ORIGINAL ARTICLE

Favipiravir Exposure in the Second and Third Trimesters of Pregnancy with COVID-19: Risk of Adverse Perinatal Outcomes: A Retrospective Cohort Study

Onanong Noomcharoen, MD[1], Thananan Chongsomboonsuk, MD[1]

[1] Department of Obstetrics and Gynecology, Queen Savang Vadhana Memorial Hospital, Thai Red Cross Society, Chon Buri, Thailand

Background: During the pandemic, Favipiravir, an oral antiviral agent, was used for COVID-19 treatment. However, its safety profile for pregnant women, especially during the second and third trimesters, is not well-established.

Objective: To assess the pregnancy outcomes and risk of congenital anomalies associated with favipiravir exposure during the second and third trimesters in COVID-19-infected pregnant women.

Materials and Methods: A retrospective cohort study was conducted at the Department of Obstetrics and Gynecology, Queen Savang Vadhana Memorial Hospital, including pregnant women beyond 14 weeks gestation who delivered between June 1, 2021, and May 31, 2022. Participants were divided into those exposed to favipiravir, which were 99 patients, and those who were not exposed, which included 115 patients. Data on maternal, obstetric, and neonatal outcomes were collected and analyzed.

Results: Out of 383 registered COVID-19-infected pregnant women, 214 were included in the analysis. No severe maternal drug reactions were observed. Favipiravir exposure was significantly associated with an increased rate of small for gestational age (SGA) infants at 13.1% versus 3.5% (OR 4.16, p=0.01). No significant differences were found in other obstetric and neonatal outcomes, including preterm delivery, cesarean delivery, or neonatal morbidity. Specific congenital anomalies such as cardiac defects and renal pyelectasis were observed in the favipiravir-exposed group, but these were not statistically significant.

Conclusion: Favipiravir exposure during the second and third trimesters was associated with an increased risk of SGA, while congenital anomalies and other perinatal outcomes did not differ significantly between groups.

Keywords: Favipiravir; Pregnancy; COVID-19; COVID-19 complicating pregnancy; Perinatal outcomes

Received 28 November 2024 | Revised 18 February 2025 | Accepted 2 April 2025

J Med Assoc Thai 2025;108(6):431-9

Website: http://www.jmatonline.com

Favipiravir, a broad-spectrum oral antiviral agent as a nucleotide analog inhibiting viral RNA polymerase activity, was first approved in Japan in 2014 as a backup choice for new and reemerging pandemic influenza[1]. However, in the initial phase of the COVID-19 pandemic crisis, when effective treatments were under investigation, favipiravir was repurposed as a potential treatment option for COVID-19 and used for emerging in many countries, such as China, Turkey, Japan, and India[2]. In Thailand, favipiravir has also been approved under the emergency procurement of the Department of Disease Control since February 2020[3-5], supported by data showing positive outcomes and promoting viral clearance, especially in patients with mild to moderate COVID-19[6]. Even though the drug does not inhibit DNA or RNA polymerase and is non-toxic to the host, preclinical animal studies have raised safety concerns during pregnancy about its potential teratogenicity and embryotoxicity, as documented in pharmaceutical reports[7,8].

However, managing COVID-19 in pregnancy in the early phase of pandemic is challenging because pregnant women are considered valuable patients. Despite their high risk for severe respiratory complications from COVID-19 due to physiological and immunological change[9], pregnant women are typically excluded from clinical trials to avoid

Correspondence to:

Noomcharoen O.

Department of Obstetrics and Gynecology, Queen Savang Vadhana Memorial Hospital, Thai Red Cross Society, 290, Jermjomphol Road, Sriracha, Chon Buri 20110, Thailand.

Phone: +66-81-9044775

Email: onanong@somdej-mec.or.th

How to cite this article:

Noomcharoen O, Chongsomboonsuk T. Favipiravir Exposure in the Second and Third Trimesters of Pregnancy with COVID-19: Risk of Adverse Perinatal Outcomes: A Retrospective Cohort Study. J Med Assoc Thai 2025;108:431-9.

DOI: 10.35755/jmedassocthai.2025.6.431-439-01780

potential maternal and fetal adverse effects[10,11]. As a result, evidence-based information on the safety and efficacy of COVID-19 drugs during pregnancy is insufficient, relying mostly on small observational studies or case series[12]. Moreover, some approved treatments are not available worldwide[5]. Hence, recommendations for managing COVID-19 in pregnancy have focused on reducing maternal morbidity and are similar to those for non-pregnant women with shared decision-making based on disease severity, patient comorbidities, and individual safety considerations[9,13].

When effective pharmacotherapy and vaccinations were not yet available, and there was lack of evidence-based treatment options, especially during the peak of the Delta and Omicron variant outbreaks, there was global concern about overwhelming the healthcare systems. According to the Thai national guidelines, favipiravir was recommended as a treatment option for pregnant women beyond 14 weeks of gestation with mild to moderate COVID-19 for a certain duration[14].

Currently, there is limited data on maternal and fetal outcomes related to favipiravir use during pregnancy, with only two case reports[15,16] and few descriptive studies among patients exposed during the periconceptional period and early gestation[17-20]. Conversely, there are no analytical clinical studies assessing the effects of favipiravir on pregnant women, particularly in the second and third trimesters, which are beyond the critical period of organogenesis. Thus, the present study aimed to achieve two objectives, 1) to provide information on pregnancy outcomes and fetal anomalies in pregnant women exposed to favipiravir during the second and third trimesters, and 2) to compare these outcomes with those of similar cohort of COVID-19-infected patients who did not receive favipiravir.

Materials and Methods

The present study was a retrospective cohort study performed within the Department of Obstetrics and Gynecology of Queen Savang Vadhana Memorial Hospital. This institute is situated in Chonburi Province, known for its high COVID-19 infection rates because of its tourist destinations and industrial district. All pregnant women registered as COVID-19 infection at the gestational age (GA) beyond 14 weeks and then subsequently delivered their offspring at the present study hospital between June 1, 2021, and May 31, 2022, were enrolled. The patients were excluded if they were treated with other antiviral agents such as remdesivir, if their treatment could not complete a standard 5-day course of favipiravir before delivery, and if the COVID-19 infection was diagnosed and treated during the postpartum period.

The present study was conducted as a complete population analysis. All eligible patients recorded within the database during a one-year period were divided into two groups according to whether favipiravir was received during the treatment of COVID-19 infection in the second to third trimester of pregnancy. The favipiravir-exposed group was defined as those prescribed a complete course of favipiravir before delivery, and the unexposed group was those not exposed to favipiravir or any other antiviral drugs and received only supportive symptomatic treatment. The present research had been approved by the Institutional Review Boards of the Queen Savang Vadhana Memorial Hospital (Study ID 024/2566). Electronic medical records and patient's antenatal documents were manually reviewed. Then, all the following data were extracted and included the demographic data and clinical characteristics including age at eligibility, gravida, parity, GA at infection, medical comorbidities, multiple gestations, and the severity of COVID-19 infection, obstetrical outcomes including GA of delivery, cesarean delivery and indications, abortion, intrauterine fetal demise, preeclampsia, fetal growth restriction, oligohydramnios, and placental abruption, and neonatal outcomes including birthweight, head circumference, length, Apgar score at 1 and 5 minutes, congenital anomaly, admitted to neonatal intensive care unit (NICU), required respiratory support, neonatal sepsis or congenital pneumonia, hypoglycemia, transient murmur, jaundice required phototherapy, neonatal death, and hospital stay. In the present study, small for gestational age (SGA) was defined as birth weight below the tenth percentile for their GA, low birth weight (LBW) as birth weight less than 2,500 g, and microcephaly as a head circumference less than the third percentile. Due to the retrospective nature, the study did not participate in the decision-making process regarding medical treatments during the study period.

The approach to diagnosing and managing COVID-19 in pregnant patients in the present study was based on the National Clinical Practice Guidelines developed by the Department of Medical Services and the Ministry of Public Health of Thailand, along with recommendations from The Thai Royal College of Obstetrics and Gynecologists at the time of patient eligibility. Diagnoses were established using RT-

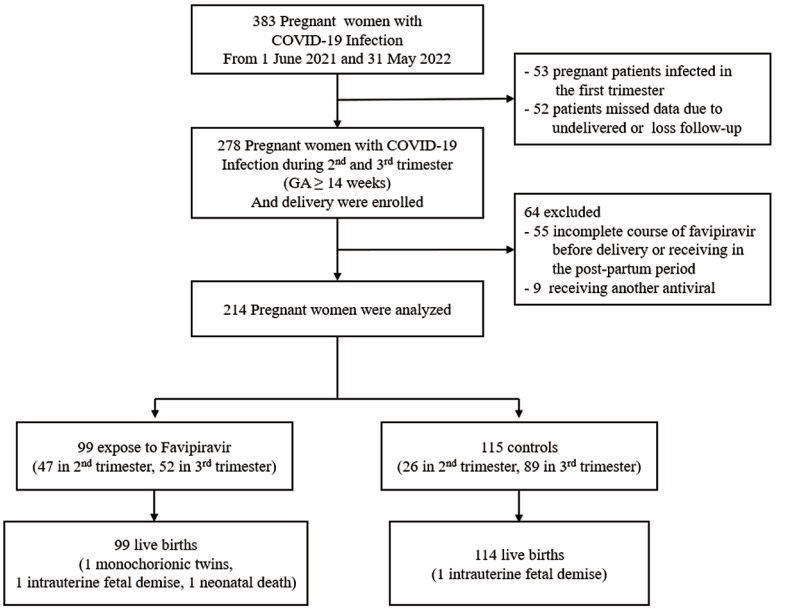

Figure 1. The flow chart of participants in the study.

PCR or rapid antigen tests for SARS-CoV-2 from nasopharyngeal swabs. Early in the pandemic, testing was confined to symptomatic patients and those with significant exposure risk. As the pandemic escalated, universal testing was implemented for all hospital admissions and medical interventions, with additional workplace screenings. At that time, Thailand's vaccination program was in the initial stages, and mRNA vaccines were not yet widely available[21]. There was also a lack of comprehensive knowledge about the effective treatment of COVID-19, particularly in pregnant women. Pregnant patients diagnosed with COVID-19 received comprehensive care from attending physicians, obstetrician teams, and infectious medicine consultants. Counseling was provided on the heightened risk of severe disease in pregnant women compared to their non-pregnant counterparts. Therefore, Favipiravir was prescribed based on clinical judgment and guidelines[19], with the consensus that its benefits outweighed the risks individually for patients beyond 14 weeks of gestation to minimize teratogenic effects.

For individuals receiving favipiravir, the regimen followed the recommended guidelines, which was 1,800 mg twice on the initial day, followed by 800 mg twice daily for five days at a minimum for patients weighing under 90 kg. Meanwhile, the recommendation for those above 90 kg was 2,400 mg twice on day one, followed by 1,000 mg twice daily for at least five days. Following recovery, the obstetric team monitored all COVID-19-infected pregnant women throughout the antenatal care period until delivery.

For statistical analysis, continuous data were presented as mean and standard deviation or median with interquartile ranges, contingent upon the data distribution. Categorical data were shown as numbers or percentages. The unpaired 2-sided Student's t-test or the Mann-Whitney U test was used to compare continuous variables, depending on data distribution, and the chi-square test was applied to compare categorical variables and to estimate odd ratios within the study group. A p-value of less than 0.05 indicated statistical significance. All analyses were conducted using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY, USA).

Results

Between June 1, 2021, and May 31, 2022, 383 pregnant women registered for COVID-19 infection were identified at the authors hospital. Of these, 278 were infected after 14 weeks of gestation and delivered the baby. Fifty-five cases were excluded due to the incomplete favipiravir course before delivery, such as during the intrapartum period or receiving favipiravir post-partum period, along with nine cases receiving another antiviral. Thus, 214 patients were analyzed, that included 99 who received favipiravir in the antepartum period, and 115 who did not (Figure 1). One patient in the favipiravir group was

Table 1. Maternal demographic and clinical characteristics among COVID-19-infected patients

Variables	Favipiravir-exposed (n=99)	Unexposed (n=115)	p-value
Maternal age at eligibility; median (IQR)	29 (21 to 33)	28 (21.6 to 33)	0.370
Gravidity; median (IQR)	2 (1 to 3)	2 (1 to 3)	0.508
Parity: nulliparous; n (%)	34 (34.3)	43 (37.4)	0.643
GA at infection; n (%)			
14 to 27 weeks	47 (47.5)	26 (22.6)	<0.001*
≥28 weeks	52 (52.5)	89 (77.4)	
Medical comorbidities; n (%)			
Obesity (BMI >30)	26 (26.3)	28 (24.3)	0.748
Asthma or active lung disease	2 (2.0)	2 (1.7)	0.880
Chronic hypertension	4 (4.0)	4 (4.3)	0.911
Pregestational diabetes	3 (3.0)	2 (1.7)	0.533
HIV	2 (2.0)	0 (0)	0.126
Thyroid disease	3 (3.0)	4 (3.5)	0.854
Multiple gestations; n (%)	1 (1.0)	0 (0.0)	0.280
Severity of COVID-19 infection; n (%)			
Required oxygen support	7 (7.1)	0 (0.0)	0.004
Critical illness or require mechanical ventilation	2 (2.0)	0 (0.0)	0.126

IQR=interquartile range; GA=gestational age; BMI=body mass index

a monochorionic diamniotic twin pregnant.

Maternal demographic and clinical characteristics of both favipiravir-exposed and unexposed groups are presented in Table 1. Most of the patients exhibited asymptomatic to mild symptoms. However, seven cases needed supportive oxygen, two cases were categorized as critical illness, and all were in the favipiravir-exposed group. Both groups demonstrated similar baselines regarding age, obstetric history, GA of infection, and comorbidity, except those in the second trimester who were more likely to receive favipiravir at 47.5% versus 22.6%. In comparison, those in the third trimester were more likely not to receive favipiravir at 52.5% versus 77.4%.

In the favipiravir-exposed group, most patients were administered the standard 5-day regimen. Notably, in six cases, the medication was extended with four cases that were prescribed a high dose for five days due to exceeding body weight, and two cases who were prescribed a high dose for ten days. During the medication administration, no severe maternal adverse reactions were identified.

Since the patient had been diagnosed with COVID-19 until delivery, obstetric outcomes are detailed in Table 2. Most patients in both groups delivered at term as the median of GA 38 weeks, with no statistically significant difference in the rate of preterm delivery, cesarean delivery and its indications, or obstetrics complications. Although patients in the favipiravir-exposed group were more likely to have preeclampsia, the difference was not statistically significant at 8.1% versus 5.2%. Unfortunately, one case in the favipiravir-exposed group, who experienced COVID-19 infection at GA 21 weeks, encountered intrauterine demise at GA 33 weeks, and another case in the unexposed group found intrauterine demise at GA 28 weeks.

As presented in Table 3, fetal outcomes showed that both groups had similar mean birthweight, head circumference, and length. Interestingly, the favipiravir-exposed group exhibited a significantly increased rate of SGA at 13.1% versus 3.5% (OR 4.16, 95% CI 1.30 to 13.20, p=0.01). The rates of LBW and microcephaly were also higher but not statistically significant. However, no differences were identified in neonatal morbidity, which included Apgar score, NICU admission, required respiratory support, neonatal sepsis, hypoglycemia, transient cardiac murmur, jaundice requiring phototherapy, and neonatal death. Notably, one case in the favipiravir-exposed group had to undergo an emergent cesarean section at 30 weeks of gestation due to fetal distress on the sixth day of COVID-19 infection. Regrettably, the newborn passed away after two days due to severe birth asphyxia. Furthermore, a supplementary multivariable logistic regression analysis adjusting for maternal comorbidities and COVID-19 severity confirmed that favipiravir exposure remained significantly associated with an increased risk of SGA (adjusted OR 4.04, 95% CI 1.25 to 13.09, p=0.020).

Table 2. Obstetrics and perinatal outcomes

Variables	Favipiravir-exposed (n=99)	Unexposed (n=115)	OR*	95% CI	p-value
GA at delivery; median (IQR)	38 (37 to 39)	38 (37 to 39)			0.756
Preterm delivery (before 37 weeks); n (%)	13 (13.3)	21 (18.3)	0.69	0.32 to 1.45	0.321
Cesarean delivery; n (%)	46 (46.5)	53 (46.1)	1.11	0.59 to 17.40	0.956
Indication for cesarean delivery; n (%)	(n=46)	(n=53)			
Previous cesarean section	10 (21.7)	13 (24.5)	0.86	0.33 to 2.19	0.743
Arrest of labor	13 (28.3)	7 (13.2)	2.59	0.93 to 7.19	0.063
Non-reassuring fetal status	7 (15.2)	13 (24.5)	0.55	0.20 to 1.53	0.250
Abnormal presentation	2 (4.3)	1 (1.9)	2.36	0.21 to 26.95	0.476
Others	8 (17.4)	12 (22.6)	0.72	0.27 to 1.95	0.516
Obstetric complications; n (%)					
Preeclampsia	8 (8.1)	6 (5.2)	1.60	0.54 to 4.77	0.398
Fetal growth restriction	2 (1.7)	3 (2.6)	1.76	0.29 to 10.79	0.533
Oligohydramnios	1 (1.0)	2 (1.7)	0.58	0.05 to 6.46	0.651
Placental abruption	0 (0.0)	1 (0.9)			0.352
Intrauterine fetal demise or abortion	1 (1.0)	1 (0.9)	1.16	0.72 to 18.84	0.915
Any obstetric complications	12 (12.1)	11 (9.6)	1.30	0.55 to 3.10	0.55

IQR=interquartile range; GA=gestational age; OR=odds ratio; CI=confidence interval
* Calculated using the chi-square test

Table 3. Neonatal outcomes

Variables	Favipiravir-exposed (n=99)	Unexposed (n=114)	OR*	95% CI	p-value
Birthweight (g); mean [SD]	2922 [586]	3011 [461]			0.215
Head circumference (cm); mean [SD]	33.14 [2.59]	33.35[1.97]			0.515
Length (cm); mean [SD]	47.51 [4.10]	47.97 [2.05]			0.294
LBW (<2,500 g); n (%)	17 (17.2)	13 (11.4)	1.61	0.74 to 3.51	0.227
SGA; n (%)	13 (13.1)	4 (3.5)	4.16	1.30 to 13.20	0.010
Microcephaly; n (%)	4 (4.0)	1 (0.9)	4.76	0.52 to 43.30	0.128
Neonatal morbidity; n (%)					
1-minute Apgar <7	10 (10.1)	5 (4.4)	2.45	0.81 to 7.43	0.104
5-minute Apgar <7	2 (2.0)	0 (0.0)			0.127
Admitted to NICU	7 (7.1)	7 (6.1)	1.16	0.39 to 3.44	0.785
Required respiratory support	12 (12.1)	12 (10.5)	1.17	0.50 to 2.74	0.713
Neonatal Sepsis or congenital pneumonia	11 (11.1)	11 (9.6)	1.18	0.48 to 2.83	0.727
Hypoglycemia	7 (7.1)	3 (2.6)	2.82	0.71 to 11.19	0.127
Transient murmur	11 (11.1)	14 (12.3)	0.89	0.39 to 2.07	0.791
Jaundice require phototherapy	21 (21.2)	17 (14.9)	1.54	0.76 to 3.11	0.231
Neonatal death	1 (1.0)	0 (0.0)			0.282
Congenital anomaly; n (%)					
Cardiac defect	3 (3.0)	1 (0.9)	3.53	3.61 to 34.51	0.278
Skin and skeletal	1 (1.0)	3 (2.6)	0.38	0.04 to 3.69	0.838
Urinary system	1 (1.0)	0 (0.0)			0.282
Genital system	1 (1.0)	1 (0.9)	1.15	0.07 to 18.68	0.920
Hospital stay (day); median (IQR)	3 (2 to 3)	3 (2 to 4)			0.209

SD=standard deviation; IQR=interquartile range; SGA=small for gestational age; LBW=low birth weight; NICU=neonatal intensive care unit; OR=odds ratio; CI=confidence interval
* Calculated using the chi-square test

Details of adverse cases and anomalies related to favipiravir exposure from the present study are summarized in Table 4. In the present study, three cases of cardiac defects were identified in the

Table 4. Adverse cases and anomalies related to favipiravir exposure from the study

Case	Age (year)	Severity of COVID infection	Total dose of expose (mg)	GA of expose (weeks)	Comorbid disease/ other exposure	Prenatal ultrasound findings	Pregnancy outcomes
Tetralogy of fallot and mild bilateral pyelectasis	28	Mild symptoms	12,800	16	- Twin B fetus of monochorionic diamniotic twins - Maternal obesity - Gestational diabetes (diet controlled)	Fetal bilateral pyelectasis at GA 24 weeks (resolved after birth)	C/S at GA 31 weeks due to preeclampsia with severe features (the co-twin A fetus was healthy)
Atrial septal defect	31	Required O2 support	10,000	36	-	Unremarkable	C/S at 36 weeks due to previous C/S with preterm labor
Patent ductus artheriosus	28	Mild symptoms	10,000	35	-	Unremarkable	C/S at GA 40 weeks due to non-reassuring fetal heart rate pattern
Sacral dimple	32	Required O2 support	10,000	31	Pregestational hypertension	Unremarkable	NL at GA 38 weeks
Undescended testis	21	Mild symptoms	10,000	36	-	Unremarkable	C/S at 37 weeks due to previous C/S
Intrauterine fetal demise at GA 33 weeks	18	Mild symptoms	10,000	21	-	Unremarkable	Fetal demise at GA 33 weeks due to an umbilical cord accident
Neonatal death	36	Mild symptoms	10,000	30	Advanced maternal age (fetal karyotype: 46, XX)	Unremarkable	C/S at GA 31 weeks due to fetal distress (day 8 of COVID-19 infection) (neonatal death on 2nd day of life due to severe birth asphyxia, sepsis, and respiratory distress syndrome

GA=gestational age; NL=normal labor; C/S=cesarean section; O2=oxygen

favipiravir-exposed group; tetralogy of Fallot, atrial septal defect, and patent ductus arteriosus. Notably, the tetralogy of Fallot case was in a twin B fetus from a monochorionic twin pregnancy, exposed to favipiravir at 16 weeks gestation, and presented with bilateral pyelectasis that resolved after birth. The co-twin A fetus was born without anomalies. Other findings included one case of undescended testis and one case of a sacral skin dimple. Despite a higher incidence of cardiac and renal anomalies in the favipiravir-exposed group, these results did not achieve statistical significance.

Discussion

In the present research, the authors focused on comparing the pregnancy outcomes of 99 women exposed to favipiravir during their second and third trimesters due to COVID-19 with 114 unexposed women. There was a significantly higher SGA in the exposed group while other obstetric and neonatal outcomes were quite similar between both groups. Specific adverse outcomes in the favipiravir-exposed group included one intrauterine fetal demise, one neonatal death, three congenital cardiac defects, one renal pyelectasis, one undescended testis, and one skin dimple in the sacral area, but they were not statistically significant compared to the unexposed group.

To the best of the authors knowledge, the present study is the most comprehensive examination of favipiravir's safety during pregnancy, being the first to focus on the second and third trimesters. The present research was a pioneering cohort study that compared pregnancy and neonatal outcomes for those exposed and unexposed to favipiravir, all within the same data pool of pregnant COVID-19 patients. This design aimed to minimize biases and confounders from COVID-19 infection, offering a clearer view of favipiravir's potential risks. Importantly, the authors first identified the significant risk of fetal SGA in the group of favipiravir exposure.

There were limitations in the present study. First, despite being one of the largest studies to date on favipiravir used during pregnancy with a complete population analysis, it may be underpowered to identify some of the minor incidences but essential outcomes. Furthermore, long-term effects on neonates need further follow up. Second, although the researchers observed cases with fetal anomalies and SGA in the favipiravir-exposed group, the study's retrospective nature limited the study ability to determine whether these outcomes were directly caused by favipiravir or if they occurred coincidentally. To address this, a supplementary multivariable regression analysis was conducted to adjust for potential confounding factors affecting the risk of SGA, including maternal underlying diseases and the severity of infection. However, the possibility

of residual confounding cannot be entirely excluded, and further prospective studies are necessary to validate these findings. Moreover, the present study also does not include safety information for the periconceptional period and the first trimester. Lastly, the study did not assess the efficacy of favipiravir in treating COVID-19. Additionally, the effects of low doses and immediate intrapartum use were not investigated because some patients with severe illness were switched to other treatments or required urgent delivery before completing the favipiravir regimen, which resulted in their exclusion from the analysis.

According to available information, there are no extensive reports on the maternal and neonatal impacts of favipiravir when exposed in the second and third trimesters of pregnancy. The first report on favipiravir use during pregnancy involved a woman at seven months gestation infected with Ebola. Tragically, she delivered her baby on the fourth day of admission and died from postpartum hemorrhage. Though the baby tested positive for Ebola, no adverse outcomes or congenital anomalies were reported[15]. Another case was documented during the early phase of the COVID-19 pandemic, involving a twin pregnant woman treated with favipiravir and convalescent plasma therapy after cesarean section, with a favorable response[16].

Subsequently, four studies from Turkey described the outcomes of 9 to 29 pregnant women exposed to favipiravir during early gestation, ranging from the periconceptional period up to 16 weeks[17-20]. Data from these studies, encompassing a total of 60 live births, report two cases of congenital cardiac defect as patent foramen ovale and aortic stenosis[19,20], three genitourinary abnormalities as pyelectasis, vesicourethral reflux, and hydronephrosis with urinoma[18,19], three cases of abortion or neonatal death[17-19], and two cases needing neurodevelopmental follow-up due to abnormal audiometry and unexplained seizures[17]. As a result, cardiac and genitourinary anomalies, along with the need for long-term follow-up, are important concerns in cases receiving favipiravir, particularly during the embryonic period.

Although the researchers also observed cardiac defects and renal pyelectasis cases, they cannot conclude that the abnormal cardiac defects and renal pyelectasis identified in the present study were solely attributed to favipiravir. The most severe case, which involved tetralogy of Fallot and pyelectasis, was a monochorionic twin. Monochorionic twins have a higher incidence of congenital heart defects and anomalies compared to singletons[22,23]. Furthermore, tetralogy of Fallot is a complex abnormality that develops during the embryonic period[24], suggesting that favipiravir might not be the direct cause in this situation. Furthermore, the other cases, including atrial septal defect, patent ductus arteriosus, sacral dimple, and undescended testis, were all exposed to favipiravir during the third trimester, leaving the clinical implications of these exposures remain unclear.

The present study found that most perinatal outcomes, including obstetric complications, cesarean sections, and neonatal morbidity, did not differ significantly between both groups, except for an increased risk of SGA in the favipiravir-exposed group. The mechanism underlying these findings remains uncertain. However, the potential effect of favipiravir on fetal bone growth should be considered. While no comparative human studies are available, animal studies have reported decreased birth weight, delayed bone development, and malformations, particularly involving skeletal anomalies and variations[7,25,26]. Notwithstanding that the rate of SGA is higher in the exposed group at 13.1% versus 3.5%, it is similar to the prevalence in the general population at 11% in high-income countries, 27% to 32.5% in low and middle-income countries, and 7% to 10.9% in Thailand[27-29]. For the LBW rate, the present study aligned with two previous studies that reported rates of 10.5% and 33%[18,19], while another study found that all patients had normal birth weight.

Given these findings, the data suggest that favipiravir might be a safe treatment option for pregnant women with mild to moderate COVID-19 infection during these trimesters. The authors recommend that pregnant women receiving favipiravir undergo regular fetal growth monitoring and detailed anomaly scans, focusing on fetal echocardiography and genitourinary system. Noticeably, the role of favipiravir in COVID-19 treatment has decreased due to controversial efficacy from subsequent clinical trials[30,31] and more robust evidence supporting the effectiveness of vaccinations and antiviral drugs, like remdesivir and nirmatrelvir/ritonavir, in pregnancy[32-34]. Nevertheless, due to its broad spectrum against RNA viruses, the safety information in pregnancy from this study remains valuable for considering the drug as a backup treatment in future pandemics.

Further research, encompassing more extensive prospective cohort studies, randomized controlled trials, and long-term outcome assessments, is

essential to validate the safety of favipiravir in pregnancy. Additionally, its potential efficacy as an outpatient therapy for pregnant individuals with mild to moderate COVID-19 manifestations or other potential viral pandemic infections in the future still needs evaluation.

Conclusion

The outcomes of the present study point towards the potential safety of Favipiravir use during the second and third trimesters of pregnancy. However, with the elevated risk of SGA and documented cases of cardiac and renal anomalies, regular monitoring of fetal growth and comprehensive anomaly scans, with an emphasis on fetal echocardiography and genitourinary system, are recommended.

What is already known about this topic?

Limited human research exists on maternal and fetal outcomes following favipiravir use in pregnancy, with only a few case reports and descriptive studies and no current data on its use during the second and third trimesters.

What does this study add?

This study identified an increased risk of SGA infants associated with favipiravir exposure in the second and third trimesters. Although certain congenital anomalies, such as cardiac defects and renal pyelectasis, were observed, these findings, along with other obstetric and neonatal outcomes, did not reach statistical significance.

Acknowledgement

The authors disclosed using artificial intelligence (AI)-assisted technologies (ChatGPT) to enhance the grammar and word flow during the manuscript preparation. The authors retain full responsibility for the content, including all text and images published in the present paper.

Conflicts of interest

The authors have no conflicts of interest.

References

1. Hassanipour S, Arab-Zozani M, Amani B, Heidarzad F, Fathalipour M, Martinez-de-Hoyo R. The efficacy and safety of Favipiravir in treatment of COVID-19: a systematic review and meta-analysis of clinical trials. Sci Rep 2021;11:11022. doi: 10.1038/s41598-021-90551-6.
2. Özlüşen B, Kozan Ş, Akcan RE, Kalender M, Yaprak D, Peltek İ B, et al. Effectiveness of favipiravir in COVID-19: a live systematic review. Eur J Clin Microbiol Infect Dis 2021;40:2575-83.
3. Rattanaumpawan P, Jirajariyavej S, Lerdlamyong K, Palavutitotai N, Saiyarin J. Real-world effectiveness and optimal dosage of favipiravir for treatment of COVID-19: Results from a multicenter observational study in Thailand. Antibiotics (Basel) 2022;11:805. doi: 10.3390/antibiotics11060805.
4. Siripongboonsitti T, Tawinprai K, Cheirsilpa K, Ungtrakul T, Krisorakun W, Chotipanich C, et al. The real-world clinical outcomes of favipiravir treatment with telemedicine monitoring in preventing disease progression in mild to moderate COVID-19 patients; a retrospective cohort study. Medicina (Kaunas) 2023;59:1098. doi: 10.3390/medicina59061098.
5. Surapat B, Kobpetchyok W, Kiertiburanakul S, Arnuntasupakul V. Use of favipiravir for the treatment of coronavirus disease 2019 in the setting of hospitel. Int J Clin Pract 2022;2022:3098527. doi: 10.1155/2022/3098527.
6. Deng W, Yang C, Yang S, Chen H, Qiu Z, Chen J. Evaluation of favipiravir in the treatment of COVID-19 based on the real-world. Expert Rev Anti Infect Ther 2022;20:555-65.
7. Ministry of Health, Labour and Welfare of Japan. Report on the deliberation results [Internet]. 2014 [cited 2024 May 30]. Available from: https://www.pmda.go.jp/files/000210319.pdf.
8. Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir - a potential treatment in the COVID-19 pandemic? J Virus Erad 2020;6:45-51.
9. The National Institutes of Health (NIH), The U.S. Department of Health and Human Services. Pregnancy, lactation, and COVID-19 therapeutics [Internet]. 2014 [cited 2024 May 30]. Available from: https://www.covid19treatmentguidelines.nih.gov/special-populations/pregnancy/.
10. Arco-Torres A, Cortés-Martín J, Tovar-Gálvez MI, Montiel-Troya M, Riquelme-Gallego B, Rodríguez-Blanque R. Pharmacological treatments against COVID-19 in pregnant women. J Clin Med 2021;10:4896. doi: 10.3390/jcm10214896.
11. Giesbers S, Goh E, Kew T, Allotey J, Brizuela V, Kara E, et al. Treatment of COVID-19 in pregnant women: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol 2021;267:120-8.
12. Louchet M, Sibiude J, Peytavin G, Picone O, Tréluyer JM, Mandelbrot L. Placental transfer and safety in pregnancy of medications under investigation to treat coronavirus disease 2019. Am J Obstet Gynecol MFM 2020;2:100159. doi: 10.1016/j.ajogmf.2020.100159.
13. Nana M, Hodson K, Lucas N, Camporota L, Knight M, Nelson-Piercy C. Diagnosis and management of covid-19 in pregnancy. BMJ 2022;377:e069739.
14. Department of Medical Services, Ministry of Public Health, Thailand. Clinical practice guideline for diagnosis, treatment and prevention of Coronavirus

Disease 2019 [Internet]. 2021 [cited 2024 May 30]. Available from: https://covid19.dms.go.th/Content/Select_Landding_page?contentId=135.
15. Caluwaerts S. Nubia's mother: being pregnant in the time of experimental vaccines and therapeutics for Ebola. Reprod Health 2017;14:157. doi: 10.1186/s12978-017-0429-8.
16. Jafari R, Jonaidi-Jafari N, Dehghanpoor F, Saburi A. Convalescent plasma therapy in a pregnant COVID-19 patient with a dramatic clinical and imaging response: A case report. World J Radiol 2020;12:137-41.
17. Cetinkaya Demir B, Albayrak O, Aslan K. The impact of coronavirus disease-19 on pregnancy outcomes, a case series. Gynecol Obstet Reprod Med 2023;29:30-5.
18. Ertem O, Guner O, Incir C, Kalkan S, Gelal A. The outcomes of favipiravir exposure in pregnancy: a case series. Arch Gynecol Obstet 2023;307:1385-95.
19. Özen B, Us Z, Toplu A, Vizdiklar C, Selalmaz Y, Çulpan Y, et al. Favipiravir does not appear to be a major teratogen: Case series from Türkiye. J Gynecol Obstet Hum Reprod 2024;53:102693. doi: 10.1016/j.jogoh.2023.102693.
20. Tırmıkçıoğlu Z. Favipiravir exposure and pregnancy outcome of COVID-19 patients. Eur J Obstet Gynecol Reprod Biol 2022;268:110-5.
21. Pairat K, Phaloprakarn C. Acceptance of COVID-19 vaccination during pregnancy among Thai pregnant women and their spouses: a prospective survey. Reprod Health 2022;19:74. doi: 10.1186/s12978-022-01383-0.
22. Balasubramanian R, Vuppalapati S, Avanthika C, Jhaveri S, Peddi NC, Ahmed S, et al. Epidemiology, genetics and epigenetics of congenital heart diseases in twins. Cureus 2021;13:e17253.
23. Hoover EA, Yamamura Y, Thompson G. Structural anomalies in multifetal gestations. Clin Obstet Gynecol 2023;66:781-91.
24. Bojórquez Martínez CA, García Murillo IM, Segón Mora S, López Mereles A. Tetralogy of Fallot: Hypoxia, the villain of the story? Birth Defects Res 2024;116:e2279.
25. Bilir A, Atay E, Firat F, Kundakci YE. Investigation of developmental toxicity of favipiravir on fetal bone and embryonic development. Birth Defects Res 2022;114:1092-100.
26. Laçin C, Turhan DO, Güngördü A. Assessing the impact of antiviral drugs commonly utilized during the COVID-19 pandemic on the embryonic development of Xenopus laevis. J Hazard Mater 2024;472:134462. doi: 10.1016/j.jhazmat.2024.134462.
27. Black RE. Global prevalence of small for gestational age births. Nestle Nutr Inst Workshop Ser 2015;81:1-7.
28. Boriboonhirunsarn D, Srikureja N. Rates of small for gestational age and low birth weight among underweight and normal weight women. Minerva Obstet Gynecol 2023;75:322-7.
29. Osuchukwu OO, Reed DJ. Small for gestational age. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2024 [cited 2020 May 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563247/.
30. Batool S, Vuthaluru K, Hassan A, Bseiso O, Tehseen Z, Pizzorno G, et al. Efficacy and Safety of Favipiravir in Treating COVID-19 Patients: A Meta-Analysis of Randomized Control Trials. Cureus 2023;15:e33676.
31. Korula P, Alexander H, John JS, Kirubakaran R, Singh B, Tharyan P, et al. Favipiravir for treating COVID-19. Cochrane Database Syst Rev 2024;2:CD015219.
32. Di Gennaro F, Guido G, Frallonardo L, Segala FV, De Nola R, Damiani GR, et al. Efficacy and safety of therapies for COVID-19 in pregnancy: a systematic review and meta-analysis. BMC Infect Dis 2023;23:776. doi: 10.1186/s12879-023-08747-2.
33. Lin CW, Liang YL, Chuang MT, Tseng CH, Tsai PY, Su MT. Clinical outcomes of nirmatrelvir-ritonavir use in pregnant women during the Omicron wave of the coronavirus disease 2019 pandemic. J Infect Public Health 2023;16:1942-6.
34. Wong CKH, Lau KTK, Chung MSH, Au ICH, Cheung KW, Lau EHY, et al. Nirmatrelvir/ritonavir use in pregnant women with SARS-CoV-2 Omicron infection: a target trial emulation. Nat Med 2024;30:112-6.