Efficacy of Tenofovir Disoproxil Fumarate in Preventing Vertical Transmission of Hepatitis B in Mothers with Chronic Hepatitis B: An Evidence-Based Case Report

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ABSTRACT

Background*: Hepatitis B virus infection is the most common cause of chronic hepatitis. Vertical transmission is the main transmission route of this virus. Current prevention involves giving newborns immune prophylaxis within 12 hours of birth. However, there is still a failure of immunoprophylaxis, especially in cases of mothers who have a high viral load or are HBeAg positive. Tenofovir disoproxil fumarate (TDF) is the first-line treatment for chronic hepatitis B and is known to reduce perinatal HBV transmission. This study aims to determine the efficacy of TDF in preventing vertical transmission in pregnant women with chronic hepatitis B.* ***Methods****: A literature search was performed on the online databases of PubMed/MEDLINE, Embase, Scopus, Cochrane, and ScienceDirect. The inclusion criteria used were pregnant women with chronic hepatitis B and using TDF antiviral as a transmission prevention therapy with the study design used in the form of a meta-analysis, systematic review, randomized or nonrandomized controlled trial. The outcome of interest was the vertical transmission rate of hepatitis B.* ***Results****: There are two studies used with a meta-analysis study design and a nonrandomized controlled trial with a good critical review result of Validity, Importance, and Applicability. TDF significantly prevented vertical transmission of hepatitis B compared to placebo. In addition, TDF was not associated with the incidence of maternal and fetal complications.* ***Conclusion****: TDF has high effectiveness in preventing vertical transmission of hepatitis B and is safe to give to pregnant women.*

Keywords: *Hepatitis B, Vertical transmission, Tenofovir Disoproxil Fumarate.*

INTRODUCTION

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). Globally, it is estimated that 3.5% of the world's population, equivalent to 257 million people, are chronically infected with hepatitis B. This disease is a major global health problem that can cause chronic infection and put individuals at high risk of death from cirrhosis and liver cancer.[1] In order to achieve the World Health Organization's (WHO) goal of eradicating hepatitis B as a public health issue by 2030, the

most important focus should be on preventing new infections.[2] The primary route of transmission for chronic hepatitis B infection is vertical or perinatal transmission from mother to child.[1,2] A newborn child should receive immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine within 12 hours of birth.[3] This immunoprophylaxis strategy has reduced the perinatal transmission rate from 85% to 5% in infants born to mothers who are positive for hepatitis B e antigen (HBeAg).[4,5] Despite the effectiveness of this strategy, there are still some infants who become infected with HBV from their mothers, especially in cases where the mother has a high viral load or is HBeAg positive.[6]

To prevent vertical transmission of HBV from mother to child, the administration of antiviral drugs such as lamivudine, telbivudine, and TDF has been attempted in pregnant women who are HBeAg positive or have a high viral load.[7,8] Previous systematic reviews and meta-analyses have concluded that lamivudine, telbivudine, and TDF significantly reduce perinatal HBV transmission compared to immunoprophylaxis alone.[9] Currently, TDF is the first-line treatment for chronic hepatitis B, while lamivudine and telbivudine are no longer recommended as preferred HBV therapies due to their low antiviral effectiveness and concerns about drug resistance.[10] A study conducted by Lin et al reported that TDF therapy with immunoprophylaxis significantly reduces perinatal HBV transmission in HBeAg-positive women with an HBV DNA load of ≥ 2×10^6 IU/mL compared to standard management with HBIG and HBV vaccination alone.[7] Another systematic review showed that TDF significantly reduces vertical HBV transmission from HBeAg-positive mothers or those carrying a large amount of HBV DNA without significant side effects.[11] However, some studies have shown the non-significant effectiveness of TDF in preventing perinatal HBV transmission compared to placebo in HBeAg-positive mothers.[12] Therefore, further research is needed to understand the role of TDF in preventing perinatal HBV transmission from high-risk mothers. In this study, the effectiveness of TDF in preventing perinatal HBV transmission in pregnant women with chronic hepatitis B will be further evaluated based on recent studies.

CASE ILLUSTRATION

Ms. NV, a 27-year-old female G1P0A0, came to the internal medicine clinic carrying laboratory results indicating HBsAg (+) during pregnancy screening. The patient did not complain of jaundice, nausea, vomiting, abdominal pain, or distended abdomen. There is no known family history of hepatitis. The patient's husband has not previously undergone diagnostic testing for hepatitis. There is no history of blood transfusion, tattoos, needle use, or illicit drug use. Physical examination reveals no jaundice and hepatomegaly. Based on laboratory tests, HBsAg (+), HBeAg (+), anti HBe (-), HBV DNA 2.3 x 107 IU/mL, SGOT 19, SGPT 28, and platelet count 285,000 were obtained. An ultrasound examination of the liver shows normal results, no masses, and normal structure. The doctor is considering the administration of tenofovir disoproxil fumarate (TDF) to prevent vertical transmission of hepatitis B from the mother to her fetus.

CLINICAL QUESTION

Could the administration of TDF prevent the vertical transmission of chronic hepatitis B in women with chronic hepatitis B?

Table 1. PICO Formulation.

Patient/Problem (P)	Intervention (I)	Comparison (C)	Outcome (O)
Pregnant women with chronic hepatitis B	Administration of Tenofovir Disoproxil Fumarate	Without antiviral drug administration	Perinatal HBV transmission
Type of Clinical Question	Therapy		
Study design	Meta-analysis, Systematic Review, atau Randomized or Non-Randomized Controlled Trial		

METHODS

Search Strategy

Literature search was conducted from January 31 to February 9, 2022. The search was performed on five electronic databases, namely PubMed/MEDLINE, Embase, Scopus, Cochrane, and ScienceDirect. The search was conducted using Medical Subject Headings (MeSH) and the Boolean operator method with the keywords "Pregnant women with chronic hepatitis B," "Tenofovir disoproxil fumarate," and "Perinatal transmission," along with their related synonyms/related terms. The search strategy is summarized in **Table 2.**

Eligibility Criteria

The included studies are those conducted on pregnant women with chronic hepatitis B, using TDF antiviral as a preventive therapy for transmission. The outcome of interest is the transmission of hepatitis B to the child. The study designs include meta-analysis, systematic review, or randomized controlled trials (RCTs). Studies will be excluded if there is a positive serology for Hepatitis C infection, HIV/AIDS, or other comorbidity. In addition, ongoing studies and unavailable full-text manuscripts will also be excluded.

Article Selection

After searching, a total of 2858 studies were found, consisting of 861 articles from PubMed/MEDLINE, 855 articles from Embase, 565 articles from Cochrane, 495 articles from Scopus, and 82 articles from ScienceDierect. After removing duplicates and screening titles, abstracts, and keywords based on PICO, and selecting based on eligibility criteria, 1 meta-analysis studies were obtained for critical appraisal.

RESULTS

Search Result

From the results of the literature search conducted, two articles met the eligibility criteria. Both studies were meta-analyses with specific characteristics for each study, which will be summarized in **Table 3**.

Table 2. Literature Search Strategy.

Database	Search Strategy	Findings
PubMed/MEDLINE	((((((Pregnant women with chronic hepatitis B[MeSH Terms]) AND (Tenofovir disoproxil fumarate[MeSH Terms])) AND (Perinatal transmission[MeSH Terms])) OR (Maternal-Child Transmission[MeSH Terms])) OR (Mother-to-Child Transmission[MeSH Terms])) OR (MTCT[MeSH Terms])) OR (Vertical Transmission[MeSH Terms])	861
Embase®	Pregnant women with chronic hepatitis B AND Tenofovir disoproxil fumarate AND perinatal transmission OR Maternal-Child Transmission OR Mother-to-Child Transmission OR MTCT OR Vertical Transmission	855
Scopus	pregnant AND women AND with AND chronic AND hepatitis AND b AND tenofovir AND disoproxil AND perinatal AND transmission OR maternal-child AND transmission OR mother- to-child AND transmission OR mtct OR vertical AND transmission	495
Cochrane	(Pregnant women with chronic hepatitis B):ti,ab,kw AND (Tenofovir disoproxil fumarate):ti,ab,kw AND (perinatal transmission):ti,ab,kw OR (Maternal-Child Transmission):ti,ab,kw OR ("mother-to-child transmission"):ti,ab,kw (Word variations have been searched)" (Word variations have been searched)	565
ScienceDirect	Pregnant women with chronic hepatitis B AND Tenofovir disoproxil fumarate AND (perinatal transmission OR Maternal-Child Transmission OR Mother-to-Child Transmission OR MTCT OR Vertical Transmission)	82

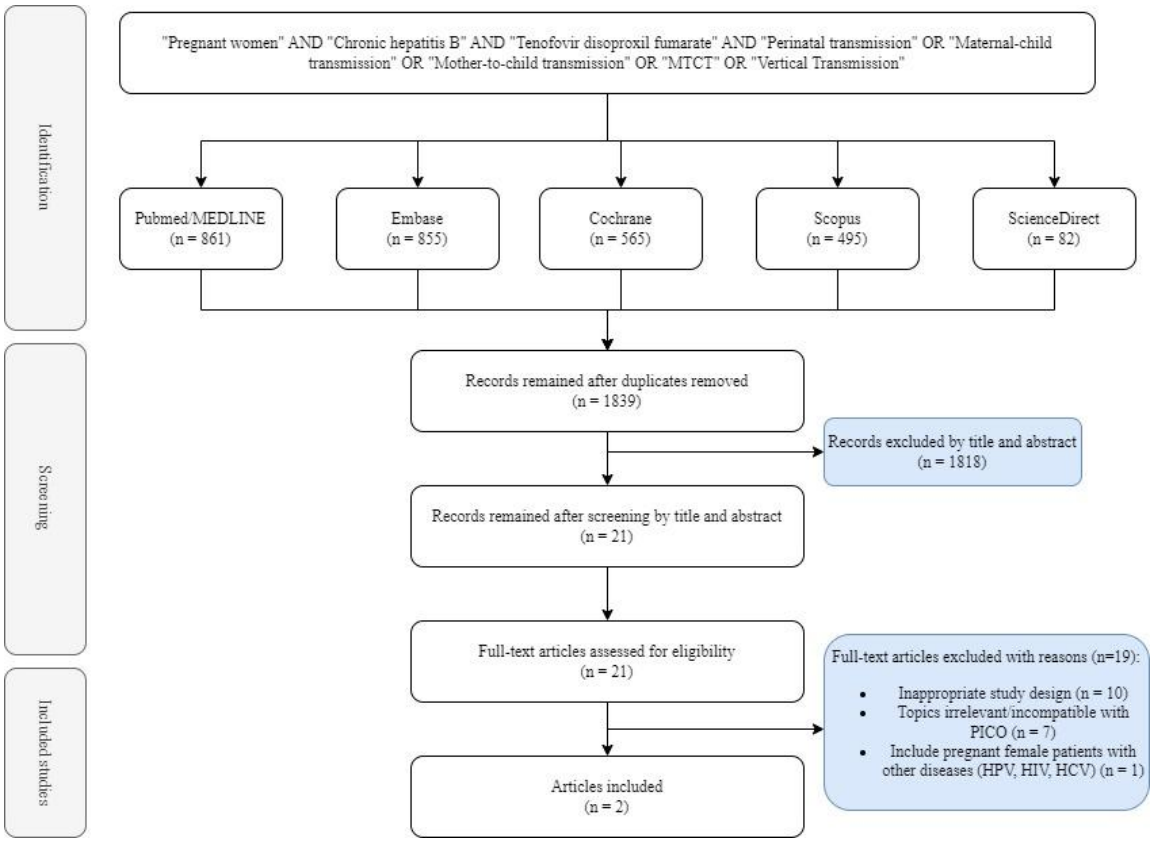

Figure 1. Searching Strategy Flowchart Diagram

Table 3. Study Characteristics

Author (Tahun)	Study Design	Population	Intervention	Comparison	Output
Funk, et al.[13](2020)	*Systematic Review and Meta-Analysis*	771 patient from 19 included studies	TDF	19 studies with placebo	Transmission rate 6 months after birth 0,25% (OR 0.09; 95% CI 0.04–0.20; I^2 = 0%).
Chen, et al[14] (2015)	*Randomized Controlled Trial*	118 patient	TDF	Placebo	At 6 months of age, the infants in the TDF group had lower rates of HBsAg positivity compared with the control group (1/65, 1.54% vs 6/56, 10.71%, respectively; P=0.0481)

Critical Appraisal

Both included studies will be further assessed using the criteria from the Centre of Evidence-Based Medicine, University of Oxford 2011 (CEBM Oxford). The aspects of the literature that will be evaluated are validity, importance, and applicability.

Validity

Table 4. Critical appraisal for Funk et al[13]

	Appraised Aspects	**Studies**
		Funk et al[13]
Validity	***What question (PICO) did the systematic review address?***	**Yes,** In the title, abstract, and introduction of the article, it can be identified that the PICO used in the study aligns with the characteristics described in the study's table.
	Is it unlikely that important, relevant studies were missed?	**Yes,** The literature search was conducted on PubMed, Embase, Scopus, and CENTRAL, without language or publication year restrictions. The literature search was also performed on Mandarin-language online databases (CNKI and Wanfang). The article also includes a PRISMA diagram accompanied by the reasons for article exclusions.
	Were the criteria used to select articles for inclusion appropriate?	**Yes,** The methods section contained inclusion and exclusion criteria, which included elements such as patient characteristics, treatment approach, comparison group, expected results, and research design.
	Were the included studies sufficiently valid for the type of question asked?	**Yes,** The article mentions that the studies identified through PubMed, Embase, Scopus, and CENTRAL were critically appraised by ALF and KY, while those identified through CNKI and Wanfang were critically appraised by YL and TZ. Subsequently, a risk of bias assessment was conducted using the Cochrane Collaboration tool for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale for non-randomized studies.
	Were the results similar from study to study?	**Yes,** According to the results section, the included studies underwent statistical evaluation using the I2 test to measure heterogeneity. The results revealed that there was no significant statistical heterogeneity among the included studies.
Importance	***What were the results?***	A meta-analysis was conducted on all the included studies, and the results of the analysis were presented in the form of a forest plot, as shown in the image below.

Figure 3 Forest plot of the included studies.[13]

	Heterogeneity?	Statistical heterogeneity assessment was performed using the I^2 test on the results of the included studies. No statistically significant heterogeneity was found among the included studies.

Table 5. Critical appraisal for Chen et al[14]

	Appraised Aspects	Studies
		Chen et al[14]
Validity	**Was the assignment of patients to treatments randomised?**	No, this study is an open-labeled non-randomized controlled trials in which the allocation of the subjects is decided by the participant willingness
	Were the groups similar at the start of the trial?	Yes, the overall parameters in the two groups at the start were similar
	Aside from the allocated treatment, were groups treated equally?	Yes, apart from the treatment being studied, all research subjects are treated equally.
	Were all patients who entered the trial accounted for? And were they analysed in the groups to which they were randomised?	Yes, there was only one subject from each group who experienced loss to follow up and each study subject was analyzed in the group that had been determined at the beginning of the study
	Were measures objective or were the patients and clinicians kept “blind” to which treatment was being received?	Unclear, there is no statement stating that neither the research subjects nor the investigators knew about the treatment being given
Importance	**What were the results?**	RR: 0.1436 [0.0178 to 1.1570] RRR: 0.856 [-0.157 to 0.982] ARR: 0.092 [0.004 to 0.2] NNT: 11 [255 to 5]

DISCUSSION

The transmission from mother to child is the main route of chronic hepatitis B infection. Vertical transmission primarily occurs through intrauterine transmission, which refers to any transmission that occurs before the onset of delivery and accounts for 13-44% of HBV transmissions. HBV vaccination and immunoglobulin therapy have been proven to only prevent infection during delivery and the postnatal period.[15] However, these methods do not affect intrauterine infection. The HBV DNA titer in pregnant women is closely related to the rate of vertical transmission and immunoprophylaxis failure. Furthermore, the suppressed immune system during pregnancy also increases the potential risk of HBV proliferation during pregnancy. Therefore, pregnant women with HBV infection, especially those who are HBeAg/HBsAg-positive with a high viral load, should control their viremia with antiviral treatment, such as TDF therapy to reduce the risk of vertical HBV transmission and maintain maternal health during pregnancy.[15,16] However, the effectiveness and safety of antiviral agents during pregnancy remain a concern.[17] In this report, a reevaluation of the efficacy and safety of TDF in preventing perinatal HBV transmission from pregnant women with chronic hepatitis B was conducted. The effectiveness of TDF in preventing perinatal HBV transmission from mother to child was assessed by examining the HbsAg positivity in infants within 6 months after birth.

Based on the conducted search, the administration of TDF can reduce vertical transmission of hepatitis B. The meta-analysis conducted by Funk et al revealed that the rate of HBV transmission in infants born to mothers receiving TDF therapy was lower compared to infants born to mothers without TDF therapy, with a transmission rate of 0.25% (OR= 0.16; 95%CI= 0.09-0.25; I^2=0%).[13] These findings are consistent with the study by Chen et al which revealed that the rate of HBV transmission in infants born to mothers receiving TDF therapy was lower compared to infants born to mothers without TDF therapy, with a transmission rate of 1,54% (RR= 0.1436; 95%CI= 0.0178 to 1.1570).[14] Both studies indicate that administering TDF to pregnant women with chronic hepatitis B effectively prevents mother to child transmission. In addition, there are meta-analysis studies by Zeleke et al also revealed that the rate of HBV infection after 6 months postpartum decreased in infants born to mothers receiving TDF treatment compared to mothers without antiviral therapy, with a transmission rate of 0.7% (RR 0.20; 95% CI 0.06–0.70; I^2 = 0%).[18] Thus, it can be concluded that giving TDF to pregnant women is effective in preventing the risk of vertical transmission of hepatitis B to their fetus.

The safety of TDF administration in preventing vertical transmission of hepatitis B in pregnant women was also considered in both included studies. The study by Funk et al found no statistical significant difference in the risk of serious adverse effects between women receiving TDF therapy and those not receiving TDF such as fetal miscarriage (RD 0.00; 95% CI: -0.01 - 0.01; I^2 = 0%), postpartum bleeding (RD 0.00; 95% CI: -0.02 - 0.02; I^2 = 0%), and postpartum hepatitis flare after discontinuation of TDF (RD -0.02; 95% CI: -0.08 - 0.04; I^2 = 0%).[13] In line with the study conducted by Funk et al, the study by Chen et al also did not find any serious side effects in pregnant mothers who were administered TDF medication to prevent vertical transmission of hepatitis B to their fetuses. Although some TDF side effects were observed, such as five cases with nausea, three with vomiting, and three with itchy skin, no study subjects discontinued the use of TDF due to these side effects. This study also identified TDF side effects in pregnant mothers by measuring the levels of creatine kinase, creatinine, and calcium in the mother's blood both before and after TDF administration.[14] The results showed no significant differences between the control and treatment groups for these three parameters. Both study findings indicate that TDF is not associated with maternal complications in pregnant women. Moreover, the study by Zeleke et al found no statistically significant difference in the risk of serious adverse effects between women receiving TDF therapy and those not receiving TDF (RR 0.91; 95% CI 0.63-1.30; I^2 = 0%). The study showed no significant difference in pregnancy complications between women treated with

TDF and those untreated, such as hypertension (RR 1.95; 95% CI 0.34-11.14; $I^2 = 0\%$), preterm rupture of membranes (RR 0.98; 95% CI 0.30-3.24; $I^2 = 0\%$), breech delivery (RR 1.00; 95% CI 0.10-9.57; $I^2 = 0\%$), and postpartum bleeding (RR 1.21; 95% CI 0.35-4.21; $I^2 = 0\%$).[18]

The safety of TDF for the fetus in mothers consuming TDF was also assessed in both included studies. The study by Funk et al indicated that TDF treatment in pregnant women with chronic hepatitis B was not associated with fetal safety concerns. The investigated outcomes in the study included neonatal death (RD 0.00; 95% CI: -0.01 – 0.01; $I^2 = 0\%$), preterm birth (RD 0.00; 95% CI: -0.02 – 0.02; $I^2 = 0\%$), and congenital abnormalities (RD 0.00; 95% CI: -0.01 – 0.01; $I^2 = 0\%$).[13] In line with the study by Funk et al, the study conducted by Chen et al also evaluated the safety of administering TDF to the fetus. This study utilized parameters including Apgar scores, congenital abnormalities, premature birth rate, serum calcium, creatinine levels, growth rates at 0, 6, and 12 months of age. Among all the safety parameters examined, no significant differences were found between the two research groups. Both studies suggest that the administration of TDF to pregnant women with chronic hepatitis B is not associated with an increased risk of preterm birth, congenital defects, and neonatal death and other TDF side effects.[14] Furthermore, The study by Zeleke et al compared the safety of infants born to mothers who did not receive TDF with those born to mothers who received TDF. The study revealed no statistically significant difference between the two groups, with low heterogeneity in all reported outcomes, including neonatal death (RR 1.34; 95% CI 0.21-8.47; $I^2 = 0\%$), congenital defects (RR 1.91; 95% CI 0.35-10.31; $I^2 = 0\%$), preterm birth (RR 0.66; 95% CI 0.31-1.40; $I^2 = 0\%$), jaundice (RR 1.41; 95% CI 0.80-2.48; $I^2 = 0\%$), and low birth weight (RR 1.96; 95% CI 0.36-10.57; $I^2 = 0\%$).[18] Thus, it can be concluded that giving TDF to pregnant women is safe. It does not interfere with pregnancy and is not associated with abnormalities in the fetus.

CONCLUSION

TDF has high effectiveness in preventing vertical transmission of hepatitis B. TDF administration is not associated with maternal complications such as postpartum bleeding, breech delivery, fetal miscarriage, and preterm rupture of membranes. Furthermore, TDF administration is also not associated with complications for the infant/fetus, such as neonatal death, congenital defects, and premature birth. Therefore, TDF can be used and recommended in pregnant women with chronic hepatitis B infection to prevent vertical transmission to the fetus. It is recommended to conduct large-scale RCT studies to further evaluate the effects of long-term therapy administration in order to obtain more comprehensive results. It is suggested that future studies must ensure subject homogeneity by establishing baseline characteristics so the studies have a valid result.

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