Correlation of viral load of Hepatitis B with the gestation period and the development of diabetes mellitus

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Abstract

Objective: To elaborate how the viral load of HBV affects the gestational diabetes mellitus (GDM).

Methods: We enrolled 196 chronic HBV-infected pregnant patients in this hospital between January 2012 and December 2017 for delivery in this study. According to the viral load of HBV-DNA, these patients were divided into the HBV-DNA negative group (n = 107, <1 × 10^3 copies/mL) and HBV-DNA positive group (n = 89, ≥1 × 10^3 copies/mL). Simultaneously, 100 HBV-free pregnant women who were admitted to the hospital for delivery were included in the control group. Before delivery, fasting venous blood was drawn from the pregnant women to perform the HBV-DNA quantification through qRT-PCR; from the 24th to 28th gestation week, all pregnant women underwent OGTT, with the third-trimester-of-pregnancy as the endpoint. Besides, we also measured the FBG, 2hPG and hemoglobin A1c (HbAIc).

Results: Among 168 pregnant patients carrying chronic HBV, viral load of 107 patients was less than 1 × 10^3 copies/mL (54.6%), and 89 not less than 1 × 10^3 copies/mL (45.4%). The incidence rates of GDM in the HBV-DNA negative group and HBV-DNA positive group were 18.7% and 19.1%, respectively, significantly higher than that in the control group (p < 0.05), while the difference of the incidence rates of GDM between two HBV-DNA groups were not significant (p > 0.05). In HBV-DNA negative group and HBV-DNA positive group, FBGs, 2hPGs and HbAIcs were respectively (6.96 ± 0.36) mmol/L and (7.04 ± 0.37) mmol/L, (10.26 ± 1.29) mmol/L and (10.16 ± 1.12) mmol/L, and (8.66 ± 0.97)% and (8.91 ± 0.90)% significantly higher than (4.57 ± 0.34) mmol/L, (6.16 ± 0.86) mmol/L, and (5.13 ± 0.57)% (p < 0.05); however, between two HBV-DNA groups, comparisons of the FBG, 2hPG and HbAlc suggested no significant differences (p > 0.05). In 196 patients carrying chronic HBV, positive correlations were identified between the viral load of HBV-DNA, and FBG, 2hPG and HbAIc (p < 0.01).

Conclusion: HBV infection can increase the incidence rate of GDM, and the viral load of HBV-DNA is correlated with the glucose level of pregnant patients.

Keywords:
Hepatitis B virus
GDM
DNA
Blood glucose

0. Introduction

Gestational diabetes mellitus (GDM) refers to the increased blood glucose that is firstly found in pregnancy, and caused by the abnormal sugar tolerance and diabetes mellitus, regardless of the treatment, or the existence after birth (Preboth, 2001). With a prevalence of 1.3–3.7% of GDM, patients are more susceptible to the pregnant hypertension, or ketoacidosis without any appropriate treatment, and simultaneously, neonates may also suffer from the premature delivery, asphyxia or hyperbilirubinemia, severely threatening the health and life of mother and baby (Schillie et al., 2013). In addition to the correlations with the genetic factors, obesity, diet habit and environment, diabetes mellitus is also associated with the infection (McNeil et al., 2014). Hepatitis B virus (HBV) has become a frequent infectious condition with, and the infectious population all over the world has outrun 2 billion, and keeps increasing (Wasley et al., 2010). Mother-to-fetus transmission is one of the three ways of HBV infection, and in China, almost 30–50% of HBV patients are infected through this way. As a particular population of pregnant women carrying HBV, chronic HBV carriers account for nearly 5% of them (Kowdley et al., 2012; Fan et al., 2014.). HBV is a kind of hepatotrophic virus, and HBV patients manifest the damages to liver. However, whether the risk of GDM in HBV-infected pregnant women is increased remains controversial, and there remain few
studies reporting the correlation between HBV viral load in the pregnant women carrying HBV and the GDM. Accumulating evidence found by Magnus and Norder (1995), Goldstein et al. (2005), and Wang et al. (2017) has shown that HBV infection also augments the risk of GDM in pregnant women. Previous studies mainly focus on the HBV infection, but there is little information regarding to the correlation between the viral load of HBV-DNA and the incidence rate of GDM as well as the blood glucose levels. Thus, in this study, we aimed to figure out the correlation between the viral load of chronic HBV pregnant carriers and the GDM, so as to provide the clinical evidence for screening the high-risk factors of GDM.

1. Material and methods

1.1. General data

We enrolled 196 chronic HBV-infected pregnant patients in this hospital between January 2012 and December 2017 for delivery in this study. Inclusion criteria: patients conforming to the diagnostic criteria for the chronic HBV carrier in Guidelines for the Prevention and Treatment of Hepatitis B Infection (2015 Edition); patients with single pregnancy; patients with no liver cirrhosis. Exclusion criteria: patients with body mass index (BMI) > 30 kg/m²; patients with Hepatitis A, C or E virus infection, or other pathogenic infection; patients complicated with the hepatic injury caused by administration of anti-tumor drugs; patients with the history of diabetes mellitus, or congenital heart disease. According to the viral load of HBV-DNA, 107 patients carrying HBV-DNA viral load < 1 x 10³ copies/mL were included in the HBV-DNA negative group, while 89 carrying HBV-DNA viral load ≥ 1 x 10³ copies/mL in the HBV-DNA positive group. Simultaneously, 100 HBV-free pregnant women who were admitted to the hospital for delivery were included in the control group. All subjects were informed of the study content, and volunteered to participate in this study by signing the consents. This study had acquired the approval from the Ethics Committee of the hospital before implementation.

1.2. Methods

1.2.1. HBV-DNA detection

Before delivery, the fasting venous blood was drawn from the pregnant women to perform the HBV-DNA quantification through qRT-PCR using the Cobas 4800 PCR apparatus, with the kit provided by Shanghai ZJ Bio-tech Co., Ltd.

1.2.2. Diagnosis of the GDM

From the 24th to 28th gestation week, all pregnant women underwent the oral glucose tolerance test (OGTT). Subjects with fasting blood glucose (FBG) and blood glucose levels at 1 h and 2 h after sugar intake less than 5.1, 10 and 8.5 mmol/L were deemed as normal, but those with these indexes exceeding the critical value as the GDM. With the third-trimester-of-pregnancy as the endpoint, we also measured the FBG, 2-hour postprandial blood glucose (2hPG) and hemoglobin A1c (HbA1c).

1.3. Statistics

SPSS 20.0 software was utilized for data analysis. Measurement data were expressed in means ± standard deviation, and comparison was carried out through the t test, while count data by chi-square test. Difference with a p < 0.05 had statistical significance.

2. Results

2.1. Comparison of the clinical data among three groups

Among three groups, the comparisons of the age, pregnancy times, delivery times and BMI of patients showed that the differences were not significant (p > 0.05; Table 1).

2.2. HBV-DNA viral load

Among 196 pregnant patients carrying chronic HBV, there were 107 patients in the HBV-DNA positive group, and 89 in the HBV-DNA negative group (45.4%).

2.3. Incidence rate of GDM

The incidence rates of GDM in two HBV-infected groups were 18.7% and 19.1%, respectively with no obvious difference (p > 0.05). When comparing to the control group, the incidence rates of GDM in two HBV-DNA groups were increased significantly (p < 0.05; Table 2).

2.4. Blood glucose

In two HBV-infected groups, significant increases were identified in the levels of FBGs, 2hPGs and HbA1cs in comparison with the control group; however, difference of the intergroup comparison between these two groups showed no statistical significance (p > 0.05; Table 3).

2.5. Correlation analysis

In 196 patients carrying chronic HBV, there was significant correlation of the viral load of HBV-DNA with th FBG, 2hPG and HbA1c (p < 0.01; Table 4).

3. Discussion

Accumulating evidence suggests that HBV infection is correlated with multiple pregnant complications, such as the spontaneous premature delivery or recurrent abortion (Mortensen et al., 2016; Candotti et al., 2012). GDM is a kind of disease particularly in pregnant women, and the blood glucose in most of GDM patients restores following the delivery, but some of them remain at a higher risk of diabetes mellitus. GDM is not only dangerous for pregnant women, but also affect the growth and development of neonates. In recent years, incidence rate of GDM keeps increasing, almost approximating the Type 2 diabetes mellitus and obesity (Hurie, Mast, and Davi, 1992; Thompson et al., 2009.). It is reported that the incidence rate of GDM has attained 16–18% (Williams et al., 2012; Weinbaum et al., 2008; Bell, 2000). Currently, the correlation between HBV infection and GDM remains controversial, while present studies concentrate on the comparison of the HBsAg
Correlation between the HBV-DNA viral load and the blood glucose.

Blood glucose levels in pregnant women in three groups (\(\times 10^{3}\) copies/mL and <1\(\times 10^{3}\)) can hardly reflect the diagnostic indicators for HBV infection, simple detection of HBsAg (+) can hardly reflect the in-vivo viral replication.

As indicated in this study, HBV infection augmented the incidence of the GDM in pregnant women. Bruce et al. (2016) reported that in pregnant women carrying HBV-DNA viral load \(\geq 1 \times 10^{3}\) copies/mL and <1 \(\times 10^{3}\) copies/mL, the incidence rates of GDM are 16.77% and 17.71%, respectively, significantly higher than 10.27% in the HBV-free pregnant women; thus, they believed that HBV infection is the major factor contributing to the increased incidence rate of GDM. Schillie et al. (2012) performed the meta-analysis for the paper regarding to the chronic HBV infection and GDM between 01/01/2009 and 31/12/2014, and they concluded that chronic HBV infection is the risk factors of GDM, but in China, this conclusion requires further verification.

Liver is one of the major metabolic organs of glucose, with the critical functions of storage, degradation and regulation of blood glucose (Shaw et al., 1989). The active replication of HBV in liver can induce the excessive infiltration of inflammatory cells and necrosis in liver cells, thereby destroying the function of liver cells. Besides, declined synthesis of glycogen synthase in liver affects the intake and utilization of glucose, which, together with the reduce generation of hepatic glycogen, can increase the blood glucose of the pregnant women (Drachman et al., 1989; Fabrizi et al., 2012). As one of the features in HBV infection, fatty degeneration of liver leads to the dysfunction in synthesis and excretion of the very low-density lipoprotein (VLDL) and a reduction in the fat utilization of liver, while hyperlipidemia is the major risk factor contributing to the increase in blood glucose, thereby resulting in GDM. HBV replication can be reflected by measuring the HBV-DNA, through which we could evaluate the active or replicative phases (Fabrizi et al., 2012; Bohlke et al., 2003). HBV is a kind of hepatotropic virus, and in the active phase, can enhance the inflammatory responses to the viral infection, resulting in the increased secretion of inflammatory factors, such as IN-2, IL-6, IL-10 or TNF-\(\alpha\) etc., thus giving rise to the inflammatory reactions, and further inducing the excessive infiltration of inflammatory cells, and damage or necrosis in hepatic cells (Bohlke et al., 2003). In addition, active replication of HBV leads to decreased synthesis of glycogen synthase, influencing the intake and utilization of glucose. Meanwhile, HBV infection may correlate with the damaged pancreatic cells, and it can damage the pancreatic secretive cell, contributing to the decrease in insulin secretion, enhanced insulin resistance and increase in blood glucose.

In this study, there was a significant correlation between the HBV-DNA viral load and the blood glucose in pregnant women. Currently, how HBV infection causes the anomaly in blood glucose has not yet been fully elucidated, and may be associated with multiple mechanism. We also explored whether the HBV-DNA viral load in different serum was correlated with the FGb and HbA1c, and found that with an increase in the HBV-DNA viral load, FGb and HbA1c were also elevated in patients, suggesting the correlation of HBV replication with the increases in FGb and HbA1c. This is possibly because the elevated HBV-DNA viral load can damage the liver of patients, thereby damping the regulation function of liver for blood glucose, and this change may be associated with the damaged pancreas. In this study, we found that the blood glucose was not increased against the elevation of HBV-DNA viral load, which might be attributed to the limited sample size. Thus, in clinical practice, for pregnant women positive to the HBV test, HBV-DNA viral load should be monitored closely, and especially for patients with a high HBV-DNA viral load, the early anti-viral treatment is recommended to control the HBV replication, so as to ameliorate the liver function and prevent the GDM.

However, this is a single-center study with a small sample size, and there remains limitation in the subjects. Thus, in the future, we wish to conduct a multi-center clinical study to perform refined comparisons among the pregnant women carrying a high viral load, so as to investigate the relevant pathogenesis regarding to the viral load and GDM.

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