Is the use of Tenofovir Dipivoxil fumarate effective and safe in preventing vertical transmission in pregnant women with chronic HBV with high viral load?

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Abstract. – OBJECTIVE: In our country, transmission from mother to baby is the most common form of transmission of viral hepatitis B. A high viral load in the mother and HBeAg positivity pose the greatest risk of transmission from mother to baby. The best way to prevent this is to try to eliminate the viral load in the mother by using a strong antiviral such as prenatal TDF in mothers with a high viral load during pregnancy. This study aimed to evaluate the efficacy and safety of TDF in pregnant women with high viral load.

PATIENTS AND METHODS: Seventy patients with hepatitis B e-antigen positive and negative were included in the retrospective study conducted in our clinic. In 35 cases, pregnant women with HBeAg (+) positive chronic HBV and HBV-DNA levels of 107 copies/mL were between 18 and 27 weeks of pregnancy. The pregnant women took 300 mg of TDF per day. There were 35 untreated HBeAg-negative, chronic HBV patients in the control group. Babies born to HBeAg-positive and HBeAg-negative mothers are given an initial dose of 200 IU of hepatitis B immune globulin (HBIG) and 20 g of recombinant hepatitis B vaccine in the first 12 hours after birth, followed by 4, 8, and 24 weeks. HBsAg and HBV-DNA findings were examined in newborn serum 28 weeks after birth.

RESULTS: Postpartum 28 weeks, none of the babies born to HBeAg-positive mothers treated with TDF had HBsAg positivity, while 3.5% of babies born to HBeAg-negative mothers and not treated with TDF had HBsAg positivity and immunoprophylaxis failure. There was no statistically significant difference between the treatment and control groups regarding maternal weight, height, gestational age, or congenital malformations (p<0.05). There was no significant difference between the side effects seen in mothers. In the examination performed at the 28th week postpartum, a statistically significant decrease in HBV-DNA levels was observed in mothers who received TDF treatment compared to those who did not (88.5%) (p<0.05). In 31 of the 35 patients receiving TDF treatment, ALT was reported to be normalized in 25 of the 35 patients who did not receive TDF treatment (p<0.05).

CONCLUSIONS: It has been observed that the use of TDF, which has a strong efficacy and high barrier, in the second and/or third trimester of pregnancy reduces transmission rates without causing side effects in both the mother and the newborn, thereby preventing vertical transmission of viral hepatitis B from the mother to child.

Key Words: Telbivudine, HBeAg, Lamivudine (LAM), Telbivudine (TBV), Newborn, Pregnancy.

Introduction

There were 1.34 million hepatitis deaths and 10 million new cases in 2015. Hepatitis B affected 257 million people globally in 2016. Prenatal care includes testing for hepatitis B. The most prevalent long-term form of hepatitis is HBV, which can spread years before symptoms show up. Chronic HBV results in cancer, cirrhosis, and liver failure. Hepatitis B surface antigen positivity was present in 257 million people in 2015, and cirrhosis and hepatocellular cancer resulted in 887,000 fatalities. Populations infected in the Eastern Mediterranean, Southeast Asia, and Europe are 3.3%, 2.0%, and 1.6%, respectively. 0.7% of Americans have an infection. After all newborns were immunized in Turkey, the 13-15% rate before the 2000s dropped to 3%.

Whether HBEAG is present (positive or negative) and the actions taken to prevent it determine the likelihood of viral hepatitis B transmission from mother to child [vaccination, Hepatitis B Immune Globulin (HBIG) or TDF]. According to a meta-analysis, ba-
abies born to mothers who are HBsAg(+)/HBeAg(-) have a transmission rate of 11.0% (7.0-15.0%), while those born to mothers who are HBsAg(+)/HBeAg(+) have a transmission rate of 84.0% (79%, 0-90). According to reports, there is no perinatal transmission rate2-7. After receiving all vaccinations (delivery dose plus three follow-up vaccinations), the likelihood of perinatal transmission was 3.8% (3.1-4.5%) for HBsAg+/HBeAg-women and 18% (10-26%) for HBsAg+/HBeAg+ mothers8. Pregnant women should be given a potent antiviral medication for a virus that spreads quickly and causes illness and death. For viral hepatitis B, antiviral therapy (TDF, viral load 200,000 IU/mL) is preferred. In addition to TDF, newborns born to mothers who have viral hepatitis B should also receive the hepatitis B vaccine and hepatitis B immunoglobulin. It is unlikely that the virus will be passed from mother to child if the viral load of HBV-DNA in the mother is less than 200,000 IU/mL. If a mother has HBV and tests positive for the hepatitis B “e” antigen (HBeAg), the likelihood that her newborn baby will contract the disease without hepatitis B immunoglobulin is 90% (HBIG). Vaccination against HBV was performed within a day from birth9,10.

Immunity during pregnancy may raise the risk of reported HBV exacerbations in pregnant women by 6-14% and in the postpartum period by 10-50%, depending on the research population. Because of this, mothers who receive antiviral therapy in the third trimester may need to have their ALT levels checked in the first six months following delivery or the first six months following the conclusion of antiviral therapy11. Due to the high maternal viral load, immunoprophylaxis with HBIG and HBV vaccines after childbirth fails to prevent VT. Pregnant women’s intrauterine HBV DNA levels and perinatal HBV transmission are related12.

The mainstays of treatment for HBV are vaccination and viral suppression because there is currently no known cure for the disease. 25% of infants whose mothers have HBV DNA levels above 200,000 IU/mL are exposed to HBV despite passive and active vaccination13-14. As a result, most recommendations encourage antiviral medications during the third trimester of pregnancy, as they appear safe and effective at preventing disease transmission from mother to child10,15. 5.3 log10 IU/mL (200,000 IU/mL) of HBV DNA is the viral load threshold during pregnancy to prevent transmission of HBV from mother to fetus if the pregnant woman’s HBV test is positive. He advises using prophylactic tenofovir (TDF) at least from the first week until delivery15. In addition to receiving three doses of the hepatitis B vaccine, including the timely delivery dose, infants born to mothers receiving TDF should also receive hepatitis B hyperimmunoglobulin (HBIG) in October16.

Two additional antivirals that are thought to be safe and effective during pregnancy are lamivudine (LAM) and telbivudine (TBV). LAM slows the decline in HBV DNA levels and has a lower resistance barrier than TDF16. TBV is effective at preventing the vertical transmission of the virus from mother to child, but safety data in nursing mothers appear to be insufficient. TBV is also linked to higher levels of creatinine kinase17. TDF is the preferred medication for treating HBV during pregnancy due to its excellent safety profile, high resistance barrier, and efficacy18-21. For six to twelve weeks following delivery, if treatment was started because of a high viral load during pregnancy, it should be continued to prevent postpartum HBV exacerbations and potential disease progression and cirrhosis18.

Patients and Methods

This retrospective study was carried out in a sizable hospital in Eastern Anatolia, a region with a high prevalence of hepatitis B. Marching between March 2017 and March 2022, 70 individuals who had been prenatally tested for chronic viral hepatitis B were included. Thirty-five patients were given 30 mg of TDF orally once daily for viral hepatitis B (Viread; Gilead cases, CA, USA). Treatment is administered between weeks 18 and 27 of pregnancy. It began in the weeks leading up to and following Dec. 12's delivery. It persisted until the following week. Thirty-five pregnant women with active hepatitis B infection who tested negative for HBeAg and did not receive TDF treatment made up the control group. The criteria for study inclusion were: pregnancy1, serum HBsAg and HBeAg positivity for at least six months2, HBV DNA levels before the start of TDF 7 log10 copies/mL3, previously treated patients4, and anemia, arrhythmia, proteinuria, or patients without gestational diabetes5. Seventy patients matched the study’s requirements6. The study included 70 patients who fit these requirements.

None of our cases had abnormal ultrasonographic findings or HIV coinfection. Pregnant women’s primary demographic and virological characteristics were tallied. In all of the cases included in the study, routine blood tests (CBC, biochemistry), urine tests, and pregnancy-related beta-HCG tests were carried out and reported. All
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pregnant women had their liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase], viral parameters (HBsAg, HBeAg, anti-HBe, HBV DNA), and creatinine levels checked at 12-week intervals in December. All mothers who participated in the study and their infants underwent regular evaluations. Infant Apgar score, anthropometric measurements, phenylketonuria, hypothyroidism, birth history, congenital anomalies, birth mode, and histories of immunoprophylaxis were reviewed and recorded in these cases at birth, just like with other infants in our clinic.

The HBV-DNA of pregnant women was examined using the Roche COBAS TaqMan HBV test (Roche Molecular Diagnostics, Branchburg, NJ, USA), which had an LLD of 50 copies/ml. In 2000, an architect (Abbott Labs, North Chicago, IL, USA) detected HBV serological markers using enzyme-linked immunosorbent assay kits with a fully automated chemiluminescence immune analyzer.

The hearing screening was evaluated using the Echo Screen (Madsen, Germering, Germany). Following breastfeeding and 72 hours after birth, blood was drawn from the heel of each infant to check for congenital phenylketonuria and hypothyroidism. After drying, the samples were taken to a lab for evaluation.

Hepatitis B immune globulin (HBIG, Hyper-HEP B solvent/detergent; Talecris Biotherapeutic, NC, USA) and 20 g of recombinant HBV vaccine (Recombivax HB; Merck Sharp and Dohme, NJ, USA) were administered following national and international treatment recommendations for all infants. HBV vaccine administered at birth, 4, 8 and 24 weeks HB vaccine (4, 8, and 24 weeks). For weeks, HBsAg and HBV DNA levels in the blood were monitored. An HBsAg test was conducted to check for a vertical transition in a newborn’s peripheral blood between 4 and 28 weeks.

After presenting the study to the board, the Malatya Turgut Ozal University non-interventional ethics committee approved it. The ethics committee acknowledged the study’s compliance with the guidelines outlined in the most recent version of the Helsinki Declaration.

**Statistical Analysis**

Stata software version 10 was used to conduct statistical analysis for this study (Computer Resource Center, Chicago, IL, USA). Analysis of variance was used to compare the measurements, which were presented as mean±standard deviation (SD). \( p<0.05 \) was considered statistically significant.

**Results**

**Characteristics of Pregnant Mothers**

All pregnant women in the study, both in the TDF-treated group and the control group, had HBV DNA levels of more than 10^7 copies per milliliter (IU/mL). The mean age of mothers was 27.2 ± 3.2 years. All pregnant women had creatinine levels in their blood that were within normal ranges. Two pregnant women with compensated cirrhosis were in each group, whether they were taking drugs or not (Table I).

**Mother results**

All 35 patients who started drug therapy got their medicine during the study and for up to 12 weeks after the study ended. Two patients with compensated cirrhosis in each group did not stop getting TDF treatment and kept getting it. The women in the treatment and control groups gave birth to healthy babies. Two mothers in each study group had gestational diabetes mellitus, which is 5.7% of the mothers in the study group. Two pregnant women with proteinuria, two with anemia, and one with arrhythmia in the TDF treatment group got better independently, without any symptoms. Two pregnant women in the treatment group who had gestational diabetes mellitus had vaginitis, which is 5.7% of the women in the treatment group.

**Table I. Maternal properties of the control group and TDF-treated group.**

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>Treated group (HBeAg +) (n=35)</th>
<th>Control group (HBeAg -) (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>27.6 ± 2.8</td>
<td>27.4 ± 3.1</td>
</tr>
<tr>
<td>HBV DNA (IU/mL)</td>
<td>8.23 log</td>
<td>8.31 log</td>
</tr>
<tr>
<td>ALT levels (U/L)</td>
<td>53 (19-77)</td>
<td>55 (22-71)</td>
</tr>
<tr>
<td>Serum creatinine levels</td>
<td>0.76 (0.6-1.0)</td>
<td>0.74 (0.6-0.96)</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>2 (5.7%)</td>
<td>2 (5.7%)</td>
</tr>
</tbody>
</table>
group. After four weeks of treatment with TDF, muscle pain and creatine kinase (CK) were found to be high in two patients. After seven weeks, they were at their highest level (370 mg/dL). This patient’s muscle function tests were normal, so it was thought that he or she had a CK elevation without any symptoms. In two cases (5.7%) treated with TDF, ALT levels went up (280 U/L and 320 U/L) at 6 and 8 weeks, but they went back to normal at 10 and 12 weeks. TDF-treated mothers exhibited significantly higher rates of HBV DNA 50 IU/mL (250 copies/mL) and ALT normalization than controls at 28 weeks postpartum (71.5% vs. 0%, p=0.001%; 82 vs. 61%, p=0.05). There was no distinction between the groups’ side effects (Table II).

In both the TDF-treated and untreated groups, three infants (11.4%) were born with a weight lower than 2,500 grams. Neither the treated nor the control newborns showed signs of congenital hearing loss, hypothyroidism, or phenylketonuria. No infants with immunoprophylaxis deficiency were found in the TDF group, whereas three babies in the control group tested positive for HBsAg (8.5%). Immunoprophylaxis failed in some cases, and the difference was statistically significant (p<0.05). All babies born to women who received TDF had anti-HBs levels higher than 100 ml IU/mL. Five infants in the control group had Anti-HBsAg levels of less than 100 ml IU/mL. Height, weight, congenital abnormalities, and gestational age exhibited no statistically significant differences between the groups that were being experimented on and those serving as controls (p>0.05) (Table III).

### Discussion

Pregnant women who are treated with antiviral drugs may be able to lower the risk of HBV being passed on to their unborn children. Antiviral drugs targeting HBV, such as TDF, during

### Table II. TDF-treated and control group maternal outcomes (%).

<table>
<thead>
<tr>
<th>Maternal outcomes</th>
<th>Treated group (n=35)</th>
<th>Control group (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA &lt; 50 IU/mL</td>
<td>71.4 (35)</td>
<td>0</td>
</tr>
<tr>
<td>Normalized ALT (U/L)</td>
<td>30 (85.7)</td>
<td>25 (71.4)</td>
</tr>
<tr>
<td>Elevated creatinine kinase (&gt; 165 mg/dL)</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>2 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>0 (0)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table III. Results of newborn to TDF-treated moms and to control mothers.

<table>
<thead>
<tr>
<th>Infant characteristics and outcomes</th>
<th>Infants of treated group mothers (n = 35)</th>
<th>Infants of control group mothers (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight &lt; 2,500 g</td>
<td>3 (8.5)</td>
<td>3 (8.5)</td>
</tr>
<tr>
<td>Congenital hearing loss</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anti-hepatitis B surface levels &gt; 100 mIU/mL</td>
<td>35 (100)</td>
<td>30 (85.7%)</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Immunoprophylaxis failure</td>
<td>0 (0)</td>
<td>3 (8.5%)</td>
</tr>
</tbody>
</table>
pregnancy can reduce the chance of vertical mother-to-child transmission by lowering HBV DNA to an undetectable level at delivery. This may be preferable to using HBIG alone at a single birth\(^9,\)\(^{20}\). Although TDF administration during the third trimester decreases HBV DNA by an impressive amount\(^8,\)\(^{21}-\)\(^{24}\), it is still required in HBIG and vaccination to avoid vertical transmission from mother to child. Nonetheless, between 24 and 27 weeks of pregnancy, TDF may be more effective at suppressing fetal growth if started early in pregnancy, in the first trimester or even earlier\(^{23,\)\(^{25}\).

Antivirals in combination with immunoprophylaxis are more effective than active or passive immunoprophylaxis alone in preventing vertical mother-to-infant transmission in trials of participants with HBV mono-infection\(^{26}\). When given to the mother in the third trimester, active and passive immunoprophylaxis, along with TDF, is cost-effective in high-income nations. There is a correlation between the amount of HBV DNA present at the beginning of treatment and how many months of TDF treatment are necessary to prevent perinatal transmission. It was predicted that TDF treatment would need to be continued for at least three months before it might interrupt vertical transmission.

A review\(^{29,\)\(^{30}\) of the research on TDF during pregnancy reveals that its first application was to stop the spread of HIV from moms with either HIV or HIV and hepatitis B virus (HBV). Numerous academic works\(^{29,\)\(^{30}\) have been written about this. This research shows a major reduction in the risk of HBV being passed from mother to child during pregnancy. When immunoprophylaxis is used with TDF treatment, a higher protection rate is provided compared to prior trials, and vertical transmission is effectively stopped\(^{21,\)\(^{23}\).

Given its strong resistance barrier, favorable safety profile, and efficacy, TDF is the preferred drug of choice for the treatment of HBV in pregnancy\(^{21,\)\(^{22}\). Postpartum HBV exacerbations, disease progression, and cirrhosis can be avoided if treatment, begun during pregnancy due to a high viral load, is maintained for 6-12 weeks after birth\(^{27,\)\(^{28}\). In our country, Ceylan et al\(^{31}\) reported that in their study comparing Tenofovir and Entecavir, those using Tenofovir achieved a better virological response than those using Entecavir.

Treatment with TDF throughout the third trimester resulted in a crucial decrease in blood HBV-DNA at birth vs. baseline, and all infants were HBsAg negative 28-36 weeks postnatal in research by Pan et al\(^8\).

Vertical transmission from mother to child was also effectively prevented in a multicenter study by Celen et al\(^{12}\) in Southeastern Anatolia, the region of our country with the highest prevalence of viral hepatitis B. This was achieved by administering HBIG + vaccine prophylaxis in addition to TDF in HBsAg-positive and HBeAg-positive pregnant women with high viral load. Reportedly, there were no severe adverse effects or congenital deformities from TDF treatment. To test whether TDF is excreted in breast milk, Ertürk et al\(^{13}\) examined 11 cases in our country in 2021. They found that TDF goes into breast milk in minimal amounts and has no effect on the infant due to its poor bioavailability rates.

Our clinic study included pregnant women 18-27 weeks along in their pregnancies who tested positive for HBeAg and had a high viral load. Starting TDF treatment between weeks of gestation and delivery, we planned to provide care for at least three months. Both the treatment group and the control group received a primary dose of 200 IU hepatitis B immune globulin (HBIG) and 20 gr recombinant HBV vaccine within the first 12 hours after birth, with subsequent doses given at four weeks, eight weeks, and 24 weeks of age, respectively, as recommended in the literature. At 28 weeks postnatal, no prophylactic failure was seen in any patients in the therapy group; HBsAg was negative in all 35 instances, and Anti-HBs levels were >100 IU/mL, as was seen in the literature. In the control group, five people had anti-HBs levels below 100 IU/mL. Again, whereas most instances in the TDF treatment group achieved HBV-DNA reduction, HBV-DNA negativity was not detected in the control group, and there was no statistically significant \((p<0.05)\).

There are now 5 indicated oral antiviral medicines for treating hepatitis B virus infection. There is no safe way to utilize any of these while pregnant. Lamivudine (LAM) and telbivudine (TBV) are two more antivirals that are safe and effective in pregnant women, apart from TDF. Lamivudine is less effective than TDF at lowering HBV DNA levels and has a lower resistance threshold\(^{14}\). Effective in preventing vertical transmission from mother to newborn, TBV may be linked to elevated creatine kinase levels and appears to have inadequate safety data in lactating women\(^5\). Other antivirals deemed safe and effective during pregnancy are LAM and TBV. LAM reduces HBV DNA levels slower than TDF and has a lower resistance barrier\(^4\). Although TBV is
effective in preventing vertical transmission from mother to newborn, it appears to have inadequate safety data in lactating moms and may be linked to elevated creatine kinase levels34.

Lamivudine therapy in late pregnancy can prevent perinatal HBV transmission in mothers with a high viral load, according to a randomized, double-blind, placebo-controlled study conducted by Xu et al14. This study demonstrated a significant reduction in the prevalence of HBsAg seropositivity (10/56, 18% vs. 23/59, 39%, \( p=0.014 \)) and detectable HBV DNA (11/11/12) in newborns receiving lamivudine + vaccination + HBIG. In infants who received placebo + vaccination + HBIG (n = 56, 27/59 - n = 20, 46%, \( p=0.003 \)), there was a significant decrease in HBIG antibody titers. After vaccination, the results of this study demonstrated that the drug lamivudine prevents vertical transmission of HBV from mothers with a high viral load to their infants14.

Similarly, Han et al35 started with the first treatment. They found that HBV DNA levels, which were 12, had significantly decreased by the end of the week. It was observed that the HBV-DNA level decreased in the following week. An open-label, prospective study was conducted to assess the effectiveness and security of TBV use in late pregnancy. In this study, the incidence of perinatal transmission was lower in infants of TBV-treated mothers at birth and seven months after birth compared to the control group, and HBV-DNA levels were undetectable in 33% of TBV-treated mothers while they were detectable in the placebo group. (0% vs. 8%); (\( p=0.002 \)). It is critical to consider both the advantages and disadvantages of antiviral medication use during pregnancy. Its use during pregnancy makes it possible for both immediate and delayed reactions. These include bringing about birth defects, impairing the baby’s long-term bone development, causing ALT levels to decline at the end of treatment, and enabling the emergence of HBV-resistant mutations. According to studies36-39 TDF can affect kidney function in people with HIV and people who already have kidney disease. In chronic HBV patients who kept their initial kidney function, three years of TDF administration did not result in nephrotoxicity.

The prevalence of birth defects at the earliest exposure, which started in the first trimester, was 3.1% for lamivudine and 2.4% for TDF, according to analyses of the Antiretroviral Pregnancy Registry (APR). Lamivudine and TDF both had a birth defect prevalence of 2.7% and 2.0%, respectively, at the time of the earliest exposure, which occurred in the second or third trimester40.

According to Shi et al41, pregnancy complications did not increase. According to Han et al35, neither women nor infants receiving telbivudine treatment have experienced any significant side effects. TDF lowers bone mineral density in children with HIV41,42. Developmental disorders or abnormal bone metabolism have not been observed in long-term safety studies in newborns exposed to TDF42,43.

The use of TDF in the second or third trimester of pregnancy completely stopped the rate of perinatal vertical transmission, according to this controlled study carried out in our clinic using TDF in pregnant women with HBeAg positive and high viral load. A week later, we discovered that it had no adverse effects on mothers or infants. This topic requires more investigation with more instances.

**Conclusions**

It has been observed that the use of TDF, which has a strong efficacy and high barrier, in the second and/or third trimester of pregnancy reduces transmission rates without causing side effects in both the mother and the newborn, thereby preventing vertical transmission of viral hepatitis B from the mother to child.

**Ethics Approval**

The study was started after obtaining the consent of Malatya Turgut Özel University Faculty of Medicine Interventional Clinical Research Ethics committee (Date: 26/05/2022, No.: 2022/100). All procedures followed the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and its later amendments.

**Funding**

The authors received no financial support for the research.

**Conflict of Interests**

There are no conflicts of interest. The authors have approved the final version of the article, including the authorship list, and do not have any relevant declarations.

**Informed Consent**

Since it is a retrospective study, verbal and written consent was obtained from the patients.
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Authors’ Contributions
HA; Study concept and design, supervision, materials, data collection and/or processing, writing, analysis and/or interpretation. MA; Statistical expertise, critical manuscript revision for important intellectual content. MA; analysis and interpretation of the data, administrative. MA, HA; technical or material support, study supervision.

Acknowledgments
We would like to thank our teachers, colleagues, nurses, allied health workers and all our employees working in hospital services and laboratories, with whom we have worked together throughout our work.

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