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Monitoring and treatment results of 88 HBsAg-positive pregnant women

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Summary

Approximately 5% of all women in the world are HBsAg-positive. Chronic hepatitis B is a problem in women of reproductive age. This paper assessed 88 HBsAg-positive pregnant women, of whom 11 began treatment during pregnancy and five became pregnant while receiving treatment. The files of HBsAg-positive pregnant women were reviewed between January 2010 and December 2013 retrospectively. From these 88 pregnant women, 72 did not receive any treatment during their pregnancy, 11 began treatment during their pregnancy, and five became pregnant while receiving treatment. Nine of these 11 pregnant women were given tenofovir disoproxil fumarate and two of them lamivudine. Ten babies of the 11 mothers that began treatment during their pregnancy were healthy, but one was lost due to preterm birth. Of the five patients who became pregnant while receiving treatment, the treatments of four women were discontinued and they were monitored during their pregnancies because mild-moderate (less than stage 3) fibrosis was found in their liver biopsy results. It is important to screen all pregnant women for hepatitis B and to assess those found HBsAg-positive. It is possible to protect both the mother and baby using appropriate approaches.

Key words: Chronic hepatitis B; Pregnancy; Treatment.

Introduction

Hepatitis B virus (HBV) infection causes more than one million cirrhosis- and hepatocellular-carcinoma-related deaths every year. This infection is a problem in women of reproductive age [1, 2]. HBsAg-positive mothers transmit the virus to their infants primarily during the perinatal period. Receiving the virus in the neonatal period results in chronicity in many cases because the infant's immune system is still immature [3-5]. In this period, the HBV DNA level and HBeAg-positivity are important for an infectious effect [4]. The risk of infection and resulting chronic hepatitis B (CHB) in the infants of HBeAg-positive mothers in developing countries are 90% [6]. On the other hand, the risk of contamination in the infant of an HBeAg-negative mother with HBV is 10–40%, and the risk of the development of CHB due to this contamination is 40–70% [4-6].

It is beyond dispute that routine vaccination of neonates against HBV can reduce the prevalence of HBV infections and HBV-related CHB, cirrhosis, and hepatocellular carcinoma [3]. The administration of hepatitis B immunoglobulin (HBIG) and hepatitis B vaccines to infants born to HBsAg-positive mothers within the first 12 hours is more than 90% protective against the occurrence of HBV infections ([7, 8]. Subsequently, it is important that all pregnant women are screened for HBV infection and those who are HBsAg-positive are assessed for treatment.

Treatment to the pregnant woman is intended to prevent the progression of liver damage, decrease the risk of hepatic exacerbation after delivery, reduce the risk of intrauterine contamination, and reduce HBV-related mortality. Therefore, hepatitis B treatment in pregnant women is an issue that should be assessed individually [3, 9]. Large-scale studies evaluating the care of pregnant women with CHB, beginning and discontinuation of their treatment indications, drug side effects, and prevention of transmission to their babies will be helpful when planning government policies.

In this study, 88 HBsAg positive pregnant women were assessed; 11 of them began treatment during their pregnancy and five of them became pregnant when receiving treatment. The authors would to stress that it is possible to protect HbsAg positive pregnant women and their babies and how important it is to closely monitor such pregnant women through appropriate care and treatment approaches.

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Materials and Methods

Study population

The files of HBsAg-positive pregnant women who presented to the Infectious Diseases and Clinical Microbiology Outpatient Clinics of Adiyaman University Faculty of Medicine, Afyon Zubeyde Hanim Maternity Hospital, Konya Numune Hospital, Selcuk University Faculty of Medicine and between January 2010 and December 2013 were reviewed retrospectively.

The following information was recorded from each patient's file: demographic data; gestational age; whether antiviral treatment was received before pregnancy and, if so, the duration of the treatment; whether antiviral treatment was started during pregnancy, the date it was started, and the antiviral used; HBV DNA levels before and during pregnancy; detailed hepatitis markers (HBsAg, HBeAg, antiHBe, antiHBcIgG, antiHCV, antiHDV, and antiHIV); and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values. The inclusion criteria comprised the following: age ≥ 18; absence of comorbid diseases; attended regular follow-ups from six to eight weeks of pregnancy; screened for syphilis, toxoplasmosis, herpes, rubella, and cytomegalovirus infections in early pregnancy; and absence of HCV, HDV, or HIV co-infections. The pregnant women included in the study were assessed in three groups: 1) those who were monitored without treatment, 2) those who began treatment during pregnancy, and 3) those who became pregnant during treatment. The postnatal files of the infants who received treatment during pregnancy were reviewed. The prophylaxis and vaccination programs administered to these infants were examined.

Ethics

This work was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. Approval was obtained from the ethical committee of Selcuk University (2014/174). Written informed consent was obtained prior to the treatment from each participant.

Statistical analysis

The data were collected retrospectively for this descriptive study. Descriptive statistics, such as mean ± standard deviations and percentage distributions were used to evaluate the data.

Results

The mean age of the 88 pregnant women who were included in the study was 26.2 ± 5.5 (17–39) years. Of the 88 women, 72 (81.8%) did not receive treatment during pregnancy. Treatment was started during pregnancy for 11 (12.5%) women, and five (5.7%) became pregnant while receiving treatment. Of the 72 women who did not receive treatment during pregnancy, 55 were inactive carriers (ALT normal, HBV DNA < 10^4 copy/ml), and 17 were patients whose HBV DNA values were 10^4–10^6 copy/ml and ALT values were not more than twice the normal. Of the 11 patients who began treatment during pregnancy, four were at the immunotolerant phase (ALT normal, HBV DNA values > 10^6 copy/ml), and seven had HBV DNA values > 10^6 copy/ml and ALT more than twice the normal. The data of the 11 patients who started treatment are presented in Table 1. The monitoring of the pregnant women who began treatment showed that there was a noticeable decrease in the viral load and a drop in liver function tests. Of the five patients who became pregnant while receiving treatment (two lamivudine [LAM], two tenofovir disoproxil fumarate [TDF], and one entecavir [ETV]), the treatments of four women were discontinued and they were monitored during their pregnancies because mild-moderate (less than stage 3) fibrosis was found in their liver biopsy results. The data of the five patients who became pregnant at the onset of treatment are given in Table 2. Since the pre-treatment liver biopsy result of the pregnant woman who received ETV treatment was stage 4 and her histological activity index (HAI) was 13, her treatment was shifted to TDF, and she was advised to continue the treatment throughout her pregnancy. However, the woman opted to discontinue the treatment and was monitored by way of monthly follow-ups. The monitoring data of the pregnant women who became

Table 1. — *Values of patients who received treatment during pregnancy at the onset of treatment.*

Patient number	Age	HBeAg	ALT	HBV DNA (u/L)	Medication (copy/ml)	Week of used starting treatment during pregnancy
1	37	Positive	141	>1.1×10^9	TDF	29
2	21	Positive	241	2.5×10^{10}	TDF	28
3	32	Positive	84	>1.1×10^9	TDF	30
4	28	Positive	21	>1.1×10^9	TDF	30
5	26	Negative	18	1.1×10^8	TDF	31
6	26	Positive	932	6.4×10^8	TDF	16
7	32	Positive	264	>1.1×10^9	TDF	29
8	24	Positive	24	>1.1×10^9	TDF	29
9	21	Positive	198	>1.1×10^9	TDF	28
10	26	Positive	31	4.4×10^8	LAM	28
11	23	Negative	89	2.5×10^8	LAM	29

ALT: alanine aminotransferase, TNF: tenofovir disoproxil fumarate, LAM: lamivudine, ALT: 0-55 u/L (normal range).

Table 2. — *Data of patients who became pregnant while receiving treatment at the beginning of pregnancy.*

Patient number	Age	Antiviral drug used	Duration of using antiviral drug (months)	Liver biopsy	HBV DNA (copy/ml)	ALT (u/L)	HBeAg
1	34	ETV	14	Stage:4 HAI:13	Negative	23	Negative
2	23	LAM	34	Stage:2 HAI:5	Negative	18	Negative
3	29	LAM	22	Stage:1 HAI:7	Negative	21	Negative
4	27	TDF	18	Stage:2 HAI:6	Negative	16	Positive
5	31	TDF	26	Stage:2 HAI:7	Negative	24	Positive

TNF: tenofovir disoproxil fumarate, LAM: lamivudine, ETV: entecavir, HAI: histological activity index.

Table 3. — *Follow-up values of patients who became pregnant while receiving treatment throughout their pregnancies.*

Age (years)	Before pregnancy		Month 1		Month 3		Month 6		Before delivery	
	HBV DNA (copy/ml)	ALT (u/L)	HBV DNA (copy/ml)	ALT (u/L)	HBV DNA (copy/ml)	ALT (u/L)	HBV DNA (copy/ml)	ALT (u/L)	HBV DNA (copy/ml)	ALT (u/L)
34	Negative	23	531	24	4.8×10^3	29	1.3×10^4	44	3.7×10^5	69
23	Negative	18	Negative	19	Negative	21	Negative	24	Negative	29
29	Negative	21	Negative	34	Negative	42	687	46	1.3×10^3	51
27	Negative	16	Negative	26	879	29	2548	37	6.6×10^3	41
31	Negative	24	Negative	23	Negative	31	4980	54	2.6×10^5	61

Table 4. — *Data of the infants of the mothers who were started treatment during pregnancy.*

Baby number	Congenital anomaly	Birth weight (g)	Week of birth	AntiHBs value at month 12 (IU/ml)
1	None	3,150	38	> 10
2	None	3,800	40	> 10
3	None	3,240	39	> 10
4	None	3,550	37	> 10
5	None	2,950	37	> 10
6	None	3,600	39	> 10
7	None	3,100	38	> 10
8	None	2,870	38	> 10
9	None	3,300	39	> 10
10	None	3,450	38	> 10
11	Ex	1,350	22	-

pregnant while receiving treatment throughout their pregnancies are given in Table 3.

Of the 11 patients who received treatment during pregnancy, seven underwent liver biopsies after delivery, fibrosis stage 3 was found in two patients, and fibrosis stage 2 was found in five patients. These women's treatments were continued, provided they agreed to forego breastfeeding. The other four patients who received treatment during pregnancy were in the immunotolerant phase. Because they were given treatment to prevent intrauterine transmission, these women's treatments were discontinued after delivery.

Of the 17 patients with HBV DNA values of 10^4–10^6 copy/ml and ALT values not more than twice the normal, 12 continued their follow-ups after delivery. Treatments were started after liver biopsies were done for eight of these patients. The biopsies were indicated according to the American Association for the Study of Liver Diseases (AASLD) criteria following the breastfeeding period. The other four patients were monitored, as liver biopsies were not indicated for them according to the AASLD criteria.

Of the infants of the 11 mothers who received treatment during pregnancy, ten were healthy and one was lost due to preterm birth. The data of these babies are presented in Table 4. Each baby was administered 200 IU of HBIG after birth and 20 μg of hepatitis B vaccine at zero, one, and six months. The physical examinations of the ten babies who returned for follow-up did not show pathology. The babies' anti-HBs values were ≥ 10 IU/ml.

Of the 72 HBsAg-positive patients, one miscarried at week 8 and one baby had Down syndrome. Of the 88 pregnant women, 29 had normal deliveries and 59 had cesarean sections.

Discussion

Approximately 5% of all women in the world are HBsAg-positive; the percentage is as low as 0.6% in regions with low endemism and is as high as 20% in regions with high endemism [10]. Although the risk of intrauterine transmission is low because the fetus is protected by the placenta, intrauterine transmission has been reported in the infants of mothers with high HBV DNA and/or HBeAg-positivity [5].

The decision whether to begin treatment in the HBsAg-positive pregnant woman is complex and requires consideration of both the woman's and the fetus' health. The decision should be supported by a combined assessment of many factors, such as the viral load, week of pregnancy, status of liver damage, and HBeAg-positivity. Studies have reported that when HBV DNA > 10^8 copy/ml, the probability of intrauterine transmission increases to 43% [11]. This rate drops to 30% when HBV DNA < 10^6 copy/ml, and decreases considerably when HBV DNA < 10^4 copy/ml [11, 12]. For this reason, the recommended general approach is to treat pregnant women whose HBV DNA values are > 10^6 copy/ml (HBeAg positive or negative) [9, 13-15]. The literature review showed that treatment was commenced for pregnant women usually when their HBV DNA values were > 10^6 copy/ml [11, 16]. The authors also found that treatment was commenced for all of the 11 pregnant women whose HBV DNA > 10^8 copy/ml (HBeAg positive or negative) in the present study. The other pregnant women were placed under follow-up throughout their pregnancies.

Antiviral drugs are effective against HBV contamination from mother to infant in pregnant women with heavy viral loads [5, 13, 16]. Of the agents to treat chronic hepatitis B in pregnant women, LAM and ETV are rated C, and TDF and telbivudine (LdT) are rated B by the FDA for safety during pregnancy. LAM, an antiviral drug with a low genetic barrier, has been used most frequently for the treatment of pregnant women with CHB [5, 17]. TDF is a safe

drug considering its high genetic barrier and low resistance; thus, its use in pregnant women has increased in recent years. LdT has a low genetic barrier, although it prevents contamination to the infant fairly well. There are limited data on the use of ETV in pregnant women [16, 18].

Many studies have been carried out on the use of these drugs. Yi *et al.* [19] reported that LAM therapy was safe and effective in pregnant women. Liu *et al.* [20], You *et al.* [21], and Han *et al.* [10] preferred LdT therapy. Celen *et al.* [22] preferred TDF therapy. The authors found in the present study that nine pregnant women received TDF and two received LAM therapy.

The treatment initiation time is an important factor among pregnant patients. Studies have shown that the antiviral therapy should begin in the third trimester (weeks 28–32 of pregnancy) [8, 12-14] . However, the results have not been much different from those of the general population in the studies investigating the risk of birth defects from LAM or TDF (2.9% and 2.4%, respectively) [10, 12, 19]. The present authors found that the initiation of treatment for pregnant women was in line with the literature; however, treatment was commenced for one woman in week 16 because her previous child was HBsAg-positive. No major anomalies were found in the babies of these patients.

There is no standard guideline for managing HBsAg-positive women who become pregnant while receiving treatment. The decision to continue the treatment must be made dependent on factors such as previous liver biopsy results, viral loads, liver function tests, and HBeAg-positivity. Treatment continuation is recommended throughout pregnancy in the presence of serious fibrosis [23, 24]. If the pregnant woman is under control for CHB (HBV DNA negative, ALT normal), and there is mild/moderate fibrosis in her liver, she can be monitored without treatment. The HBV DNA and liver function tests of the pregnant women whose treatments are discontinued should be monitored closely for exacerbations that may occur during pregnancy. These patients should also be assessed for resuming treatment, if necessary [19, 25]. Kim *et al.* [25] investigated 12 pregnant women whose treatments were discontinued because they became pregnant. They observed viral rebound in some of the patients and severe hepatic flares in others after the discontinuation of the treatment. In the present study, the treatments were discontinued in four patients who became pregnant, and further appropriate antiviral therapy was proposed to a patient whose biopsy result showed advanced fibrosis. In the follow-ups of four patients whose treatments were discontinued and one patient who refused treatment, no indications were found for beginning treatment.

The post-delivery follow-ups and breastfeeding periods are as important as the monitoring carried out during pregnancy in HBsAg-positive pregnant women. The treatments of pregnant women who have post-delivery liver biopsy indications should be designed according to their biopsy results. If a mild fibrosis is found in the liver, the treatment can be stopped in the first month after delivery. However, if there is advanced fibrosis, continuation of the treatment is recommended. In cases where the treatment is continued, breastfeeding should be avoided [8, 23]. The present authors found that seven of 11 patients who received treatment during pregnancy were administered biopsies after pregnancy. The other four patients were in the immunotolerant phase, thus their treatments were discontinued at one month after delivery and they were placed under follow-up.

The progress of HBV infection is similar in pregnant and non-pregnant women [24]. Some studies have reported fetal complications, such as preterm births, stillbirths, and miscarriages [26]. Celen *et al.* [22] reported no difference in fetal complications between the groups receiving and not receiving treatment. The present authors found that one of the HBsAg-positive pregnant women had an eight-week miscarriage, one infant had Down syndrome, and one infant in the treatment group died due to premature birth. These observations were not different from the normal population.

Cesarean section is not superior to normal delivery in HBsAg-positive pregnant women [10, 27]. Han *et al.* [10] found that the rate of cesarean section was high in HBsAg-positive pregnant women. The present authors found that 29 of the pregnant women had normal deliveries and 59 had cesarean sections. Thirty-nine of these patients had deliveries by cesarean section due to their previous cesarean section histories, one due to preterm delivery (at week 22) and 19 due to reasons such as early membrane rupture.

The major limitation of the present study was that it was retrospective; therefore, the authors could not reach many of the infants of pregnant women who had been monitored before the onset of treatment. Hence, they could not compare the infants of the mothers who received and did not receive treatment.

In conclusion, because hepatitis B caught in the intrauterine or early childhood period has a high rate of chronicity, it is important to screen all pregnant women for hepatitis B and to assess those found HBsAg-positive. It is possible to protect both the mother and baby using appropriate approaches.

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