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The pregnancy outcomes of women with SARS-CoV-2 infection in the first trimester ---a longitudinal cohort study

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Abstract

Background In recent years, severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection has been prevalent worldwide. Pregnant women belong to a special group, and it is very important for clinicians to pay attention to the impact of SARS-CoV-2 infection on pregnancy outcomes. However, there are limited studies on the impact of SARS-CoV-2 infection on pregnancy outcomes during the first trimester.

Objective To investigate the effect of SARS-CoV-2 infection in the first trimester on pregnancy outcomes.

Methods Clinical information of pregnant women whose last menstrual period was between October 1, 2022, and April 1, 2023, and who were registered in the Obstetrics and Gynecology department of Peking University International Hospital, was analyzed. Among them, 498 pregnant women with SARS-CoV-2 infection in the first trimester were included in the study group; while a total of 654 pregnant women with no SARS-CoV-2 infection in the first trimester were included in the control group. Mann Whitney U test, $\chi 2$ test, Fisher's exact probability method, and multivariate logistic regression were used to analyze the impact of SARS-CoV-2 infection on pregnancy outcomes during the first trimester.

Results A total of 30 cases in the study group experienced pregnancy loss before 28 weeks of gestation, and 468 cases delivered. In the control group, 41 cases experienced pregnancy loss before 28 weeks of gestation, and 613 cases delivered. The rates of pregnancy loss in the two groups were 6.02% and 6.27%, respectively, with no statistically significant difference between the two groups ($P > 0.05$). There was no statistically significant difference ($P > 0.05$) in the baseline data (delivery age, pre-pregnancy body mass index, gestational age, and parity) between the two groups. The rates of neonatal malformation, premature birth, premature rupture of membranes, postpartum hemorrhage, cesarean section, small for gestational age infants, low birth weight infants, macrosomia, and neonatal asphyxia were compared, with no statistically significant difference between the two groups ($P > 0.05$). However, the incidence of gestational hypertension in the study group was significantly higher than that in the control group ($P = 0.012$).

Conclusions In this single center study, we found that SARS-CoV-2 infection in the first trimester may increase the risk of gestational hypertension, while the incidences of other adverse pregnant outcomes such as premature birth, premature rupture of membranes, cesarean section, postpartum hemorrhage, small for gestational age infants, low

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birth weight infants, and neonatal asphyxia did not significantly increase compared with women without SARS-CoV-2 infection in the first trimester.

Keywords SARS-CoV-2 infection, The first trimester, Pregnancy outcomes

Introduction

The COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global health crisis [1, 2]. Currently, there is still controversy regarding whether pregnancy increases susceptibility to SARS-CoV-2 infection [3, 4], but existing data suggests that pregnancy is a risk factor for severe COVID-19 [5, 6]. Due to the unique physiological adaptation of pregnant women's physiological changes and maternal-fetal interactions, the impact of SARS-CoV-2 on maternal health and pregnancy outcomes has attracted widespread attention. Previous reports were mainly focused on the impact of SARS-CoV-2 infection in the acute affection period, or mid and late pregnancy, with limited research on the relationship between SARS-CoV-2 infection in the first trimester and pregnant outcomes. Some studies have stratified pregnancy outcomes based on gestational age in the context of SARS-CoV-2 infection or have only analyzed a few pregnancy outcome indicators such as miscarriage [7–10]. We conducted a longitudinal cohort study, which analyzed the pregnancy outcomes of pregnant women with or without SARS-CoV-2 infection in the first trimester, aiming to explore the impact of the first trimester SARS-CoV-2 infection on pregnancy outcomes and provide data support for clinical prevention and risk assessment.

Materials and methods

Study design

Clinical information of pregnant women whose last menstrual period was between October 1, 2022, and April 1, 2023, and who were registered in the Obstetrics and Gynecology department of Peking University International Hospital, was analyzed. Among them, 498 pregnant women with SARS-CoV-2 infection in the first trimester were included in the study group. A total of 654 pregnant women with no SARS-CoV-2 infection in the first trimester were included in the control group. This study was reviewed and approved by the Ethics Committee of Peking University International Hospital (2023-KY-0033-01) in accordance with the Declaration of Helsinki, with signed consents from all the subjects for usage of their data.

Data collection

Demographic and clinical data of the subjects, including gestational age, gravidity, parity, pre-pregnancy body mass index (BMI), pregnancy loss (embryo arrest, fetal malformation, intrauterine fetal death, etc.), delivery mode, delivery weeks, neonatal length, neonatal weight, total labor duration, neonatal malformation, precipitous labor, premature birth, macrosomia, small for gestational age infants, low birth weight infants, neonatal asphyxia, placental adhesion, premature rupture of membranes, postpartum hemorrhage, oligohydramnios, gestational hypertension, preeclampsia, et al., were all recorded in the study. Women with a positive reverse transcription-polymerase chain reaction (PCR) for SARS-CoV-2 during the 13^{+6} weeks of gestation were classified as infected.

Statistical analysis

SPSS 26.0 statistical software was used for statistical analysis. Because the gestational age of delivery in this study was non-normal distribution data, the results were expressed in the median and quartile range and Mann Whitney U test was used. The counting data was described using percentages. Fisher's exact probability method was used for the comparison of the rate of neonatal asphyxia between the two groups, while $\chi 2$ test was used for the comparison of the other counting data between the two groups. Multivariate logistic regression analysis was used to evaluate the correlation between the SARS-CoV-2 infection and pregnancy outcomes, with $P < 0.05$ indicating statistically significant differences.

Results

The baseline data between the two groups of pregnant women

A comparison of baseline data between the two groups that delivered was conducted. The differences in gestational age, pre-pregnancy BMI, gravidity and parity between the two groups were not statistically significant ($P > 0.05$), as shown in Table 1.

Among the women with SARS-CoV-2 infection in the first trimester, 429 cases (429/468, 91.67%) were vaccinated against COVID-19. The symptoms of pregnant women with COVID-19 were listed Table 2. Their clinical manifestations were mild or moderate, and no severe or critically ill cases occurred. 185 cases (185/468,39.53%) took antipyretic drugs such as acetaminophen orally, and the conditions of most people improved after 3 ~ 5 days.

Pregnant loss between the two groups

Among the pregnant women with SARS-CoV-2 infection in the early pregnancy, a total of 30 cases experienced pregnancy loss before 28 weeks of gestation, with the rate 6.02% (30/498). Among them, 22 cases experienced embryonic arrest, and copy number variation (CNV)

Table 1 The baseline data between the two groups of pregnant women

	The study group *n* = 468	The control group *n* = 613	χ2	*P*
Gestational age (years)	n(%)	n(%)		
≥ 18–35	348(74.36)	491(80.10)	5.441	0.066
≥ 35–40	102(21.79)	100(16.31)		
≥ 40	18(3.85)	22(3.59)		
Pre-pregnancy BMI (kg/m^2)				
<18.5	44(9.40)	61(9.95)	5.102	0.164
≥ 18.5–25	351(75.00)	473(77.16)		
≥ 25–28	46(9.83)	38(6.20)		
≥ 28	27(5.77)	41(6.69)		
Gravidity				
<3	407(86.97)	523(85.32)	4.620	0.439
≥ 3	61(13.03)	90(14.68)		
Parity				
<1	354(75.64)	441(71.94)	1.867	0.172
≥ 1	114(24.36)	172(28.06)		

Table 2 Symptoms in patients with COVID-19

Fever (77%)
Headache (34%)
Sore throat (38%)
Cough (38%)
Fatigue (32%)
Rhinorrhea and/or nasal congestion (32%)
Anosmia or other smell abnormalities (15%)
Myalgias (38%)
Diarrhea (4%)
Nausea/vomiting (4%)

genetic testing was done on 9 cases of miscarriage tissue: 3 cases were negative, 2 cases were trisomy 22, 1 case was trisomy 18, 1 case was dup (7) (q36.2q36.3) del (14) (q31.3q32.3), and 2 cases were of uncertain clinical significance. 7 cases experienced induced labor due to fetal malformations or chromosome abnormality (2 cases of trisomy 21, 1 case of multiple malformations with negative CNV, 1 case of cleft lip and palate with negative CNV, 1 case of 47, XXY, 1 case of achondroplasia with *FGFR3* mutation, and 1 case of cervical cystic hygroma with 45, X), and 1 case experienced intrauterine death caused by Listeria infection at 16 weeks of gestation.

Among the pregnant women without SARS-CoV-2 infection in the early pregnancy, 41 cases experienced pregnancy loss before 28 weeks of gestation, with the rate 6.27% (41/654). Among them, 32 cases had embryonic arrest (CNV genetic testing was done on 15 cases of miscarriage tissue: negative in 5 cases, trisomy 22 in 2 cases, trisomy 16 in 2 cases, trisomy 13 in 1 case, trisomy 18 in 1 case, trisomy 21 in 2 cases, 45, X in 2 cases). 3 cases experienced premature rupture of membranes before 24 weeks of gestation, inevitably leading to miscarriage. 2 cases experienced intrauterine fetal death at 16 weeks of gestation and 20 weeks of gestation. 4 cases experienced induced labor due to fetal malformations or chromosome abnormality (1 case of trisomy 21, 1 case of fetal skeletal dysplasia, 1 case of trisomy 18, and 1 case of cervical cystic hygroma of 45, X). There was no statistically significant difference in the rate of pregnancy loss between the two groups ($P > 0.05$).

The malformations between the two groups

Among pregnant women with SARS-CoV-2 infection in the early pregnancy, a total of 23 cases delivered with birth defects or malformations, with the rate of 4.62% (23/498). Among them, there were 7 cases of cardiac malformations (1 case of right heart dysplasia with ventricular septal defect; 2 cases of patent ductus arteriosus with patent foramen ovale; 2 cases of ventricular septal defect; 2 cases of patent foramen ovale), 3 cases of finger malformations (1 case of polydactyly, 1 case of syndactyly, and 1 case of polydactyly and syndactyly), 7cases of auriculofacial malformations (3 cases of preauricular fistula, 1 case of bilateral accessory ear, 1 case of left accessory ear malformation combined with right small ear malformation and facial transverse fissure, 1 case of accessory ear combined with right facial cleft, and 1 case of right earlobe fissure). There were 6 cases of urinary system malformations (2 cases of hypospadias, 1 case of horseshoe kidney, 1 case of duplicate kidney, 1 case of cryptorchidism, and 1 case of hydronephrosis).

Among pregnant women without SARS-CoV-2 infection in the early pregnancy, a total of 36 cases developed birth defects, with a birth defect rate of 5.50% (36/654). Among them, there were 12 cases of cardiac malformations (3 cases of ventricular septal defect, 3 cases of ventricular septal defect combined with patent foramen ovale, 4 cases of simple patent foramen ovale, 1 case of patent ductus arteriosus combined with patent foramen ovale, 1 case of simultaneous ventricular septal defect, patent foramen ovale, tricuspid valve insufficiency and pulmonary arterial hypertension), 2 cases of respiratory malformations (1 case of congenital pulmonary sequestration, 1 case of pulmonary cystadenoma), 2 cases of finger malformations (1 case of finger vegetations, 1 case of syndactyly), and 15 cases of auriculofacial malformations (8 cases of accessory ear, 3 cases of preauricular fistula, 1 case of right accessory ear combined with preauricular fistula, 1 case of left folded ear, 1 case of auricular malformation with external ear canal accessory ear, and 1 case of right external auricular malformation), 3 cases of urinary system malformations (2 cases of hypospadias and 1 case of left cryptorchidism), and two other malformations (1 case of cervical hydrocystoma, and 1 case of lymphatic malformation). There was no statistically

Table 3 Pregnancy outcomes between the two groups

	The study group *n* = 468	The control group *n* = 613	Z/χ2	*P*
Delivery weeks [M(P_{25} ~ P_{75}),w]	39(38 ~ 40)	39(38 ~ 40)	-0.005	0.996
Delivery mode[n(%)]				
Vaginal delivery	304(64.96)	411(67.05)	1.798	0.407
Forceps	28(5.98)	26(4.24)		
Cesarean section	136(29.06)	176(28.71)		
Total labor duration [M(P_{25} ~ P_{75}), min]	470(291 ~ 699)	410(292 ~ 655)	-1.732	0.083
Precipitate labor [n(%)]	13(2.78)	20(3.26)	0.211	0.646
Placental adhesion [n(%)]	20(4.27)	29(4.73)	0.128	0.720
Premature rupture of membranes [n(%)]	95(20.30)	126(20.55)	0.011	0.918
Postpartum hemorrhage [n(%)]	35(7.48)	42(6.85)	0.158	0.691
Oligohydramnios [n(%)]	13(2.78)	19(3.10)	0.757	0.096
HDP [n(%)]	24(5.13)	11(1.79)	9.415	0.002
Gestational hypertension[n(%)]	13(2.78)	5(0.82)	6.240	0.012
Preeclampsia [n(%)]	11(2.35)	6(0.98)	3.226	0.072

HDP: hypertensive disorders of pregnancy (including gestational hypertension and preeclampsia)

Table 4 Neonatal outcomes between the two groups of pregnant women

	The study group *n* = 468	The control group *n* = 613	Z/χ2	*P*
Preterm birth [n(%)]	24(5.13)	37(6.04)	0.411	0.522
Macrosomia [n(%)]	17(3.63)	18(2.94)	0.410	0.522
Small for gestational age infants [n(%)]	17(3.63)	24(3.92)	0.058	0.809
Low birth weight infants [n(%)]	19(4.06)	24(3.92)	0.015	0.904
Neonatal asphyxia [n(%)]*	2(0.43)	5(0.82)	0.705	0.350
Neonatal length [M(P_{25} ~ P_{75}), cm]	50(49 ~ 51)	50(49 ~ 51)	-0.883	0.377
Neonatal weight [M(P_{25} ~ P_{75}), g]	3230(3000 ~ 3500)	3280(2970 ~ 3480)	-0.668	0.504

Note: * Fisher's exact probability test

significant difference in the rate of malformations between the two groups $P > 0.05$).

Pregnancy outcomes between the two groups

Pregnancy outcomes such as delivery mode, total labor duration, the rates of precipitate labor, placental adhesions, premature rupture of membranes, postpartum hemorrhage, oligohydramnios, gestational hypertension and preeclampsia, et al., were compared between the two groups. There was no statistically significant difference ($P > 0.05$) between the two groups, except gestational hypertension and hypertensive disorders of pregnancy (HDP). The rates of gestational hypertension and HDP in the study group were statistically higher than those in control group ($P = 0.012$, $P = 0.002$), as shown in Table 3.

Neonatal outcomes between the two groups of pregnant women

The rates of preterm birth, macrosomia, small for gestational age infants, low birth weight infants, neonatal asphyxia, and neonatal length and weight were compared between the two groups. And there were no statistically significant differences ($P > 0.05$), as shown in Table 4. However, among the study group, the rates of adverse birth weight were slightly higher (macrosomia: 3.63%, low birth weight: 4.06%) compared to the control group (macrosomia: 2.94%, low birth weight: 3.92%).

Multivariate logistic regression analysis of pregnancy outcomes between the two groups

The results of the multivariate logistic regression analysis showed a significant increase in the risk of gestational hypertension (aOR = 3.68, 95%CI: 1.26–10.78) and hypertensive disorders of pregnancy (aOR = 2.96, 95%CI:1.42–6.18)in the study group, while the other maternal and neonatal outcomes were not significantly different between the two groups ($P > 0.05$), after adjusting for confounding factors such as age, gestational week, parity, and pre-pregnancy BMI, et al., as shown in Table 5.

Discussion

Due to the limited data of viral transmission, prevention and treatment, the clinical management of pregnancy complicated with viral infection is challenging. COVID-19, as a newly emerged viral infectious disease in 2019, has increased clinical concerns about the course of SARS-CoV-2 infection in pregnant women, such as the safety of medication use, delivery modes, pregnancy

Table 5 Multivariate logistic regression analysis of pregnancy outcomes between the two groups

	aOR, (95%CI)	*P* value
Gestational hypertension	3.68(1.26–10.78)	0.017
Preeclampsia	2.35(0.86–6.44)	0.096
HDP	2.96(1.42–6.18)	0.004
Premature rupture of membranes	0.98(0.72–1.32)	0.873
Oligohydramnios	0.91(0.44–1.88)	0.803
Postpartum hemorrhage	1.06(0.66–1.69)	0.822
Placental adhesion	0.92(0.51–1.67)	0.784
Cesarean section	1.00(0.75–1.32)	0.981
Precipitate labor	0.99(0.48–2.08)	0.985
Preterm birth	0.86(0.51–1.47)	0.579
Neonatal asphyxia	0.55(0.10–2.93)	0.482
Small for gestational age infants	0.90(0.48–1.71)	0.754
Low birth weight infants	1.08(0.58–2.01)	0.813
Macrosomia	1.24(0.62–2.48)	0.540

HDP: hypertensive disorders of pregnancy (including gestational hypertension and preeclampsia)

outcomes, and the risk of obstetric complications. This poses significant challenges to the clinical management and guidance of pregnant women [11].

During pregnancy, the maternal immune system undergoes complex changes to establish and maintain tolerance to the fetus, while still protecting itself from pathogenic invasion. The impact of SARS-CoV-2 infection on the maternal-fetal interface and the fetus is not yet clear. A recent review suggests that infection with SARS-CoV-2 during pregnancy can activate the maternal-fetal immune interface through vertical transmission, potentially leading to short-term and long-term effects on fetal development, including the central nervous system [12]. However, other studies suggest that SARS-CoV-2 infection does not compromise the physiological function of the maternal-fetal interface immunity [13]. So far, there has been no definitive evidence obtained regarding the vertical transmission rate of COVID-19 [14–16]. However, even without direct infection, SARS-CoV-2 can cause vascular damage leading to ischemic placental injury, thereby causing adverse pregnancy outcomes. Multiple studies have reported that the frequency of maternal vascular perfusion abnormalities in the placenta of SARS-CoV-2 infected pregnant women is higher [17–20].

In our study, we didn't find the first trimester SARS-CoV-2 infection significantly increase the risk of pregnancy loss such as embryo arrest. The latest two meta-analyses also showed that first and second trimester SARS-CoV-2 infection did not increase the risk of miscarriage [10, 21], which was consistent with our results. Similarly, our data is also insufficient to indicate an increased risk of congenital malformations associated with SARS-CoV-2 infection during pregnancy. An observational cohort study of 92 pregnant women with SARS-CoV-2 infection and 292 pregnant women without SARS-CoV-2 infection showed that SARS-CoV-2 infection in the first trimester was not associated with severe congenital fetal malformations [22]. However, a study indicated that maternal infection with SARS-CoV-2 during the 5th and 6th weeks of embryonic development may be associated with eye deformities in newborns [23].

Previous studies have shown that SARS-CoV-2 infection significantly increases the risk of adverse outcomes in pregnant and postpartum women. However, due to the differences in race, virus strains, infection timing, and sample size, the research conclusions are still inconsistent. The meta-analysis of 42 studies including 438,548 pregnant women by WEI et al. [24] showed that, compared with pregnant women without SARS-CoV-2 infection, women with SARS-CoV-2 infection had increased risk of preeclampsia, preterm labor and stillbirth. Also, compared with those with mild COVID-19, the incidences of pre-eclampsia, preterm labor, gestational diabetes mellitus and low birth weight of newborns in women with severe COVID-19 increased. A study by METZ et al. [25] showed that compared with asymptomatic COVID-19 pregnant women, pregnant women with severe COVID-19 had significantly increased risk of cesarean section, gestational hypertension, and premature birth, while pregnant women with mild to moderate COVID-19 had no increased adverse perinatal outcomes. Another study showed that pregnant women with severe SARS-CoV-2 infection had a significantly increased risk of premature birth and preeclampsia [26]. A study from Estonia showed that positive SARS-CoV-2 testing during pregnancy was associated with higher rates of stillbirth and neonatal mortality, but not with the occurrence of preeclampsia, cesarean section, or premature birth [27]. This suggests that the impact of SARS-CoV-2 infection on pregnancy outcomes may be related to the severity of COVID-19 symptoms or disease course.

In our study, all cases were mild and moderate COVID-19 cases, with no severe or critically ill cases, and we found that there was no significant correlation between the first trimester SARS-CoV-2 infection and the rates of cesarean section, precipitate labor, placental adhesions, premature rupture of membranes, postpartum hemorrhage, oligohydramnios, premature birth, et al., which was consistent with most research results. But there was still controversy over the impact of the first trimester SARS-CoV-2 infection on preterm birth. A cohort study found that SARS-CoV-2 infection in early, mid, or late pregnancy increased the risk of preterm birth ($p < 0.05$), and this effect was obvious among pregnant women infected with SARS-CoV-2 in early and mid-pregnancy [28]. Another cohort study included 402 pregnant women with SARS-CoV-2 infection in the early and middle stages of pregnancy and 11,705 pregnant women

without SARS-CoV-2 infection, and found that the rate of preterm birth less than 37 weeks of gestation increased, while that of less than 34 weeks didn't show significantly different [29]. However, TRILLA et al. [30]found that SARS-CoV-2 infection in the first trimester did not increase the incidence of premature birth. Our study also suggested that SARS-CoV-2 infection in the first trimester does not increase the incidence of premature birth. However, due to different races, differences in the types of virus strains, and different infected stages, further prospective exploration with multiple populations and large sample is still needed in the future.

In addition, in our study, after adjusting for confounding factors such as age, gravidity, parity, and pre-pregnancy BMI, multivariate logistic regression analysis found that the incidence of gestational hypertension in pregnant women with SARS-CoV-2 infection in the first trimester was significantly higher than that in pregnant women without SARS-CoV-2 infection, although there was no statistically significant difference in the incidence of preeclampsia between the two groups. A meta-analysis found pregnant women with SARS-CoV-2 related symptoms had a significantly higher incidence of preeclampsia than asymptomatic women [31], although this study did not conduct stratified analysis based on gestational age at the time of SARS-CoV-2 infection. A study was conducted to analyze the correlation between SARS-CoV-2 infection during pregnancy and HDP, with stratification based on the gestational week and severity of SARS-CoV-2 infection. The study indicated that compared with infection in the later stages of pregnancy, early pregnancy infection with SARS-CoV-2 may increase the risk of HDP [32]. A retrospective cohort study found that the incidence of HDP increased during the COVID-19 pandemic, regardless of COVID-19 infection status, and that the increase was higher among White individuals compared to African Americans [33]. Papageorghiou et al. [34] found that COVID-19 during pregnancy was strongly associated with preeclampsia, especially among nulliparous women. This association was independent of any risk factors and preexisting conditions.

The mechanism by which this occurs is still unclear. Several mechanisms could explain how SARS-CoV-2 infection during pregnancy might be involved in the pathogenesis of preeclampsia. Firstly, cellular entry of SARS-CoV-2 is facilitated by binding of viral spike proteins to Angiotensin Converting Enzyme 2 (ACE2) receptors on host membranes [35]. The ACE2 receptor is an important component of the Renin-Angiotensin System (RAS) which converts angiotensin II (Ang II) into angiotensin 1 to 7. The binding of SARS-CoV-2 to ACE2 receptors causes down-regulation of the RAS, increased Ang II and decreased levels of the vasodilatory angiotensin 1–7. The RAS significantly modulates uteroplacental blood flow through the balance of its vasoconstrictive and vasodilatory pathways [36], which may contribute to the etiopathogenesis of HDP. SARS-CoV-2 infection could lead to reduced expression of ACE2, resulting in downregulation of the AT2R and PlGF and upregulation of the AT1R, AT1-AA, and sFlt-1 arms of the RAS cascade [37, 38]. Also, potential SARS-CoV-2 interactions with placental proteins such as Milk Fat MFGE8, PLAT, and PAR2, which may play key roles in trophoblast invasion, migration, proliferation, and differentiation processes [39]. Secondly, SARS-CoV-2 infection also causes endothelial damage in various organs directly or indirectly through the host's inflammatory responses [40] and placental factors causing systemic maternal endothelial dysfunction are believed to play a significant role in the pathogenesis of preeclampsia [41]. Beys-da-Silva et al. [42] found that SARS-CoV-2 infection upregulates sFlt-1 and endoglin, vasoconstrictive peptides, nitric oxide modulators, and prothrombotic-related molecules. Thirdly, the fundamental model of the pathophysiology of preeclampsia is that early poor placental perfusion leads to the release of anti-angiogenic and inflammatory mediators, which in turn cause endothelial dysfunction [3, 43]. In preeclampsia, the failure of physiological remodeling of the decidual vessels can also lead to reduced placental perfusion [41]. Multiple studies have reported that the frequency of maternal vascular perfusion abnormalities in the placenta of SARS-CoV-2 infected pregnant women is higher [17–20]. Radan et al. [44] found that the incidence of low placental weight increased among those infected with the novel coronavirus during pregnancy. A retrospective cohort study further identified chronic villitis as the most distinctive histopathological manifestation associated with maternal SARS-CoV-2 infection. This placental inflammation pattern involves damage to vasculosyncytial membranes within chorionic villi, critical structures responsible for gas exchange and nutrient transfer. The observed pathological changes suggest potential mechanisms of placental impairment even in cases where vertical transmission to the fetus does not occur [45]. This can also explain the correlation to a certain extent. However, there were also different research conclusions. TRILLA et al. [30] found that the presence of SARS-CoV-2 infection in first trimester did not increase the incidence of preeclampsia. HUGHES et al. [29] also found that there was no significant difference in the incidence of gestational hypertension or severe preeclampsia among pregnant women infected with SARS-CoV-2 in the early and mid-pregnancy compared with SARS-CoV-2 negative individuals. The inconsistent results may be related to factors such as racial differences in the study population, different virus subtypes, different infection phases, and lack of stratified analysis.

In this study, we didn't find obvious correlations between the first trimester SARS-CoV-2 infection and adverse neonatal outcomes such as neonatal asphyxia, abnormal neonatal length and weight, et al. We couldn't get the long-term childhood outcome data, given the relatively recent onset of the pandemic in China. Numerous studies have investigated the short-term and long-term effects of maternal SARS-CoV-2 infection on all aspects of offspring, but definitive conclusions remain elusive. The neurological effect of SARS-CoV-2 infection has been a key focus of recent research. A small case-control study by Aldrete Cortez et al. found that maternal SARS-CoV-2 infection in the third trimester was associated with lower early motor repertoire performance in infants aged 3 to 5 months [46]. A cohort study revealed that in utero exposure to severe maternal SARS-CoV-2 infection could significantly delay neurodevelopment at 12 months of age, potentially mediated by DNA methylation at birth [47]. A narrative review incorporating 10 studies and a meta-analysis of 3 studies revealed that while infants exposed to SARS-CoV-2 in utero did not show an overall increased risk of developmental delays up to 17 months of age compared to unexposed counterparts, they exhibited significantly lower scores in specific domains, such as fine motor skills and problem-solving abilities, when compared with either unexposed infants or pre-pandemic cohorts [48]. However, findings across studies have been heterogeneous. One study reported no significant differences in communication, gross motor, fine motor, problem-solving, or personal-social skills at 6 months of age between exposed and unexposed infants [49]. Similarly, prenatal SARS-CoV-2 infection was not associated with neurodevelopmental differences at 12 months of age in other studies [50, 51]. Additionally, a cohort study found no significant differences in neurodevelopmental screening outcomes through 24 months postpartum [52].

Some scholars have conducted studies regarding auditory and ophthalmological impacts in children, but definitive conclusions remain elusive. A study demonstrated that the majority of pediatric cases exhibited normal audiological outcomes [53], while Celik et al. found that the infants exposed to SARS-CoV-2 in utero had dysfunction of the medial olivocochlear efferent system [54]. One study [53] found that approximately 15% of children had retinal abnormalities, such as bilateral choroidal perfusion abnormalities, capillary occlusion, and bilateral vascular tortuosity, while another study found that there was no increased risk of ocular abnormalities in neonates born to mothers with COVID-19 [55]. However, the above two studies lacked a control group [55].

Several limitations should be acknowledged in our study. Firstly, this is a single center study, with participants relatively from Beijing and its surrounding areas, which may limit the extrapolation of our results. Multi-center studies with larger sample sizes are needed to validate and expand upon these results. Secondly, some pregnant women who were infected with SARS-CoV-2 during the first trimester terminated their pregnancies artificially, resulting in missing data of pregnancy outcomes for these participants. Unfortunately, this study was based on the Obstetrics data extracted from the hospital's electronic information system, so data on artificial termination of pregnancy were not available. Therefore, our conclusions should be interpreted with caution and limited to the population of women who continued their pregnancies. Thirdly, the research subjects included in this study were pregnant women who were registered in our hospital after intrauterine live fetuses, so the incidence of embryo arrest was lower than the actual situation, and the results were slightly biased.

Future research may include the following aspects. Firstly, prospective, large-scale and multicenter studies with long-term follow-up are needed to better understand the maternal and fetal outcomes following SARS-CoV-2 infection during pregnancy. Additionally, efforts should focus on analyzing the mechanisms by which maternal infection results in adverse outcomes and affects offspring health, specifically examining placental function, placental blood perfusion, and fetal epigenetics, using mechanistic models. Investigating how these factors impact fetal development and contribute to long-term health outcomes will be essential for identifying key pathways and potential targets for intervention.

Conclusion

In this single center study, we found that SARS-CoV-2 infection in the first trimester may increase the risk of gestational hypertension, while the incidences of other adverse pregnant outcomes such as premature birth, premature rupture of membranes, cesarean section, postpartum hemorrhage, small for gestational age infants, low birth weight infants, and neonatal asphyxia did not significantly increase compared with women without SARS-CoV-2 infection in the first trimester. This conclusion needs further validation through prospective, large sample, and multi-center studies.

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No.

Author contributions

Jiangtao Hu, Ju Li and Jing Wang drafted the manuscript; Zhi Li collected the clinical data; Jiangtao Hu and Zhi Li analyzed the data; Li Lin and Jing Wang designed the study. All authors have agreed to be personally accountable for their own contributions. All authors read and approved the final manuscript.

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Data availability
Data and materials involved in this study are available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate
This study was reviewed and approved by the Ethics Committee of Peking University International Hospital (2023-KY-0033-01) in accordance with the Declaration of Helsinki, with signed consents from all the subjects for usage of their data.

Consent for publication
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Competing interests
The authors declare no competing interests.

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References

1. V'Kovski P, et al. Coronavirus biology and replication: implications for SARS-CoV-2. Nat Rev Microbiol. 2021;19(3):155–70.
2. Yang H, Rao Z. Structural biology of SARS-CoV-2 and implications for therapeutic development. Nat Rev Microbiol. 2021;19(11):685–700.
3. Narang K, et al. SARS-CoV-2 infection and COVID-19 during pregnancy: A multidisciplinary review. Mayo Clin Proc. 2020;95(8):1750–65.
4. Allotey J, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320.
5. Lim MJ, et al. Pregnancy and severe ARDS with COVID-19: epidemiology, diagnosis, outcomes and treatment. Semin Fetal Neonatal Med. 2023;28(1):101426.
6. Kleinwechter HJ, et al. COVID-19, pregnancy, and diabetes mellitus. Z Geburtshilfe Neonatol. 2024;228(1):17–31.
7. Khalil A, et al. SARS-CoV-2 infection in pregnancy: A systematic review and meta-analysis of clinical features and pregnancy outcomes. EClinicalMedicine. 2020;25:100446.
8. Knight M, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: National population based cohort study. BMJ. 2020;369:m2107.
9. Abu-Amara J, et al. Contracting COVID-19 in the first and second trimester of pregnancy: what we know - a concise qualitative systematic review. Arch Med Sci. 2021;17(6):1548–57.
10. van Baar JAC, et al. COVID-19 in pregnant women: a systematic review and meta-analysis on the risk and prevalence of pregnancy loss. Hum Reprod Update. 2024;30(2):133–52.
11. Şahin D, et al. Pregnancy and COVID-19: prevention, vaccination, therapy, and beyond. Turk J Med Sci. 2021;51(Si–1):3312–26.
12. Li J, Yao J, Yang Z. Effects of maternal SARS-CoV-2 infection during pregnancy on fetal development. Am J Reprod Immunol. 2024;92(2):e13911.
13. Hsieh LE, et al. SARS-CoV-2-specific T cell responses and immune regulation in infected pregnant women. J Reprod Immunol. 2022;149:103464.
14. Oliveira KF, et al. Vertical transmission and COVID-19: a scoping review. Rev Bras Enferm. 2021;74(suppl 1):e20200849.
15. Sharma R, et al. Perinatal outcome and possible vertical transmission of coronavirus disease 2019: experience from North India. Clin Exp Pediatr. 2021;64(5):239–46.
16. Duran P, et al. COVID-19 and newborn health: systematic review. Rev Panam Salud Publica. 2020;44:e54.
17. Rebutini PZ, et al. Association between COVID-19 pregnant women symptoms severity and placental morphologic features. Front Immunol. 2021;12:685919.
18. Corbetta-Rastelli CM, et al. Analysis of placental pathology after COVID-19 by timing and severity of infection. Am J Obstet Gynecol MFM. 2023;5(7):100981.
19. Wong YP, Khong TY, Tan GC. The effects of COVID-19 on placenta and pregnancy: what do we know so far?? Diagnostics (Basel), 2021; 11(1).
20. Shanes ED, et al. Placental pathology after SARS-CoV-2 infection in the Pre-Variant of concern, Alpha / Gamma, delta, or Omicron eras. Int J Surg Pathol. 2023;31(4):387–97.
21. Rodriguez-Wallberg KA, et al. Outcomes of SARS-CoV-2 infection in early pregnancy-A systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2024;103(5):786–98.
22. Hernández-Díaz S, et al. First trimester COVID-19 and the risk of major congenital malformations-International registry of coronavirus exposure in pregnancy. Birth Defects Res. 2022;114(15):906–14.
23. Morhart P, et al. Maternal SARS-CoV-2 infection during pregnancy: possible impact on the infant. Eur J Pediatr. 2022;181(1):413–8.
24. Wei SQ, et al. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. CMAJ. 2021;193(16):E540–8.
25. Metz TD, et al. Disease severity and perinatal outcomes of pregnant patients with coronavirus disease 2019 (COVID-19). Obstet Gynecol. 2021;137(4):571–80.
26. Lai J, et al. SARS-CoV-2 and the subsequent development of preeclampsia and preterm birth: evidence of a dose-response relationship supporting causality. Am J Obstet Gynecol. 2021;225(6):689–e6931.
27. Veerus P, et al. SARS-CoV-2 infection during pregnancy and perinatal outcomes in Estonia in 2020 and 2021: A register-based study. Acta Obstet Gynecol Scand. 2024;103(2):250–6.
28. Piekos SN, et al. The effect of maternal SARS-CoV-2 infection timing on birth outcomes: a retrospective multicentre cohort study. Lancet Digit Health. 2022;4(2):e95–104.
29. Hughes BL, et al. First- or second-trimester SARS-CoV-2 infection and subsequent pregnancy outcomes. Am J Obstet Gynecol. 2023;228(2):e2261–9.
30. Trilla C, et al. First-Trimester SARS-CoV-2 infection: clinical presentation, inflammatory markers, and obstetric outcomes. Fetal Diagn Ther. 2022;49(3):67–76.
31. Conde-Agudelo A, Romero R. SARS-CoV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis. Am J Obstet Gynecol. 2022;226(1):68–e893.
32. Parker SE, et al. Trimester and severity of SARS-CoV-2 infection during pregnancy and risk of hypertensive disorders in pregnancy. Hypertens Pregnancy. 2024;43(1):2308922.
33. Lanier AL, et al. Racial differences in hypertensive disorders in pregnancy during the COVID-19 pandemic. Pregnancy Hypertens. 2024;36:101113.
34. Papageorghiou AT, et al. Preeclampsia and COVID-19: results from the INTERCOVID prospective longitudinal study. Am J Obstet Gynecol. 2021;225(3):e2891–28917.
35. Wan Y, et al. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on Decade-Long structural studies of SARS coronavirus. J Virol. 2020;94(7). https://doi.org/10.1128/jvi.00127-20
36. Lumbers ER, et al. Causes and consequences of the dysregulated maternal Renin-Angiotensin system in preeclampsia. Front Endocrinol (Lausanne). 2019;10:563.
37. Verma S, et al. SARS-CoV-2 colonization of maternal and fetal cells of the human placenta promotes alteration of local renin-angiotensin system. Med. 2021;2(5):575–e5905.
38. Sayad B, et al. Pregnancy, preeclampsia, and COVID-19: susceptibility and mechanisms: A review study. Int J Fertil Steril. 2022;16(2):64–9.
39. Seethy AA, et al. Potential SARS-CoV-2 interactions with proteins involved in trophoblast functions - An in-silico study. Placenta. 2021;103:141–51.
40. Varga Z, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395(10234):1417–8.
41. Tomimatsu T et al. Preeclampsia: maternal systemic vascular disorder caused by generalized endothelial dysfunction due to placental antiangiogenic factors. Int J Mol Sci, 2019;20(17).
42. Beys-da-Silva WO, et al. The risk of COVID-19 for pregnant women: evidences of molecular alterations associated with preeclampsia in SARS-CoV-2 infection. Biochim Biophys Acta Mol Basis Dis. 2021;1867(3):165999.
43. Burton GJ, et al. Pre-eclampsia: pathophysiology and clinical implications. BMJ. 2019;366:l2381.
44. Radan A-P, et al. Low placental weight and altered metabolic scaling after severe acute respiratory syndrome coronavirus type 2 infection during pregnancy: a prospective multicentric study. Clin Microbiol Infect. 2022;28(5):718–22.

45. Gabby LC, et al. Chronic villitis as a distinctive feature of placental injury in maternal SARS-CoV-2 infection. Am J Obstet Gynecol. 2025;232(1):e1231–12312.
46. Aldrete-Cortez V, et al. Infants prenatally exposed to SARS-CoV-2 show the absence of fidgety movements and are at higher risk for neurological disorders: A comparative study. PLoS ONE. 2022;17(5):e0267575.
47. Hill RA, et al. Investigating the impact of severe maternal SARS-CoV-2 infection on infant DNA methylation and neurodevelopment. Mol Psychiatry, 2024.
48. Pinheiro G, et al. Effects of intrauterine exposure to SARS-CoV-2 on infants' development: a rapid review and meta-analysis. Eur J Pediatr. 2023;182(5):2041–55.
49. Shuffrey LC, et al. Association of birth during the COVID-19 pandemic with neurodevelopmental status at 6 months in infants with and without in utero exposure to maternal SARS-CoV-2 infection. JAMA Pediatr. 2022;176(6):e215563.
50. Favre G, et al. Neurodevelopmental outcomes of infants after in utero exposure to SARS-CoV-2 or mRNA-COVID-19 vaccine compared with unexposed infants: a COVI-PREG prospective cohort study. Clin Microbiol Infect. 2025;31(2):266–73.
51. Firestein MR, et al. Assessment of neurodevelopment in infants with and without exposure to asymptomatic or mild maternal SARS-CoV-2 infection during pregnancy. JAMA Netw Open. 2023;6(4):e237396.
52. Jaswa EG, et al. Utero exposure to maternal COVID-19 and offspring neurodevelopment through age 24 months. JAMA Netw Open. 2024;7(10):e2439792.
53. Buonsenso D, et al. Short- and mid-term multidisciplinary outcomes of newborns exposed to SARS-CoV-2 in utero or during the perinatal period: preliminary findings. Eur J Pediatr. 2022;181(4):1507–20.
54. Celik T, et al. Evaluation of cochlear functions in infants exposed to SARS-CoV-2 intrauterine. Am J Otolaryngol. 2021;42(4):102982.
55. Kiappe OP, et al. Ocular assessments of a series of newborns gestationally exposed to maternal COVID-19 infection. JAMA Ophthalmol. 2021;139(7):777–80.

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