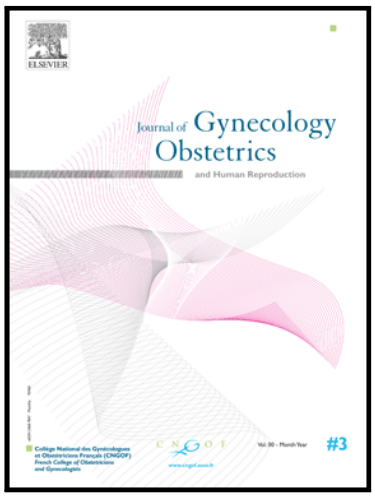

FAVIPIRAVIR DOES NOT APPEAR TO BE A MAJOR TERATOGEN: CASE SERIES FROM TÜRKİYE

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PII: S2468-7847(23)00160-5
DOI: https://doi.org/10.1016/j.jogoh.2023.102693
Reference: JOGOH 102693

To appear in: *Journal of Gynecology Obstetrics and Human Reproduction*

Received date: 6 May 2023
Revised date: 9 October 2023
Accepted date: 17 November 2023

Please cite this article as: BERNA ÖZEN , ZEYNEP US , AYLİN TOPLU , CANER VIZDIKLAR , YASEMİN SELALMAZ , YEKTA ÇULPAN , ZEHRANUR TURGAN AŞIK , MERT KAŞKAL , BÜŞRA NAZLI AÇIKGÖZ , MEDİNE GÜLÇEBİDİRİZ OĞLU , ATİLA KARAALP , FİLİZ ONAT , HASAN RACİ YANANLI , REZZAN GÜLHAN , FAVIPIRAVIR DOES NOT APPEAR TO BE A MAJOR TERATOGEN: CASE SERIES FROM TÜRKİYE, *Journal of Gynecology Obstetrics and Human Reproduction* (2023), doi: https://doi.org/10.1016/j.jogoh.2023.102693

FAVIPIRAVIR DOES NOT APPEAR TO BE A MAJOR TERATOGEN: CASE SERIES FROM TÜRKİYE

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Abstract

Introduction: Favipiravir has gained attention during the Coronavirus Disease-2019 pandemic due to its potential antiviral effect against Severe Acute Respiratory Syndrome Coronavirus-2. Favipiravir has been identified as a teratogen in animal studies, but there is limited human data. We aimed to evaluate the pregnancy outcomes of women exposed to favipiravir during the pandemic.

Material and Methods: Pregnant women who were exposed to favipiravir and applied to Marmara University School of Medicine Medical Pharmacology Outpatient Clinic Teratology Information Service between December 2020-September 2021 are included in the study. The demographic information, medical and obstetric histories of patients were acquired during admission, the outcomes of the pregnancies and the characteristics of the infants were gathered by regular phone calls. The infants whose parents consented were evaluated by a pediatrician for general well-being and congenital anomalies.

Results: 22 pregnant women were included in this study. 81.8% received the recommended favipiravir dose (8000 mg in 5 days), in the first trimester. Two patients were lost to follow-up, there was one elective termination and 19 live births. Congenital anomalies were found in 2 infants, one of whom had 9q34 duplication syndrome. Except for these, all newborns examined by the pediatrician were healthy.

Discussion: Within a limited case series, a subset of the infants exposed to favipiravir prenatally were followed up to 1 year of age. Two infants exhibited congenital malformations that cannot be directly linked to favipiravir due to confounding variables. Considering the limited data published, favipiravir does not appear to be a major teratogen.

Keywords: favipiravir, pregnancy, Covid-19, teratogen, congenital anomaly

Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which emerged in December 2019 in China, was identified to cause severe viral pneumonia [1]. The World Health Organization (WHO) named the disease as Coronavirus Disease 2019 (COVID-19) and on March 2020, declared it a pandemic [2]. Various drugs that are previously approved for other indications and have antiviral activity against SARS-CoV-2 in vitro or in observational studies were used empirically in COVID-19 treatment throughout the world, such as hydroxychloroquine [3], favipiravir [4],[5], remdesivir [6], lopinavir, and ritonavir [7]. Early in the pandemic, favipiravir was used in outpatient and inpatient clinics with some special permissions and distributed to the patients by the filiation teams assigned by the Turkish Ministry of Health [8, 9]. However, these drugs except remdesivir are later discontinued due to a lack of sufficient evidence or adverse effects, and treatment guidelines are revised and updated [10].

Favipiravir is an antiviral agent that inhibits the RNA polymerase enzyme, approved for the treatment of influenza in Japan and China [11]. In animal studies, favipiravir caused post-implantation fetal loss, decreased fetal and placental weight, unspecified abnormalities of the head, brain, heart, and tail, as well as unidentified cardiac and thymic abnormalities in mice and rats. Fetal edema and ascites occurred in all fetuses in an experiment with pregnant monkeys when favipiravir was given at a dose of 200 mg/kg/day, whereas cleft palate occurred in 2 of 5 fetuses [12]. However, human data are scarce and consist of only four case series (Table 1) with a total of 58 pregnancies exposed to favipiravir [13-16].

This study aims to provide information about the outcomes of pregnant women who used favipiravir unaware of their pregnancy and consulted our medical pharmacology outpatient clinic. We report the data on prenatal drug exposure, pregnancy course and outcome, the variables about the infant's health, the pediatric examination results if available, and the general well-being of infants.

Material and methods

We collected data on pregnant women exposed to favipiravir and admitted directly or consulted to the Medical Pharmacology Outpatient Clinic at Marmara University School of Medicine, Pendik Research and Training Hospital during the COVID-19 pandemic between December 2020 and September 2021. The study protocol was approved by the Marmara University School of Medicine Ethics Committee (08.10.2021, 09.2021.1161).

Medical Pharmacology Outpatient Clinic provides an information service about the teratogenic effects of drugs to pregnant women and physicians, as well as the adverse effects of drugs, drug-drug interactions, and dose adjustment in special conditions. When the patients are admitted to the clinic, an information form is completed, including data on demographics, medical and obstetric history, and drug exposure. Information about the course and outcome of pregnancy and information about the infants are obtained by regular phone calls 1 month after the first visit, at the expected delivery date, and after delivery.

Data collection

Gestational week at the first visit, age, height, weight, and body mass index of patients, folic acid use, comorbidities and concomitant drug usage, paternal exposure, and radiation exposure were recorded in the information form. The favipiravir dose and duration of the exposure and its relation to gestational week, estimated date of delivery, last menstrual period, and family history of congenital anomalies were questioned. After the first visit, patients were called regularly to obtain information about the pregnancy course, prenatal ultrasonography (USG) outcomes, other prenatal diagnoses or complications in pregnancy if present, the date of delivery, the infant's gestational week at birth, sex, birth weight, height, and head circumference, and the general well-being of infants regularly checked by their family physicians. Any difficulties during delivery, congenital malformations, neonatal complications, poor neonatal adaptation, APGAR scores, and neonatal intensive care unit/cuvette histories were investigated. Mothers were also questioned about any developmental problems, growth

retardation, lactation and feeding status of the infants, and drug usage during breastfeeding if present.

Additionally, families were offered a physical examination of the infant by a pediatrician at the Marmara University School of Medicine, Department of Pediatrics, at the end of the study period. The infants whose parents agreed to pediatric evaluation were examined for their general well-being and major congenital malformations.

Categorical data were shown as percentages and digits. The mean and range (min.–max.) were used to describe continuous variables. Delivery before the 37th gestational week was accepted as preterm [17].

Results

Between December 2020 and September 2021, 127 pregnant women consulted for drug counseling at our unit. We identified 22 cases exposed to favipiravir, and all were included in the present study. The general demographics of the patients are presented in Table 2. Of the 22 cases, 20 were in the first trimester at the time of exposure (Figure 1), and 63.6% were in the 5th–8th week of their pregnancies (Table 3). One of the pregnant women had applied at the 20th week of gestation when she became aware of her pregnancy. Her exposure to favipiravir was in the 15th week of gestation.

The favipiravir treatment recommended by the Ministry of Health involved a 3200 mg loading dose on the first day, followed by a 1200 mg/day maintenance dose for 4 days, for a total dosage of 8000 mg in 5 days [8]. The total dose of favipiravir was received by 81.8% of the cases. Half of the pregnant women had also been treated with other medicines along with favipiravir. Nonsteroidal anti-inflammatory drugs took the lead among concomitant drug groups (Table 3).

The prenatal medical characteristics of the patients are given in Table 4. Among the 22 pregnant women, two were lost to follow-up. Prenatal USG evaluation of three out of 20 pregnancies reported pathologies related to fetuses (Table 4), and two of them were born with multiple anomalies (Cases 5 and 9). The third patient, whose prenatal suspected diagnosis was Down syndrome, was lost to follow-up, and the outcome is not known. Out of 20 patients, four

had a family history of congenital anomalies. Two infants with congenital anomalies in our report were from these patients.

There were 19 live births recorded, as one of the pregnant women had an elective termination. Infant characteristics are shown in Table 5. Out of 19 infants, 14 (73.7%) were born via cesarean section, and three of the infants presented in abnormal positions during the labor: two were breech presentations and one was an arm-elbow presentation. The mean gestational age of the newborns was 38 weeks (min.—max.: 35–41 weeks). Six (31.6%) of the 19 infants were preterm. The mean weight of infants at birth was 3273 g (min.—max.: 2080–3940 g). Out of 19 infants, two had cardiac and renal congenital malformations (Cases 5 and 9).

Case 5 was diagnosed prenatally at the 20th gestational week with USG imaging which revealed a hyperechoic focus in the left ventricle, and the diameters of the renal pelvises were measured abnormal. The mother had also migraine, hyperthyroidism, depression, multiple drug use (venlafaxine, hydroxyzine), and a history of consanguineous marriage with a history of congenital anomalies in the family. At the 41st week, an emergency cesarean section was indicated due to breech presentation. The newborn had normal percentile measurements and did not need to be admitted to the neonatal intensive care unit. After birth, the urinary system USG was performed at 8 weeks of age. Both kidneys' pelvicalyceal structures were normally dilated, and the right kidney's AP diameter was 6.5 mm and the left kidney's diameter was 7.5 mm. Due to an unidentified defect in his heart and bilateral hydronephrosis, he was being monitored by pediatric nephrologists and pediatric cardiologists. His diagnosis at 6 months of age was vesicoureteral reflux with uropathy and grade 2 hydronephrosis for both kidneys. At the age of 13 months, in the urinary system USG the right kidney pelvicalyceal system was reported to be grade 1 dilated, and the left kidney pelvicalyceal system grade 1-2 dilated. His pediatric cardiology examinations revealed no heart anomalies.

Case 9 was followed for 9q34 duplication syndrome and congenital malformations. The diagnosis was made prenatally at the 7th gestational month by amniocentesis. The same genetic condition was present in his uncle's son. 9q34 duplication syndrome is marked by

psychomotor developmental impairment, morphological deformities (on the face and extremities), and various congenital malformations, such as musculoskeletal system, ophthalmic, heart, and rarely renal disorders, in affected children [18]. However, these problems differ depending on the affected region of the chromosome and the type of duplication. We do not know for certain the degree of duplication in this infant.

In several case reports with 9q34 duplication, anomalies of heart, kidney, and urogenital system have been reported at different levels [18-21]. In this case, septa in the urinary bladder and cystic formation in the left kidney were seen in the prenatal USG examination. He was born at the 36th week of gestation via emergency cesarean surgery with renal and cardiac malformations and had a history of neonatal intensive care unit for 1 month. When he was 2 months old, according to the corrected gestational age, he had a catheter (nephrostomy) on his right kidney because of the cystic left kidney and septa in his urinary bladder. Hospitalization diagnoses for the patient were antenatal left multicystic dysplastic kidney, right congenital hydroureteronephrosis (with nephrostomy), posterior urethral valve, and congenital vesico-uretero-renal reflux. He had aortic stenosis and was followed by pediatric cardiologists. When he was 5.5 months old, he underwent pyelostomy due to bilateral hydronephrosis and left urinoma. Until he was 2 years old, he could urinate with the help of a vesicostomy between the umbilicus and genitalia. He continued to be followed by pediatric cardiology due to aortic dilatation. His growth and development were below expectations.

Six of the 19 infants had neonatal jaundice. Two of them had been treated with phototherapy for one night. Three (15.7%) of the 19 infants had a neonatal intensive care unit history (Table S2).

The mothers of four out of 19 infants agreed to the pediatric evaluation. All the infants examined by the pediatrician were evaluated as healthy (Cases 1, 4, 7, and 17). The head circumference percentile of Case 17 was found to be lower than the weight and height percentiles. His head circumference, growth and development were found normal by the family physician in the control examination performed 3 months later.

Among the infants whose health and development have been followed, three have reached 12 months and four have reached 10 months of age.

Supplemental tables provide detailed data for each pregnant patient and their gestation periods (Table S1) and the follow-up of each infant (Table S2). According to the most recent examination reports, only two babies (Cases 5 and 9) still had malformations and needed routine follow-ups.

Discussion

In the present study, we report on 22 pregnancies exposed to favipiravir during the COVID-19 pandemic, resulting in 19 live births, 1 elective termination, and 2 cases that were lost to follow-up. Among the prominent results, 6 out of 19 infants (31.6%) were preterm, and 10 out of 19 pregnancies (52.6%) had medical indications for cesarean deliveries. There were two infants (10.5%) with cardiac and renal congenital anomalies (Cases 5 and 9); one (Case 9) had a rare genetic syndrome. Two term newborns were weighing less than 2500 grams; one was the baby with the genetic syndrome (Case 9), and the other's mother (Case 3) had a history of smoking in addition to favipiravir exposure. This baby later reached the normal percentile.

The congenital malformation rate in this study was found 10.5% (2 out of 19 cases). The previous studies about the rate of congenital malformations in COVID-19-infected pregnancies suggested no increase in malformation rates compared to the normal population (2% and 3.3%) [22, 23]. Although the congenital malformation rate seemed high in our study, the small number of our patient group (n=19), presence of confounding factors (family history of genetic disorder and multiple drug exposure) and the lack of a control group make it difficult to reach a definitive conclusion about the teratogenicity of favipiravir.

The preterm birth rate in our study was 31.6%, comparable to 27.0% reported in another study on 92 pregnant women with COVID-19 diagnosis [16]. Both outcomes were more than twice as high as Türkiye's preterm birth rate of 12.2% for 2021 [24]. A similar pattern was observed with cesarean section rates. The rate of cesarean sections in our case series (73.6%) was higher than the rate of cesarean sections in Türkiye, which was 58.4% in 2021 [25]. Moreover, ten (52.6%)

of the deliveries were medically indicated cesarean sections due to malpresentation of the fetuses, the diagnosis of developmental delay, the weight loss of the baby, fetal tachycardia or pre-natal preeclampsia, or the diagnosis of lumbar hernia in a pregnant woman. Multiple studies have demonstrated that pregnant patients with a diagnosis of COVID-19 have a higher risk of preterm birth and cesarean section than those without the diagnosis [26, 27]. A recent comparative study from Türkiye evaluated the pregnancy outcomes in the presence or absence of COVID-19 infection during pregnancy. The rate of preterm birth was found to be 30.3% and the rate of cesarean section was 76.9% among the COVID-19 positive group, similar to our sample, whereas the corresponding rates for the negative group were 12.0% and 44.0%, respectively [28]. It can be concluded that the high rate of preterm birth and cesarean sections in this report can be related to COVID-19 although the effect of favipiravir exposure cannot be ruled out.

Two infants out of 19 had congenital anomalies (Cases 5 and 9) in parallel with the previous reports, which were cardiac and renal anomalies (Table 1). Case 9 had a rare genetic syndrome (9q34 duplication syndrome). It has been reported that, although rare, congenital malformations, including heart, renal and genitourinary anomalies at different levels, are seen in 9q34 duplication syndrome [18-21]. Since there are few cases in the literature attributable to both cardiac and renal conditions, and the degree of duplication in this infant has not been determined, therefore it is not known whether his severe congenital anomalies are due to the genetic syndrome he has or to favipiravir exposure prenatally.

The mother of Case 5 had comorbidities (migraine, hyperthyroidism, and depression), multiple drug usage (venlafaxine, hydroxyzine) and a history of consanguineous marriage with congenital anomalies in the family. Although the infant had a prenatal diagnosis of renal and cardiac abnormality, postnatally follow-ups revealed that cardiac pathology was resolved at 13 months of age. These pathologies cannot be directly associated with favipiravir exposure.

Limitations

The small sample size of patients makes it difficult to reach a definitive conclusion regarding the impact of favipiravir on pregnancy outcomes. Furthermore, there is a lack of information about the prognosis of pregnant women who had Covid-19 and were not administered favipiravir therapy for comparative analysis. One additional constraint pertains to the fact that the follow-up data for most infants were acquired through telephone communication with their mothers. During the volatile and unpredictable course of the pandemic, it was challenging to persuade all families to bring their infants to the hospital for pediatric evaluations. Therefore, it is difficult to state that we have attained precise data regarding infant health, although there are studies indicating that specific variables, such as preterm birth, cesarean delivery, and birth weight, were reliable data obtained by telephone follow-up [29, 30].

Conclusion

This case series, along with limited previous reports, suggest that favipiravir does not have a major teratogenic effect. Although congenital anomalies in terms of cardiac and renal pathologies were reported in two out of the 19 infants exposed prenatally to favipiravir, one of these infants (Case 5) had a history of consanguineous marriage and was exposed to multiple drugs in addition to favipiravir. The other infant (Case 9) had a diagnosis of a rare genetic syndrome and a family history of genetic anomalies. Nevertheless, it is recommended that the utilization of favipiravir during pregnancy should be avoided unless the use of the drug is considered essential.

Declaration of Interest

The authors of this publication confirmed that they had no financial or personal connections that could be seen to have influenced the research presented in this paper.

Acknowledgement

We are thankful to all the patients who accepted to talk and give information and to the pediatrician physicians of the Marmara University Education and Research Hospital who evaluated the infants to be called for the general examination.

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Table 1. Reports of pregnancies exposed to favipiravir

Year and country of publication	Indication	Number of cases	Pregnancy outcomes
Caluwaerts, 2017, Belgium	Ebola virus infection	1	1 live birth. No congenital anomaly
Tirmikcioglu, 2022, Türkiye	Covid-19	29	5 elective abortions, and 25 live births (2 of them were premature births). Only 1 infant has been identified with patent foramen ovale as a congenital abnormality. All other physical characteristics were found within normal parameters during birth and the first four months of life.
Ertem, 2022, Türkiye	Covid-19	9	2 elective terminations, 1 spontaneous abortion, and 6 live births (1 was born extremely preterm and reported the death on the 5th day of NICU admission). There were no congenital abnormalities. Only in one newborn mild pelviectasis in the left kidney was detected prenatally, and in the postnatal third-month control of the infant the renal pelvis diameter was measured within normal ranges without any interventions.

Cetinkaya, 2022, Türkiye	Covid-19	19*	8 elective abortions and 11 live births (1 premature birth). Nasal bone hypoplasia and ventriculomegaly were detected in 1 child born prematurely due to premature rupture of membranes. The other 10 pregnancies resulted in live newborns, 2 of them had neonatal anomalies (one had an abnormal auditory test and the other had unexplained seizures). The authors could not determine if favipiravir caused these abnormalities. No follow-up data were supplied for these infants in the article.
Total		58	43 live births (4 preterm births), 15 elective terminations, 1 spontaneous abortion. 1 patent foramen ovale 1 mild pelviectasis 1 nasal bone hypoplasia and ventriculomegaly

* 19 out of 92 pregnant women with COVID-19 diagnoses were exposed to favipiravir.

Table 2. Maternal characteristics, n=22

Maternal Characteristics	**Study population, n (%)**
Mean age, years (min.-max.)	30.5 (21-39)
Mean height, cm (min.-max.) *	162.8 (150-170)
Mean weight, kg (min.-max.) *	73.9 (44-100)
Chronic disease	
No	14 (63.6%)
Yes	6 (27.2%)
Unknown	2 (9%)
Folic acid use	
No	4 (18.1%)
Yes	14 (63.6%)
Unknown	4 (18.1%)
Smoking	
No smoking history	18 (81%)
Smoking during pregnancy	2 (9%)
Smoking before pregnancy	1 (4.5%)
Unknown	1 (4.5%)
Gravidity **	
1	5 (23.8%)
2	5 (23.8%)
3	3 (14.2%)
4 and above	8 (38%)
Parity **	
0	6 (28.5%)
1	5 (23.8%)
2	5 (23.8%)
3	3 (14.2%)
4	2 (9.5%)
Previous miscarriages **	
0	14 (66.6%)
1	4 (19%)
2	2 (9.5%)
3	1 (4.7%)
Previous stillbirth **	
No	21 (100%)
Yes	_

Previous children with birth defects	
No	21 (95.4%)
Yes	_
Unknown	1

*: n=20; **: n=21

Table 3. Favipiravir use in pregnant women in the study, n=22

Favipiravir dose exposure, mg	**Study population, n (%)**
3200	1 (4.5%)
3800	1 (4.5%)
5600	2 (9%)
8000	18 (81.8%)
Time of exposure	
Preconception	1(4.5%)
1st trimester (0-13th week)	20 (90.9%)
All or none (in first 4 weeks)	5 (22.7%)
5th-8th weeks	14 (63.6%)
2nd trimester	1 (4.5%)
Concomitant use of drugs	
No	11 (50%)
Yes	11 (50%)
	Number of patients & Case numbers
Nonsteroidal anti-inflammatory drugs	7 (7, 8, 13, 15, 17, 20, 21)
Paracetamol	4 (7, 13, 15, 21)
Antibacterial drugs	4 (7, 13, 14, 21)
Nasal decongestants	4 (7, 14, 15, 21)
Antihistamine drugs	4 (5, 7, 14, 15)
Cough and cold medicines	3 (7, 14, 21)
Medroxyprogesterone acetate	2 (2, 7)
Antiplatelet drugs/anticoagulants	2 (13, 20)
Proton pump inhibitors and anti-reflux drugs	2 (14, 18)
Antidepressants	2 (5, 18)
Corticosteroids (nasal spray)	Case 14
Antispasmodics	Case 14
Antipsychotics	Case 18
Levothyroxine	Case 13

Table 4. Prenatal medical characteristics, n=20

Prenatal USG	**n (%)**
No pathology	17 (85%)
Pathology present	3 (15%)
Complications during pregnancy	
No complication	16 (80%)
Nausea and gestational diabetes	1 (5%)
Preeclampsia	1 (5%)
Anemia, stomach cramps	1 (5%)
Unknown	1 (5%)
History of congenital anomalies in the families	
No	15 (75%)
Yes	4 (20%)
Unknown	1 (5%)
Concomitant radiation exposure	
No	18 (90%)
Yes (2 chest X-rays and 1 wrist X-ray)	1 (5%)
Unknown	1 (5%)

Table 5. Infant characteristics, n=19	
Gestational week at birth	
Preterm	6 (31.6%)
Term	13 (68.4%)
Type of delivery	
Normal vaginal birth	5 (26.3%)
Elective cesarean section	4 (21%)
Medically indicated cesarean section	10 (52.6%)
Sex of infants	
Female	9 (47.3%)
Male	10 (52.6%)
Weight at birth	
<2500 g	2 (10.5%)
2500-3000 g	2 (10.5%)
>3000 g	15 (78.9%)
Congenital malformations	
No	17 (89.4%)
Yes, cardiac and renal anomalies	2 (10.5%)

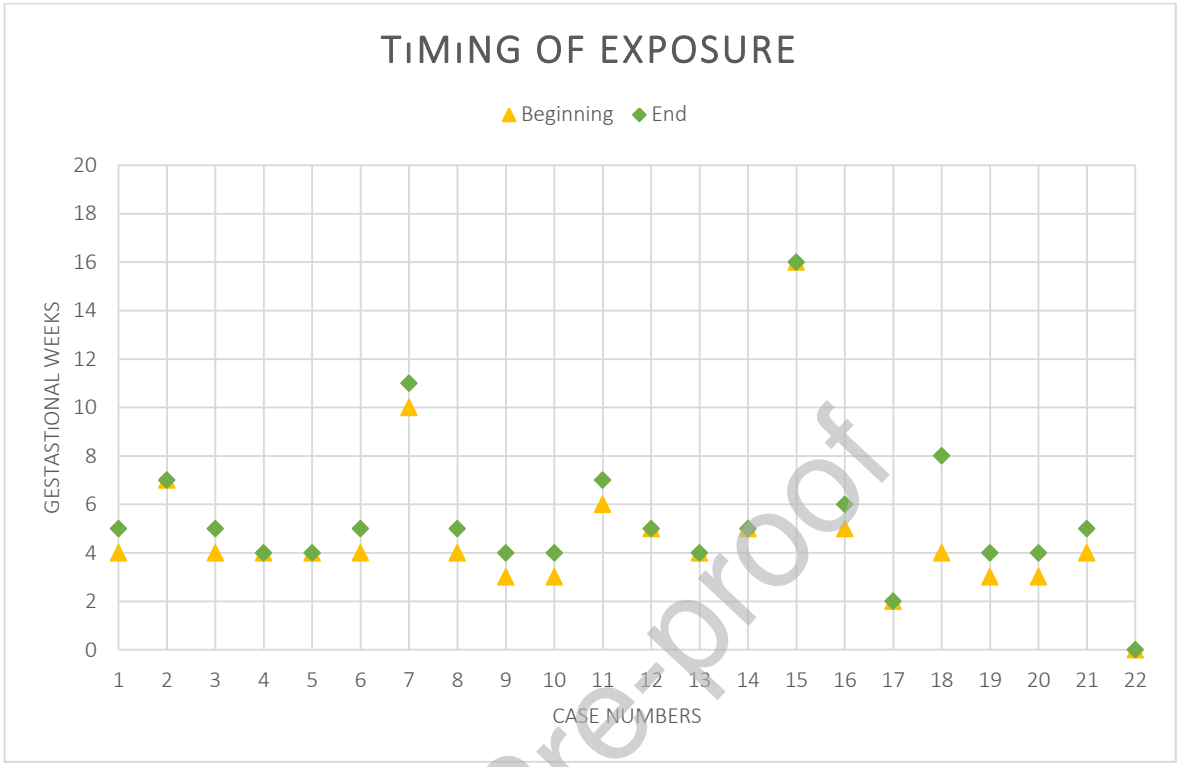

Figure 1. Timing of favipiravir exposure during pregnancy

Disclosure of Interests

The authors of this publication confirmed that they had no financial or personal connections or interests that could be seen to have influenced the research presented in this paper.