Short-term pregnancy outcomes and drug interactions after simultaneous exposure to Nematavir/Ritonavir (Paxlovid) and immunosuppressants in pregnant women

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Abstract

**Background** In the context of the coronavirus disease 2019 (COVID-19) pandemic, pregnant women, especially those who have been receiving long-term immunosuppressive therapy, are considered at high risk for developing severe COVID-19. However, there are limited available data regarding the safety of Paxlovid for the treatment of novel coronavirus infection during pregnancy. Moreover, it should be noted that the ritonavir component of paxlovid acts as a potent cytochrome P4503A (CYP3A) inhibitor that can significantly increase the blood concentrations of various drugs metabolized by paxlovid. When combined with immunosuppressive agents, this interaction may lead to drug toxicity and other adverse reactions. This article presents three cases illustrating short-term pregnancy outcomes and drug interactions resulting from simultaneous exposure to both paxlovid and immunosuppressive agents.

**Methods** Through an initial series of reports on three pregnant women concurrently exposed to paxlovid and immunosuppressive drugs, such as cyclosporine and tacrolimus, we conducted an analysis of short-term delivery outcomes and discussed potential interactions between paxlovid and immunosuppressive drugs. By integrating pharmacogenomics and therapeutic drug concentration monitoring, this study facilitates the formulation, adjustment, and monitoring of drug therapy while also providing a comprehensive review of the literature.

**Results** After simultaneous exposure to paxlovid and immunosuppressive agents during pregnancy, the short-term pregnancy and neonatal outcomes of the two pregnant women were favourable, consistent with the majority of studies. Unfortunately, one pregnant woman delivered a preterm infant at 26 gestational weeks (GW), resulting in adverse outcomes unrelated to the administration of paxlovid. Furthermore, the use of paxlovid in pregnant women significantly inhibited the metabolism of cyclosporine and tacrolimus, leading to increased drug exposure and potential side effects. This interaction is associated with genetic polymorphisms, such as those in the CYP3A5*3, CYP3A4*18B, and ABCB1 genes, and with a unique physiological state during pregnancy.

**Conclusions** Pregnant women who concurrently use paxlovid, cyclosporine, and tacrolimus should promptly adjust the drug dosage to mitigate potential drug toxicity. Given the distinctive physiological conditions during pregnancy, it is advisable to incorporate genetic testing into pharmacokinetics and therapeutic drug monitoring. The integration of these two strategies constitutes a pivotal approach to achieving precision medicine for pregnant women.

Background

In the context of the COVID-19 pandemic, pregnant women are considered vulnerable due to their increased susceptibility to severe COVID-19 and associated complications such as intensive care unit (ICU) hospitalization, mechanical ventilation, premature delivery, and stillbirth [1]. Pregnant women receiving long-term immunosuppressants face an even greater risk, complicating their management in relation to severe COVID-19. Paxlovid is an oral antiviral medication used for treating novel coronavirus infection. Administering paxlovid within 5 days of symptom onset significantly reduces hospitalization and mortality in patients with mild to moderate symptoms who have risk factors for progressing to severe COVID-19 [2]. However, there are limited safety data available regarding its use during pregnancy, and there is a lack of clinical trials and studies. Given the unique physiology of pregnant women, caution must be exercised when using medications due to considerations such as pharmacokinetics, vertical transmission risks, drug toxicity concerns, and postpartum care requirements. Currently, there is global controversy within the medical community regarding whether paxlovid can be safely administered during pregnancy [3].

The ritonavir component of paxlovid is a potent inhibitor of CYP3A that can significantly increase the blood concentration of various drugs metabolized by CYP3A4. Concurrent use of these drugs may lead to drug toxicity and other adverse reactions [4–6]. For example, Stader et al. reported that ritonavir increased the dose of antiviral therapy in recipients with hepatitis C virus infection after liver transplantation and that therapeutic levels were maintained when the cyclosporine dose was reduced to 20% of the previous regimen [7]. However, whether paxlovid and immunosuppressants such as cyclosporine, tacrolimus have similar interactions between pregnant women with unique physiological conditions and nonpregnant women has not been reported.

The primary objective of this article was to evaluate the influence of paxlovid on pregnancy and delivery outcomes and to explore the potential interactions between paxlovid and immunosuppressive drugs. The impact of these interactions on COVID-19 disease outcomes and maternal and neonatal outcomes was investigated. The integration of pharmacogenomic techniques and therapeutic drug concentration monitoring (TDM) methods can help guide the development and adjustment of drug treatment plans for pregnant women. Additionally, a comprehensive literature review and analysis were conducted to provide clinical guidance and references for similar complex cases in pregnant women.

Methods

**Design**

This descriptive study enrolled pregnant women with COVID-19 infection and long-term immunosuppressant use who were admitted to the obstetrics department of a large tertiary hospital in southern China from January 1, 2023, to December 1, 2023.

**Participants**

Patients eligible for paxlovid treatment included those who were diagnosed with mild-to-moderate COVID-19 (confirmed by a positive nasopharyngeal polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), who exhibited symptoms of COVID-19 infection within the past five days, and who had no contraindications to the medication.

**Data collection**
The patients provided informed consent to participate in this study. Subsequently, interviews were conducted with infected pregnant women to assess symptoms associated with COVID-19, and these symptoms were documented in medical records. Furthermore, clinical data, including maternal age, gestational age, pregnancy complications, usage of immunosuppressive medication, COVID-19 vaccination status, and the onset of symptoms at paxlovid initiation, were extracted from the electronic medical records of all participants. Following treatment administration, comprehensive information on treatment efficacy was collected, encompassing the duration and outcome of COVID-19 symptoms as well as any adverse drug reactions. Patients underwent close monitoring throughout pregnancy and the postpartum period. The following data were collected to assess maternal and fetal short-term outcomes: maternal complications during delivery, neonatal complications, the Apgar score, and admission to the ICU or neonatal intensive care unit (NICU).

**Results**

1. **Maternal and fetal short-term outcomes**

During the study period, three patients were eligible for inclusion in the descriptive analysis (Table 1). Patient 1 and patient 3 were diagnosed with systemic lupus erythematosus (SLE) complicated by pregnancy, while patient 2 had undergone kidney transplantation complicated by pregnancy. Patient 1 who received cyclosporine had an AA genotype for ABCB1 and CYP3A4*18B genotypes. The CYP3A5*3 genotype of patient 2 who took tacrolimus was GG. Patient 3 received hydroxychloroquine tablets. These three pregnant women had a mean gestational age of 30 weeks and had all completed vaccination with an inactivated SARS-CoV-2 vaccine. These patients were identified as candidates for paxlovid treatment due to their main symptoms, including sore throat, fever, and mild cough associated with COVID-19. All patients agreed to receive oral administration of paxlovid (300 mg of nirmatavir/100 mg of ritonavir) twice daily for five days. The average time from the onset of symptoms to treatment was two days. During the treatment period, one patient experienced adverse reactions such as nausea, vomiting, and diarrhea, while the other two tolerated the medication without immediate side effects. Antiviral therapy resolved symptoms after an average duration of four days without progressing to severe disease (Table 1).

Patient 1, the patient underwent a cesarean section at 36+6 GW due to suspected fetal distress. This resulted in the delivery of a neonate weighing 1820 g who was subsequently diagnosed with neonatal hypoglycemia, premature ultralow birth weight, and hypospadias. After an eleven-day hospitalization period, the newborn was discharged. Patient 2 underwent an emergency cesarean section at 26+3 GW due to suspected placental abruption and cord blood flow disconnection, resulting in the delivery of a newborn weighing 650 g. The neonate was admitted to NICU for management of extremely low birth weight, neonatal respiratory distress syndrome, neonatal intracranial hemorrhage, neonatal acidosis and neonatal hyperbilirubinemia. Despite exhaustive efforts by the medical staff, the infant’s condition did not improve as expected. Due to the poor prognosis of the newborn, the parents asked for automatic discharge, and the medical team will continue to provide support and care for the family. Patient 3, a healthy newborn weighing 3040 g was delivered vaginally at 38 GW due to fetal maturity without any complications related to paxlovid treatment during delivery (Table 2).

2. **The drug interactions of paxlovid with cyclosporine and tacrolimus.**

The Patient 1 was diagnosed with SLE and had been experiencing progressive thrombocytopenia for two months. Upon consultation with the physician, immunotherapy using cyclosporine at a dosage of 50 mg q12h was initiated. The patient's ABCB1 genotype was AA, and her CYP3A4*18B genotype was also AA. When paxlovid-related anti-coronavirus treatment began, the clinical pharmacist considered factors such as the patient’s drug metabolism genotype, drug interaction characteristics, and timing of cyclosporine steady-state blood concentration. It was recommended that during days one to five of paxlovid treatment, the dose of cyclosporine should be reduced to 25 mg bid while closely monitoring its blood concentration after achieving a steady state. The target trough concentration range was set between 50 and 150 ng/ml [8,9]. However, due to various factors, timely adjustment of the drug dosage did not occur in this particular case. Five days after initiating paxlovid therapy, the blood concentration of cyclosporine reached 550 ng/ml, which was accompanied by elevated blood pressure compared to that at admission (118/78 mmHg on admission vs. 153/93 mmHg at present). Moreover, the patient exhibited facial flushing as well as abdominal pain and distention. The clinical pharmacist suggested that cyclosporine should be stopped immediately and restarted until the concentration of cyclosporine drops to the target range. Three days after cessation of cyclosporine therapy, the patient's abdominal pain, distension, and other symptoms resolved, and her blood pressure returned to normal (123/76 mmHg). At this juncture, the measured blood concentration of cyclosporine was 127.3 ng/ml, which fell within the effective therapeutic range required for managing the patient's condition. The prognosis for both the mother and child was favourable.

The patient 2, who underwent renal transplantation, had been receiving long-term tacrolimus 2 mg q12h therapy, to prevent organ rejection. The patient’s CYP3A5*3 genotype was GG. Considering the drug metabolism genotype and potential drug interactions, the clinical pharmacist recommended discontinuing tacrolimus during the first to fifth days of paxlovid treatment. On the sixth day (one day after paxlovid was stopped), the blood concentration of paxlovid was reevaluated, and dosage adjustments were made accordingly. Prior to initiating paxlovid therapy, the blood concentration of tacrolimus was measured at 7.3 ng/ml. On the first day after paxlovid was discontinued, the blood concentration was 5.50 ng/ml, which remained within the effective range of 4-8 ng/ml for this patient's disease [10]. Consequently, immunosuppressive therapy with half of the original dose of tacrolimus (1.0 mg q12h) was resumed. Blood concentrations were monitored every 2-4 days until eventually returning to the initial dose on day 3 following withdrawal from paxlovid treatment. Unfortunately, due to his mother's illness, the newborn was born prematurely at 26* GW with an extremely low birth weight. The infant experienced severe complications after birth and had a poor prognosis, which led the parents to request voluntary discharge.

Patient 3 was a pregnant woman with SLE who had been receiving long-term hydroxychloroquine therapy for immunomodulation. No drug interaction was observed between paxlovid and hydroxychloroquine, necessitating no adjustment in dosage during the combined treatment. The patient’s SLE condition remained controlled and stable throughout anti-coronavirus therapy, ultimately resulting in the successful delivery of a healthy full-term newborn.

**Discussion**

1. **The efficacy and safety of paxlovid in pregnant women**
A descriptive study based on real-world data demonstrated that out of 11 pregnant women who received a short 5-day course of paxlovid, 7 successfully completed the treatment. All patients who received paxlovid experienced symptom relief without requiring additional treatment. Throughout the treatment period, all patients tolerated the medication well, with no immediate adverse reactions reported, except for one patient who experienced nausea. Furthermore, there were no observed adverse effects on fetal or neonatal health [11]. Another study involved 12 pregnant women who underwent a short 5-day course of paxlovid. Adverse effects included dysgeusia (n=11, 91.7%), diarrhea (n=2, 16.7%), and mild abdominal pain (n=1, 8.3%). Eleven patients delivered successfully with favourable outcomes for both the mother and fetus, while one patient was still in her pregnancy stage [12]. In a study conducted at the Johns Hopkins Institute for Clinical and Translational Research involving 47 pregnant women aged between 22 and 43 years, among the group of patients who initiated paxlovid within days 0-5 after symptom onset (30 patients), two individuals (4.3%) discontinued the medication before completing their prescribed course due to adverse effects; specifically, excessive fetal growth and polyhydramnios were observed in one patient (2.1%), while oligohydramnios developed in another patient (which also accounted for approximately 2%). The remaining participants tolerated the medication well throughout its administration period. In total, twenty-five patients (53.2%) were discharged following the completion of paxlovid treatment [13] (Table 3).

In our study, the two pregnant women demonstrated favourable short-term pregnancy and neonatal outcomes, consistent with previous research findings [14,15,16]. However, the woman who underwent kidney transplantation delivered a preterm infant at 26* GW, resulting in unfavourable neonatal outcomes. Currently, there is extensive documentation indicating that pregnancies in kidney transplant recipients present significant risks to the mother, fetus, and transplanted kidney. The primary risk factors include abortion, infection, proteinuria, preeclampsia, premature delivery, foetal growth restriction, stillbirths and neonatal malformations [14]. Based on previous evidence-based research, it is probable that the adverse outcomes of neonates delivered by this woman can be primarily attributed to her mother's medical history rather than her use of the paxlovid device. The present study represents the initial report on short-term pregnancy outcomes and fetal effects in three pregnant women who were concurrently exposed to both paxlovid and immunosuppressive agents. Despite these encouraging findings, further investigations are necessary to evaluate the effectiveness and safety of oral antiviral therapies against various COVID-19 variants during pregnancy, as well as their long-term impact on maternal and neonatal outcomes.

Therefore, based on the evaluation of paxlovid's mechanism of action, real-world study data, and recommendations from domestic and international authorities, it is recommended that a risk-benefit assessment be conducted for pregnant women with COVID-19. This assessment may encompass various factors, such as comorbid medical conditions, body mass index ≥35, unvaccinated status, and prolonged use of immunosuppressive agents. Based on the risk-benefit assessment, paxlovid is recommended for eligible pregnant women [15]. Paxlovid is a relatively safe option during pregnancy.

2. Interactions between paxlovid and calcineurin inhibitors

Ritonavir, a protease inhibitor for human immunodeficiency virus type 1 in paxlovid, does not exhibit activity against the major protease of SARS-CoV-2. Instead, it increases the plasma concentration of nematavir by inhibiting its CYP3A-mediated metabolism [4-5]. As a potent and irreversible inhibitor of CYP3A, ritonavir may interact with drugs metabolized by this hepatic enzyme or inhibitors/inducers, leading to either enhancement or attenuation of the combined drugs' effects [16].

Both cyclosporine and tacrolimus are calcineurin inhibitors (CNIs) and exhibit significant interactions with ritonavir through CYP3A metabolism and P-glycoprotein transport. Pharmacokinetic studies have demonstrated that coadministration of CNIs with ritonavir (100 mg) resulted in a 57-fold increase in total exposure to tacrolimus and a 5.8-fold increase in total exposure to cyclosporine [17]. According to the "Clinical Pharmacy Guidelines for Antiviral Treatment of Novel Coronavirus Pneumonia" issued by the Guangdong Pharmaceutical Association of China [16], it is recommended that the daily dose of cyclosporine be reduced by 80% during days 1-5 of paxlovid treatment combined with CNIs; tacrolimus administration should be suspended, and the blood concentration of CNIs should be reevaluated as soon as possible after the completion of paxlovid therapy to guide dose adjustments for restarting treatment. Studies have indicated that when tacrolimus is combined with ritonavir, its inhibitory effect reaches peak levels shortly after exposure, resulting in a sudden increase in tacrolimus trough concentration within 48 hours following ritonavir use [18,19]. After ritonavir is discontinued, its inhibitory effect decreases significantly by 46%-61% within the first 24 hours and by 70%-90% from the second to fifth days; however, it may take up to three weeks for enzyme function to fully recover [20].

The dose of cyclosporine was not adjusted when paxlovid was initiated in Patient 1, leading to increased blood concentrations of cyclosporine and subsequent incidents of high blood pressure, abdominal pain, and other adverse reactions caused by drug overdose. The dose of tacrolimus was appropriately adjusted when paxlovid was initiated in patient 2, resulting in the maintenance of tacrolimus blood concentrations within the therapeutic range even after the discontinuation of paxlovid. Our study further confirmed that paxlovid significantly affects the plasma concentration of CNIs. Previous studies have demonstrated a notable interaction between paxlovid and immunosuppressants in nonpregnant individuals [21,22]. Our study is the first to report that paxlovid can significantly increase the blood concentrations of cyclosporin and tacrolimus in pregnant women. Therefore, when paxlovid is combined with CNIs, the dose should be adjusted over time, and the blood concentration should be closely monitored to avoid drug toxicity.

3. The pharmacogenomic factors influencing CNI therapy

The genomics of cyclosporine strains that have been extensively investigated include the activity of P-glycoprotein in ABCB1 and the metabolic enzyme activity of CYP3A4 [23,24]. Studies conducted by Crettol, Lee et al. have demonstrated that individuals with the AA genotype of ABCB1 exhibit reduced P-glycoprotein activity, leading to increased concentrations of cyclosporine and necessitating lower doses to achieve target drug levels [25,26]. In our study, the patients 1 who received cyclosporine had a low risk for hepatotoxicity due to their AA genotype for CYP3A4*18. Despite a significant increase in cyclosporine concentration during treatment resulting from drug interactions, no hepatotoxicity was observed. The patient's ABCB1 genotype was AA, indicating slow metabolism. Even though they were administered a dose equivalent to 2.2 mg/kg/day (50 mg bid), which did not meet the recommended therapeutic dose for SLE (3.5 mg/kg/day), the concentration reached a stable level of 127.3 ng/ml (>100 ng/ml), indicating that patients with an AA genotype for ABCB1 require lower doses of cyclosporine than those with a normal genotype.
Several studies have reported that the blood concentration of tacrolimus can be influenced by CYP3A5 gene polymorphisms [27,28]. For instance, Provenzani et al. reported that renal transplant patients with the CYP3A5*3 *1/*1 and *1/*3 genotypes required higher doses of tacrolimus to achieve blood drug concentrations comparable to those of patients with the CYP3A5*3 *3/*3 genotype [27]. In our study, the patients in Patient 2 who carried the GG genotype for CYP3A5*3 of tacrolimus were considered slow metabolizers. Therefore, the initial dose of cyclosporine in this patient should be cautiously initiated from the minimum dosage, as it is recommended that the required dosage is lower than that of the normal genotype population[29].

The implementation of TDM has played a crucial role in mitigating the adverse reactions associated with CNIs to some extent. However, it is important to note that TDM exhibits a certain degree of delay and can only be conducted after medication administration. Prior to initiating CNI therapy, it is imperative to employ genetic detection technology to determine the genotypes of CYP3A5*3, CYP3A4*18B, and ABCB1 to ascertain patients' metabolic profiles and predict the initial dosage requirements for CNIs. Subsequently, based on TDM results, individualized medication dosages can be adjusted accordingly to optimize clinical efficacy while minimizing the occurrence of adverse events. The field of pharmacogenomics serves as a prospective tool for determining the initial dosage of medication for individual patients. Given the unique physiological state during pregnancy, genotype polymorphisms and individual variations in drug response, it is crucial to integrate genetic testing with TDM for therapeutic drug monitoring to guide precision medicine specifically tailored for pregnant women.

**Limitations and future research directions**

This study has limitations, and caution is warranted when interpreting the results. First, due to the limited safety data on drug use in pregnant women with specific conditions, the analysis involving paxlovid included a small number of patients. Second, in patient 2, the patient required termination of pregnancy due to an emergency situation, and the duration of paxlovid practice was close to the time of delivery, so the effect of paxlovid on pregnancy outcome was limited. However, the timely administration of paxlovid resulted in a reduced impact of COVID-19 infection on the mother and resulted in a favourable prognosis. In Case 1, various factors contributed to a delay in adjusting the cyclosporine dosage, leading to elevated concentration levels and adverse reactions such as abdominal pain and increased blood pressure. After prompt intervention, positive progress was demonstrated by the patient. Fourth, due to the time urgency, the primary focus of this study was on the short-term outcomes of both mothers and fetuses, while their long-term outcomes require further follow-up and attention from our research team. In the future, our team will still need to increase the sample size and conduct multicenter studies to enhance the reliability of the research findings. Additionally, further studies are required to assess the effectiveness and safety of paxlovid against various COVID-19 variants during pregnancy.

**Conclusion**

Our study is the first to provide a comprehensive analysis of short-term pregnancy and foetal outcomes in pregnant women concurrently exposed to paxlovid and immunosuppressant medications.

Additionally, our study revealed that when pregnant women use paxlovid combined with cyclosporine or tacrolimus, it significantly inhibits the metabolism of CNIs and increases their exposure to the patient's body. In clinical practice, it is imperative to adjust dosages when using these drugs concomitantly to prevent drug toxicity caused by excessively high concentrations. Close monitoring of blood concentration levels is also essential. Moreover, considering the distinctive physiological characteristics of pregnant patients, integrating pharmacogenomic information and TDM into clinical practice for treatment plan formulation, adjusting drug doses, and monitoring the patient play important roles in achieving precision medicine for pregnant women.

**Abbreviations**

GW  
Gestational Weeks  
CYP3A4  
Cytochrome P4503A4  
COVID-19  
Coronavirus Disease 2019  
SLE  
Systemic lupus erythematosus  
IUC  
intensive care unit  
NICU  
Neonatal Intensive Care Unit  
CNIs  
Calcineurin inhibitors  
TDM  
Drug Concentration Monitoring.

**Declarations**

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**Authors' contributions**

XM Z contributed to sample collection, patient management, original draft preparation, and finalization of the manuscript. QY H provided comments and collected the data. LQ M: Conceptualization and functionalization of the manuscript. SN Z and FF F: Sample collection and literature review. Y F provided comments and revised the manuscript. CH Y: conceived the research, made comments and revised the manuscript. All the authors have read and approved the final manuscript.

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**Availability of data and materials**

For further details, the corresponding author can be contracted.

**Ethical approval and consent to participate**

The collection and use of the materials for research purposes were approved by the Medical Ethics Committee of Nanfang Hospital, which is affiliated with Southern Medical University (ID: NEEC2023-116) and is registered with ChiCTR2300071187). All the data were collected from the patients after providing written informed consent. All methods were carried out in accordance with relevant guidelines and regulations.

**Consent for publication**

Written informed consent for the photographs and their subsequent publication in this series was obtained from the patient.

**Competing interests**

The authors declare no competing interests.

**References**


Tables

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (y)</th>
<th>Gravida</th>
<th>Para</th>
<th>Gestational Age at COVID-19 Diagnosis (wk)</th>
<th>Vaccination Status</th>
<th>Symptom Status at Diagnosis</th>
<th>The time from symptom onset to treatment (d)</th>
<th>Duration of COVID-19 Symptoms (d)</th>
<th>Treatment side Effects</th>
<th>Prognosis of COVID-19</th>
<th>Pregnant women be admitted to ICU</th>
<th>Immunosuppressive drugs</th>
<th>Genotype</th>
</tr>
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<tbody>
<tr>
<td>Case1</td>
<td>27</td>
<td>G1P0</td>
<td>16 0/7</td>
<td>vaccinated</td>
<td>sore throat, Mild cough</td>
<td>2</td>
<td>3</td>
<td>None</td>
<td>Get better</td>
<td>None</td>
<td>Cyclosporin ABCB CYP3A5 AA</td>
<td>Tacrolimus CYP3A5 GA</td>
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</tr>
<tr>
<td>Case2</td>
<td>26</td>
<td>G2P0</td>
<td>26 1/7</td>
<td>vaccinated</td>
<td>cough, fever</td>
<td>3</td>
<td>4</td>
<td>Nausea, vomiting, diarrhea</td>
<td>Get better</td>
<td>None</td>
<td>Hydroxychloroquine</td>
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<td></td>
</tr>
<tr>
<td>Case3</td>
<td>37</td>
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<td>34 1/7</td>
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<td>cough, fever</td>
<td>1</td>
<td>4</td>
<td>None</td>
<td>Get better</td>
<td>None</td>
<td>Hydroxychloroquine</td>
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</table>

Table 2. Maternal and fetal outcomes
<table>
<thead>
<tr>
<th>Patients</th>
<th>Pregnancy Status</th>
<th>Gestational Age at Delivery (wk)</th>
<th>Mode of Delivery</th>
<th>Complications during delivery</th>
<th>Birth Weight (g)</th>
<th>Apgar score</th>
<th>The newborn admitted to NICU</th>
<th>Neonatal Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Delivered</td>
<td>36 6/7</td>
<td>Cesarean section</td>
<td>Intrauterine distress; hypoxemia.</td>
<td>1820</td>
<td>29</td>
<td>None</td>
<td>Premature ultralow birth weight; Low blood glucose; Hypospadias</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Delivered</td>
<td>26 3/7</td>
<td>Cesarean section</td>
<td>Placental abruption; Cord blood was drained; Puerperal infection</td>
<td>650</td>
<td>21</td>
<td>Yes</td>
<td>Premature ultralow birth weight infants; Neonatal intracranial hemorrhage; Neonatal acidosis; Neonatal jaundice; Vitamin D deficiency</td>
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<tr>
<td>Patient 3</td>
<td>Delivered</td>
<td>38 0/7</td>
<td>Vaginal</td>
<td>None</td>
<td>3040</td>
<td>30</td>
<td>Yes</td>
<td>None</td>
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</table>

Table 3. Summary of research studies on the safety of Paxlovid use during pregnancy

<table>
<thead>
<tr>
<th>Title</th>
<th>Type of Study</th>
<th>Number of participants (people)</th>
<th>Gestational age (median)</th>
<th>Vaccination Status</th>
<th>Dosage of Paxlovid</th>
<th>Treatment Side Effects</th>
<th>Pregnancy Outcomes</th>
<th>Complications during delivery</th>
<th>Neonatal Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term Pregnancy Outcomes After Nirmatrelvir-Ritonavir Treatment for Mild-to-Moderate Coronavirus Disease 2019 (COVID-19) (Published in 2022)</td>
<td>Descriptive study</td>
<td>7</td>
<td>26³w</td>
<td>6 vaccinated (4 of them second dose)</td>
<td>Nirmatrelvir(300 mg)-Ritonavir(100 mg) po q12h 5d</td>
<td>One patient developed dysgeusia and stopped treatment after 2 days</td>
<td>Three labor Four pregnant</td>
<td>None</td>
<td>Non</td>
</tr>
<tr>
<td>Nirmatrelvir-Ritonavir (Paxlovid) for Mild Coronavirus Disease 2019 (COVID-19) in Pregnancy and Lactation. (Published in 2023)</td>
<td>Cross-sectional study</td>
<td>12</td>
<td>26w</td>
<td>/</td>
<td>Adverse effects were 91.7%, dysgeusia (n=11, 91.7%), diarrhea (n=2, 16.7%), and mild abdominal pain (n=1, 8.3%)</td>
<td>Eleven labor One pregnant</td>
<td>None</td>
<td>Non</td>
<td></td>
</tr>
<tr>
<td>Analysis of Clinical Outcomes of Pregnant Patients Treated With Nirmatrelvir and Ritonavir for Acute SARS-CoV-2 Infection (Published in 2022)</td>
<td>Descriptive study</td>
<td>47</td>
<td>28 ⁴w</td>
<td>40 were vaccinated (21 with the second dose and 3 with the third dose)</td>
<td>Two patients (4.3%) discontinued the medication before completing treatment due to adverse effects.</td>
<td>Twenty-five labor Twenty-two pregnant</td>
<td>One patient developed excessive fetal growth and polyhydramnios; One patient (2.1%) developed oligohydramnios</td>
<td>Non</td>
<td></td>
</tr>
</tbody>
</table>