

Safety of the BBIBP-CorV COVID-19 Vaccine in Relation to Adverse Clinical Outcomes in Newborns: A Prospective Cohort Study

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Objective: The aim of this study is to evaluate the safety of preconception inoculation with an inactivated SARS-CoV-2 vaccine with respect to adverse birth outcomes in newborns, to elucidate the potential association between inactivated COVID-19 vaccination and birth outcomes, and to provide scientific evidence to inform future vaccine policy development.

Methods: In this study, a prospective cohort design is adopted, including 913 mother–infant pairs among 2243 pregnant and postpartum women who delivered between January 2023 and May 31, 2023, at You'ai Hospital and the Maternal and Child Health Hospital in Urumqi. On the basis of the number of preconception doses of an inactivated SARS-CoV-2 vaccine, Poisson regression models were used to analyse the safety of preconception vaccination in terms of adverse birth outcomes in newborns.

Results: Among 913 participants, 13.8% were unvaccinated (n=126), while 1-, 2-, and 3-dose BBIBP-CorV recipients accounted for 2.4% (n=22), 17.9% (n=163), and 65.9% (n=602), respectively. Stratified analysis revealed no increased risk of adverse neonatal outcomes in any vaccinated group vs unvaccinated group (1-dose: RR 1.07 [0.67–1.71]; 2-dose: 1.02 [0.80–1.31]; 3-dose: 1.03 [0.84–1.26]). Sensitivity analysis confirmed that there were no significant differences.

Conclusion: This study provides substantial evidence that prepregnancy BBIBP-CorV vaccination poses no safety concerns for neonatal outcomes. Clinically, these findings suggest that obstetricians should recommend COVID-19 vaccination during preconception counselling as a protective measure for future pregnancies. Public health implications include (1) supporting the integration of inactivated vaccines into prepregnancy health care programs to enhance immunity before gestation and (2) informing national policies to accelerate vaccine coverage among women of childbearing age, thereby reducing maternal–foetal risks in potential pandemics.

Keywords: SARS-CoV-2, inactivated COVID-19 vaccine, neonatal, vaccine safety, vaccine safety evaluation

Introduction

Novel coronavirus pneumonia (COVID-19) is caused by novel coronavirus, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a highly contagious acute respiratory infectious disease.^{1,2} Vaccination against COVID-19 is widely regarded as one of the most effective means to contain the spread of the epidemic and reduce the burden on health.³ As of August 18, 2022, the World Health Organization (WHO) approved emergency use authorizations for four types of vaccines: mRNA vaccines, adenovirus vector vaccines, inactivated virus vaccines, and recombinant protein vaccines.⁴ Global vaccine distribution disparities persist: mRNA platforms dominate high-income countries (85% supply), while inactivated vaccines (BBIBP-CorV, etc.) serve 72 LMICs. Despite the accumulation of safety data, pregnant women are frequently excluded from clinical trials because of foetal safety concerns,^{5,6} exacerbating vaccine hesitancy in this population, particularly in terms of prepregnancy and trimester-specific vaccination timing.

Current evidence suggests that maternal COVID-19 vaccination during pregnancy does not increase the risk of adverse neonatal outcomes.^{7–11} A large Israeli cohort (n=4,399) revealed comparable incidences of gestational age at delivery, small-for-gestational-age infants, and respiratory complications between vaccinated and unvaccinated groups,¹² whereas multinational studies confirmed no increased risks of stillbirth, congenital abnormalities, or NICU admission.^{13–15} Notably, data from a Boston cohort indicated trimester-dependent efficacy, with late-pregnancy immunization enhancing infant protection through antibody transfer.¹⁶ However, critical gaps persist: (1) safety data for prepregnancy inactivated vaccination remain scarce; (2) trimester-specific risk profiles are inadequately quantified; and (3) systematic validation in high-coverage populations is lacking.

This study was conducted in Urumqi, Xinjiang, which experienced an Omicron variant-dominated COVID-19 infection peak between December 2022 and February 2023. The Urumqi vaccination campaign was launched in August 2021, and the full-course vaccination rate was significantly higher than the national average. Urumqi operates a comprehensive three-tier maternal and child health care network. All participants received standardized antenatal care at either a tertiary specialized hospital (Urumqi Maternal and Child Health Hospital) or a general hospital obstetrics department (You'ai Hospital), with first-trimester registration rates exceeding 95% and a 100% institutional delivery rate. This high-coverage perinatal health care system may enhance the generalizability of findings to regions with similar medical resource allocation.

In this prospective cohort study, the neonatal safety of prepregnancy BBIBP-CorV vaccination was evaluated. By comparing birth outcomes between vaccinated and unvaccinated women in Urumqi's high-coverage system, we address critical evidence gaps regarding how preconception inactivates vaccine safety, empowers obstetricians to recommend preconception vaccination during fertility counselling, leveraging its dual benefit for maternal and neonatal protection, and provides evidence for integrating inactivated vaccines into national prepregnancy health care frameworks, accelerating vaccine equity in resource-varied settings.

Methods

Study Design and Setting

This prospective cohort study was conducted from February 2023 to May 2023 at Urumqi You'ai Hospital and Maternal and Child Health Hospital. This study follows the guidelines of the Enhanced Epidemiological Observational Study Reporting (STROBE). The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Committee of Xinjiang Medical University, and written informed consent was obtained from the participants. The survey questionnaire was designed on the basis of a literature review,¹⁷ as well as expert evaluations from epidemiological and obstetric experts. Prior to official distribution, a pilot test was conducted to collect feedback, refine the questionnaire, and evaluate its clarity, logic, scientific validity, and accuracy. The pregnant women who participated in the study joined the research group during their first prenatal examination. On-site health care professionals collected detailed information including basic demographic data, SARS-CoV-2 exposure history, vaccination status, and adverse clinical outcomes in newborns through structured questionnaires, face-to-face interviews, and telephone follow-up. The detailed questionnaire used in this study is provided in [Supplementary Figure S1](#).

This study specifically evaluated the safety of prepregnancy vaccination. Women were considered exposed to the vaccine if they received one or more doses of the BBIBP-CorV-inactivated COVID-19 vaccine within the 3 months immediately preceding conception. Conception was estimated based on the first day of the last menstrual period (LMP) and confirmed by first-trimester ultrasound dating. This preconception window was selected to capture women who were vaccinated while actively planning pregnancy, ensuring that the vaccination occurred prior to embryonic exposure. Only vaccinations administered during this defined prepregnancy period were included in the exposed groups. Women who received any vaccine dose during their current pregnancy were excluded from the analysis to isolate the effects of prepregnancy exposure.

Inclusion and Exclusion Criteria

Inclusion criteria:

- (1) Pregnant women who gave birth at You'ai Hospital and Maternal and Child Health Hospital in Urumqi from February 2023 to May 2023;
- (2) Age range from 18 to 45 years;
- (3) COVID-19 nucleic acid and/or antibody tests were negative during pregnancy;
- (4) Only women who were vaccinated with BBIBP-CorV ≤ 3 months before pregnancy were included.

Exclusion criteria:

- (1) Serologically confirmed prior SARS-CoV-2 exposure (IgG+) led to exclusion, regardless of symptoms;
- (2) Pregnant women who terminated their pregnancy;
- (3) Pregnant women with multiple pregnancies;
- (4) Pregnant women who use drugs that may affect foetal development during pregnancy, such as certain antibiotics and antiepileptic drugs;
- (5) Vaccination during pregnancy.

Ethical Statement

This study was approved by the Xinjiang Medical University Institutional Review Board. On-site health care professionals collected individual baseline information and other relevant data, and written informed consent was obtained from the participants. All the research data were completely anonymized to ensure confidentiality.

Variable Definitions

The outcome measure of this study is the composite adverse birth outcome of newborns,¹⁸ which consists of seven nonweighted measures:

- (1) Neonatal complications, including bronchopulmonary dysplasia, hypoxic-ischaemic encephalopathy, sepsis, anaemia requiring blood transfusion, patent ductus arteriosus, intraventricular haemorrhage, necrotizing enterocolitis, and retinopathy of prematurity;
- (2) Transfer to neonatology for any reason;
- (3) Severe perinatal outcomes, with one of the following situations occurring: Hospitalization of the newborn in the ICU, the presence of birth defects, or intrauterine or neonatal death;
- (4) Low birth weight infants (born weighing less than 2500 grams);
- (5) Rapid assessment results of newborn health status (5-minute Apgar score below 10 points);
- (6) Whether to breastfeed;
- (7) Whether to give birth by caesarean section.

Statistical Analysis

To control for and adjust for multiple potential confounding variables, such as basic demographic information and the medical history of pregnant women, this study used Poisson regression to evaluate the true relationship between vaccine exposure and adverse birth outcomes among newborns. This method can effectively handle sparse data and provide accurate estimates of event rates. Through stepwise regression, factors such as age, body mass index, husband's age, ethnicity, occupation as a health care worker, education level, medical insurance status, pregnancy season, number of diseases during pregnancy, sleep conditions during late pregnancy, smoking exposure, and alcohol consumption during pregnancy were selected as confounding variables and included in the model. The data were grouped according to the dose of vaccination (0, 1, 2, and 3 doses) and described using descriptive statistical methods.

Basic distribution characteristics of the four research groups are presented. Continuous data are represented as the mean and interquartile range (IQR), whereas categorical data are represented as the count and percentage. Clinically meaningful differences were prespecified as follows: absolute risk difference (ARD) $\geq 5\%$, number needed to harm (NNH) ≤ 30 (based on FDA pregnancy registry guidelines), and relative risk (RR).

The data input was completed using EpiData software (version 3.1), and all the statistical analyses were performed using R statistical software (version 4.3.1).

Results

1. Baseline characteristics at the first prenatal visit (prepregnancy vaccination completed)

Among the included participants, 126 (13.8%) were unvaccinated, 22 (2.4%) received only one dose of the vaccine, 163 (17.9%) received two doses of the vaccine, and 602 (65.9%) received three doses of the vaccine (Figure 1).

Key demographic differences are summarized in Table 1:

Clinically relevant variations included the following: Unvaccinated women had higher rates of overweight (26.2% vs $\leq 15\%$ vaccinated) and comorbidities (14.3% vs $\leq 11.6\%$), and vaccinated groups showed higher natural conception planning (68.2–83.6% vs 90.5%). Notable homogeneity: There were no significant differences in age distribution, ethnicity, or health care access across groups.

2. Stratified analysis of the vaccine and primary outcomes

Table 2 summarizes the safety of maternal preconception vaccination with 0 (reference), 1, 2, or 3 doses of the inactivated COVID-19 vaccine on composite adverse neonatal outcomes. Poisson regression analysis revealed no increased risk for any vaccinated group versus the unvaccinated group: 1-dose: RR 1.07 (95% CI: 0.67–1.71); 2-dose: RR 1.02 (95% CI: 0.80–1.31); and 3-dose: RR 1.03 (95% CI: 0.84–1.26). Subgroup analyses stratified by maternal age, prepregnancy BMI, comorbidities, and adverse lifestyle factors (smoking, alcohol use, and late sleep) consistently revealed no statistically significant differences: Maternal age >33 years: All vaccinated groups exhibited a nonsignificant reduction in risk (1-dose: RR 0.99 [0.41–2.39]; 2-dose: RR 0.97 [0.58–1.61]; 3-dose: RR 0.98 [0.67–1.45]). Overweight/

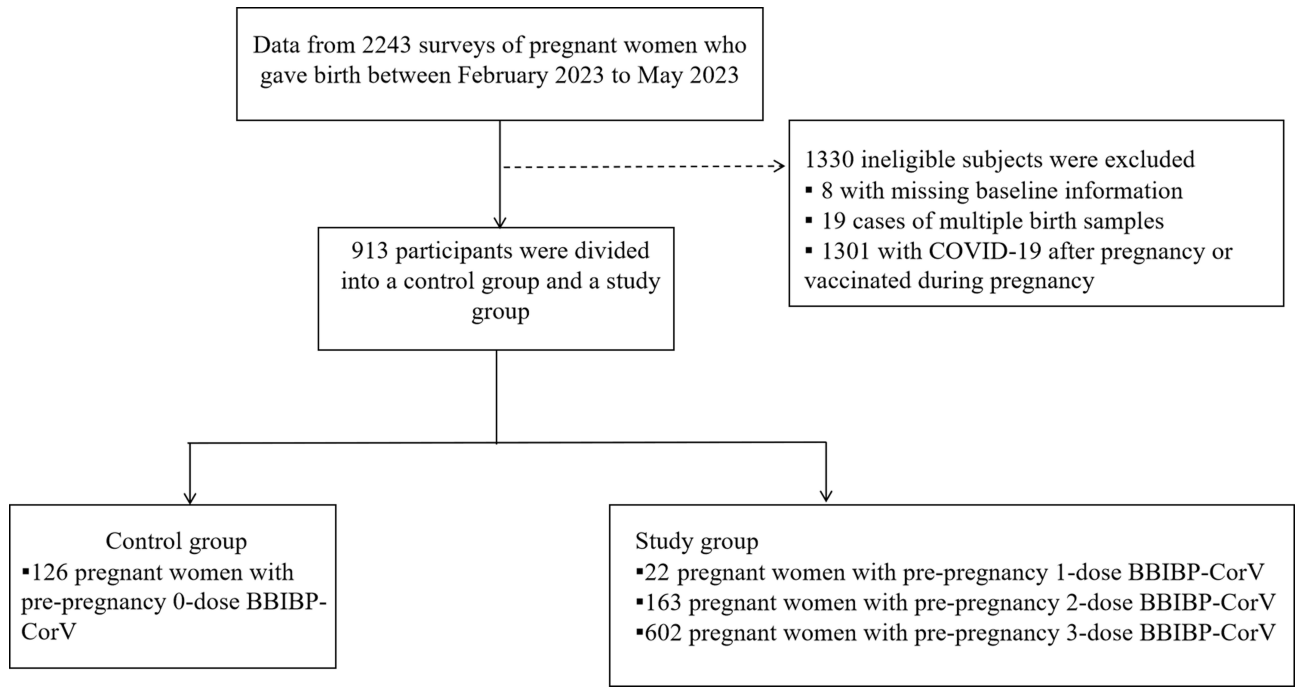


Figure 1 Flowchart of sample selection.

Table 1 Baseline Population Characteristics

Characteristics	Vaccine Status After Pregnancy (Column %)			
	Women with 0 Dose	Women with 1 Dose	Women with 2 Doses	Women with 3 Doses
Total	126 (13.8%)	22 (2.4%)	163 (17.9%)	602 (65.9%)
Maternal age group				
< 20 yr	0	0	2 (1.2%)	2 (0.3%)
20–29 yr	56 (44.4%)	11 (50.0%)	68 (41.7%)	256 (42.5%)
30–35 yr	48 (38.1%)	7 (31.8%)	73 (44.8%)	257 (42.7%)
> 35 yr	22 (17.5%)	4 (18.2%)	20 (12.3)	87 (14.5%)
Maternal median age, yr [IQR]	30.00 [27.00, 34.00]	29.50 [27.00, 34.00]	30.00 [27.00, 33.00]	30.00 [27.00, 33.00]
^aPaternal age group				
< 20 yr	0	0	0	1 (0.2%)
20–35 yr	94 (74.6%)	16 (72.7%)	126 (77.3%)	457 (75.9%)
> 35 yr	32 (25.4%)	6 (27.3%)	37 (22.7%)	144 (23.9%)
Paternal median age, yr [IQR]	32.00 [29.00, 36.00]	31.00 [28.75, 39.25]	32.00 [29.00, 35.00]	32.00 [29.00, 35.00]
Ethnicity				
Han	81 (64.3%)	16 (72.7%)	109 (66.9%)	411 (68.3%)
Uyghurs	32 (25.4%)	5 (22.7%)	22 (13.5%)	114 (18.9%)
Hui	10 (7.9%)	0	17 (10.4%)	57 (9.5%)
Other ethnic minorities	3 (2.4%)	1 (4.5%)	15 (9.2%)	20 (3.3%)
Occupation				
Healthcare worker	1 (0.8%)	1 (4.5%)	3 (1.8%)	37 (3.7%)
Non-healthcare occupations	91 (72.2%)	14 (63.6%)	121 (74.2%)	465 (77.2%)
Unemployed	34 (27.0%)	7 (31.8%)	39 (23.9%)	100 (16.6%)
Highest education level				
Secondary school or below	28 (22.2%)	7 (31.8%)	46 (28.2%)	144 (23.9%)
Associated degree	44 (34.9%)	6 (27.3%)	47 (28.8%)	170 (28.2%)
Undergraduate degree	47 (37.3%)	8 (36.4%)	65 (39.9%)	258 (42.9%)
Master degree or above	7 (5.6%)	1 (4.5%)	5 (3.1%)	30 (5.0%)
Public medical insurance				
Insured	101 (80.2%)	15 (68.2%)	16 (9.8%)	66 (11.0%)
Not insured	25 (19.8%)	7 (31.8%)	16 (9.8%)	66 (11.0%)
Marital status				
Yes	121 (96.0%)	20 (90.9%)	158 (96.9%)	586 (97.3%)
No	5 (4.0%)	2 (9.1%)	5 (3.1%)	16 (2.7%)

(Continued)

Table 1 (Continued).

Characteristics	Vaccine Status After Pregnancy (Column %)			
	Women with 0 Dose	Women with 1 Dose	Women with 2 Doses	Women with 3 Doses
Season of pregnancy in 2022				
Spring: March - May	7 (5.6%)	2 (9.1%)	9 (5.5%)	35 (5.8%)
Summer: June - August	106 (84.1%)	18 (81.8%)	143 (87.7%)	520 (86.4%)
Fall: September - November	13 (10.3%)	2 (9.1%)	11 (6.7%)	47 (7.8%)
Median maternal height, cm [IQR]	162.00 [160.00, 165.00]	165.00 [161.50, 168.00]	163.00 [160.00, 168.00]	163.00 [159.00, 166.00]
Median maternal weight, kg [IQR]	59.00 [51.45, 68.00]	55.50 [52.75, 62.25]	57.10 [52.00, 65.00]	57.00 [52.00, 65.00]
Maternal body mass index group at the start of pregnancy				
Underweight: < 18.5 kg/m ²	13 (10.3%)	2 (9.1%)	17 (10.4%)	61 (10.1%)
Normal weight: 18.5–24.9 kg/m ²	76 (60.3%)	18 (81.8%)	121 (74.2%)	431 (71.6%)
Overweight: 25–30 kg/m ²	33 (26.2%)	2 (9.1%)	22 (13.5%)	90 (15.0%)
Obesity: > 30 kg/m ²	4 (3.2%)	0	3 (1.8%)	20 (3.3%)
Median maternal BMI, kg/m² [IQR]	22.28 [19.81, 25.40]	20.56 [19.37, 22.90]	21.45 [19.37, 24.00]	21.67 [19.69, 23.96]
Number of pre-existing conditions				
0	107 (84.9%)	20 (90.9%)	138 (84.7%)	528 (87.7%)
1	18 (14.3%)	2 (9.1%)	23 (14.1%)	70 (11.6%)
> 1	1 (0.8%)	0	2 (1.2%)	4 (0.7%)
Previous pregnancy				
Yes	83 (65.9%)	14 (63.6%)	94 (57.7%)	322 (53.5%)
No	43 (34.1%)	8 (36.4%)	69 (42.3%)	280 (46.5%)
Previous miscarriage				
Yes	54 (42.9%)	10 (45.5%)	68 (41.7%)	194 (32.2%)
No	72 (57.1%)	12 (54.5%)	95 (58.3%)	408 (67.8%)
Mode of pregnancy				
Planned natural pregnancy	114 (90.5%)	15 (68.2%)	132 (81.0%)	503 (83.6%)
Unplanned natural pregnancy	7 (5.6%)	3 (13.6%)	23 (14.1%)	74 (12.3%)
Artificial insemination	5 (4.0%)	4 (18.2%)	8 (4.9%)	25 (4.2%)
Self-reported status of sleep late during pregnancy^b				
Yes	16 (12.7%)	2 (9.1%)	18 (11.0%)	79 (13.1%)
No	110 (87.3%)	20 (90.9%)	145 (89.0%)	523 (86.9%)
Self-reported first-hand or secondary smoking exposure during pregnancy				
Yes	76 (60.3%)	9 (40.9%)	81 (49.7%)	353 (58.6%)
No	50 (39.7%)	13 (59.1%)	82 (50.3%)	249 (41.4%)

(Continued)

Table 1 (Continued).

Characteristics	Vaccine Status After Pregnancy (Column %)			
	Women with 0 Dose	Women with 1 Dose	Women with 2 Doses	Women with 3 Doses
Self-reported alcohol intake during pregnancy				
Yes	4 (3.2%)	0	4 (2.5%)	15 (2.5%)
No	122 (96.8%)	22 (100.0%)	159 (97.5%)	587 (97.5%)
Delivery Hospital				
Urumqi Maternal & Child	58 (46.0%)	11 (50.0%)	78 (47.9%)	298 (49.5%)
You'ai Hospital	68 (54.0%)	11 (50.0%)	85 (51.1%)	304 (50.5%)

Notes: Data are presented as n (%), or median [IQR] unless otherwise specified. ^aAdvanced paternal age (eg, >40 years) is associated with an increased risk of de novo mutations. ^bDefined as bedtime ≥23:00.

Abbreviation: IQR, interquartile range.

Table 2 Stratified Analysis of the Safety of Maternal Vaccination with 0, 1, 2, and 3 Doses of Vaccine for Adverse Birth Outcomes (Primary Outcome) in Newborns

Stratification	Composite Outcome of Neonatal Morbidity and Mortality				
	Subjects with Outcome (%)	Total Subjects	Abs. Risk Diff.	Relative Risk Reduction (95% CI)	
				Crude	Adjusted [§]
Overall					
Women with 0 dose (ref.)	116 (92.1%)	126	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	22 (100.0%)	22	7.9%	1.08 [0.68, 1.71]	1.07 [0.67, 1.71]
Women with 2 doses	155 (95.1%)	163	3.0%	1.03 [0.81, 1.31]	1.02 [0.80, 1.31]
Women with 3 doses	572 (95.0%)	602	2.9%	1.03 [0.84, 1.26]	1.03 [0.84,1.26]
Maternal age from 20 to 33 years					
Women with 0 dose (ref.)	83 (89.2%)	93	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	16 (100.0%)	16	10.8%	1.12 [0.65, 1.91]	1.14 [0.66, 1.95]
Women with 2 doses	126 (94.7%)	133	5.5%	1.06 [0.80, 1.40]	1.07 [0.80, 1.41]
Women with 3 doses	431 (93.8%)	459	4.6%	1.05 [0.83, 1.33]	1.06 [0.83, 1.35]
Maternal age > 33 years					
Women with 0 dose (ref.)	33 (100.0%)	33	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	6 (100.0%)	6	0.0%	1.00 [0.41, 2.38]	0.99 [0.41, 2.39]
Women with 2 doses	29 (96.9%)	30	−3.1%	0.96 [0.58, 1.59]	0.97 [0.58, 1.61]
Women with 3 doses	141 (98.6%)	143	−1.4%	0.98 [0.67, 1.44]	0.98 [0.67,1.45]
Underweight at the start of pregnancy: BMI < 18.5 kg/m ²					
Women with 0 dose (ref.)	11 (84.6%)	13	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	2 (100.0%)	2	15.4%	1.18 [0.26, 5.33]	1.19 [0.24, 5.75]

(Continued)

Table 2 (Continued).

Stratification	Composite Outcome of Neonatal Morbidity and Mortality				
	Subjects with Outcome (%)	Total Subjects	Abs. Risk Diff.	Relative Risk Reduction (95% CI)	
				Crude	Adjusted [§]
Women with 2 doses	17 (100.0%)	17	15.4%	1.18 [0.55, 2.52]	1.20 [0.55, 2.64]
Women with 3 doses	60 (98.3%)	61	13.7%	1.16 [0.61, 2.21]	1.14 [0.59, 2.23]
Normal weight at the start of pregnancy: BMI ranging from 18.5 to 24.9 kg/m²					
Women with 0 dose (ref.)	70 (92.1%)	76	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	18 (100.0%)	18	7.9%	1.08 [0.64, 1.82]	1.07 [0.63, 1.83]
Women with 2 doses	116 (95.8%)	121	3.7%	1.04 [0.77, 1.40]	1.03 [0.76, 1.40]
Women with 3 doses	410 (95.1%)	431	3.0%	1.03 [0.80, 1.33]	1.02 [0.79, 1.33]
Overweight or obesity at the start of pregnancy: BMI of 25 kg/m² or above					
Women with 0 dose (ref.)	35 (94.5%)	37	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	2 (100.0%)	2	5.5%	1.05 [0.25, 4.39]	1.03 [0.24, 4.33]
Women with 2 doses	22 (88.0%)	25	-6.5%	0.93 [0.54, 1.58]	0.92 [0.54, 1.58]
Women with 3 doses	102 (92.7%)	110	-1.8%	0.98 [0.66, 1.43]	0.99 [0.67, 1.47]
No pre-existing condition					
Women with 0 dose (ref.)	100 (93.4%)	107	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	20 (100.0%)	20	6.6%	1.07 [0.66, 1.72]	1.05 [0.65, 1.71]
Women with 2 doses	132 (95.6%)	138	2.2%	1.02 [0.78, 1.32]	1.01 [0.78, 1.33]
Women with 3 doses	502 (95.0%)	528	1.6%	1.01 [0.82, 1.26]	1.02 [0.82, 1.26]
At least 1 pre-existing conditions					
Women with 0 dose (ref.)	16 (84.2%)	19	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	2 (100.0%)	2	15.8%	1.18 [0.27, 5.16]	1.19 [0.25, 5.73]
Women with 2 doses	23 (92.0%)	25	7.8%	1.09 [0.57, 2.06]	1.11 [0.58, 2.15]
Women with 3 doses	70 (94.5%)	74	10.3%	1.12 [0.65, 1.93]	1.16 [0.65, 2.04]
No self-reported exposure to smoking, alcohol, or sleep late during pregnancy					
Women with 0 dose (ref.)	47 (97.9%)	48	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	11 (100.0%)	11	2.1%	1.02 [0.53, 1.96]	1.03 [0.52, 1.98]
Women with 2 doses	74 (94.8%)	78	-3.1%	0.96 [0.67, 1.39]	0.97 [0.67, 1.40]
Women with 3 doses	216 (97.2%)	222	-0.7%	0.99 [0.72, 1.36]	0.99 [0.72, 1.37]
Any self-reported exposure to smoking, alcohol, or sleep late during pregnancy					
Women with 0 dose (ref.)	69 (88.4%)	78	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	11 (100.0%)	11	11.6%	1.13 [0.59, 2.13]	1.15 [0.61, 2.18]
Women with 2 doses	81 (95.2%)	85	6.8%	1.07 [0.78, 1.48]	1.08 [0.77, 1.49]
Women with 3 doses	356 (93.6%)	380	5.2%	1.05 [0.81, 1.37]	1.06 [0.82, 1.37]

obesity (BMI ≥ 25 kg/m²): Nonsignificant risk reduction in the 2-dose (RR 0.93 [0.54–1.58]) and 3-dose (RR 0.98 [0.66–1.43]) groups. No reduction was observed in the underweight/normal-weight subgroup. No adverse effects on lifestyle factors were detected in the 2-dose (RR 0.96 [0.67–1.39]) and 3-dose (RR 0.99 [0.72–1.36]) groups. Subgroups with comorbidities or unhealthy lifestyles showed no difference in risk between vaccinated and unvaccinated mothers.

3. Stratified analysis of the vaccine and secondary outcomes

Sensitivity analysis was conducted on the individual outcomes of major adverse events, as shown in Table 3. The results revealed that compared with unvaccinated pregnant women, pregnant women who received a vaccination had a lower incidence of adverse outcomes such as caesarean section delivery, but there was no significant difference between the two groups. There were no statistically significant differences observed between the vaccinated and unvaccinated groups in terms of outcomes related to neonatal complications, transfer to neonatology for treatment, severe perinatal outcomes, low birth weight infants, 5-minute Apgar scores below 10, or breastfeeding status.

Table 3 Safety of BBIBP-CorV Vaccine for Pregnant and Maternal Women on Single Adverse Clinical Outcome (Secondary Outcome) of Newborns

Stratification	Secondary Outcome				
	Subjects with Outcome (%)	Total Subjects	Abs. Risk Diff.	Relative Risk Reduction (95% CI)	
				Crude	Adjusted [§]
Against outcome of Neonatal complications					
Women with 0 dose (ref.)	0	126	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	0	22	0.0%	Not calculated	Not calculated
Women with 2 doses	0	163	0.0%	Not calculated	Not calculated
Women with 3 doses	3 (0.49%)	602	0.5%	Not calculated	Not calculated
Against outcome of Transferred to neonatology for treatment					
Women with 0 dose (ref.)	9 (7.1%)	126	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	4 (18.1%)	22	11.0%	2.54 [0.78, 8.26]	2.56 [0.77, 8.48]
Women with 2 doses	13 (7.9%)	163	0.8%	1.11 [0.47,2.61]	1.09 [0.46, 2.56]
Women with 3 doses	53 (8.8%)	602	1.7%	1.23 [0.60, 2.49]	1.18 [0.58, 2.41]
Against outcome of Severe perinatal outcomes					
Women with 0 dose (ref.)	0	126	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	0	22	0.0%	0	0
Women with 2 doses	0	163	0.0%	0	0
Women with 3 doses	0	602	0.0%	0	0
Against outcome of Low birth weight infant					
Women with 0 dose (ref.)	2 (1.5%)	126	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	1 (4.5%)	22	3.0%	2.86 [0.26, 31.58]	2.83 [0.25, 32.06]
Women with 2 doses	3 (1.8%)	163	0.3%	1.16 [0.19, 6.93]	1.16 [0.19, 7.01]
Women with 3 doses	11 (1.8%)	602	0.3%	1.15 [0.25, 5.19]	1.21 [0.26, 5.50]

(Continued)

Table 3 (Continued).

Stratification	Secondary Outcome				
	Subjects with Outcome (%)	Total Subjects	Abs. Risk Diff.	Relative Risk Reduction (95% CI)	
				Crude	Adjusted [§]
Against outcome of 5-minute Apgar score below 10 points					
Women with 0 dose (ref.)	2 (1.5%)	126	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	0 (0%)	22	−1.5%	0	0
Women with 2 doses	2 (1.2%)	163	−0.3%	0.77 [0.10, 5.48]	0.75 [0.11, 5.37]
Women with 3 doses	12 (1.9%)	602	0.4%	1.25 [0.28, 5.61]	1.20 [0.26, 5.39]
Against outcome of Whether or not by breast milk					
Women with 0 dose (ref.)	105 (83.3%)	126	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	19 (86.3%)	22	3.0%	1.03 [0.63, 1.68]	1.01 [0.62, 1.66]
Women with 2 doses	144 (88.3%)	163	5.0%	1.06 [0.82, 1.36]	1.04 [0.81, 1.35]
Women with 3 doses	498 (82.7%)	602	−0.6%	0.99 [0.80, 1.22]	0.99 [0.80, 1.23]
Against outcome of Whether to produce by caesarean section					
Women with 0 dose (ref.)	60 (47.6%)	126	0.0% (ref.)	0% (ref)	0% (ref)
Women with 1 dose	8 (36.3%)	22	−11.3%	0.76 [0.36, 1.59]	0.78 [0.37, 1.66]
Women with 2 doses	60 (36.8%)	163	−10.8%	0.77 [0.54, 1.10]	0.80 [0.56, 1.15]
Women with 3 doses	276 (45.8%)	602	−1.8%	0.96 [0.72, 1.27]	0.98 [0.74, 1.30]

Discussion

Since the outbreak of COVID-19, global efforts to develop vaccines have been critical for pandemic control. Pregnant women were initially excluded from clinical trials because of foetal safety concerns, resulting in limited evidence regarding the safety of prepregnancy vaccination.^{19–23} Our prospective cohort study provides robust evidence that prepregnancy vaccination with the BBIBP-CorV inactivated vaccine does not increase the risk of adverse neonatal outcomes.

Evidence suggests that prepregnancy vaccination can lead to the production of antibodies that persist into pregnancy, enabling placental transfer and providing passive immunity for newborns.²⁴ Studies have documented detectable maternal immune responses and antibody transfer to umbilical cord blood following vaccination, indicating a potential protective effect for infants.²⁵ Furthermore, comparative analyses have demonstrated that vaccinated individuals generate stronger binding and neutralizing antibody responses than both their infected and unvaccinated counterparts do, without evidence of associated safety concerns for mothers or newborns.²⁶ Importantly, vaccine-induced immune responses can be effectively transferred to the foetus, supporting the protective role of prepregnancy vaccination.²⁷

In this study, we did not report any severe perinatal outcomes (including neonatal admission to the ICU, birth defects, or intrauterine or neonatal mortality) in either the vaccinated or unvaccinated groups. However, in the analysis of single adverse neonatal outcomes, the incidence rate of low birth weight infants in the vaccination group was significantly greater than that in the unvaccinated group, which may be related to the sample size. However, the difference between the two groups was not significant. These findings are consistent with the findings of Shimabukuro and Theiler et al, whose cohort compared unvaccinated pregnant women with vaccinated pregnant women and reported that adverse pregnancy outcomes for pregnant women and adverse outcomes for newborns (neonatal stillbirth, low birth weight

infants, congenital abnormalities) did not vary with vaccination status. In addition, a retrospective cohort study included all individuals who gave birth at Israel's largest delivery centre between January and June 2021 and applied multivariate analysis to find no differences between vaccinated (mid- or late pregnancy) and unvaccinated individuals in terms of delivery and neonatal complications, incidence of infants smaller than normal for gestational age, or neonatal respiratory complications.²⁸ A large, multicentre, retrospective cohort study in the United States revealed that COVID-19 vaccination during pregnancy was not associated with increased risk of premature delivery or small-for-gestational-age infants at birth.^{29–31} We also reported that vaccination reduced C-sections by 11.3% (ARR=11.3%; NNT=8.8), preventing 1 surgery per 9 women vaccinated. Pregnant women who have not been vaccinated may have a higher incidence of underlying diseases or other social psychological factors, such as fear of childbirth, which may lead to a higher caesarean section rate.³² In addition, sociocultural background may play an important role in the decision-making process related to caesarean section. Pregnant women who have not been vaccinated may face fear or misunderstanding because of a lack of vaccine-related information, which may affect their decision-making regarding delivery methods. In contrast, pregnant women who have been vaccinated are more likely to receive positive support and information from health care providers, thereby promoting the choice of natural childbirth.³³ Although we observed a higher caesarean section rate in the unvaccinated group than in the vaccinated group, the difference was not significant. The call for further research pertains broadly to maternal health and delivery outcomes (eg, caesarean drivers, postpartum haemorrhage, and gestational comorbidities) and not solely to caesarean delivery. Future investigations should prioritize the following: vaccine timing effects on delivery outcomes (eg, caesarean rates, preterm birth, and perineal injury); maternal health parameters (eg, placental pathology, inflammatory markers, and long-term cardiometabolic impacts); confounding social determinants (eg, vaccine hesitancy linked to birth plan choices). Finally, a nonsignificant reduction in the incidence of 5-minute Apgar scores less than 10 was observed in the 2-dose group compared with the unvaccinated group. These findings should be interpreted with caution because of the limited subgroup size and the absence of statistical significance. Similarly, a large population-based cohort study from Ontario, Canada, revealed no significant association between COVID-19 vaccination and low 5-minute Apgar scores,³⁴ supporting the overall safety profile of prepregnancy vaccination.

This study has several limitations. The single-centre design and regional sampling may affect the generalizability of the findings and introduce selection bias. Additionally, variations in the timing of prepregnancy vaccination relative to conception were not fully analysed for their potential impact on neonatal outcomes. Nevertheless, the consistent safety profile observed across all dose groups strengthens the evidence supporting the safety of prepregnancy vaccination. Future multicentre studies with larger sample sizes and longer follow-up periods are warranted to further validate these findings and explore the optimal timing of prepregnancy vaccination.

In summary, this study provides evidence that prepregnancy vaccination with the BBIBP-CorV vaccine is not associated with an increased risk of adverse neonatal outcomes. These findings offer reassuring clinical data supporting the safety of prepregnancy vaccination for maternal and infant health. We recommend that health care providers incorporate this evidence into preconception counselling to promote vaccination. Public health policies should consider including inactivated vaccines in prepregnancy care programs to improve coverage. Further large-scale, multicentre studies are warranted to confirm these results and optimize vaccination timing.

Data Sharing Statement

Data Availability Statement: Due to ethical restrictions and patient confidentiality concerns, the raw data underlying this study cannot be made publicly available. Interested researchers may apply for access to the de-identified dataset by submitting a methodologically sound proposal to the corresponding author Kai Wang at wangkaimath@sina.com. Data requests will be assessed and approved by the ethics committee of Xinjiang Medical University.

Ethics Approval

The collection of specimens, epidemiological and clinical data for SARS-CoV-2 infected individuals and their close contacts is a part of a continuing public health investigation of COVID-19 outbreaks, ruled in the Protocol on the Prevention and Control of COVID-19 by the National Health Commission of the People's Republic of China, Ethical

approval was obtained from the Institutional Review Board of Xinjiang Medical University (Ethical Approval Number: XJYKDXR20230327001), and written informed consent was obtained from the participants.

Consent of Information Collection

Individual verbal consent was obtained when collecting personal information and human samples by governmental healthcare professionals in the field.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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