission of HBV

The 2019 guidelines of the Vietnam's Ministry of Health (VMOH), the World Health Organization (WHO), and global associations recommend prescribing TDF to pregnant women with HBV DNA >200,000 IU/mL (or 10^6 copies/mL) to prevent MTCT of HBV. The VMOH and EASL (European Association for the Study of the Liver) also suggest using qHBsAg levels (>10^4 IU/mL) when HBV DNA testing is unavailable. The WHO and APASL (Asian Pacific Association for the Study of the Liver) 2022 guidelines further propose considering HBeAg positivity as a criterion when HBV DNA testing is not accessible.

2.6. Research on postpartum active hepatitis in pregnant women with chronic HBV infection

2.6.1. Research in the world

Most global studies on postpartum AH in pregnant women with chronic HBV infection are retrospective cohort studies

conducted in the United States and China. Only one prospective cohort study was carried out in North America between 2011 and 2016. Overall, the reported rates of AH and HF vary across studies, depending on the defined ALT threshold for HF (ALT ≥2 times or ≥5 times the ULN). Even with the same ALT threshold, the reported rates of HF differ significantly between studies. Additionally, a 2017 retrospective study in Beijing, China, identified HBeAg positivity and gestational diabetes as risk factors for postpartum AH

2.6.2. Research in Vietnam

Only one retrospective study (2015-2017) reported postpartum flares up to 2 months postpartum, with limited data on longer-term outcomes.

3. Participants and research methods

3.1. Design: Retrospective and prospective cohort study.

3.2. Participants

- Target population: Pregnant women with chronic HBV infection.
- Study population: Pregnant women with chronic HBV infection who were examined and monitored at the Hospital for Tropical Diseases during the study period.

3.3. Location and Duration: Hepatology Unit, Hospital for Tropical Diseases, from November 2019 to November 2022.

- Retrospective: from November 2019 to August 2022
- Prospective: from Septemper 2022 to November 2022

3.4. Sample size

- ***Objective 1***: Describe the epidemiological characteristics and viral markers of all eligible cases recruited during the study period.
- ***Objective 2***: Use the sample size calculation formula to

estimate the incidence rate with relative precision. The required sample size for Objective 2 is **171 patients**.

- ***Objective 3***: Use the formula for cohort studies to estimate the relative risk. The required sample size for Objective 3 is **290 patients**.

Among the pregnant women with chronic HBV infection to be recruited, approximately 10% are anticipated to have ALT levels more than twice the ULN at the time of enrollment. These cases will be excluded when analyzing *the incidence rate* of *postpartum active hepatitis* (AH). Additionally, it is estimated that around 20% of participants will be lost to follow-up. Therefore, the planned sample size for the study is **380 patients**.

3.5. Sampling criteria

- Inclusion criteria:
  - Pregnant women with chronic HBV infection
  - Not on antiviral therapy
  - At 25±2 weeks of gestation
  - Consenting to participate
- Exclusion Criteria:
  - Co-infection with HCV and/or HIV
  - Have a history of psychiatric illness.

3.6. Implementation procedure

Eligible pregnant women were invited to participate in the study. The sampling method used was convenience sampling. After signing the consent form and providing information via a data collection form, blood samples were taken for testing

following the procedures and the 2019 guidelines of the Vietnam's Ministry of Health (VMOH). Pregnant women were scheduled to receive their test results (including HBV DNA levels) within a week (when the gestational age was no greater than 28 weeks). The results were explained by a physician who provided comprehensive counseling.

Pregnant women were scheduled for at least one follow-up visit before delivery, typically around 34 weeks (±2 weeks). Postpartum follow-up lasted 12 months, with four follow-up visits approximately 12 weeks (±4 weeks) apart or more frequently, depending on the patient's condition. For women prescribed prophylactic TDF, discontinuation was considered between 4 to 12 weeks postpartum, as per VMOH's guideline.

3.7. Variables

- Variables related to maternal characteristics: age, residence, education, occupation, gravidity, time since HBV diagnosis, history of antiviral use, family history of HBV infection, HBeAg status, HBV DNA levels, qHBsAg levels, AST, and ALT.
- Outcome variables: Active hepatitis (AH, ALT> 2 ULN) and hepatitis flare (HF, ALT> 5 ULN).

3.8. Data Collection and Analysis

Data entry via EpiData and analysis using Stata 17.

3.9. Ethical Considerations

This is an observational, non-interventional study that adheres to ethical principles in research and has been approved

by the Institutional Ethics Committee of the Hospital for Tropical Diseases (Approval No. 48/HĐĐĐ, dated on December 2nd, 2019).

4. Results

4.1. Epidemiological characteristics and viral markers of chronic HBV infection in pregnant women visiting the Hospital for Tropical Diseases

4.1.1. Socio-demographic characteristics of pregnant women participating in the study

A total of 375 eligible pregnant women were recruited into the study from December 2019 to April 2021. The average age was 29 years (equal to the median), with the youngest being 18 years and the oldest 43 years. Among them, 56.5% (212/375) were under 30 years old.

4.1.2. Epidemiological characteristics and HBV-related history of pregnant women with chronic HBV infection

Multiparous pregnant women accounted for 52%. A total of 19.5% of women were classified as overweight or obese before pregnancy (BMI ≥23). There were 6 cases with a history of fatty liver and 14 cases of gestational diabetes during this pregnancy.

Regarding HBV-related history, 12.5% of pregnant women had previously used antiviral drugs, with a statistically significant higher proportion in the group prescribed TDF during this pregnancy (16.9% compared to 7.2%, p=0.015). Among the 47 women with a history of antiviral use, 83% had taken antivirals to prevent MTCT of HBV. Nearly half of the study participants (46.4%) had a family history of HBV infection (father, mother, or siblings), of which 41 out of 174 (39%) had at least one family member, specifically their mother, infected with HBV (Table 3.2).

4.1.3. Characteristics of HBV markers and transaminases in pregnant women with chronic HBV infection at the assessment of Tenofovir disoproxil fumarate prescription

Most pregnant women in the non-TDF group had qHBsAg $\leq 10^4$ IU/mL (163/167 cases). In the TDF group, 21.6% (45/208) of pregnant women had qHBsAg $\leq 10^4$ IU/mL (Figure 3.1).

Of the 290 pregnant women who underwent abdominal ultrasound to assess liver condition, 13 cases (4.5%) were found to have fatty liver.

Table 3.3. Characteristics of HBV markers and transaminases in pregnant women with chronic HBV infection at the assessment of tenofovir disoproxil fumarate prescription

Variables	Non-TDF (N=167)	TDF (N=208)	Total (N=375)	p*
HBeAg (+)†, n (%)	24 (14.4)	198 (96.1)	222 (59.5)	**<0.001**
HBV DNA (IU/mL)‡, n (%)				**<0.001**
<2000	130 (77.8)	2 (1.0)	132 (35.3)	
2000-200,000	37 (22.2)	2 (1.0)	39 (10.4)	
.>200,000	0 (0)	203 (98.0)	203 (54.3)	

Variables	Non-TDF (N=167)	TDF (N=208)	Total (N=375)	p*
qHBsAg (IU/mL), median (IQR)	922 (216 - 1,923)	25,663 (11,771 - 38,765)	5,097 (923 – 27,541)	**<0.001**
AST (U/L), median (IQR)	19 (16 – 22)	21 (18 – 27)	20 (17 – 25)	**<0.001**
ALT (U/L), median (IQR)	14 (12 – 20)	18 (14 – 27)	16 (13 – 22)	**<0.001**
ALT > 2× ULN, n (%)	2 (1.2)	14 (6.7)	16 (4.3)	**0.008**

*: p-values from Wilcoxon rank sum test for continuous variables; Pearson's Chi-squared test or Fisher's exact test for categorical variables.

†HBeAg: TDF group and total was 206 and 373, respectively.

‡HBV DNA: Non-TDF group, TDF group, and total was 167, 207, and 374, respectively. One pregnant women had HBV DNA >200,000 IU/mL tested by a non-study laboratory, so the HBV DNA results of this case were not included in the analysis.

IQR: interquartile range; ULN: upper limit of normal

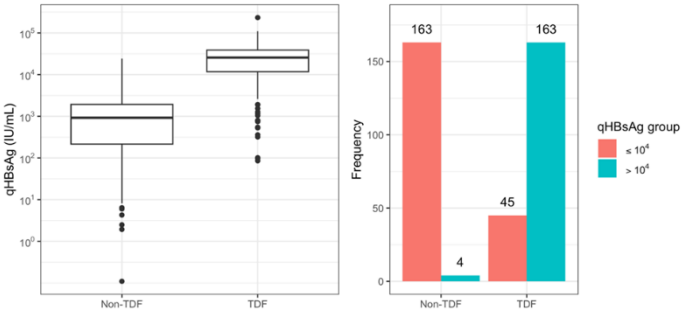

Figure 3.1. Characteristics of qHBAg in pregnant women with chronic HBV infection at the assessment of tenofovir disoproxil fumarate prescription

4.1.4. Correlation between qHBsAg and HBV DNA in pregnant women with chronic HBV infection

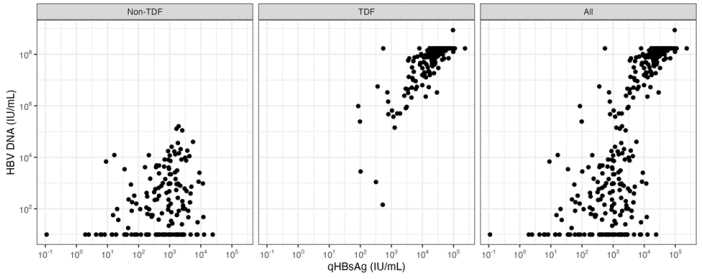

Figure 3.2. Correlation between qHBsAg and HBV DNA in pregnant women with chronic HBV infection

There was a strong correlation between qHBsAg and HBV DNA (r= 0.79, 95% CI = 0.75–0.83). The results also showed a strong correlation in the TDF group (r= 0.81, 95% CI = 0.76–

0.85), but a relatively weak correlation in the non-TDF group (r= 0.24, 95% CI = 0.09–0.38) (Figure 3.2).

4.2. The incidence rate of postpartum active hepatitis

4.2.1. The incidence rate of postpartum active hepatitis by the characteristics of pregnant women with chronic HBV infection

The incidence rate of postpartum AH within 12 months postpartum in women with chronic HBV infection was 2.92 per 100 person-months. There was no difference in the incidence rate of postpartum AH when compared across age groups, parity (multiparous/primiparous), pre-pregnancy BMI, gestational diabetes, or fatty liver. Among the 67 cases of postpartum AH within 12 months, approximately 1/5 (14/67) were hepatitis flares. The incidence rate of postpartum AH was significantly higher in pregnant women with HBV DNA >200,000 IU/mL, qHBsAg $>10^4$ IU/mL, HBeAg positivity, and ALT >1ULN (upper limit of normal) at enrollment compared to the other group.

4.2.2. The cumulative incidence of postpartum active hepatitis

The cumulative incidence of postpartum AH increased over time at 3 months, 6 months, 9 months, and 12 months postpartum. The cumulative incidence rose most rapidly during the 2–3 months postpartum period. The cumulative incidence of postpartum AH was higher in the group of pregnant women with HBeAg positivity, HBV DNA >200,000 IU/mL, and qHBsAg $>10^4$ IU/mL compared to other groups. Additionally, pregnant women with ALT levels above the ULN (>25 U/L or >1×ULN) at enrollment had a higher cumulative incidence of postpartum

AH than those with normal ALT levels (≤25 U/L) (Figures 3.3, 3.4, 3.5, and 3.6).

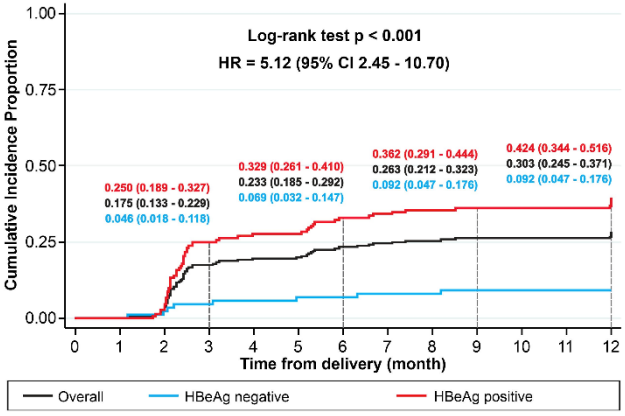

Figure 3.3. The cumulative incidence of postpartum active hepatitis by HBeAg status in pregnancy

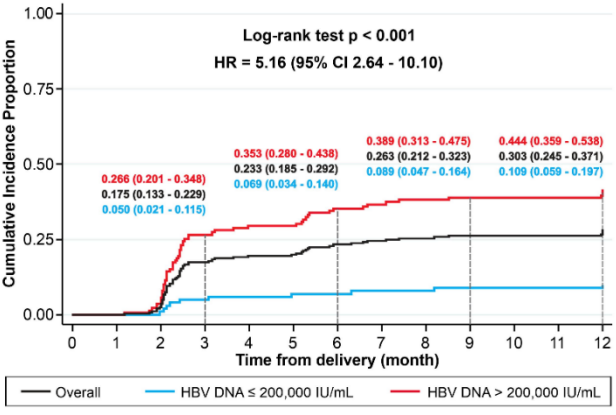

Figure 3.4. The cumulative incidence of postpartum active hepatitis by HBV DNA level in pregnancy

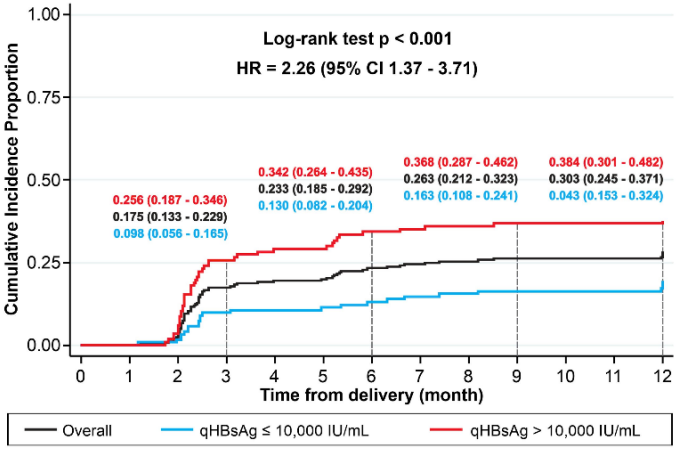

Figure 3.5. The cumulative incidence of postpartum active hepatitis, stratified by qHBsAg level in pregnancy

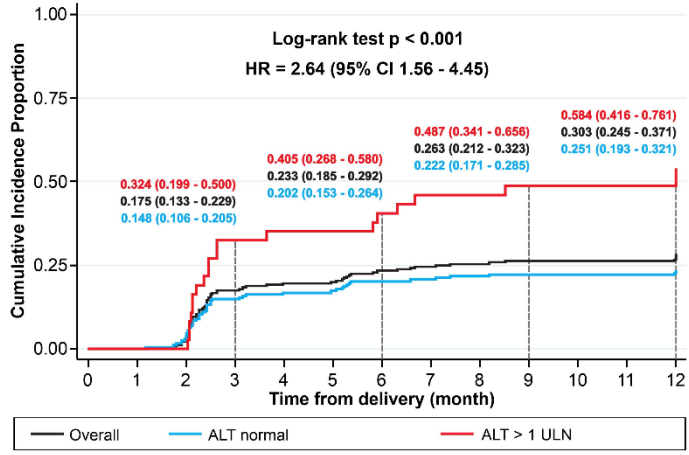

Figure 3.6. The cumulative incidence of postpartum active hepatitis by ALT level in pregnancy

4.3. Risk factors of postpartum active hepatitis

Table 3.10. The association between HBV characteristics of pregnant women and postpartum active hepatitis (N = 240)

Variables	HR (95% CI)	p
TDF prescription in this pregnancy		
No	1	
Yes	4.86 (2.48 – 9.52)	**<0.001**
Ever used antiviral drugs		
No/Unknown	1	
Yes	1.66 (0.85 – 3.26)	0.137
Steatosis (n=178)		
No	1	
Yes	0.49 (0.07 – 3.59)	0.486
HBeAg		
Negative	1	
Positive	5.12 (2.45 – 10.70)	**<0.001**
HBV DNA (IU/mL)		
≤200,000	1	
>200,000	5.16 (2.64 – 10.10)	**<0.001**
Log(qHBsAg) (IU/mL)	1.27 (1.13 – 1.44)	**<0.001**
qHBsAg (IU/mL)		
$\leq 10^4$	1	
$>10^4$	2.26 (1.37 – 3.71)	**0.001**
ALT	1.06 (1.04 – 1.09)	**<0.001**
ALT		
Normal	1	
> 1 ULN	2.64 (1.56 – 4.45)	**<0.001**

ULN: upper limit of normal; HR: Harzard Ratio;
CI: Confident Interval.

Univariate analysis results showed that factors associated with postpartum AH in pregnant women with chronic HBV infection included: HBeAg status, HBV DNA levels, qHBsAg levels, indication for TDF therapy during pregnancy, and ALT levels at enrollment (Table 3.10).

To assess the true impact of the aforementioned factors on postpartum AH, multivariate Cox regression analysis was used to control for potential confounding variables, as identified in the literature or considered significant in clinical practice: age, parity, gestational diabetes, pre-pregnancy BMI, and fatty liver. The results showed that HBeAg positivity, HBV DNA >200,000 IU/mL, and qHBsAg $>10^4$ IU/mL were risk factors for postpartum AH in pregnant women with chronic HBV infection (Figure 3.8).

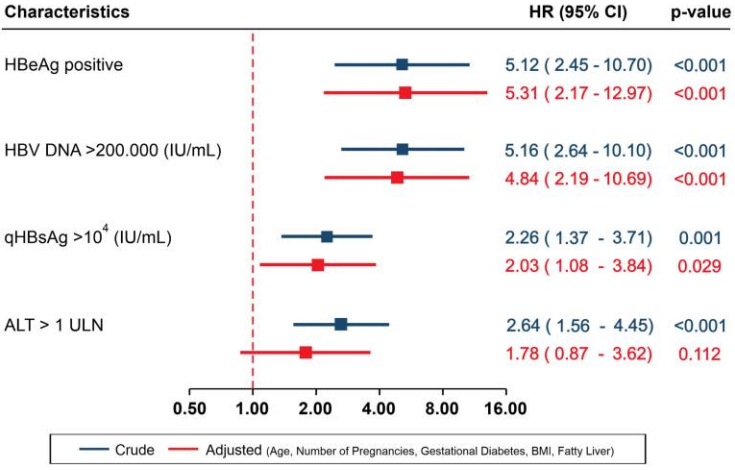

Figure 3.8. Risk factors of postpartum active hepatitis in pregnant women with chronic HBV infection

5. Discussion

5.1. Epidemiological characteristics and viral markers of chronic HBV infection in pregnant women visiting the Hospital for Tropical Diseases

5.1.1. Socio-demographic characteristics of pregnant women participating in the study

Our study results, along with other studies conducted nationally and internationally, indicate that pregnant women with chronic HBV infection have an average age of approximately 30 years, with the majority being under 30. Most of the participants resided in Ho Chi Minh City and had completed high school. Over half of the women had a normal pre-pregnancy BMI, with only a small proportion having fatty liver or gestational diabetes.

5.1.2. Epidemiological characteristics and HBV-related history of pregnant women with chronic HBV infection

The family history of HBV in pregnant women with chronic HBV infection who participated in the study aligns well with the HBV infection patterns in high-endemic regions, where vertical transmission from mother to child is a significant route, leading to outcomes such as hepatocellular carcinoma (HCC) and cirrhosis.

5.1.3. Characteristics of HBV markers and transaminases in pregnant women with chronic HBV infection at the assessment of Tenofovir disoproxil fumarate prescription

The proportion of pregnant women who had a TDF prescription in our study (55.5%) is similar to the findings of

L.T.B. Ngoc in Ho Chi Minh City in 2020, higher than the results reported by N.M. Khue, and lower than those from a study in Australia.These differences may be attributed to variations in study locations. The proportion of pregnant women with HBeAg positivity also differs when compared to other studies, potentially due to differences in study locations and time periods.

In our study, the indication for TDF was primarily based on HBV DNA >200,000 IU/mL (the threshold for prophylactic treatment), with 21.6% (45/208) of pregnant women needing TDF despite having qHBsAg $\leq 10^4$ IU/mL (Figure 3.1). Thus, in cases where pregnant women have qHBsAg $>10^4$ IU/mL, physicians can confidently prescribe TDF for prophylactic treatment to prevent mother-to-child HBV transmission. Conversely, if qHBsAg $\leq 10^4$ IU/mL, physicians should rely on HBV DNA test results to decide whether to prescribe TDF for prophylaxis.

5.1.4. Correlation between qHBsAg and HBV DNA in pregnant women with chronic HBV infection

The correlation between qHBsAg and HBV DNA in pregnant women with chronic HBV infection in our study is similar to that reported by several authors. A strong correlation was clearly demonstrated when analyzing the entire cohort of pregnant women ($r = 0.79$) and in the group indicated for TDF therapy ($r = 0.81$) (Figure 3.2).

5.2. The incidence rate of postpartum active hepatitis

5.2.1. The incidence rate of postpartum active hepatitis by the characteristics of pregnant women with chronic HBV infection

The reported incidence rates of postpartum AH vary widely across studies. Even when using the same ALT elevation thresholds, these rates differ between studies. Variations can be attributed to differences in study locations, study designs (retrospective or prospective), data collection periods, postpartum follow-up durations, and the upper limit of normal (ULN) for ALT applied. Studies in the United States typically use an ALT ULN of 19 or 20 U/L, while studies in China often apply an ALT ULN of 40 U/L.

5.2.2. The cumulative incidence of postpartum active hepatitis

The cumulative incidence increased significantly during the first 6 months postpartum, with the fastest increase observed between 2–3 months postpartum. This pattern is similar to other cohort studies worldwide and is explained by immune system changes during pregnancy, followed by immune recovery postpartum. The cumulative incidence of postpartum AH over time was higher in groups with HBeAg positivity, HBV DNA levels above 200,000 IU/mL, qHBsAg levels over 10^4 IU/mL, and ALT levels above 1 ULN (>25 U/L) at enrollment compared to other groups ($p < 0.001$).

From a pathological perspective, HBeAg positivity reflects active viral replication, often associated with high HBV DNA levels, while qHBsAg correlates strongly with HBV DNA. Thus, the cumulative incidence of postpartum AH tends to increase with higher viral loads during pregnancy. Additionally, elevated ALT levels during pregnancy have been previously reported to be associated with postpartum AH.

5.3. Risk factors of postpartum active hepatitis

5.3.1. HBeAg

Several studies worldwide have identified HBeAg positivity as a risk factor for postpartum active AH, consistent with our findings. The progression of AH or HF, which causes liver cell damage, is considered the result of complex interactions between HBV, hepatocytes, and the patient's immune cells. A significant parallel increase in HBV DNA and HBeAg levels in the serum, along with the accumulation of viral proteins in cells, is observed weeks before the onset of HF.

5.3.2. HBV DNA

Some studies have not found a correlation between HBV DNA levels and postpartum active AH, potentially due to insufficient sample sizes or issues with sampling and postpartum follow-up in retrospective studies. However, many studies have demonstrated that HBV DNA is a risk factor for postpartum AH in pregnant women with chronic HBV infection. Liu (2018), using a study design similar to ours, reported that HBV DNA was the only independent prognostic factor for postpartum AH at 3 months. HBV DNA is considered a risk factor for postpartum

AH, as explained by numerous studies, due to immune system changes in mothers during pregnancy and postpartum, which may be associated with viral reactivation in women with chronic HBV infection.

5.3.3. qHBsAg

We did not find information on qHBsAg in other global studies on postpartum AH in pregnant women with chronic HBV infection, possibly because the research results have not been published.

6. Conclusion and recommendations

6.1. Conclusion

6.1.1. Epidemiological characteristics and viral markers of chronic HBV infection in pregnant women

- The median age of pregnant women participating in the study was 29, with 52% being multiparous.

- 12.5% of pregnant women had a history of antiviral use, primarily for the prevention of MTCT of HBV.

- 39% of pregnant women had mothers infected with HBV.

- 55.5% of pregnant women with chronic HBV infection were indicated TDF to prevent mother-to-child HBV transmission and/or to treat CHB in the mother.

- HBeAg positivity accounted for approximately 60% of the total study sample, with 96% belonging to the group of women indicated for TDF therapy.

- About 1/5 of the women in the group requiring TDF prescription had qHBsAg $\leq 10^4$ IU/mL.

6.1.2. The incidence rate of postpartum active hepatitis in chronic HBV infection in pregnant women

- The incidence rate of postpartum AH within 12 months postpartum in women with chronic HBV infection was 2.92 per 100 person-months, and it was higher in women with HBeAg positivity, HBV DNA >200,000 IU/mL, qHBsAg $>10^4$ IU/mL, and ALT > 1 ULN at enrollment ($p < 0.001$).

- The cumulative incidence of postpartum active hepatitis increased over time at 3 months, 6 months, 9 months, and 12 months postpartum, with the fastest increase occurring during the 2-3 months postpartum period.

- The cumulative incidence of postpartum AH was higher in pregnant women with HBV DNA >200,000 IU/mL, qHBsAg $>10^4$ IU/mL, and HBeAg positivity, as well as in those with elevated ALT levels at enrollment compared to those with normal ALT levels ($p < 0.001$).

- Among the 67 cases of postpartum AH within 12 months, approximately 1/5 (14/67) were hepatitis flares (HF).

6.1.3. Risk factors of postpartum active hepatitis in chronic HBV infection in pregnant women

There are three risk factors for postpartum active hepatitis in pregnant women with chronic HBV infection, which are:

- HBeAg (+), HR= 5.31 (95%CI= 2.17 – 12.97)
- HBV DNA >200.000 IU/mL, HR= 4.84 (95%CI= 2.19 – 10.69)
- qHBsAg $>10^4$ IU/mL, HR= 2.03 (95%CI= 1.08 – 3.84).

6.2. Recommendations

1) It is necessary to have a strategy for screening and assessing HBV infection in pregnant women in order to develop effective treatment and prevention plans for mother-to-child transmission of HBV.

2) Chronic HBV-infected pregnant women should be counseled to undergo regular postpartum follow-up visits every 1–3 months, especially during the first six months after delivery, in order to detect postpartum hepatitis flares and provide timely and appropriate management. This is particularly important for women with risk factors for postpartum hepatitis flares, such as HBeAg positivity, HBV DNA levels >200,000 IU/mL, and qHBsAg levels $>10^4$ IU/mL.

3) Consider including in the national guideline management strategies for postpartum women with chronic HBV infection who have ALT levels greater than 2 times ULN within 1–3 months after delivery.

4) A multidisciplinary collaboration involving obstetrics, infectious diseases and hepatology should be established to optimize the care and management of pregnant women with chronic HBV infection.

LIST OF AUTHOR'S PUBLICATIONS RELATED TO THE THESIS

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