EBioMedicine 26 (2017) 152–156

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

Liver Dysfunction during Pregnancy and Its Association of With Preterm Birth in China: A Prospective Cohort Study

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ARTICLE INFO

Article history:
Received 5 October 2017
Received in revised form 4 November 2017
Accepted 16 November 2017
Available online 21 November 2017

Keywords:
Preterm birth
Liver function tests
Hepatitis B virus
Cohort study

ABSTRACT

Background: Liver dysfunction is common in pregnancy but its association with adverse pregnancy outcomes such as preterm birth (PTB) remains unclear.
Methods: A prospective cohort of HBV-infected or uninfected pregnant women attending antenatal care was recruited at Nantong Maternal and Child Health Hospital between January 1, 2012, and June 30, 2016. Liver function tests (LFTs) were monitored through pregnancy. The primary outcomes were PTB and very PTB (delivery prior 37 and 32 weeks' gestation respectively). Poisson regression was used to estimate adjusted risk ratios (RR) for women with HBV infection and LFT abnormalities.
Results: Among 36,755 pregnant women (1,113 HBV carriers and 35,642 non-HBV subjects), 3,519 (9.57%) had abnormal LFTs. The commonest cause for liver dysfunction during pregnancy was non-alcoholic fatty liver diseases (NAFLD, 51.3%). Abnormal aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and two folds upper limit of normal total bilirubin (RR and 95%CI: 2.73, 1.30–5.76; 2.24, 1.35–3.31; 2.01, 1.22–3.31 respectively), rather than HBsAg positivity, were identified as independent risk factors for preterm birth. Besides, GGT abnormality was associated with increased risk of very PTB.
Conclusions: We suggest that surveillance of LFTs among pregnant women should be warranted, given the increased risk of PTB.

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1. Introduction

Preterm birth (PTB, delivery prior 37 weeks' gestation) or premature birth remains a leading cause for neonatal morbidity and mortality, as well as a wide array of long-term sequelae (Saigal and Doyle, 2008). Worldwide, an estimated 15 million babies are born premature annually and the number is increasing, with rates varying from 5% to 18% across countries (Goldenberg et al., 2008).

Chronic hepatitis B virus (HBV) infection is highly endemic in China. The seroprevalence rate of hepatitis B surface antigen (HBsAg) was reported 6.71% among pregnant women in our province (Zhang et al., 2010). Several studies, including our previous studies, explored the incidence of PTB in women with HBV infection, but the results are inconsistent (Chen et al., 2015; Connell et al., 2011; Cui et al., 2016a,b; Salemi et al., 2014; Sirilert et al., 2014). Recently, a large-scale population-based cohort study suggested that pre-pregnancy HBV infection may be associated with increased risk for preterm delivery (Liu et al., 2017). Moreover, three reviews suggested minimally but significantly increased risk of preterm birth among HBV carriers (Cui et al., 2016b; Huang et al., 2014; Ma et al., 2017). However, It should be stressed that chronic HBV infection is also a major cause of liver dysfunction (e.g. rise in serum aminotransferase and bilirubin), which may have serious consequences by itself (Than and Neuberger, 2013). The impact of liver dysfunction on preterm birth has not been systematically documented and remains unclear.

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https://doi.org/10.1016/j.ebiom.2017.11.014
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In the current study, we conducted a hospital-based cohort study to determine whether liver function test (LFT) abnormalities, as well as chronic HBV infection, were associated with increased risk of PTB.

2. Methods

2.1. Study Cohort

A prospective cohort was recruited at the Nantong Maternal and Child Health Hospital affiliated to Nantong University, China between January 1, 2012 and June 30, 2016. The medical history as well as supporting clinical and laboratory information were collected at baseline. All pregnant women aged 18 to 50 years were screened. Exclusion criteria were (1) multiple pregnancy; (2) positivity for antibodies against hepatitis C virus (HCV), human immunodeficiency virus (HIV), toxoplasma (TOX), rubella virus (RV), cytomegalovirus (CMV) or herpes simplex virus (HSV-1/2), positivity for rapid plasma reagin test/RPR (indicating active syphilis infection); (3) pre-existing chronic diseases such as diabetes mellitus (DM), hypertension or heart diseases; (4) spontaneous or induced abortion; (5) lost to follow-up or incomplete data. HBV carriers were defined as those who had positive HBsAg for at least 6 month.

This study was performed according to the Declaration of Helsinki and approved by the Institutional Review Board of the Nantong Maternal and Child Health Hospital affiliated to Nantong University, China. Written informed consents were obtained from all participants.

2.2. Procedures

This study was conducted during January 2012 to April 2017. Data on maternal demographic characteristics were collected from questionnaires completed by women at the first antenatal visit. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and total bilirubin (TBiL) were measured with an automatic biochemical analyzer (AU2700, Olympus, Japan). Serological tests for HBsAg and hepatitis B e antigen (HBeAg) were done by enzyme linked immunoassays on a random-access analyzer (Architect i2000; Abbott Diagnostics, USA). Liver function tests were assessed as routine in all pregnancies. All recruited women had baseline LFT performed and at least one subsequent test. Additional LFTs were requested by the obstetric staff or general clinical practitioners. The medical aspects of the pregnancy were followed-up as clinically appropriate. Other investigations included hepatobiliary ultrasonography, serum bile acids, hepatitis A, C, E serology, autoantibodies, etc.

Abnormal LFT was defined as at least one result of the four markers (ALT, AST, GGT, total bilirubin) greater than its upper limit of normal (ULN), i.e. ALT > 40 U/L or AST > 40 U/L or GGT > 50 U/L or total bilirubin > 17.1 μmol/L. Diagnoses of non-alcoholic fatty liver diseases (NAFLD), intrahepatic cholestasis of pregnancy (ICP), pre-eclampsia/eclampsia, haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, and acute fatty liver of pregnancy (AFLP) were made according to relevant guidelines (Chalasani et al., 2012; Tran et al., 2016).

2.3. Outcomes

The primary outcome was preterm birth. The definitions of PTB, very PTB and extremely PTB were spontaneous or medically indicated labor occurring at <37, 32, and 28 weeks of gestation respectively, according to the World Health Organization (WHO) guidelines (WHO, 2015). The participants were followed-up until the end of pregnancy.

2.4. Statistical Analysis

Statistical analyses were conducted using Stata 14.0 (Stata Corp., TX, USA). Continuous or categorical data were compared using Student's *t*-test or Chi-square test respectively. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated using the 'cs' command in Stata to describe the association between each outcome category and potential risk factors. All tests were two-sided, and the significance level was set at 0.05.

According to hepatitis B virus infection status, participants were divided into two or three groups. HBsAg negative indicated no infection with HBV (control group); HBsAg positive women (exposure group) were further divided into HBeAg negative (exposure group 1) and HBeAg positive (exposure group 2) subgroups. Poisson regression models, as we described elsewhere (Qin et al., 2016), were used to estimate RRs of PTB for women with HBV infection or LFT abnormality. In model 1, we adjusted for age categories (18–24 years, 25–29 years, 30–34 years, 35–39 years, or 40–50 years). In model 2, we additionally adjusted for pre-pregnancy BMI categories (<18.5 kg/m^2, 18.5–23.9 kg/m^2, 24.0–27.9 kg/m^2, or ≥28.0 kg/m^2), levels of education (high school or under, college or above), history of pregnancy (first gestation) and history of adverse pregnancy outcomes (spontaneous or induced abortion, preterm birth or stillbirth). In model 3, in addition to those factors included in model 2, we also adjusted for HBV infection status (HBsAg negative, HBsAg positive and HBeAg negative, HBsAg and HBeAg double positive), LFT abnormality categories.

2.5. Role of the Funding Source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Participant Characteristics and Pregnancy Outcomes

A total of 44,906 pregnant women were screened during their first trimester of pregnancy at Nantong Maternal and Child Health Hospital affiliated to Nantong University, China. Of these, 6,242 were excluded: due to multiple pregnancy in 1,518 subjects; due to other infection in 2,496 subjects; due to concurrent medical complications (DM, hypertension or heart diseases) in 841 subjects, due to spontaneous or induced abortion in 2,787 subjects. Thereafter, 37,264 pregnant women were recruited in this study, including 1,115 HBV carriers and 36,149 non-HBV subjects. Most of the enrolled subjects received at least three health examinations and were followed-up until delivery. Five hundred and nine subjects were excluded because of lost to follow-up (292 subjects) or incomplete data (217 subjects). Finally, 36,755 subjects, with 1,113 HBV carriers and 35,642 non-HBV subjects, were included (Fig. 1).

The demographic and clinical characteristics were listed in Table 1. The median age of all participants was 26 years (IQR 25–29). 6.38% of the subjects were aged 35 years or more, 62.04% had an education level of college or above, and 61.41% were in their first pregnancy. However, baseline characteristics for the HBV carrier and non-HBV groups were not comparable in terms of history of gestation, abortion.

The main pregnancy outcomes were also listed in Table 1. The incidence of preterm birth was significantly higher in HBV carrier group than that in the non-HBV group (9.70% vs 7.16%, $P = 0.018$). Meanwhile, for incidence of very PTB and extremely PTB, there was no significant difference between the two groups.

3.2. Distribution of Preterm Birth Cases in Women With LFT Abnormality

Of these 36,755 women, 3,519 (9.57%) had at least one abnormal liver function test result. The commonest liver disease observed in pregnancy here was NAFLD (1,805/36,755, 4.91%). The onset of liver dysfunction occurred mostly during the first and third trimesters. The incidence of ICP, preeclampsia/eclampsia and HELLP syndrome were

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