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# The impact of delivery mode on MTCT of hepatitis B virus after Tenofovir disoproxil fumarate implementation in Thailand

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## Abstract

The Hepatitis B virus remains a major public health problem around the world, especially in developing countries. In Asia, the prevalence of the hepatitis B virus is more than 8%. In Thailand, thousands of children under the age of 5 years have HBV infection from mother-to-child transmission. Infants infected with HBV from their mothers are at risk of developing hepatocellular carcinoma and hepatic cancer at 90%. Since 2017, Thai national guidelines have recommended that mothers with high viral loads or hepatitis B e antigen (HBeAg) positivity use tenofovir disoproxil fumarate (TDF) prevent HBV transmission to their babies. However, there are few studies in Thailand on the effect of mode of delivery on mother-to-child transmission in pregnant women receiving TDF. The cross-sectional study in Thai hospitals investigated TDF's effect on mother-to-child Hepatitis B transmission and mode of delivery. This study also collected interview data from hospitals when hepatitis B infants were diagnosed. 342 pregnant women with HBsAg positive were included in this study. There were 342 mothers and infants in the study, and 212 of the infants (61.99%) were born through normal labor, 117 or 34.21 % were delivered via caesarean section, and 13 (3.8%) were delivered with the usage of forceps and a vacuum. However, C/S infants had a mother-to-child transmission rate of 2.56 percent (3/177). Two of their infected infants were delivered to mothers who received TDF for 9 weeks, while the other two were born to mothers whose mothers did not receive TDF. Furthermore, one infant born to a mother who did not receive TDF had a viral load of 17,000,000 IU/ml. All infants were vaccinated with HBV, whereas none of the three infected infants received HBIG. Conversely, we discovered that none of the infants receiving HBIG were infected through mother-to-child transmission.

**Keywords:** HBV, mother-to-child transmission, Tenofovir disoproxil fumarate, mode of delivery

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# Introduction

Hepatitis B virus remains a major public health problem around the world, an estimated 2 billion people, or 30% of the population infected with Hepatitis B virus (Goldstein, Zhou, Hadler, Bell, Mast, Margolis, 2005) In each year, about 600,000 people died from liver cancer, cirrhosis and liver failure related to hepatitis B (Shepard, Simard, Finelli, Fiore, Bell, 2006; World Health Organization, 2009). According to previous research, infants have a 90% chance of becoming chronic carriers after HBV infection, and children under the age of three have a 50% chance (Ma, Alla, Li, Mynbaev, Shi, 2014; Yi, Chen, Huang, Zhou, Fan, 2016). In Thailand the rate of HBV infection among women who pregnant is still at a high rate of 11.19 cases per 100,000 people (Khamduang, Kongyai, Hongjaisee, 2019). Since 2017, Thai national guidelines have recommended that mothers with high viral load or HBeAg positivity use Tenofovir disoproxil fumarate (TDF) to prevent HBV transmission from mother to child. In Thailand, thousands of children under the age of five are infected with HBV by their mothers, resulting in a 0.1 prevalence of HBV infection (Department of Disease Control, 2018). Hepatitis B virus transmission from mother to child is thus a cause of chronic hepatitis. Infants infected with HBV from their mothers have a 90% chance of developing hepatocellular carcinoma and hepatic cancer. In addition, studies on reducing the risk of early mother-to-child transmission of hepatitis B virus revealed that cesarean sections significantly reduce the risk of HBV MTCT (OR = 0.26; 95% CI = 0.07–0.95; P = 0.042) (Peng, Wan, Liu, Li, Du, 2018). However, there are few studies in Thailand on the effect of delivery mode after TDF treatment on mother-to-child transmission.

# Methods

The cross-sectional study in Thailand hospitals aimed to evaluate the effect of TDF on the prevention of mother-to-child Hepatitis B transmission and the mode of delivery in Thailand. However, this study also collected in-depth interview information through questionnaires sent to hospitals when infants with hepatitis B were identified. This study included 342 pregnant women who were diagnosed with Hepatitis B Surface Antigen (HBsAg) positivity between 2018 and 2020. Hepatitis B Surface Antigen (HBsAg) positivity in pregnant women and infants born from Hepatitis B Surface Antigen (HBsAg) positive mothers were the inclusion criteria for this study. Using a case record form, information was collected and recorded from hospitals around Thailand. Nurses and doctors complete all case record forms. The case record form collected information on the mother's general characteristics, details of her hepatitis B infection, TDF treatment and untreated, and mode of delivery; the infant's information included general characteristics, vaccination status, and breastfeeding status. All statistical analysis was carried out using Stata software version 14. The collected information is presented in the form of numbers and percentages together with descriptive data. The study was conducted in accordance with the standards and was approved by the Ministry of Public Health (MOPH) Ethical Committee No.505/2564.

# Results

The most of 342 mothers (50.29%) were between 21 to 30 years old. 84.21% of pregnant women did not have an underlying condition. 65.20 percent of pregnant women had no pre-pregnancy family plans. 61.11% of mothers during pregnancy had ANC visits five or more times, while 52.34 % were diagnosed with HBV During pregnancy, the level

of viral load before TDF was 6.43 percent, and the volume of viral load higher than 200,000 IU/ml was 47.66 %. A total of 168 HBeAg data show that 97 mothers were HBeAg positive, or 57.74%, and had a viral load prior to receiving TDF greater than or equal to 200,000 IU/ml, or 75.86%, with most of them delivering by normal labor, or 61.99%There were 145 mothers with hepatitis B who received TDF, or 42.40 %, and 197 mothers who did not receive the treatment or 57.60 %. TDF adherence was 55.17 % among 145 mothers who received the treatment at 4 weeks.

**Table 1** *General characteristics of Mothers*

| Factor | Number | Percent |
|---|---|---|
| **Age (Years) (Median=30, MAX =44, Min =14), (n=342)** | | |
| ≤ 20 | 10 | 2.92 |
| 21-30 | 172 | 50.29 |
| ≥ 31 | 160 | 46.78 |
| **Underlying disease (n=342)** | | |
| Yes | 54 | 15.79 |
| No | 288 | 84.21 |
| **Family planning (n=342)** | | |
| No | 119 | 34.80 |
| Yes | 223 | 65.20 |
| **ANC visit (n=342)** | | |
| 1- 4 times | 133 | 38.89 |
| ≥5 times | 209 | 61.11 |
| **Diagnose HBV (n=342)** | | |
| Before pregnancy | 163 | 47.66 |
| During pregnancy | 179 | 52.34 |
| **HBeAg** status **(n=168)** | | |
| HBeAg Negative | 71 | 42.26 |
| HBeAg Positive | 97 | 57.74 |
| **Viral load before TDF (IU/ml), (n=29)** | | |
| < 200,000 | 7 | 24.14 |
| ≥ 200,000 | 22 | 75.86 |
| **Mode of delivery (n=342)** | | |
| Normal Labor | 212 | 61.99 |
| Caesarean Section | 117 | 34.21 |
| Forceps delivery and vacuum extraction | 13 | 3.80 |
| **TDF received (n=342)** | | |
| Mothers receive TDF | 145 | 42.40 |
| Mothers not receive TDF | 197 | 57.60 |
| **TDF-taking duration (n=145)** | | |
| < 4 weeks | 65 | 44.83 |
| ≥ 4 weeks | 80 | 55.17 |

According to Table 2, 51.75 percent of infants born to hepatitis B-infected mothers were female. 63.74% of infants were exclusively breastfeeding, whereas 94.44% of

infants received HBIG and 94.44% received both the HBV and HBIG vaccines. And according to HBsAg results, 3 postnatal newborns, or 0.88% of the total 342 infants, were born with mother-to-child transmission of Hepatitis B.

**Table 2** *General characteristics of infants*

| Factor | Number | Percent |
|---|---|---|
| **Gender (n=342)** | | |
| Male | 165 | 48.25 |
| Female | 177 | 51.75 |
| **Exclusive breastfeeding (n=342)** | | |
| Yes | 218 | 63.74 |
| No | 124 | 36.26 |
| **HBV Vaccine (n=342)** | | |
| Yes | 342 | 100 |
| **HBIG (n=342)** | | |
| Yes | 323 | 94.44 |
| No | 19 | 5.56 |
| **HBV and HBIG (n=342)** | | |
| Yes | 323 | 94.44 |
| No | 19 | 5.56 |
| **HBsAg (n=342)** | | |
| Positive | 3 | 0.88 |
| Negative | 339 | 99.12 |

Among the 342 infants, 117 were delivered via Caesarean Section, 212 through normal labor, and 13 with forceps delivery and vacuum extraction. HBsAg-positive infants were 2.56 % of those delivered by Caesarean section, whereas HBsAg-negative infants were 97.44 percent.

In Table 3, 0.8% of infants were infected with hepatitis B from mother-to-child transmission. One infant was not tested for HBeAg, one has been negative for HBeAg, and one was positive. The HBeAg test is positive. One HBeAg-positive case had a maternal viral load of 17,000,000 IU/ml before being treated with TDF. Two out of three mothers do not receive TDF treatment. 9 weeks of TDF were treated to one mother, which is beyond than the 4 weeks recommended by the Thai Ministry of Public Health. Two of the three mothers do not have family planning, and all three people are known case of HBV. The mother who received the TDF treatment during pregnancy was an unknown case of HBV and did not utilize family planning.

In an analysis of 117 infants (2.56%) born through cesarean section, 3 were found to have been infected. Also, 114 infants (97.44) were not affected from mother to child. In accordance with Thailand's policy encouraging HBV-infected mothers to have their infants delivered by cesarean section to reduce the likelihood of mother-to-child transmission, all three HBV-infected infants were delivered by cesarean section. In this study, however, we reported that children born by cesarean section were also infected through mother-to-child transmission.

**Table 3:** *General characteristics of mothers by mode of delivery*

| Factor | Caesarean Section (n=212) | Normal Labor (n=117) | Forceps delivery and vacuum extraction (n=13) |
|---|---|---|---|
| | Number (%) | Number (%) | Number (%) |
| **Age (Years)** | | | |
| < 20 | 0 | 9 (90.00) | 1 (10.00) |
| 21-30 | 49 (28.49) | 119 (69.19) | 4 (2.33) |
| ≥ 31 | 68 (42.50) | 84 (52.50) | 8 (5.00) |
| **Underlying disease** | | | |
| Yes | 20 (37.04) | 32 (59.26) | 2 (3.70) |
| No | 97 (33.68) | 180 (62.50) | 11 (3.82) |
| **Family planning** | | | |
| Yes | 77 (34.53) | 135 (60.54) | 11 (4.93) |
| No | 40 (33.61) | 77 (64.71) | 2 (1.68) |
| **ANC visit (n=342)** | | | |
| 1- 4 times | 77 (34.53) | 135 (60.54) | 11 (4.93) |
| ≥5 times | 40 (33.61) | 77 (64.71) | 2 (1.68) |
| **Diagnose HBV (n=342)** | | | |
| Before pregnancy | 47 (29.19) | 106 (65.84) | 8 (4.97) |
| During pregnancy | 70 (38.67) | 106 (58.56) | 5 (2.76) |
| **HBeAg (n=168)** | | | |
| HBeAg Negative | 25 (35.21) | 40 (56.34) | 6 (8.45) |
| HBeAg Positive | 32 (32.99) | 65 (67.01) | 0 |
| **Viral load before TDF (IU/ml), (n=29)** | | | |
| < 200,000 | 4 (57.14) | 3 (42.86) | 0 |
| ≥ 200,000 | 12 (54.55) | 10 (45.45) | 0 |
| **TDF received** | | | |
| Mothers receive TDF | 52 (35.86) | 93 (64.14) | 0 |
| Mothers not receive TDF | 65 (32.99) | 119 (60.41) | 13 (6.60) |
| **Adherence TDF (n=145)** | | | |
| < 4 weeks | 24 (36.92) | 41 (63.08) | 0 |
| ≥ 4 weeks | 28 (35.00) | 52 (65.00) | 0 |

**Table 4** *General characteristics of infants by mode of delivery*

| Factor | Caesarean Section (n=212) | Normal Labor (n=117) | Forceps delivery and vacuum extraction (n=13) |
|---|---|---|---|
| | Number (%) | Number (%) | Number (%) |
| **Gender** | | | |
| Male | 58 (35.15) | 99 (60.00) | 8 (4.85) |
| Female | 59 (33.33) | 113 (63.84) | 5 (2.82) |
| **Exclusive breastfeeding** | | | |
| Yes | 133 (31.01) | 80 (36.70) | 5 (2.29) |
| No | 79 (63.71) | 37 (29.84) | 8 (6.45) |
| **HBV Vaccine** | | | |
| Yes | 212 (61.99) | 117 (34.21) | 13 (3.80) |
| **HBIG** | | | |
| Yes | 198 (61.30) | 113 (34.98) | 12 (3.72) |
| No | 14 (73.68) | 4 (21.05) | 1 (5.26) |
| **HBV and HBIG** | | | |
| Yes | 198 (61.30) | 113 (34.98) | 12 (3.72) |
| No | 14 (73.68) | 4 (21.05) | 1 (5.26) |
| **HBsAg** | | | |
| Positive | 0 | 3 (100) | 0 |
| Negative | 212 (62.54) | 114 (33.63) | 13 (3.83) |

**Table 5** *Characteristics of mothers of HBV- infected infants (n=3,0.88%)*

| Case | HBeAg | Viral Load (IU/ml) | TDF Treatment | Adherence TDF | Known case of HBV | Family planning |
|---|---|---|---|---|---|---|
| 1 | No Test | - | No | No | No | No |
| 2 | Negative | - | Yes | 9 weeks | No | No |
| 3 | Positive | 17,000,000 | No | No | No | Yes |

**Table 6** *Characteristics of HBV-infected infants and mode of delivery*

| Case | Delivery | HBV (Doses) | HBIG* | Exclusive breastfeeding |
|---|---|---|---|---|
| 1 | C/S | L/F | No | Yes |
| 2 | C/S | 3 | No | Yes |
| 3 | C/S | 3 | No | Yes |

L/F = lost to follow-up, C/S = Cesarean Section

* No cases of mother-to-child transmission from infants receiving both HBV vaccine and HBIG.

## Conclusion and Discussion

From the data collection of 342 mothers with HBsAg positive from 2018 to 2020 in Thailand, the overall mother-to-child transmission rate of hepatitis B was 0.88%. We have All infants infected from mother to child were delivered by cesarean section. We also found that infants who received the HBIG and HBV vaccines at birth were protected. Transmission of infection from mother to child. However, studies have shown that emergency cesarean section delivery could not reduce the chance of hepatitis B being passed from mother to child.

The results were similar to latest research that showed a prevalence of mother-to-child transmission is 0.88. In accordance with previous studies, the study also found that two out of three women whose mothers were not treated for TDF had a mother-to-child transmission. For example, a study of mothers with HBV DNA levels greater than 200,000 IU/ml during the third trimester discovered that TDF-taking mothers had a lower mother-to-child transmission rate than non-TDF-taking mothers (Jourdain et al., 2018). The findings were also consistent with previous research on the rate of hepatitis B transmission from mother to child after TDF treatment. In a Chinese study, mothers with a high viral load had a 0.7 mother-to-child transmission rate of hepatitis B after receiving TDF (Wang et al., 2019). It was related to the study by Calvin Q, who conducted a randomized controlled trial to compare TDF-taking and non-TDF-taking mothers and found that the TDF-taking group had a lower mother-to-child transmission rate than the non-TDF-taking group with statistical significance (Pan et al., 2016). Furthermore, the findings were consistent with a meta-analysis of 1578 articles, which found that taking TDF during pregnancy reduced the risk of hepatitis B infection in infants born to hepatitis B mothers and was effective in preventing hepatitis B infection, particularly in those resistant to lamivudine (Song et al., 2019). Gonzague's RCT study in Thailand with 328 mothers from 28 weeks to two months postpartum observed that the mother-to-child transmission rate of hepatitis B after receiving TDF was 3%, whereas the placebo group had a 6% rate (Jourdain et al., 2018). As a result, there was no statistically significant difference. Finally, a Chinese study on the efficacy of TDF in preventing mother-to-child transmission discovered that TDF-using mothers could effectively reduce mother-to-child transmission (Cui, Woodring, Chan, Xu, 2018).

Receiving HBIG and HBV vaccines was consistent with previous studies, such as one that established that receiving HBIG and HBV vaccines within 1 hour of birth could prevent

mother-to-child transmission of hepatitis B. It was consistent with a Panpan study, which discovered that providing HBIG and HBV vaccines within 12 hours of birth could reduce mother-to-child transmission by 90%. (Yi et al., 2016). This was similar to the study's finding that no infant who received HBIG and HBV vaccines within 12 hours of birth became infected through mother-to-child transmission. A study conducted in the United States of America found that giving HBIG and HBV vaccines to high-risk infants reduced mother-to-child transmission better than receiving the plasma-derived vaccine (Stevens et al., 2017), which agreed with a study by Zhe, who conducted a systematic review study and found that having given HBIG and HBV vaccines to pregnant women who tested positive for HBsAg could prevent mother-to-child transmission of hepatitis B (Chen, Zeng, Liu, Wu, Zhang, 2020). Furthermore, a study comparing HBIG 100 IU and 200 IU doses among hepatitis B mothers discovered that using HBIG 100 IU at birth could prevent mother-to-child transmission of hepatitis B (Wei et al., 2018). In Thailand, however, not all infants born to mothers infected with HBV vaccine receive HBIG. This study highlights the importance of receiving combined HBIG and HBV vaccine to prevent mother-to-child transmission.

We recommend to the mother Antiviral drug treatment was offered at least four weeks before delivery, and cesarean section was elective. The treatment of HBV vaccinations in combination with HBIG is suggested for all infants born to mothers infected with HBV.

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