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# Effect of Paxlovid on Skeletal System Morphogenesis in Animal Model Rat (Morphological Study)

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## Abstract

**Background:** Paxlovid, an investigational oral therapeutic comprising Nirmatrelvir (NMV) and Ritonavir, is being developed to treat SARS-CoV-2 infections and reduce the risk of severe disease, hospitalization, and mortality. This study evaluates the effects of Paxlovid on the skeletal morphogenesis of rat fetuses at doses up to 1000 mg/kg/day, adhering to the International Council for Harmonisation guidelines for embryo-fetal development studies.

**Methods:** In this morphological study of the morphogenesis of the skeletal system, Pregnant rats were allocated into four groups (one control and three subjected to varying treatment levels). fetal weight, crown-rump length (CRL), and abdominal circumference (AC) were measured. Skeletal abnormalities were assessed using double staining with Alizarin red S and Alcian blue. Data were evaluated using Microsoft Excel. One-way analysis of variance (ANOVA) was performed to compare fetal weight, CRL, and AC among the experimental groups and the control group. When significant differences were detected, Tukey's Honestly Significant Difference (HSD) test was used for post hoc comparisons. Statistical analysis was conducted using XLSTAT 2016 software, and a p-value of $< 0.05$ was considered statistically significant.

**Results:** Results indicated that mothers in the Paxlovid treatment groups experienced less weight gain compared to controls (252 ± 19.84 g, 224.1 ± 14.1 g, 232.1 ± 15.5 g, 246.2 ± 12.8 g, respectively, on GD21). On GD (gestational day) 21, fetuses from treatment groups exhibited reduced weight (3.5 ± 0.6 g, 1.7 ± 0.8 g, 1.8 ± 0.8 g, 2.5 ± 0.3 g, respectively), CRL (35 ± 3.8 mm, 25.9 ± 6.5 mm, 26.36 ± 6.2 mm, 31.58 ± 2.2 mm, respectively), and AC (12.2± 1.2 mm, 9.9 ± 1.4 mm, 9.8 ± 1.6 mm, 11 ± 1 mm, respectively) compared to controls; however, no skeletal abnormalities were detected through staining methods.

**Conclusion:** The findings suggest that while there are observable effects on maternal weight and fetal growth parameters, the administration of Paxlovid did not result in skeletal system abnormalities in the embryos. This research indicates a minimal risk of fetal harm associated with Paxlovid use, reinforcing its safety profile regarding fetal development. These results contribute to the understanding of Paxlovid's implications for pregnant individuals and support its potential therapeutic use against SARS-CoV-2.

**Keywords:** Paxlovid, Skeletal system, SARS-CoV-2, COVID-19, Rat

***Conflicts of Interest:*** *None declared*
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## Introduction

The coronavirus has always been one of the challenges facing mankind throughout history. Over the past 2 decades, two new COVID-19 infections, Severe Acute Respiratory Syndrome CoV (SARS-CoV) and Middle East

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***↑What is "already known" in this topic:***
Humans have historically contended with coronaviruses, deploying vaccines and therapeutics for defense. Due to frequent mutations and the emergence of variants, continuous development of updated vaccines and antiviral agents is essential to effectively counteract these rapidly evolving pathogens, ensuring sustained protection against COVID-19 and related coronavirus infections.

***→What this article adds:***
Paxlovid, a potent antiviral for COVID-19, is vital for safeguarding high-risk populations, including pregnant individuals. This study investigates its effects on rat fetal development to assess safety and teratogenic risks, offering critical data on its potential suitability for antenatal use.



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Respiratory Syndrome (MERS-CoV) have emerged that have caused serious medical conditions. Throughout the SARS-CoV endemic, over 8,000 individuals were infected globally, with close to 800 fatalities recorded, indicating a mortality rate of approximately 10%. While MERS-CoV recorded more than 857 reported cases with 334 associated mortalities, giving a Fatality rate of about 35% (1, 2).

COVID-19, resulting from infection with SARS-CoV-2, posed one of the most serious threats to global health and well-being. In the last five years, which started in 2019 and has continued until now, it can be said that it has been one of the biggest challenges of the last five years, both in terms of treatment and in terms of economics and politics in the entire human society. As of December 12, 2021, over 269 million infections and 5.3 million fatalities have been attributed to the COVID-19 pandemic (3). Many drugs were made for treatment, and many vaccines for prevention, which continue to be made to this day. Paxlovid is one of these drugs, and it can be said that it is the newest one that was made by Pfizer Pharmaceutical Company and introduced to the world (4, 5).

Paxlovid is made from the combination of two drugs, nirmatrelvir and ritonavir (300 mg, 100 mg), which is considered one of the effective drugs in the treatment of COVID-19 disease. According to ritonavir, which is a CYP3A4 inhibitor, inhibiting CYP3A4 increases the concentration and persistence of Nirmatrelvir in the blood. In addition to its primary mechanism of inhibiting the SARS-CoV-2 main protease (Mpro), Paxlovid may influence several other molecular pathways. Nirmatrelvir, the active antiviral component, disrupts viral replication by targeting a critical protease enzyme, thereby preventing processing of viral polyproteins. Ritonavir, a pharmacokinetic enhancer, inhibits cytochrome P450 enzymes, particularly CYP3A4, which can alter the metabolism of various co-administered drugs. Beyond this, emerging evidence suggests that Paxlovid may modulate host immune responses, potentially affecting inflammatory signaling pathways such as NF-κB and cytokine production. Additionally, some studies propose off-target effects on cellular proteases or kinases, which could influence cell signaling and apoptosis pathways (6, 7).

During embryonic development, most skeletal elements exist as cartilage templates. Over time, these are systematically dismantled and rebuilt as bone, a transformation that lasts until the growth plates unite during adolescence (8).

The formation of a skeleton with many bones in different shapes and sizes, and the growth of these bones from the embryonic period to adulthood, is a complex process that includes many genes (9). The skeletal system is an organ derived from the mesoderm, and its formation begins with mesenchymal condensation, in which chondrocytes are used to form cartilage and osteoblasts are used to form bone (10, 11).

Considering that one of the most sensitive communities that can be exposed to the disease (COVID-19), is pregnant women. It is very important to investigate the possible side effects of Paxlovid on the fetus. Due to the human fetus that is the continuation of the human race, it is very important to determine the side effects of new drugs, including Paxlovid, on the fetus in order to avoid possible harm to it, according to the previous studies on Nirmatrelvir, which was in the field of morphogenesis of the skeletal system (5). Here, we report the results of studies on the effect of Paxlovid on the reproduction and morphogenesis of the skeletal system of rat embryos.

## Methods

The study was performed in compliance with laboratory regulations in the Anatomy and Histology Laboratories of the Faculty of Veterinary Medicine, Ardakan University, Yazd Province, under the supervision of an accredited Institutional Animal Care and Use Committee. This study received ethical clearance from the Ardakan University Ethics Committee (ethics code: IR.ARDAKAN.REC.1403.035).

### *Preparation of medicine*

For embryo-fetal development (EFD) and fertility studies, Paxlovid tablets (Composed of Nirmatrelvir and Ritonavir) were completely powdered. For each dose, the required amount of drug powder was completely prepared in 10 ml of distilled water for each group. Subsequently, 1 ml of the drug was provided to each rat by gavage. For each study, Paxlovid concentrations were assessed and validated in the dosing formulas.

### *Animals*

In this study, 40 pregnant female Wistar rats, aged 11-13 weeks, were provided (based on the observation of vaginal plaque) from the Yazd Institute of Reproductive Sciences. The Laboratory rodent feed (Envigo Teklad Global Diet) for the rats was provided by the Yazd Institute of Reproductive Sciences and was freely available. Drinking water from the municipal system, treated using reverse osmosis, was freely available to the animals. The laboratory environmental conditions were set at 30%-70% relative humidity, 20-25°C temperature, and a 12-hour light/dark cycle for all groups.

### *Embryo-fetal development studies in rats*

GD 0 – GD 7:

1. First group: The control group received no treatment. (They received daily food and water)
2. Second group: Experimental group 1 received the drug administered at 60 mg/kg/day by gavage daily.
3. Third group: Experimental group 2 received the drug administered at 200 mg/kg/day by gavage daily.
4. Fourth group: Experimental group 3 received the drug at a high dose of 1000 mg/kg/day by daily intragastric administration.

GD 8 – GD 17:

1. First group: The control group received no treatment. (They received daily food and water)
2. Second group: Experimental group 1 received the drug administered at 100 mg/kg/day by gavage daily.
3. Third group: Experimental group 2 received the drug administered at 300 mg/kg/day by gavage daily.
4. Fourth group: Experimental group 3 received the drug at a high dose of 1000 mg/kg/day by daily intra-





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gastric administration.

### Experimental design and treatment administration

The rats were weighed in the laboratory using a scale, and their weight was 196-250 grams. After weighting, they were randomly divided into 4 groups (n = 10 per group). The drug was administered to rats in two periods with different doses. The first period, which included the first week of pregnancy (GD 0 - GD 7), was administered at 0, 60, 200, and 1000 mg/kg/day to rats by gavage. The second period, which included GD 8 to GD 17, was administered at 0, 100, 300, and 1000 mg/kg/day to rats by gavage. Nirmatrelvir dosing was conducted up to 1000 mg/kg/day, adhering to ICH guideline recommendations (5). The doses used in our study were based on previous pharmacological data and guidelines, with the highest administered dose being 1000 mg/kg/day as the limit dose in accordance with ICH standards. The lower doses of Paxlovid were selected to evaluate dose-dependent effects.

### Sampling

Blood samples were collected from maternal rats on GD 17 to determine Paxlovid systemic concentration. The sampling method was as follows: at the beginning of GD 17 and before drug gavage, a blood sample was collected from the tail. Half an hour after drug gavage, a second sampling was performed from the tail, and similarly, blood sampling was performed one hour, two hours, and four hours after drug gavage, respectively. The tail snip method was used for sampling.

### Empirical data

Throughout every study, researchers recorded physiological indicators, tracked mass, and measured dietary intake. Details of the experimental framework, pharmacokinetic profiling, and statistical procedures for the fertility and rat EFD investigations have been outlined in prior publications (12, 13).

On GD 21, maternal rats were euthanized (via Chloroform), and then the fetuses were evacuated. Post-euthanasia, pregnant rats were examined visually for the pelvic, thorax, visceral organs, ovarian, and uterine contents to determine the number of dead or live fetuses. After extraction and clearing, the embryos were measured for weight, CRL, and AC. CRL and AC were measured using digital calipers. After euthanasia (via Chloroform), to observe the skeletal system, the skin and adipose tissue were carefully removed, and the internal organs of the embryos were removed. They were then fixed in 10% formalin for 5 days. Following evisceration, cleared, and dual staining using Alizarin Red S and Alcian Blue, they were assessed for skeletal malformations by means of a stereo microscope (14-16).

### Statistical analyses

In this study, Excel was used to evaluate the data (weight, CRL, and AC). One-way analysis of variance (ANOVA) was utilized to contrast the difference in weight, CRL, and AC of embryos of the treatment groups and the control group, and if significant, the Tukey test (HSD) was used for standardization. The differences between groups were analyzed using XLSTAT 2016 software, and the significance level in all fetal analyses was $P<0.05$.

## Results

### Clinical examination of rats

All rats were observed for physical signs throughout the study, and no mortality was observed. Rats were purchased based on the observation of vaginal plaque.

### Checking the body weight of maternal rats

The mothers' weights were examined on three different days, namely GD 7, GD 14, and GD 21. According to the examination of the rats' weights, pregnant rats gained weight on GD 21 compared to GD 7. However, the weight gain of pregnant rats in the control group was greater than that of the three experimental groups. The lowest weight gain was in experimental group 1 with doses of 60 and 100 mg ($P$ = 0.020) (Table 1). Maternal mean systemic exposure levels demonstrated variability across treatment groups, with higher variability at lower doses and relatively stable levels at the highest dose (Table 2).

### Clinical evaluation of fetuses

On GD 21, after removing the embryos from the uterus and examining their appearance, no abnormalities were observed. However, in experimental group 2, all embryos from a mother were very small, black, and dead (Table 3).

### Fetal weight assessment

The 21-day-old embryos were weighed immediately after they were removed from the uterine horns. The embryos of all experimental groups that received different doses of the drug weighed less than those of the control group. By evaluating the weight of the embryos of all four groups, we concluded that the lowest average weight of the embryos was in experimental group 1 (60 / 100 mg / kg / day), which was markedly lower than the control group ($P < 0.001$). Also, embryos of experimental group 2

*Table 1.* Maternal body weight

| Gestation Day | GD 7 | GD 14 | GD 21 |
|---|---|---|---|
| 0 | 215.6 ± 26.9 | 204.2 ± 33.3 | 252 ± 19.84 |
| 60,100 mg/kg/day (g)* | 216.6 ± 14.9 | 211.6 ± 14.5 | 224.1 ± 14.1 |
| 200,300 mg/kg/day (g) | 223.6 ± 14.6 | 220.6 ± 15.6 | 232.1 ± 15.5 |
| 1000 mg/kg/day (g) | 219.2 ± 6.7 | 214.7 ± 3.2 | 246.2 ± 12.8 |

P (*) < 0.05
(g) = grams; GD = Gestation Day
Data presented as mean per group ± standard deviation





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*Table 2.* Maternal mean total systemic exposure

| mg/kg/day | Mean Systemic Exposure (µg/mL) |
|---|---|
| 100 | 289.6 ± 121.9 |
| 300 | 296.7 ± 112.4 |
| 1000 | 209.1 ± 21.5 |

(200 / 300 mg / kg / day) had a very low average weight, which was markedly lower than that of the untreated group ($P < 0.001$). Embryos of experimental group 3 (1000 mg / kg / day) also had a significantly lower average weight ($P < 0.001$) than the control group (Table 3).

### Assessing fetal Crown Rump Length (CRL)

The average CRL of the embryos in all three experimental groups showed a decrease compared to the control group. The average CRL of experimental group one was markedly diminished relative to the untreated group ($P < 0.001$). Also, the average CRL of experimental group 2 embryos was significantly less than the average CRL of untreated group embryos ($P < 0.001$). The average CRL of the embryos in experimental group 3 was also significantly less than the average CRL of the embryos in the untreated group ($P < 0.001$) (Table 3).

### Assessing fetal abdominal circumference (AC)

Examination of the fetal AC in all three experimental groups showed that their average was less than that of the control group. In this way, the average fetal AC of experimental group 1 was less than that of the control group and was completely significant ($P < 0.001$). Also, the average size of the AC embryos from experimental group 2 was markedly diminished relative to the untreated group ($P < 0.001$). The average fetal AC in experimental group 3 was also less than the average AC of the control group and was significant ($P < 0.001$) (Table 3).

### Double-staining fetal observations

No skeletal abnormalities were observed in all three experimental groups (60/100, 200/300, 1000 mg/kg/day) with dual staining using Alizarin Red S and Alcian Blue (Figures 1, 2).

## Discussion

In this study, Paxlovid (Nirmatrelvir, Ritonavir) was not associated with malformations or reduced offspring survival following maternal administration. The sole observation was weight loss, CRL, and AC size of rat fetuses, as well as less weight gain during the mothers' pregnancy.

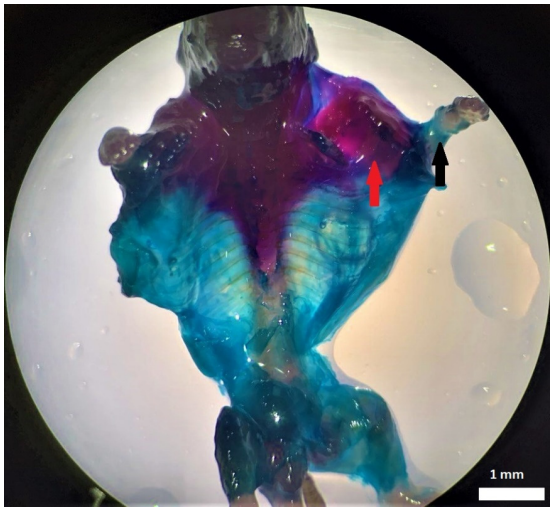


*Figure 1.* Alizarin Red S and Alcin Blue double staining
A newborn fetus after 21 days of pregnancy. The red arrow in the image indicates the bone regions that have successfully absorbed the alizarin red S dye, resulting in a prominent red coloration. This highlights the areas of calcified bone tissue where calcium deposits are present, confirming the sites of ossification and mineralization during the developmental stage under investigation. Conversely, the black arrow points to the cartilaginous regions that have taken up the Alcian blue dye, which binds specifically to glycosaminoglycans within the cartilage matrix. This staining pattern delineates the unossified, cartilage-rich areas that are still undergoing endochondral ossification. The differential staining allows for a clear distinction between calcified bone and cartilage tissues, facilitating the understanding of skeletal development and the spatial relationship between these tissue types within the specimen. Such staining techniques are essential in developmental biology studies to assess the progression of ossification and cartilage formation during growth stages.

Low fetal body weight is in agreement with developmental delay and occurs after drug exposure during organogenesis. Compared to humans, the 5-day period required for Paxlovid treatment is less than 2% (treatment for 5 days within a 280-day pregnancy) throughout human pregnancy. Moreover, fetal weight loss in rats occurred at exposure to a dose 10 times higher than the predicted human dose; Therefore, the lower weight of the rat fetus is not considered a significant risk to humans. There was also no effect on maternal fertility or preimplantation fetal development. In summary, the studies conducted show that Nirmatrelvir demonstrates positive fertility and developmental safety, evidenced by the lack of clinically significant influence on the fertility of female rats, as well

*Table 3.* Maternal data, fetal weight, CRL, and AC from the rat embryo-fetal development study.

| Mg/kg/day dose | 0 | 60/100 | 200/300 | 1000 |
|---|---|---|---|---|
| Number of pregnant rats | 5 | 9 | 8 | 4 |
| Maternal food consumption (g/day) | 205.5 ± 20.1 | 206.6 ± 15.6 | 201.4 ± 14.4 | 207.8 ± 17.6 |
| Live fetuses | 5.8 ± 4.1 | 8.7 ± 4.6 | 8.6 ± 4.6 | 11.5 ± 5.3 |
| Dead fetus | 0 | 7 | 0 | 0 |
| Fetal weight (g)* | 3.5 ± 0.6 | 1.7 ± 0.8 | 1.8 ± 0.8 | 2.5 ± 0.3 |
| Fetal CRL (mm)** | 35 ± 3.8 | 25.9 ± 6.5 | 26.36 ± 6.2 | 31.58 ± 2.2 |
| Fetal AC (mm)*** | 12.2 ± 1.2 | 9.9 ± 1.4 | 9.8 ± 1.6 | 11 ± 1 |

P (*, **, ***) < 0.001
(g) = grams; GD = Gestation Day; mm = millimeter
Data presented as mean per group ± standard deviation





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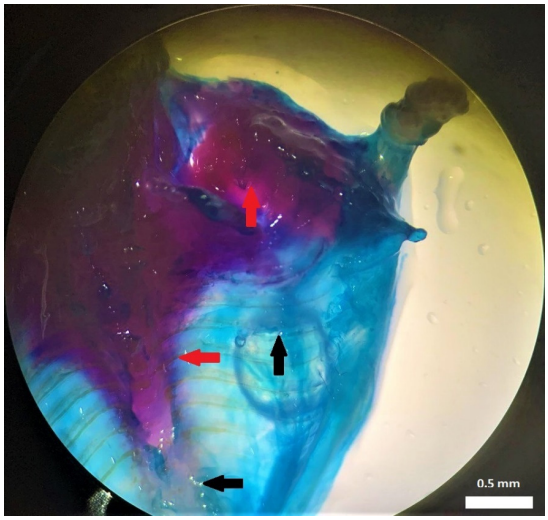


*Figure 2.* Alizarin Red S and Alcin Blue double staining
A newborn fetus after 21 days of pregnancy. The red arrow in the image denotes osseous regions that have effectively incorporated alizarin red S, a dye that selectively binds to calcium deposits in mineralized bone matrix. This results in a distinct red staining pattern, marking areas of active ossification and calcification within the developing skeletal tissue. The observed staining confirms the presence of mature, mineralized bone at these sites. In contrast, the black arrow identifies chondrogenic regions stained with Alcian blue, which exhibit high affinity for sulfated glycosaminoglycans (GAGs) within the cartilaginous extracellular matrix. This staining demarcates zones of unossified cartilage, indicative of ongoing endochondral ossification. The differential application of alizarin red S and Alcian blue enables clear morphological discrimination between mineralized bone and hyaline cartilage, providing critical spatial and structural insights into skeletal development.

as the absence of abnormalities in fetal skeletal tissue histology, along with the lack of findings in a genetic toxicology test of Nirmatrelvir (5, 17).

Over the past two decades, two new COVID-19 infections, SARS-CoV in 2002 and MERS-CoV in 2012, have emerged that provoked severe human illnesses. During the SARS-CoV epidemic, more than 8,000 people were affected around the world, and about 800 deaths were recorded, indicating about 10% deaths. At the same time, MERS-CoV recorded more than 857 confirmed cases and 334 deaths, with about 35% deaths. So far, SARS-CoV-2 represents the seventh human-infecting species of the Coronavirus group. The key signs of the SARS-CoV-2 infection, which involve fever, fatigue, and cough, are comparable to those of two past coronavirus infections (1, 2).

Many vaccines, including Pfizer, Moderna, Sinopharm, and AstraZeneca, were distributed to prevent SARS-CoV-2, which were more or less effective against COVID-19. Also, various drugs, including Molnofavir, Remdesivir, Ribavirin, Favipiravir, Nirmatrelvir, and Paxlovid, were introduced to treat COVID-19, one of the most effective of which was Paxlovid. On December 22, 2021, the US Food and Drug Administration granted approval in the U.S. for contingency use of Paxlovid for mild to moderate 2019 coronavirus infections in populations at risk over 12 years of age weighing equal to or exceeding 40 kg in the first 5 days of signs and symptoms appearance (18). The National Institutes of Health suggests that Paxlovid be prescribed to eligible pregnant women based on evidence of a therapeutic index. This evaluation may consider BMI, vaccination status, and factors predisposing to acute COVID-19 illness (19). The NIH does not suggest against prescribing Paxlovid in the lactation phase, but advocates that the benefits of lactation, the necessity of the drug, and the infant's potential exposure to COVID-19 infection be considered (19).

The Maternal-Fetal Medicine Association in the U.S. endorses the consumption of Paxlovid during pregnancy in certain circumstances, given its substantial drug interface profile, but the Canadian administration advises against the use of Paxlovid during pregnancy unless advised otherwise by a health care professional. The Canadian government also recommends that women who are not pregnant utilize birth control while consuming Paxlovid and assigns the judgment on whether Paxlovid can be used during breastfeeding to the health care professional. Paxlovid is not recommended for use during pregnancy and breastfeeding by medical associations in Europe, the United Kingdom, Germany, Australia, and New Zealand (4).

The lack of genotoxicity for Nirmatrelvir represents a major factor in determining pregnancy risks of antiviral pharmaceuticals. Corresponding to Nirmatrelvir and Paxlovid, Remdesivir, an RNA polymerase inhibitor reliant on viral RNA, authorized for the care of inpatients with COVID-19, showed no developmental toxicity observed in rat fetuses at the maximum dosage evaluated (20 mg/kg/day) (5, 20).

Reproductive and maturational preservation of Nirmatrelvir has been evaluated in just one animal study. The possible impacts of NMV on embryonic growth in rats and rabbits and on fecundity and initial fetal growth in rats were evaluated up to a limiting dosage (1000 mg / kg / day). The evaluation reported no acute maturational toxic effects in both animals. In addition, the research reported no impacts on early embryogenesis and fertility in rats. In Catlin et al.'s study, the lack of weight observed in the fetuses of rabbits is similar to the effect of Paxlovid (NMV, Ritonavir) on the fetuses of rats, in terms of weight accumulation in the research (5).

Nirmatrelvir inhibits the major protease of SARS-CoV-2 (17), inhibits viral replication, and necessitates concurrent use with Ritonavir, an HIV-1 protease and CYP3A blocker, to achieve sufficient therapeutic plasma concentrations. The mechanism of action of Nirmatrelvir shows a minimal hazard of toxicity. As Ritonavir is a significant and extensively utilized antiviral agent for HIV, there is much evidence on its impact on gestation period. A recent analysis of 34 historical group studies found that protease inhibitor-based antiretroviral therapy for HIV was correlated with elevated risk of small-for-gestational-age infants but does not raise the risk of premature labor or other unfavorable fetal results (4, 21).

Other drugs such as Ribavirin (RBV) and Favipiravir (FAV) were also used to treat SARS-CoV-2, but because





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of their teratogenicity, their administration to pregnant women was problematic. Additional antiviral drugs (RBV and FAV) are accomplished through focusing on viral RNA. The complexes have been illustrated to have teratogenicity in diverse species. Ribavirin has been reported to be embryo lethal and toxic in rats, rabbits, and guinea pigs (22, 23). Also, the teratogenicity of Favipiravir has been documented in monkeys, rats, and rabbits (5). This mutagenesis mechanism, which leads to the antiviral activity of these compounds, can lead to subsequent integration and mutational change of the host genome (24, 25).

Pregnant women are at risk of severe disease from coronavirus infection, also COVID-19 infection during pregnancy raises the risk of delivering before term. Moreover, they can be more susceptible to complications or spontaneous abortion. These necessitate antiviral treatments and highlight the importance of potential treatments during pregnancy (26, 27).

Paxlovid could be a significant alternative to diminish the complications arising from severe COVID-19 infection in susceptible and unvaccinated individuals, upon careful analysis of the potential benefits and risks for every patient, but additional research is required to evaluate its efficacy in pregnant and lactating women (4).

Given the absence of observable abnormalities in the skeletal system of rat fetuses and the limited adverse effects, primarily a slight reduction in crown-rump length, abdominal circumference, and fetal weight, further investigation into high-dose Paxlovid administration is warranted. Additionally, subsequent studies should evaluate drug toxicity during pregnancy and its potential effects on human fetal development.

## Conclusion

All these data did not show any abnormality of the morpho-skeletal system due to Paxlovid, and only weight loss, CRL, and AC were observed in fetuses. Data from this study, as well as existing data, suggest little Possible fetal toxicity related to Paxlovid, which contains NMV, a strong and specific blocker of the primary SARS-CoV-2 protease, used alongside Ritonavir, which boosts drug levels. Although rat models do not fully replicate human physiology and clinical outcomes, they are widely accepted as valuable preliminary models for understanding underlying biological mechanisms and assessing potential therapeutic effects. The use of rats in this study allows for controlled experimentation and provides foundational data that can inform future research. We acknowledge that further validation in human studies is necessary to confirm the translatability of our findings. However, the hazards and possible advantages of Paxlovid use in pregnancy ought to be reviewed with a medical professional.

### *Authors' Contributions*

AA, MM, and ES were involved in the planning and development of the experimental work. MR and ARG performed the data processing and statistical evaluations. All authors participated in reviewing the findings and contributed to the preparation of the final manuscript.

### *Ethical Considerations*

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### *Acknowledgment*

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### *Conflict of Interests*

The authors declare that they have no competing interests.

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