Maternal Chronic HBV Infection Would Not Increase the Risk of Pregnancy-Induced Hypertension – Results from Pregnancy Cohort in Liuyang Rural China

Xin Huang¹, Hongzhuan Tan¹*, Xun Li¹, Shujin Zhou², Shi Wu Wen¹,³, Meiling Luo¹

¹. Department of Epidemiology and Health Statistics, School of Public Health, Central South University, Changsha, Hunan, China, 2. Liuyang Municipal Hospital of Maternal and Child Health, Beizheng, Liuyang, Hunan, China, 3. OMNI Research Group, Department of Obstetrics and Gynecology, University of Ottawa, Ottawa, Ontario, Canada

*tanhz99@qq.com

Abstract

The relationship between maternal HBV (hepatitis B virus) infection and pregnancy-induced hypertension (PIH) is inconclusive. Few studies have been conducted in rural areas of China. In order to examine the association between maternal chronic HBV infection and risk of PIH in Liuyang rural area China, we enrolled 6,195 eligible pregnant women in 2010–2011 in selected 14 towns of Liuyang on their first prenatal visit to local maternity care unit. A total of 461 subjects (7.44% (95%CI: 6.79%, 8.10%)) were identified with positive HBsAg status (exposed group) and 5734 were non-HBV carriers (unexposed group). Multivariate log-binomial regression models were used to estimate the risk of PIH, gestational hypertension (GH), and preeclampsia (PE) in relation to maternal chronic HBV infection. There are total of 455 subjects diagnosed with PIH (7.34% (95%CI: 6.70%, 7.99%)), including 371 GH (5.99% (95%CI: 5.40%, 6.58%)) and 81 PE (1.31% (95%CI: 1.07%, 1.64%)). The crude risk ratio between PIH, GH, PE and maternal HBV infection were 1.20 (95%CI: 0.88, 1.64), 1.30(95%CI: 0.93, 1.81) and 0.79 (95%CI: 0.32, 1.93), respectively. After adjustment for gravidity history, abortion history, family history of Diabetes Mellitus (DM) and family history of hypertension, positive HBsAg status was still not significantly associated with PIH (RR=1.18, 95%CI: 0.87, 1.62), GH (RR=1.27, 95%CI: 0.91, 1.78) or PE (RR=0.79, 95%CI: 0.32, 1.95). Additional adjustment for maternal age, marital status, parity history, family history of DM, Body Mass Index at first antenatal visit, folic acid supplementation, smoking status during pregnancy and economic status of living area, multivariate analysis provided similar results. In conclusion, our study found that maternal chronic HBV infection prevalence rate is 7.4% among Liuyang rural area and there
is no significant association between maternal HBV infection and the risk of PIH, GH or PE.

**Introduction**

More than 400 million people in the worldwide are chronically infected with Hepatitis B virus [1, 2]. The majority of them live in Asia Pacific including China [3]. In China, the prevalence of hepatitis B surface antigen (HBsAg) in individuals aged 1–59 years was 7.2% [4]. Consequently, chronic HBV infection affects a significant number of Chinese pregnant women. Maternal asymptomatic infection with HBV has been strongly associated with increased risk of medical complications during pregnancy, for example, antepartum hemorrhage and gestational diabetes mellitus [5–13]. The relationship between chronic HBV infection and risk of pregnancy-induced hypertension (PIH), however, remains unclear.

PIH, which includes gestational hypertension (GH) and preeclampsia (PE), is a major cause of maternal, fetal, and neonatal morbidity and mortality [14, 15]. Furthermore, PIH could increase the risk of long-term cardiovascular diseases of both mothers and their children [16, 17]. PIH became the second leading cause of maternal death in China, which accounted for 13.8% and 8.8% of total maternal deaths in urban and rural areas, respectively [18]. Although significant efforts have been made, little is known about the etiology of PIH.

Early published studies have reported a conflicting association between maternal chronic HBV infection and PIH. Some studies found a significantly positive association between maternal HBV infection and PIH [5], some reported no association between GH or PE and HBV [6–12], while others found a significantly negative association between GH, PE and HBV [13, 19, 20]. In addition, previous studies have been done in USA [6, 7], Germany [8], Israel [9], Iran [5], Thailand [10] and Hong Kong [11–13, 19, 20]. To our best knowledge, no study in China mainland rural area has been reported. The incidence of PIH varied between different races [21, 22] and the prevalence of HBV infection varied not only between different countries [2, 23], but also within different areas of the same country [24, 25]. The findings from previous studies might not be generalizable to Chinese rural population. Given the inconsistent relationship between chronic HBV infection and PIH and the paucity of studies in China rural area, we conducted a study in Liuyang, Hunan, China, to examine the association between HBV and PIH among China rural population.
Methods

Study population

Data for this study were collected within our pre-conception cohort in Liuyang which was designed to study pregnancy induced hypertension and gestational diabetes mellitus. Liuyang is a ‘county-level city’ with 4 city districts and 33 towns. It is located in northeast Hunan Province and under the jurisdiction of Changsha City. Economic status and population size of rural areas in China have wide variation. According to the outcome of Changsha statistical survey [26], multi-stage sampling method was used to select the study subjects. Firstly, based on local GDP level, all 33 towns of Liuyang County were stratified into high, middle and low income areas. Secondly, according to the overall population size ratio of those areas (4:4:5), four towns from 10 high income townships, 5 from 12 middle income townships and 5 from 11 low income townships were selected. All pregnant women (6,693) living in those selected 14 towns of Liuyang from January 2010 to December 2011 were asked to participate in the cohort on their first prenatal visit to local maternity care unit. Of them, 6,237 subjects (93%) were followed to childbirth. Furthermore, women who gave multiple births, still birth, or who had chronic hypertension or chronic hepatitis C virus infection were also excluded, which yielded a final sample size of 6,195.

Data collection and variable definition

Our data collection has consisted of two components: antenatal care booklet collection and hospital chart review. In rural China, all pregnant women were offered with maternal healthcare based on three-level network system (county hospital, the township hospitals and village clinics). Information on antenatal care would be routinely recorded in an antenatal care booklet since first prenatal visit by certified doctors or nurses. This booklet was kept by individual during pregnancy and should be handed in to local maternity care unit in town after childbirth for the process of applying for birth certification. We collected antenatal care booklets of all subjects in township maternity care unit every month. And subjects’ hospital medical records were linked to their booklets as long as they give birth at hospitals. General information on maternal demographic characteristics, health status, blood pressure (BP) during pregnancy, obstetric history and antenatal care records could be obtained from antenatal care booklets. Information on maternal complications was abstracted from antenatal care booklets and hospital records.

Maternal hepatitis B surface antigen (HBsAg) status was part of the routine antenatal care in Liuyang and will be routinely reconfirmed when pregnant women were hospitalized for childbirth. HBsAg was screened by enzyme linked immunosorbent assay (ELISA) kit. Maternal chronic infection with HBV was defined as positive HBsAg status on antenatal record. In Liuyang, BP was measured 3 times by certified nurse, using standardized mercuric-column sphygmomanometer at each prenatal visit in a sitting position after 5 minutes of
rest, and the time interval between successive pairs of BP measurements was 2
minutes. GH was defined as systolic BP (SBP) $\geq 140$ mmHg and/or diastolic BP
(DBP) $\geq 90$ mmHg, occurring for the first time after 20 weeks of gestation. PE
was defined as SBP $\geq 140$ mmHg and/or DBP $\geq 90$ mmHg, concurrent with
proteinuria ($\geq 0.3$ g in a 24-hour urine specimen or $\geq 1+$ on dipstick in two urine
samples) after 20 weeks of gestation. PIH was defined as a combination of GH and
PE. According to HBsAg status, subjects were classified into HBsAg positive
(exposed) and HBsAg negative (unexposed) groups.

**Ethics statement**
The study protocol was reviewed and approved by the Central-South University’s
Ethical and Confidentiality Committee. All participants provided written
informed consent.

**Statistical analysis**
Chi-square tests were used to compare the distributions of maternal character-
istics between exposed and unexposed group. Crude risks of PIH by different
maternal characteristics and their 95% confidence intervals (CI) were estimated
based on normal approximation method. Multivariate log-binomial regression
models were used to calculate risk ratios (RR) and 95%CI for the association
between HBV infection and risk of PIH, GH and PE. Potential confounding
variables included maternal age ($<25$, $25–34$, and $\geq 35$ years), marital status
(unmarried or married), gravidity ($\leq 1$, $>1$), nulliparous (yes or no), abortion
history (yes or no), family history of DM (yes or no), family history of
hypertension (yes or no), BMI at first antenatal visit ($<18.5$, $18.5–24.9$, and
$\geq 25$ kg/m$^2$), folic acid supplement intake during pregnancy (yes or no), smoking
during pregnancy (yes or no) and economic status of living area (high, middle
and low income area). Additional adjustment for alcohol consumption, infant
gender, weight gain during pregnancy did not result in material changes of the
observed associations and thus were not included into the final models (results
not shown). Statistical significance was assessed at the 5% level (two-tail test). All
analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary,
NC).

**Results**
Of the 6,195 study subjects, 461 (7.44% (95%CI: 6.79%, 8.10%)) subjects were
with positive HBsAg status (Table 1). Compared to unexposed group, HBsAg
positive carriers were more likely to be multigravida, having abortion history and
family history of hypertension. There were no significant differences in the
distribution of maternal age, marital status, parity history, family history of DM,
BMI at first antenatal visit, taking folic acid supplement during pregnancy,
Table 1. Distribution of selected characteristics of subjects between maternal HBV carriers and non-HBV carriers, Liuyang, Hunan, China, 2012.

| Characteristics               | HBsAg (-) | HBsAg (+) | \( \chi^2 \) | \( P \) |
|-------------------------------|-----------|-----------|--------------|--------|
|                              | N=5734    | %         | N=461        | %      |        |
| Age (years)                   |           |           |              |        |
| <25                           | 3520      | 61.39     | 282          | 61.17  | 0.032  | 0.984 |
| 25–34                         | 2072      | 36.14     | 167          | 36.23  |        |       |
| ≥35                           | 142       | 2.48      | 12           | 2.60   |        |       |
| Marital status                |           |           |              |        |
| Unmarried                     | 186       | 3.24      | 11           | 2.39   | 1.020  | 0.313 |
| Married                       | 5548      | 96.76     | 450          | 97.61  |        |       |
| Gravidity                     |           |           |              |        |
| ≤1                            | 2492      | 43.46     | 176          | 38.18  | 4.966  | 0.026 |
| >1                            | 3234      | 56.40     | 285          | 61.82  |        |       |
| Nulliparous                   |           |           |              |        |
| No                            | 1758      | 30.66     | 149          | 32.32  | 0.553  | 0.457 |
| Yes                           | 3976      | 69.34     | 312          | 67.68  |        |       |
| Abortion history              |           |           |              |        |
| No                            | 3928      | 68.50     | 281          | 60.95  | 11.165 | 0.001 |
| Yes                           | 1806      | 31.50     | 180          | 39.05  |        |       |
| Family history of DM          |           |           |              |        |
| No                            | 5719      | 99.74     | 458          | 99.35  | 2.231  | 0.135 |
| Yes                           | 15        | 0.26      | 3            | 0.65   |        |       |
| Family history of hypertension|           |           |              |        |
| No                            | 5662      | 98.74     | 449          | 97.40  | 5.791  | 0.016 |
| Yes                           | 72        | 1.26      | 12           | 2.60   |        |       |
| BMI at first antenatal visit (kg/m²) |       |           |              |        |
| <18.5                         | 1253      | 21.85     | 85           | 18.44  | 3.020  | 0.221 |
| 18.5–24.9                     | 3861      | 67.34     | 322          | 69.85  |        |       |
| ≥25                           | 620       | 10.81     | 54           | 11.71  |        |       |
| Folic acid supplement         |           |           |              |        |
| No                            | 1743      | 30.40     | 145          | 31.45  | 0.225  | 0.636 |
| Yes                           | 3991      | 69.60     | 316          | 68.55  |        |       |
| Smoking                       |           |           |              |        |
| No                            | 5686      | 99.16     | 459          | 99.57  | 0.867  | 0.352 |
| Yes                           | 48        | 0.84      | 2            | 0.43   |        |       |
| Economic status of living area|           |           |              |        |
| High income                   | 1664      | 29.0      | 130          | 28.2   | 0.157  | 0.924 |
| Middle income                 | 1780      | 31.0      | 146          | 31.7   |        |       |
| Low income                    | 2290      | 39.9      | 185          | 40.1   |        |       |

Abbreviations: HBsAg, hepatitis B virus antigen; BMI, body mass index; DM, diabetes mellitus.

doi:10.1371/journal.pone.0114248.t001
| Characteristics          | Observed population | GH/PE | GH | PE |
|-------------------------|---------------------|-------|----|----|
|                         | N                   | Risk(%) (95%CI) | Risk(%) (95%CI) | Risk(%) (95%CI) |
| Overall                 | 6195                | 7.34 (6.70, 7.99) | 5.99 (5.40, 6.58) | 1.36 (1.07, 1.64) |
| Age (years)             |                     |                   |                |                |
| <25                     | 3802                | 5.76 (5.02, 6.50) | 4.81 (4.13, 5.49) | 0.95 (0.64, 1.25) |
| 25–34                   | 2239                | 8.71 (7.54, 9.88) | 6.97 (5.91, 8.02) | 1.74 (1.20, 2.28) |
| ≥35                     | 154                 | 26.62 (19.64, 33.60) | 20.78 (14.37, 27.19) | 5.84 (2.14, 9.55) |
| Marital status          |                     |                   |                |                |
| Unmarried               | 197                 | 6.60 (3.13, 10.07) | 5.08 (2.01, 8.14) | 1.52 (0.00, 3.23) |
| Married                 | 5998                | 7.37 (6.71, 8.03) | 6.02 (5.42, 6.62) | 1.35 (1.06, 1.64) |
| Gravidity               |                     |                   |                |                |
| ≤1                      | 2668                | 7.27 (6.29, 8.26) | 5.96 (5.06, 6.86) | 1.31 (0.88, 1.74) |
| >1                      | 3527                | 7.40 (6.54, 8.26) | 6.01 (5.23, 6.80) | 1.39 (1.00, 1.78) |
| Nulliparous             |                     |                   |                |                |
| No                      | 1907                | 7.18 (6.03, 8.34) | 5.82 (4.77, 6.87) | 1.36 (0.84, 1.88) |
| Yes                     | 4288                | 7.42 (6.63, 8.20) | 6.06 (5.35, 6.78) | 1.35 (1.01, 1.70) |
| Abortion history        |                     |                   |                |                |
| No                      | 4209                | 7.44 (6.64, 8.23) | 5.94 (5.23, 6.65) | 1.50 (1.13, 1.86) |
| Yes                     | 1986                | 7.15 (6.02, 8.28) | 6.09 (5.04, 7.14) | 1.06 (0.61, 1.51) |
| Family history of DM    |                     |                   |                |                |
| No                      | 6177                | 7.32 (6.67, 7.97) | 5.97 (5.38, 6.56) | 1.34 (1.06, 1.63) |
| Yes                     | 18                  | 16.67 (0.00, 33.88) | 11.11 (0.00, 25.63) | 5.56 (0.00, 16.14) |
| Family history of hypertension |           |                   |                |                |
| No                      | 6111                | 7.22 (6.57, 7.87) | 5.87 (5.29, 6.46) | 1.34 (1.05, 1.63) |
| Yes                     | 84                  | 16.67 (8.70, 24.64) | 14.29 (8.80, 21.77) | 2.38 (0.00, 5.64) |
| BMI at first antenatal visit (kg/m²) | |                   |                |                |
| <18.5                   | 1338                | 5.68 (4.44, 6.92) | 4.86 (3.71, 6.01) | 0.82 (0.34, 1.31) |
| 18.5–24.9               | 4183                | 6.67 (5.91, 7.43) | 5.36 (4.67, 6.04) | 1.31 (0.97, 1.66) |
| ≥25                     | 674                 | 14.84 (12.15, 17.75) | 12.17 (9.70, 14.63) | 2.67 (1.45, 3.89) |
| Folic acid supplement   |                     |                   |                |                |
| No                      | 1888                | 9.22 (7.91, 10.52) | 7.84 (6.63, 9.05) | 1.38 (0.85, 1.90) |
| Yes                     | 4307                | 6.52 (5.79, 7.26) | 5.18 (4.52, 5.84) | 1.35 (1.00, 1.69) |
| Smoking                 |                     |                   |                |                |
| No                      | 6145                | 7.32 (6.67, 7.97) | 5.97 (5.38, 6.56) | 1.35 (1.06, 1.64) |
| Yes                     | 50                  | 10.00 (1.68, 18.32) | 8.00 (0.48, 15.52) | 2.00 (0.00, 5.88) |
| Economic status of living area |           |                   |                |                |
| High income             | 1794                | 7.02 (5.84, 8.21) | 5.91 (4.82, 7.00) | 1.28 (0.08, 1.80) |
| Middle income           | 1926                | 7.63 (6.45, 8.82) | 5.54 (4.55, 6.54) | 1.40 (0.09, 1.93) |
| Low income              | 2475                | 7.35 (6.33, 8.38) | 5.79 (4.89, 6.68) | 1.37 (0.09, 1.83) |

Abbreviations: BMI, body mass index; DM, diabetes mellitus; CI, confidence intervals.

doi:10.1371/journal.pone.0114248.t002
exposure to active smoking and economic status of living area between the exposed and unexposed groups.

There are total of 455 subjects diagnosed with PIH (7.34% (95% CI: 6.70%, 7.99%)), including 371 GH (5.99% (95% CI: 5.40%, 6.58%)) and 81 PE (1.31% (95% CI: 1.07%, 1.64%)) (Table 2). Crude risks of PIH by other different maternal characteristics were also showed in Table 2. Those with age over 35, family history of hypertension, BMI at first antenatal visit over 25 or not taking folic acid supplement during pregnancy were having higher risks of PIH than others.

The crude risks of PIH and GH among positive HBsAg carrier were 8.68% and 7.59% respectively, which is higher than that unexposed group (7.24% and 5.86%) (Table 3). Meanwhile, the risk of PE among positive HBsAg carrier was 1.08% lower than that unexposed group (1.38%). However, none of the risks difference between those two groups were statistical significant. After adjustment for gravidity history, abortion history, family history of DM and family history of hypertension, positive HBsAg status was still not significantly associated with PIH (RR = 1.18, 95% CI: 0.87, 1.62), GH (RR = 1.27, 95% CI: 0.91, 1.78) or PE (RR = 0.79, 95% CI: 0.32, 1.95). Additional adjustment for maternal age, marital status, parity history, family history of DM, BMI at first antenatal visit, folic acid supplementation, smoking and economic status of living area, multivariate analysis provided similar results (Table 3).

Only 5 subjects (1% of HBsAg positive carriers) suffered with chronic active HBV infection, others were chronic carriers with normal liver function. We also tried to exclude those chronic active infection subjects. This sensitive analysis reached the same conclusion (data not shown).

Discussion

Our population based on cohort study shows that maternal chronic HBV infection prevalence rate is 7.4% (95% CI: 6.79%, 8.10%) among Liuyang rural area. This prevalence rate is similar to the overall population of China 7.2% (95% CI: 6.67%, 7.70%) [4] and those women of childbearing age (15–49) in Jiangsu, China (6.71% (95% CI: 6.10%, 7.30%)) [27] or in Northwest China (7.2% (95% CI: 6.0%, 8.5%)) [24]. But it is lower than women of childbearing age in Hainan, China (9.5% (95% CI: 8.99%, 10.02%)) [28] and pregnant women in Hong Kong (10.0% (95% CI: 9.78%, 10.18%)) [19]. According to the study in China, the rate of mother-to-child transmission of HBV was 7.3% [29]. Therefore, the high maternal HBV infection rate in our study area would remain a serious concern. Timely administration of the HBV vaccine combined with hepatitis B immune globulin need to be administered to at risk individuals [30].

There are 11 previously published studies that had assessed the association between maternal HBV infection and risk of PIH and reached inconsistent conclusion. Of those 11 studies, 2 were multi-center based [6, 7] and 9 were single hospital based [5, 8–13, 19, 20]. Those 2 multi-center based studies were conducted in US and observed the same results as our population based cohort
One was conducted by Reddick et al. [6], they used the discharge registry data from 1054 hospitals across 37 states, enrolled 297,664 subjects with 814 HBV carriers. After adjustment for maternal age, race and other confounding variables, no association was observed between maternal HBV infection and PE (OR = 0.91, 95%CI: 0.57, 1.4). The other one was conducted in Florida [7], using births certification and hospital discharge linked data and enrolled 1,670,369 subjects with 1,458 HBV carriers, also found no significant association for HBV and GH or PE. Studies done by Sirilert et al. in Thailand [10], Lobstein et al. in Germany [8], Safir et al. in Israel [9], Wong et al. [11] and Tse et al. [12] in Hong Kong also support this conclusion. However, a case-control study in Iran [5], enrolled 450 HBV carriers and 450 controls observed increased risk of PIH with maternal HBV infection (OR = 4.2, 95%CI: 2.2, 8.1). In contrast to all of the aforementioned studies, Lao et al. [19] enrolled 86,537 subjects with 8,634 HBV carriers in a teaching hospital in Hong Kong found that maternal HBV infection could reduce the risk of PIH (OR = 0.79, 95%CI: 0.66, 0.95) and PE (OR = 0.71, 95%CI: 0.56, 0.91). And other two studies in Hong Kong [13, 20] also supported this negative association. All of those single hospital based studies were conducted in hospitals with great annual delivery rate. The potential patients served by those hospitals may differ from those served by regular community hospitals. In another words, the admission rate of non-HBV carriers with PIH in those hospitals may differ from that of HBV carriers with PIH. We speculated that this discrepancy might involve selection bias and result in the inconsistence results.

Previous studies have demonstrated that HBV infection could increase the risk of atherosclerosis [31], however this association was secondary to the liver dysfunction associated with HBV infection rather than HBsAg positivity itself [32], though HBV infection could induce a proinflammatory effect. 99% of our study population was chronic HBV carrier with normal liver function. The simple HBV infection without liver dysfunction may not initiate or aggravate vascular damage and causes atherosclerosis, which were the key the process of PE. The association between maternal chronic active HBV infection and PIH may need further investigation.

Our study has several strengths in comparison with previous studies of the field. It was the population-based prospective cohort study with reduced selection bias.

### Table 3. Association between maternal HBV infection and pregnancy-induced hypertension, Liuyang, China, 2012.

|       | HBsAg + | HBsAg - | Crude RR (95%CI) | Adjusted RR a (95%CI) | Adjusted RR b (95%CI) |
|-------|---------|---------|------------------|-----------------------|-----------------------|
| N=461 |         |         |                  |                       |                       |
| GH/PE | 40      | 415     | 1.20 (0.88, 1.64) | 1.18 (0.87, 1.62)     | 1.17 (0.85, 1.59)     |
| GH    | 35      | 336     | 1.30 (0.93, 1.81) | 1.27 (0.91, 1.78)     | 1.25 (0.90, 1.76)     |
| PE    | 5       | 79      | 0.79 (0.32, 1.93) | 0.79 (0.32, 1.95)     | 0.80 (0.32, 1.96)     |

aAdjustment covariates are gravidity, abortion history, family history of hypertension.

bAdjustment covariates are maternal age, marital status, gravidity, parity, abortion history, family history of DM, family history of hypertension, BMI at first antenatal visit, folic acid supplementation, smoking, economic status of living area.

Abbreviations: GH, gestational hypertension; PE, preeclampsia; HBsAg, hepatitis B virus antigen; RR, risk ratio; CI, confidence intervals.

doi:10.1371/journal.pone.0114248.t003
The data contained detailed information on maternal demographic and medical and some pregnancy information allowing adjustment for several important potential confounding factors simultaneously. Diagnosis of GH/PE in our study was based on medical records not self-report, which minimized potential disease misclassification. However, the limitation of our study should be considered when interpreting the study findings. Our data did not include information on HbcAg, HBeAg or HBV DNA levels. Therefore, we were not able to determine whether the replicating virus had an effect on onset of PIH. Only 5 subjects suffered chronic active HBV infection, this limitation did not allow us to do further research on the association between chronic active HBV infection and PIH. Lack of information on the date of diagnosis of PIH limited our ability to examine the association by early and later onset PE, which might have different etiologies. The incidence of PE and PIH and prevalence of HBV infection among Chinese population are quite different from that of Caucasians, genetic differences may play a dominant role. Hence, the generalizability of our results may be limited to Chinese population.

Conclusions
Our study found that maternal chronic HBV infection prevalence rate is 7.4% among Liuyang rural area and there is no significant association between maternal HBV infection and the risk of PIH, GH or PE.

Acknowledgments
We thank the health workers in maternity and childcare units in Liuyang for their assistance in the fieldwork.

Author Contributions
Conceived and designed the experiments: XH HT SWW. Analyzed the data: XH XL ML. Contributed reagents/materials/analysis tools: XH SZ XL ML. Wrote the paper: XH HT SWW. Managed and coordinated field work: SZ.

References
1. McMahon BJ (2005) Epidemiology and natural history of hepatitis B. Semin Liver Dis 25 Suppl 1: 3–8.
2. Sarin SK, Kumar M (2010) Epidemiology, Screening, and Natural History of Chronic Hepatitis B Infection. In: Shetty K, Wu GY, editors. Chronic Viral Hepatitis 2nd ed. Lippincott, Williams, and Wilkins (Philadelphia): Humana Press. pp. 185–241.
3. Hudu SA, Malik YA, Niazlin MT, Harmal NS, Sekawi Z (2013) An Overview of Hepatitis B Virus Surface Antigen Mutant in the Asia Pacific. Curr Issues Mol Biol 16: 69–78.
4. Liang X, Bi S, Yang W, Wang L, Cui G, et al. (2009) Epidemiological serosurvey of hepatitis B in China—declining HBV prevalence due to hepatitis B vaccination. Vaccine 27: 6550–6557.
5. Gargari SS, Hantouchzadeh S, Zendehdel N, Jamal A, Aghdam H (2009) The Association of Maternal HBsAg Carrier Status and Perinatal Outcome. Hepat Mon 9: 180–184.
6. Reddick KL, Jhaveri R, Gandhi M, James AH, Swamy GK (2011) Pregnancy outcomes associated with viral hepatitis. J Viral Hepat 18: e394–398.

7. Connell LE, Salihu HM, Salemi JL, August EM, Weldeeselasse H, et al. (2011) Maternal hepatitis B and hepatitis C carrier status and perinatal outcomes. Liver Int 31: 1163–1170.

8. Lobstein S, Faber R, Tillmann HL (2011) Prevalence of hepatitis B among pregnant women and its impact on pregnancy and newborn complications at a tertiary hospital in the eastern part of Germany. Digestion 83: 76–82.

9. Safir A, Levy A, Sikuler E, Sheiner E (2010) Maternal hepatitis B virus or hepatitis C virus carrier status as an independent risk factor for adverse perinatal outcome. Liver Int 30: 765–770.

10. Sirilert S, Traisrisilp K, Sirivatanapa P, Tongsong T (2014) Pregnancy outcomes among chronic carriers of hepatitis B virus. Int J Gynaecol Obstet 126: 106–110.

11. Wong S, Chan LY, Yu V, Ho L (1999) Hepatitis B carrier and perinatal outcome in singleton pregnancy. Am J Perinatol 16: 485–488.

12. Tse KY, Ho LF, Lao T (2005) The impact of maternal HBsAg carrier status on pregnancy outcomes: a case-control study. J Hepatol 43: 771–775.

13. Lao TT, Chan BC, Leung WC, Ho LF, Tse KY (2007) Maternal hepatitis B infection and gestational diabetes mellitus. J Hepatol 47: 46–50.

14. Backes CH, Markham K, Moorehead P, Cordero L, Nankervis CA, et al. (2011) Maternal preeclampsia and neonatal outcomes. J Pregnancy 2011: 214365.

15. Chen XK, Wen SW, Smith G, Yang Q, Walker M (2006) Pregnancy-induced hypertension is associated with lower infant mortality in preterm singletons. Bmj 113: 544–551.

16. Brown DW, Dueker N, Jamieson DJ, Cole JW, Wozniak MA, et al. (2006) Preeclampsia and the risk of ischemic stroke among young women: results from the Stroke Prevention in Young Women Study. Stroke 37: 1055–1059.

17. Irgens HU, Reisaeter L, Irgens LM, Lie RT (2001) Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. Bmj 323: 1213–1217.

18. Liang J, Zhu J, Dai L, Li X, Li M, et al. (2010) Maternal mortality in China, 1996-2005. Int J Gynaecol Obstet 110: 93–96.

19. Lao TT, Sahota DS, Cheng YK, Law LW, Leung TY (2013) Maternal hepatitis B surface antigen status and incidence of pre-eclampsia. J Viral Hepat 20: 343–349.

20. To WW, Cheung W, Mok KM (2003) Hepatitis B surface antigen carrier status and its correlation to gestational hypertension. Aust N Z J Obstet Gynaecol 43: 119–122.

21. Rao AK, Daniels K, El-Sayed YY, Moshesh MK, Caughey AB (2006) Perinatal outcomes among Asian American and Pacific Islander women. Am J Obstet Gynecol 195: 834–838.

22. Gong J, Savitz DA, Stein CR, Engel SM (2012) Maternal ethnicity and pre-eclampsia in New York City, 1995–2003. Paediatr Perinat Epidemiol 26: 45–52.

23. Lu FM, Li T, Liu S, Zhuang H (2010) Epidemiology and prevention of hepatitis B virus infection in China. J Viral Hepat 17 Suppl 1: 4–9.

24. Ji Z, Wang T, Shao Z, Huang D, Wang A, et al. (2014) A population-based study examining hepatitis B virus infection and immunization rates in Northwest China. PLoS One 9: e97474.

25. Liu J, Fan D (2007) Hepatitis B in China. Lancet 369: 1582–1583.

26. Changsha City Bureau of Statistics, National Bureau of Changsha Survey Organization (2010) Changsha Statistical Yearbook 2010 (in Chinese). Beijing: China Statistics Press: 417–426.

27. Zhang S, Li RT, Wang Y, Liu Q, Zhou YH, et al. (2010) Seroprevalence of hepatitis B surface antigen among pregnant women in Jiangsu, China, 17 years after introduction of hepatitis B vaccine. Int J Gynaecol Obstet 109: 194–197.

28. Zhang Y, Fang W, Fan L, Gao X, Guo Y, et al. (2013) Hepatitis B surface antigen prevalence among 12,393 rural women of childbearing age in Hainan Province, China: a cross-sectional study. Virol J 10: 25.
29. Li F, Wang Q, Zhang L, Su H, Zhang J, et al. (2012) The risk factors of transmission after the implementation of the routine immunization among children exposed to HBV infected mothers in a developing area in northwest China. Vaccine 30: 7118–7122.

30. Poland GA, Jacobson RM (2004) Clinical practice: prevention of hepatitis B with the hepatitis B vaccine. N Engl J Med 351: 2832–2838.

31. Ishizaka N, Ishizaka Y, Takahashi E, Toda Ei E, Hashimoto H, et al. (2002) Increased prevalence of carotid atherosclerosis in hepatitis B virus carriers. Circulation 105: 1028–1030.

32. Sung J, Song YM, Choi YH, Ebrahim S, Davey SG (2007) Hepatitis B virus seropositivity and the risk of stroke and myocardial infarction. Stroke 38: 1436–1441.