

Association of COVID-19 vaccination before conception with maternal liver function during early pregnancy: a cohort study of 7745 Chinese pregnant women

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ABSTRACT

Multicenter case series has reported patients with hepatic injury following COVID-19 vaccination, which raised concern for the possibility of vaccine-induced liver dysfunction. We aimed to assess the impact of COVID-19 vaccination on liver function of pregnant women, who may be uniquely susceptible to vaccine-induced liver dysfunction. We conducted a retrospective cohort study at a tertiary hospital in Shanghai, China. Vaccine administration was obtained from the electronic vaccination record. Serum levels of alanine transaminase (ALT), aspartate transaminase (AST), total bile acid (TBA) and total bilirubin (TBIL) in early pregnancy were determined by enzymatic methods. Among the 7745 included pregnant women, 3832 (49.5%) received at least two doses of an inactivated vaccine. COVID-19 vaccination was significantly associated with higher levels of maternal serum TBA. Compared with unvaccinated pregnant women, the mean TBA levels increased by 0.17 $\mu\text{mol/L}$ ($\beta = 0.17$, 95% CI, 0.04, 0.31) for women who had been vaccinated within 3 months before the date of conception. Moreover, COVID-19 vaccination was significantly associated with an increased risk of maternal hyperbileacidemia. The risk of hyperbileacidemia increased by 113% (RR = 2.13; 95% CI, 1.17-3.87) for pregnant women who had been vaccinated within 3 months before conception compared with unvaccinated pregnant women. However, when the interval from complete vaccination to conception was prolonged to more than 3 months, COVID-19 vaccination was not associated with serum TBA levels or maternal hyperbileacidemia. Our findings suggest that vaccination with inactivated COVID-19 vaccines more than 3 months before conception have no detrimental effects on maternal liver function in early pregnancy.

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused a major public health crisis since early 2020 [1]. Vaccination is the most important method of pandemic control [2]. As of June 1, 2022, more than 5 billion persons have been vaccinated with coronavirus disease 2019 (COVID-19) vaccines worldwide [3]. Despite the high COVID-19 vaccination coverage, potential vaccine-induced adverse effects, especially for pregnant women who were excluded from the initial randomized controlled trials testing the safety and efficacy of COVID-19 vaccines, have not yet been fully characterized [4].


The side effects related to COVID-19 vaccines are typically mild and usually resolve within 1–3 days after vaccination. These side effects include local adverse events (injection site pain, swelling and redness) and systemic reactions (fever, fatigue, headache and myalgia) [5, 6]. In addition, COVID-19

vaccination has also been linked to the development of some autoimmune diseases, such as Graves' disease, myocarditis and immune thrombocytopenic purpura [7–14]. Recently, a multicenter case series reported 16 patients with hepatic injury following mRNA-based COVID-19 vaccination [15]. Although the causality could not be proven, it raised concern for the possibility of vaccine-induced liver injury. However, no study has reported the effect of COVID-19 vaccination on liver function among pregnant women, who may be uniquely susceptible to vaccine-induced liver dysfunction.

In China, pregnant women are not recommended to receive COVID-19 vaccines. Using data from a retrospective cohort study of 7745 Chinese pregnant women, we examined the association of COVID-19 vaccination before conception with maternal liver function in early pregnancy. We hope our findings will add safety information related to COVID-19

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vaccination for pregnant women or women who are trying to conceive.

Materials and methods

Study participants

This retrospective cohort study was conducted at the Shanghai First Maternity and Infant Hospital, which is one of the largest prenatal health care providers in China, with more than 25000 deliveries per year. Participants were pregnant women who were registered at the hospital's department of obstetrics from September 2021 to January 2022. The flowchart of participant enrolment is shown in [Figure 1](#). Briefly, 12076 singleton pregnant women who received liver function assessments in early pregnancy were screened for eligibility. We excluded 4331 pregnant women with chronic disease before pregnancy, women who did not provide vaccination information, women who did not complete vaccination before pregnancy and women who received adenoviral-vectored vaccines. Ethics approval was obtained from the Ethics Committee of the Shanghai First Maternity and Infant Hospital.

Exposure

Vaccine administration data were collected from each participating woman's electronic vaccination record. These data included the vaccine type and manufacturer, number of vaccine doses and date of vaccination. In China, the most commonly used COVID-19 vaccines are inactivated virus vaccines. Therefore, we focused on inactivated COVID-19 vaccines. Participating pregnant women were categorized as exposed if they received at least two doses of an inactivated vaccine before conception. Since pregnant women are not recommended to receive COVID-19 vaccines in China, no unvaccinated participating pregnant women received the vaccine after conception.

Assessment of covariates

Demographic characteristics regarding maternal age (MA), body weight and height before pregnancy, and reproductive history, such as maternal parity (nulliparous or multiparous), abortion history (yes or no) and mode of conception (conceived naturally or conceived through the use of artificial reproductive technology), were extracted from the hospital's electronic medical record system. Gestational age (GA) at the time of the liver function assessment was calculated from the last menstrual period to the date of the liver function assessment. Prepregnancy body mass index (BMI) was calculated as weight (kg) divided by body height in metres squared (m^2) and was

classified into three categories: underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), and overweight or obese (BMI \geq 25.0 kg/m^2).

Outcomes

The main outcome of interest was maternal liver function, which was assessed by measuring serum levels of alanine transaminase (ALT), aspartate transaminase (AST), total bile acid (TBA) and total bilirubin (TBIL) during early pregnancy. The laboratory reference ranges of ALT, AST, TBA and TBIL were 1–40 U/L, 2–40 U/L, 0–10 μ mol/L and 0–17.1 μ mol/L, respectively. The diagnostic standards for hyperbileacidemia were serum levels of TBA higher than 10 μ mol/L.

Statistical analysis

According to their vaccination status, all participating pregnant women were categorized into vaccinated and unvaccinated groups. The general characteristics of the two groups are presented as percentages (%) and were compared using the chi-square test. Continuous serum ALT, AST, TBA and TBIL are depicted as the mean \pm SD and were compared between the two groups using the two-sample t test.

We first conducted multiple linear regression models to assess the associations of COVID-19 vaccination with serum levels of ALT, AST, TBA and TBIL. In linear regression models, vaccination status (yes/no) was fitted as an independent variable, whereas each liver function parameter was fitted as a dependent variable. We considered GA at the time of the liver function assessment, MA, parity, mode of conception, abortion history and prepregnancy BMI as potential confounders. Given one study observed that the binding and neutralizing antibodies declined over time 3 months after receiving two doses of an inactivated virus vaccine [16], based on the time intervals from complete vaccination to the date of conception, vaccinated participants were further divided into two subgroups: \leq 3 months and $>$ 3 months since vaccination. We then estimated the association between the time intervals and each liver function parameter with the unvaccinated group serving as a reference.

We subsequently performed multivariable log-binomial regression analysis to estimate the relative risk (RR) and 95% CI for the associations of COVID-19 vaccination with a dichotomous outcome: maternal hyperbileacidemia. We adjusted for the same confounders as those in linear regression analysis. In log-binomial regression analysis, the association between the time intervals from complete vaccination to the date of conception and the risk of maternal

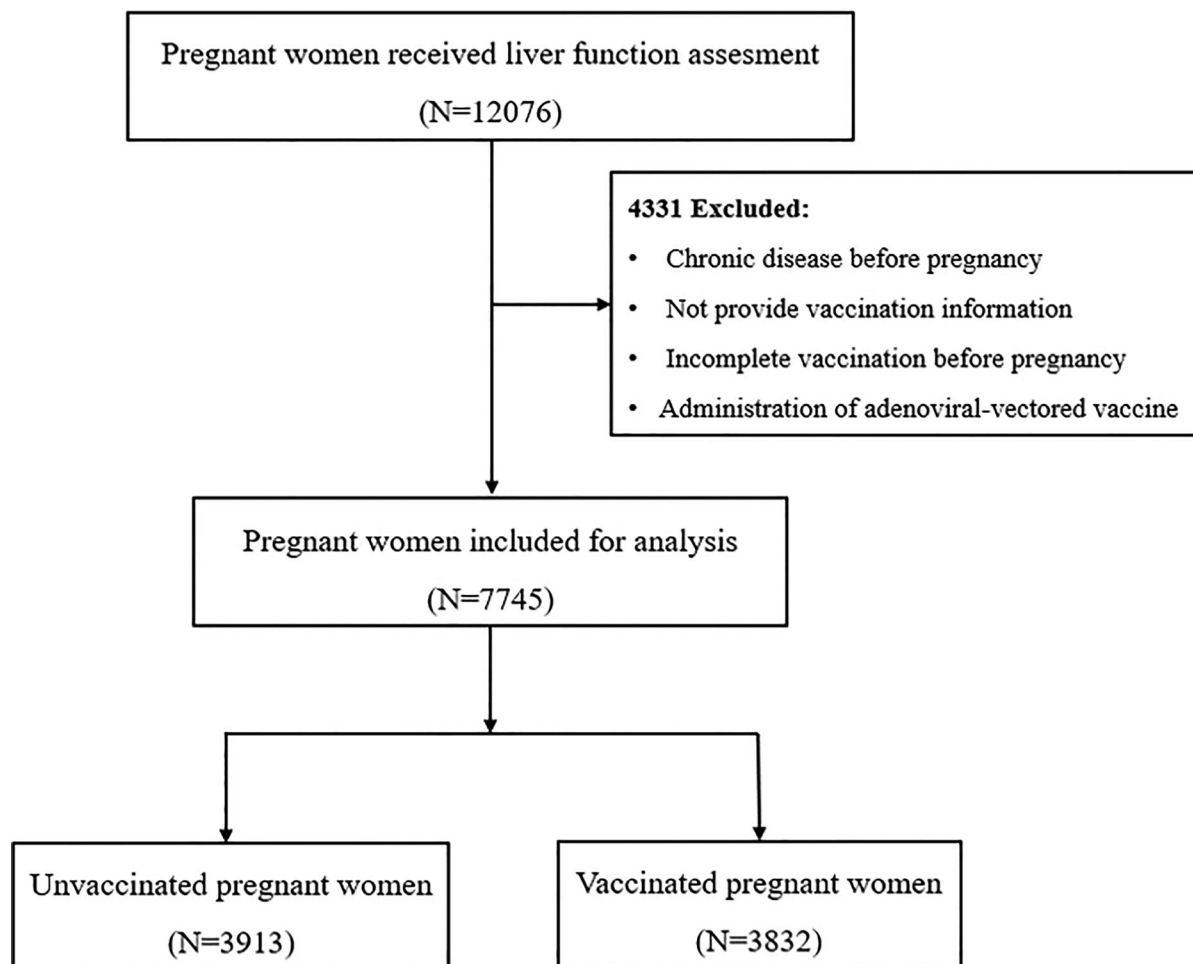


Figure 1. The flow chart of participants enrolment. A total of 7745 pregnant women were included in the final analysis. Among the 7745 participating pregnant women, 3832 (49.5%) received at least two doses of an inactivated vaccine.

hyperbileacidemia was also estimated with the unvaccinated group serving as the reference.

As a sensitivity analysis to address the confounding effects of liver dysfunction in a previous pregnancy, we replicated all linear regression models restricted to nulliparous pregnant women. Another sensitivity analysis was conducted to ensure that the observed associations were not confounded by the mode of conception by replicating linear regression models to participating women who conceived naturally. In a third sensitivity analysis, we replicated regression models restricted to participants with no prior history of abortion. All statistical analyses were performed using R statistical software version 3.2.3 (R Project for Statistical Computing), and a 2-sided $P < 0.05$ was considered significant.

Results

Demographic characteristics of the participants

After exclusion, 7745 pregnant women were included in the final analysis. As shown in Table S1, there was no significant difference in MA, parity, prepregnancy BMI or mode of conception between the included

and excluded subjects. However, the prevalence of abortion was slightly higher in the included subjects than in the excluded subjects (24.2% vs. 21.9%, $P = 0.004$). The general characteristics of the included subjects are summarized in Table 1. Of the 7745 included pregnant women, 3832 (49.5%) completed vaccination before conception (1636 completed vaccination within 3 months of conception, and 2196 completed vaccination before 3 months of conception), while 3913 (50.5%) did not receive any COVID-19 vaccine before their liver function assessment. The vaccinated and unvaccinated groups did not differ in MA or prepregnancy BMI. However, compared with the unvaccinated pregnant women, the vaccinated pregnant women were more likely to be multiparous and less likely to have a prior abortion history or conceive through the use of ART.

Distribution of serum levels of ALS, AST, TBIL and TBA

Serum levels of ALT, AST, TBIL and TBA were measured and compared between the vaccinated and unvaccinated groups (Table 2). The mean (\pm SD) ALS, AST, TBA and TBIL levels of the 7745

Table 1. General characteristics of the participating pregnant women.

Characteristics ^a	Total (N = 7745)	Vaccination		p-value ^b
		Yes (N = 3832)	No (N = 3913)	
Maternal age				
< 35	6521 (84.2%)	3251 (84.8%)	3270 (83.6%)	0.125
≥ 35	1224 (15.8%)	581 (15.2%)	643 (16.4%)	
Parity				
Nulliparous	6197 (80.0%)	2804 (73.2%)	3393 (86.7%)	< 0.01**
Multiparous	1548 (20.0%)	1028 (26.8%)	520 (13.3%)	
Pregnancy BMI				
< 18.5	959 (12.4%)	487 (12.7%)	472 (12.1%)	0.176
18.5-24.9	5939 (76.7%)	2950 (77.0%)	2989 (76.4%)	
≥ 25	847 (10.9%)	395 (10.3%)	452 (11.6%)	
Mode of conception				
The use of ART	247 (3.2%)	40 (1.0%)	207 (5.3%)	< 0.01**
Natural Conception	7498 (96.8%)	3792 (99.0%)	3706 (94.7%)	
Abortion history				
Yes	1874 (24.2%)	780 (20.4%)	1094 (28.0%)	< 0.01**
No	5871 (75.8)	3052 (79.6%)	2819 (72.0%)	

^aValues are shown as percent (%).

^bp-values were calculated by chi-square test.

** $p < 0.01$.

participating pregnant women were 19.13 ± 18.54 $\mu\text{mol/L}$, 19.61 ± 8.39 $\mu\text{mol/L}$, 2.26 ± 2.27 U/L and 9.27 ± 3.49 U/L, respectively.

Analyses of the differences in serum liver function parameters between the two groups showed that serum levels of ALT (18.59 vs. 19.66, $P = 0.011$) and AST (19.37 vs. 19.84, $P = 0.012$) were significantly lower in vaccinated pregnant women than in vaccinated pregnant women. In contrast, serum levels of TBA (2.33 vs. 2.20, $P = 0.022$) and TBIL (9.42 vs. 9.13, $P < 0.001$) were significantly higher in vaccinated pregnant women than in vaccinated pregnant women.

Association of COVID-19 vaccination with serum levels of ALS, AST, TBIL and TBA

The adjusted associations of COVID-19 vaccination with serum levels of ALT, AST, TBA and TBIL are presented in Table 3. We found that COVID-19 vaccination was not significantly associated with serum levels of ALT, AST or TBIL. COVID-19 vaccination was significantly associated with higher levels of serum TBA. Compared with unvaccinated pregnant women, pregnant women who had been vaccinated within 3 months before the date of conception showed an increase in the mean TBA level of 0.17 U/L ($\beta = 0.17$, 95% CI, 0.04, 0.31). However, when the time interval from complete vaccination to the date of conception was prolonged to more than 3 months,

COVID-19 vaccination was not associated with serum levels of TBA.

Sensitivity analysis

In the sensitivity analysis, when restricting the analysis to nulliparous pregnant women, the associations of COVID-19 vaccination with TBA were similar to those observed in all participating pregnant women (Table S2). Further limiting the analysis to pregnant women who conceived naturally yielded generally similar findings (Table S3). In addition, compared with the main results, the observed associations did not change significantly when limiting the analysis to pregnant women with no prior history of abortion (Table S4).

Association of COVID-19 vaccination with risk of maternal hyperbileacidemia

Given that linear regression analysis demonstrated that COVID-19 vaccination was associated with higher serum levels of TBA, we sought to examine the associations of COVID-19 vaccination with the risk of maternal hyperbileacidemia. As shown in Table 4, COVID-19 vaccination was associated with an increased risk of maternal hyperbileacidemia. In the adjusted model, compared with unvaccinated pregnant women, women who had been vaccinated

Table 2. Distribution of serum ALT, AST, TBA and TBIL in early pregnancy.

Characteristics ^a	Total (N = 7745)	Vaccination		p-value ^b
		Yes (N = 3832)	No (N = 3913)	
ALT (U/L)	19.13 ± 18.54	18.59 ± 17.20	19.66 ± 19.75	0.011 *
AST (U/L)	19.61 ± 8.39	19.37 ± 8.02	19.84 ± 8.72	0.012 *
TBA ($\mu\text{mol/L}$)	2.26 ± 2.27	2.33 ± 2.43	2.20 ± 2.10	0.022 *
TBIL ($\mu\text{mol/L}$)	9.27 ± 3.49	9.42 ± 3.61	9.13 ± 3.36	< 0.001**

^aValues are shown as mean (\pm SD).

^bp-values were calculated by student's t-test.

* $p < 0.05$, ** $p < 0.01$.

Table 3. Effect estimates (95% CI) of serum ALT, AST, TBA and TBIL levels associated with COVID-19 vaccination before conception.

	Unvaccinated	Vaccinated	Time interval from vaccination to pregnancy	
			≤ 3 months	> 3 months
ALT	0 (Reference)	-0.16 (-1.01, 0.69)	-0.14 (-1.22, 0.94)	-0.18 (-1.18, 0.82)
AST	0 (Reference)	-0.04 (-0.43, 0.34)	0.14 (-0.35, 0.63)	-0.19 (-0.64, 0.26)
TBA	0 (Reference)	0.07 (-0.04, 0.18)	0.17 (0.04, 0.31) *	-0.01 (0.13, 0.12)
TBIL	0 (Reference)	0.05 (-0.11, 0.21)	0.05 (-0.16, 0.25)	0.05 (-0.14, 0.24)

^aAdjusted for GA at the time of liver function assessment, maternal age, parity, model of conception, abortion history and pre-pregnancy body mass index.
* $p < 0.05$.

within 3 months before the date of conception had a risk of maternal hyperbileacidemia that increased by 113% (RR = 2.13; 95% CI, 1.17, 3.87). However, when the time interval from complete vaccination to the date of conception was prolonged to more than 3 months, COVID-19 vaccination was not significantly associated with maternal hyperbileacidemia.

Discussion

The most intuitive expected toxicity of COVID-19 vaccines is related to immune activation. Therefore, the side effects are usually mild and self-limiting, and very few serious adverse events are reported [17]. In this cohort of 7745 Chinese pregnant women, we provided a comprehensive assessment of the effect of COVID-19 vaccination on maternal liver function in early pregnancy. We found that pregnant women who had been vaccinated within 3 months before the date of conception had higher serum TBA levels than those who had not been vaccinated. In addition, we found that COVID-19 vaccination within 3 months before the date of conception was associated with an increased risk of maternal hyperbileacidemia. Since higher serum TBA is considered to be an indicator of hepatobiliary impairment or disease [18], our findings might suggest the possibility of COVID-19 vaccine-induced liver injury.

Although rare, evidence of liver injury related to COVID-19 vaccination has emerged recently. In a multicenter case series, Shroff H et al. reported 16 patients with liver injury following mRNA-based COVID-19 vaccination. Of the 16 patients, 13 demonstrated a hepatocellular pattern of liver injury [15]. In another study, Dumortier J reported a case of a liver

transplant recipient who presented mild liver injury after the first dose of an mRNA vaccine. In addition to liver injury, a growing number of case reports reporting individuals who developed autoimmune hepatitis following mRNA-based COVID-19 vaccination have begun to emerge, and molecular mimicry is supposed to be the potential mechanism underlying vaccine-induced autoimmune conditions [19–26].

Our study is the first to examine the association of COVID-19 vaccination before conception with liver function among pregnant women. We observed higher levels of serum TBA and an increased risk of maternal hyperbileacidemia in association with COVID-19 vaccination within 3 months before the date of conception. The observed association of COVID-19 vaccination with serum TBA was consistent with a recent study conducted by Liu et al. With 11 healthy adult volunteers, they observed significantly elevated serum levels of TBA at Day 7 after the first dose of an inactivated COVID-19 vaccine [27].

The mechanisms through which inactivated vaccines impact liver function have not been elucidated. Similar to SARS-CoV-2 infection, vaccinated with mRNA COVID-19 vaccines could also trigger autoimmune responses through cross-reactivity with host cells [28], which may induce liver injury with autoimmune features. In addition, one study observed an enrichment of T cells in different areas of the liver that were reactive to mRNA COVID-19 vaccine [29]. The activation of intrahepatic T cells may lead to immune-mediated liver injury [30]. Although inactivated vaccines have lower immunogenicity than mRNA vaccines [31], they may trigger similar immune and autoimmune responses. We hypothesized that the alterations in maternal liver function might be attributed to inactivated vaccine-induced immune and autoimmune responses, especially the responses within 3 months after receiving two-dose inactivated vaccines.

Considering that the estimated increase in serum TBA is relatively small (0.17 U/L), the clinical relevance of the present findings merits further discussion. Our findings do not intend to discourage health care providers from prescribing inactivated COVID-19 vaccines to women who are trying to conceive. In contrast, we raise awareness about the potential adverse effects of COVID-19 vaccination on liver function among pregnant women and suggest that

Table 4. Relative risk of maternal hyperbileacidemia associated with COVID-19 vaccination before pregnancy.

	Model, RR (95% CI)	
	Crude model	Adjusted model ^a
Unvaccinated	1.00 (Reference)	1.00 (Reference)
Vaccinated	1.79 (1.06, 3.02) *	1.62 (0.95, 2.78)
Time interval		
≤ 3 months	2.37 (1.31, 4.26) **	2.13 (1.17, 3.87) *
> 3 months	1.36 (0.73, 2.56)	1.22 (0.64, 2.34)

^aAdjusted for GA at the time of liver function assessment, maternal age, maternal parity, mode of conception, abortion history and pre-pregnancy body mass index.

* $p < 0.05$, ** $p < 0.01$.

COVID-19 vaccination should be performed more than 3 months before the date of conception.

Bearing certain limitations, our results should be interpreted with caution. First, although the sample size is quite large ($N = 7745$), our study is an observational study and the existence of residual confounders may not be ruled out. Second, due to the retrospective design of the present study, we could not assess the antibody levels of each participant. However, no participant had ever been infected with SARS-CoV-2 before the date of their liver function assessment, and therefore, no participant in the unvaccinated group developed natural antibodies. Third, all vaccinated pregnant women received inactivated COVID-19 vaccines, and we could not compare the effect of different types of COVID-19 vaccines on maternal liver function. Fourth, all participating pregnant women were from one of the largest cities in China, and most participants were of Han ethnicity, which may limit the generalizability of our findings.

Our study provides the first evidence that vaccination with inactivated COVID-19 vaccines more than 3 months before conception does not result in any detrimental effects on maternal liver function in early pregnancy. Our findings may contribute to the mounting evidence that supports the safety of COVID-19 vaccination in pregnant women or women who are trying to conceive.

Authors contributions

The study was designed by LPJ and YZ. Acquisition, analysis, or interpretation of data were done by LPJ and YZ. Drafting of the manuscript was done by YZ and YBZ. Statistical analysis was done by YZ and YBZ. YZ, YBZ, YCZ, ZYZ, YJZ, MYL and XS provided administrative, technical and material support. LPJ obtained the funding and had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the reviewing and approved the final version.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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