

Tenofovir in the management of chronic hepatitis B infection during pregnancy

Abstract

Chronic hepatitis B infection has a worldwide distribution, with approximately 350 million infected persons. While become more of an issue during pregnancy concerning maternal and fetal well-being and the influence of pregnancy itself on the course of the disease; natural history of chronic hepatitis B infection during pregnancy has not been clearly established. This paper reports the outcome of pregnancy in a patient with chronic hepatitis B infection who discontinued double antiviral treatment since she wanted to get pregnant but then administered tenofovir disoproxil fumarate (TDF; 245mg/day) monotherapy at the 32nd gestational week.

Özet

Kronik Hepatit B enfeksiyonu dünyada 350 milyon kişiyi etkilemiş yaygın bir enfeksiyondur. Gebelikte anne ve bebek sağlığı ve gebelik süreci için önemli bir sorun olan kronik Hepatit B enfeksiyonunun gebelikteki doğal seyri henüz açıkça tesbit edilememiştir. Bu yazı, Hepatit B enfeksiyonu için ikili antiviral tedavi almakta iken, gebelik planlamasıyla antiviral tedaviyi kesen bir hastanın, gebeliğin 32. haftasında tekrar tenofovir disoproxil fumarate (TDF; 245 mg/gün) tedavisine başlanması ile gebeliğin seyrini bildirmektedir.

Keywords:

tenofovir,Hepatitis B, Pregnancy

tenofovir,Hepatit B, gebelik

20 **Introduction**

21 Affecting 350 to 400 million individuals worldwide, Hepatitis B virus (HBV) remains a global
22 health problem despite proper vaccination (1,2) because acquirement of the infection resides
23 either perinatal or in early childhood exposure in half of the infected population in countries with
24 high rates of HBeAg-positive infections in women of child-bearing age (3).

25 Pregnancy is known as an immunological counterbalance between maternal tolerance of paternal
26 and fetal MHC antigens and that of maintaining immune-competence for defense against
27 microbes and other antigens (4). Hepatitis B infection during pregnancy has been associated with
28 special terms and conditions such as maternal and fetal effects of hepatitis B, effects of
29 pregnancy itself on the course of hepatitis B infection, treatment of hepatitis B during pregnancy
30 and prevention of perinatal infection (5). That's why; the question arises about what to do if a
31 young woman on therapy becomes pregnant or plans to become pregnant (6).

32 To be familiar with the natural history of chronic HBV infection in the peri-partum period has
33 been considered essential as the detection and management of abnormal liver function in the
34 pregnant female is an uphill struggle (4). Nevertheless much has been documented about peri-
35 natal mother to newborn transmission of HBV and the possible modes of prevention but data
36 concerning the effect of chronic maternal infection on pregnancy outcome as well as the effect of
37 pregnancy on maternal HBV disease in the chronically infected mothers are limited and
38 controversial (3,4,7). From this point of view, this paper presents the outcome of pregnancy in a
39 patient with chronic hepatitis B infection who was administered tenofovir disoproxil fumarate
40 (TDF; 245 mg/day) monotherapy at the 32nd gestational week due to risks related to high viral
41 load.

42

43 **Case report**

44 A 28-year-old woman was identified with HBsAg positivity, HBeAg positivity, HBV DNA level
45 of > 640 000 000 copies/mL (Roche-Combas-Taqman), minimally high levels of ALT 51 IU/L
46 (5-45 IU/L) and Delta Ab negativity at her initial diagnosis of hepatitis during family screen for
47 the disease which was primarily detected in his father. She had been on follow up in our clinic
48 since July 2005. Pre-treatment liver biopsy revealed Hepatic Activity Index (HAI) of 12 and the
49 diagnosis of fibrosis 3 (Ishiac score) chronic hepatitis B with HBeAg positivity and HBV DNA >
50 640 000 000. Pegylated interferon 2a (180 µg/week; s.c.) was initiated on July 11 2006. There
51 was no decline in HBV DNA titers despite normalization of ALT- AST levels after 2 months.
52 Treatment was discontinued after 20 weeks due to determination of HBV DNA 640 000 000
53 copies/mL and HBeAg (+) as well as significant side effects of interferon including depression,
54 severe headache, weight loss, hair loss and skin lesions at the injection site. Lamivudin (100
55 mg/day; oral) treatment was initiated. Later on adefovir (10 mg/day; oral) was added to the
56 treatment due to failure to expected decrease in the viral load with antiviral monotherapy. Normal
57 ALT levels, HBV DNA titers of 10 000 copies/mL and ongoing HBeAg positivity were evident
58 on the last evaluation despite ongoing combined treatment with lamivudin and adefovir. The
59 patient admitted to our department at this stage as a married woman for 4 years planning for a
60 pregnancy.

61 Risk of rapid progression to cirrhosis during drug-free periods due to lack of complete
62 suppression of the viral load and the high hepatic activity together with fibrosis in the past course
63 of the disease necessitated rigorous pregnancy planning in terms of well being of both baby and
64 the mother. Pregnancy under ongoing antiviral treatment was not approved by the patient as well
65 as the physician due to high risk associated with adefovir therapy. Therefore, pregnancy was

66 planned with deferral of antiviral drugs.
67 Antiviral drugs were discontinued. Patient became pregnant after four months during which HBV
68 DNA was measured to be >640 000 000 copies/mL. Increase in ALT during drug-free period was
69 gradual as recorded to be 63 IU/L (5-45 IU/L) in the first month and 126 IU/L (5-45 IU/L) in the
70 last month of the pregnancy. Mutation analysis for drug resistance was performed due to
71 established increase in HBV DNA titers. After DNA isolation 80, 173, 180, 181, 204, 236
72 numbered codons of HBV polymerase gene was screened by multiplex PCR method during
73 mutation analysis. Additionally, mutation analysis was also performed for RT gene (amino acids
74 from 131 to 210) and S gene (amino acids from 119 to 201). No mutation was observed
75 indicating absence of drug resistance. Tenofovir disoproxil fumarate (TDF; 245 mg/day; oral)
76 was initiated at the 32nd week of pregnancy. Preterm delivery occurred at 37th gestational week
77 due to severe urinary infection related to kidney stone. Hepatitis B Immunoglobulin and vaccine
78 were administered to the newborn baby who is still healthy without any problems. ALT levels
79 were normalized at the second month of TDF treatment after high levels ranged high between
80 100 IU/L and 130 IU/L (5-45 IU/L) for the initial months. HBV DNA titer measured to be >640
81 000 000 copies/mL at the beginning of the tenofovir treatment was determined to regress to <300
82 copies/mL at the 4th month of the treatment. The patient is still on TDF (245 mg/day)
83 monotherapy without any sign of decompensation of her liver disease with ALT levels of
84 normal range. Immunization schedule was completed in the baby who has high titer Anti-HbsAb
85 positivity.

86 **Discussion**

87 Owing to several challenges of hepatitis B treatment in pregnancy including contraindications
88 related to interferon use and lack of detailed evaluations concerning use of nucleoside analogs

89 with activity against HBV in pregnant women, patients on antiviral therapy for hepatitis B are
90 recommended to practice birth control (6). What is more, tenofovir and telbivudine are
91 considered “Category B”, indicating that they have been found to be safe in animal models and
92 there is limited data in humans, whereas lamivudine, adefovir, and entecavir are considered
93 “Category C”, indicating that their safety has not been shown adequately either in animal models
94 or humans (6).

95 In this regard, it is well-advised to defer therapy until after delivery in order to avoid fetal
96 exposure to the therapeutic agents unless maternal liver disease requires treatment, or a
97 pregnancy occurs in a woman already receiving a medication for HBV (5). Thus, antiviral
98 therapy during pregnancy was documented to be an option for women with high viral loads as
99 long as comprehensive discussion of risks and benefits has been considered since limited data are
100 evident while use of lamivudine, tenofovir, or telbivudine starting early in 3rd trimester of
101 pregnancy becomes the common strategy for therapy (8).

102 Based on safety data in pregnancy which are most robust with lamivudine and tenofovir
103 compared with other therapies (8), use of tenofovir in pregnancy was documented to be
104 associated with a risk not higher than other antiretroviral drugs or the general population in the
105 first trimester of pregnancy (9). As a matter of fact, selection of TDF (245 mg/day) for the
106 management of high viremia persist to late pregnancy in our patient seems reasonable based on
107 published reports signifying potent inhibitory activity of TDF against the wild-type and drug-
108 resistant mutants in the treatment of hepatitis (10,11) as well as consideration of the drug in
109 “Category B” indicating safety in animal models despite limited data in humans (6). In fact,
110 among agents classified as FDA pregnancy risk category B, only tenofovir received this

111 classification based on data collected in human exposure (8). The clinical trial with tenofovir in
112 pregnant women consisting 879 women in their first trimester and 501 in the second and third
113 trimester revealed the rate of birth defects associated with tenofovir to 2.2%, which is similar to
114 the background rate (9). Furthermore continuation of TDF treatment after delivery is also in line
115 with the recommendations concerning use of antiviral therapy after delivery with respect to
116 indications expressed in available HBV guidelines (5).

117 Accordingly, despite gradual and slow rise in ALT levels observed in our patient during the
118 course of pregnancy, persistently high levels of viral load necessitated the implementation of
119 antiviral therapy at the 32nd gestational week in correlation with the past history of the disease
120 lacking complete suppression of the viral load as long as 4 year-follow up.

121 Several local and systemic non-specific suppressor mechanisms operating during pregnancy to
122 down-regulate maternal immune responses (12) for fetal protection were also documented to
123 affect the evolution of chronic HBV infection (13). Hence, it has been stated that a relatively
124 immune-compromised state in the second and third trimesters of pregnancy associated with high
125 levels of adrenal corticosteroids may facilitate viral replication leading to the increase in viral
126 load (5). Therefore while considered to do well during pregnancy in general, women with chronic
127 hepatitis B infection may also suffer from high viremia which was documented to reach a peak in
128 the third trimester of pregnancy (13) reducing maternal immune-competence and thus disturbing
129 the orchestration of an immune-clearance of HBV (4).

130 Since maternal HBeAg positivity, HBsAg titer and HBV DNA level are considered among the
131 risk factors for transplacental transmission of HBV (14), our administration of HBIG and HBV
132 vaccine which is a regimen considered to be effective in preventing transmission of hepatitis B in

133 more than 95% of children, seems to be in line with current recommendations for prevention of
134 maternal-infant transmission of hepatitis B (6, 15).

135 Albeit 80% of preterm births have been considered to be spontaneous resulting from maternal
136 infection or inflammation, uteroplacental ischemia or hemorrhage, uterine over-distension, and
137 immunologically mediated processes (16), the effects of chronic HBV infection on pregnancy
138 outcomes have not been clearly defined and the data are controversial.

139 In this context, while lack of any significant differences was reported in terms of gestational age
140 at delivery, birth weight, incidence of prematurity, neonatal jaundice, congenital anomalies and
141 perinatal mortality in HBsAg-positive women when compared to controls (17), retrospective
142 evaluation of chronic maternal HBV infection on pregnancy outcome revealed that a chronic
143 HBV infection in the pregnant woman may contribute to premature birth because of low grade
144 inflammation due to the release of pro-inflammatory cytokines (7,17). Whilst still subject to
145 further investigation, pregnancy outcome in our case supports the suggested association of
146 pregnancy of a mother with chronic HBV infection with preterm delivery (5,17).

147 Actually, decreased possibility of materno-fetal transmission as well as low probability of birth
148 defects was the key factors effective in convincing mother to use TDF during pregnancy.

149 Nevertheless she questioned the possible role of TDF treatment in premature birth of her baby
150 which in fact occurred due to severe urinary infection related to kidney stone.

151 In conclusion, the findings of our case report suggest that deferral of antiviral therapy until
152 delivery during pregnancy in chronic hepatitis B infection lacking complete suppression of viral
153 load is likely to be associated with a gradual serum ALT elevation and an abrupt and persistent
154 increase in viral load reaching a peak in the third trimester necessitating implementation of

155 antiviral treatment. Hence, TDF monotherapy (245 mg/day) seems to be safe and effective in
156 achievement of a pronounced reduction in persistently high maternal viral load to < 300
157 copies/mL which is much better than before the pregnancy and the normalization of hepatic
158 enzymes even after a treatment-free period lasting almost for a year. When considered from fetal
159 point of view, contribution to the prevention of materno-fetal transmission during pregnancy
160 seems another success of TDF monotherapy. While large scale, prospective studies are necessary
161 to clarify the interplay of pregnancy and chronic hepatitis B, the role of closer follow-up on
162 chronic HBV-infected, pregnant females seems non-ignorable for the effective management of
163 the disease to avoid potentially serious maternal morbidity and mortality.

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