Archives of Gynecology and Obstetrics
https://doi.org/10.1007/s00404-022-06615-z

MATERNAL-FETAL MEDICINE

The outcomes of favipiravir exposure in pregnancy: a case series

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Received: 16 March 2022 / Accepted: 6 May 2022

Abstract

Purpose As in vitro and in vivo studies reported antiviral efficacy against RNA viruses, favipiravir, a pyrazinecarboxamide derivative, has become one of the treatment options for COVID-19 in some countries including Turkey. Preclinical studies demonstrated the risk for teratogenicity and embryotoxicity. Hence, the drug is contraindicated during pregnancy. Although limited in numbers, case-based evaluations indicate that favipiravir might not be a major teratogen in human pregnancies. This study aimed to present and analyze the outcomes of favipiravir exposure during pregnancy.

Methods In this case series, the outcomes of nine pregnancies that were referred to the Teratology Information Service of Dokuz Eylul University Faculty of Medicine, Department of Medical Pharmacology between 01 April 2020 and 30 November 2021 were retrospectively evaluated.

Results One spontaneous abortion, two elective terminations, one preterm live delivery and five term live deliveries were detected. The premature newborn was reported dead on the 5th day of neonatal intensive care unit admission. Physiological jaundice and transient respiratory distress were recorded in two term infants. One term infant was antenatally diagnosed with renal pelviectasis, but the findings resolved postnatally without requiring intervention.

Conclusion The data indicate that favipiravir is not likely to be a major teratogen. Yet, it is not possible to draw a definite conclusion due to methodological limitations. Favipiravir exposures during pregnancy should be followed up closely and the outcomes should be reported consistently.

Keywords Favipiravir · Pregnancy outcomes · Teratogen

Introduction

Upon recognition of Coronavirus disease-2019 (2019-nCoV), COVID-19, as an outbreak that constitutes a Public Health Emergency of International Concern by the World Health Organisation on 30 January 2020, the first case in Turkey was confirmed by Republic of Turkey Ministry of Health on 10 March 2020 [1]. Due to a lack of confirmed effective curative or prophylactic agents, researchers focused on repurposing approved drugs in search of the fastest route to fight the COVID-19 pandemic.

Favipiravir is an oral pyrazinecarboxamide derivative antiviral drug that was licensed in Japan in 2014 for the treatment of influenza infection. The active metabolite of the drug, ribofuranosyl 5′-triphosphate (T-705RTP), is a nucleoside analogue that hinders viral replication by inhibiting RNA-dependent RNA polymerase [2, 3].

Both in vitro and in vivo studies reported antiviral efficacy of favipiravir against several RNA viruses. Although scientific evidence regarding the efficacy of favipiravir in COVID-19

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Published online: 27 May 2022

treatment was sparse, the drug has been approved by the National Medical Products Administration of China as the first anti-COVID-19 agent in March 2020 [3, 4]. Soon after, on 23 March 2020, favipiravir was included in the COVID-19 Guideline for Management of Adult Patients, a guideline designed to ensure a standardized approach throughout the country, by the Republic of Turkey Ministry of Health. A dose regiment of 1600 mg twice daily on day 1, followed by 600 mg twice daily for 4 days was recommended [5, 6]. As subsequent clinical researches demonstrated that favipiravir was not superior to standard supportive care in terms of reducing COVID-19 related hospitalization rates or mortality, favipiravir was dropped from the COVID-19 Guideline for Management of Adult Patients on revision dated 20 December 2021 [7–9]. It was also noted that the drug could be used when the treating physician deems necessary, as some of the clinical researches reported reduced duration of symptoms [7, 10].

Favipiravir use is contraindicated during pregnancy. Preclinical studies indicate that the drug has a risk for teratogenicity and embryotoxicity. Early embryonic death was observed in rats [11, 12]. Embryo-fetal developmental studies conducted on mice, rats, rabbits, and monkeys were indicative of teratogenic effects, decreased number of live fetuses and lower birth weight [11]. Due to extremely limited data on the safety of favipiravir use in human pregnancies, the use of the drug is not recommended in pregnant women or women planning pregnancy [2]. A retrospective study conducted in Turkey reports that 29 pregnancies exposed to favipiravir resulted in 25 live births, one minor congenital cardiac anomaly (foramen ovale) and two preterm deliveries. In foramen ovale case, the mother was reported to have oligohydramnios at 35th week, but delivery was at term. The study also indicates that birth weight, length and head circumferences of the infants were within the normal range. Acknowledging that data are limited to draw a definite conclusion, the author concluded that favipiravir might not be defined as a major teratogen [13]. Another study from Turkey, which revealed the findings of seven out of 20 pregnancies of favipiravir exposure, showed that one infant had bilateral renal pelvicalyceal dilatation and cardiac malformation, while the other had fetal distress requiring neonatal intensive care unit (NICU) admission [14].

This study aimed to present and analyze the outcomes of favipiravir exposure in pregnancy. Our data may contribute to the limited body of knowledge regarding the safety of the drug in pregnancy.

Methods

This is a case series of our Teratology Information Service. Teratology Information Service of Dokuz Eylul University Faculty of Medicine, Department of Medical Pharmacology has been providing consultation to approximately 150 patients annually since 2005. The Service provides evidence-based risk assessment of various exposures during pregnancy or breastfeeding to women who are referred by physicians, mainly obstetricians. Detailed information regarding exposures, maternal demographics, medical history, and obstetric anamnesis is obtained and recorded at the first visit to the Teratology Information Service. After 2 months following the estimated delivery date, information regarding the rest of the gestational period and the infant are obtained via phone call. All mothers are informed that their records can be used for scientific purposes, providing their identities remain hidden.

All records of the pregnant women who were referred to our Teratology Information Service between 01 April 2020 and 30 November 2021 were retrospectively evaluated. The records of the patients who completed their gestational period were included in the study. Demographics, maternal/family medical history, all exposures during pregnancy, complications, pregnancy outcomes (spontaneous abortus, elective termination, stillbirth, term/preterm birth, mode of delivery), characteristics of the infant (sex, weight, and length at birth), neonatal complications and congenital anomalies were recorded to data record form. The exposed comedications were classified according to their pharmacological classes. The active ingredients in combined preparations were individually evaluated.

Gestational weeks at the time of delivery and exposures were calculated based on fetal ultrasonography or last menstrual period in the absence of an available fetal ultrasonography record. Spontaneous loss of the fetus before the 20th week of pregnancy was defined as miscarriage and a non-viable delivery after the 20th week was referred as stillbirth. Delivery before 37th gestational week was considered as preterm birth and low birth weight was defined as a birth weight of less than 2500 g. Preterm births were sub-categorized into extreme preterm (< 28 weeks), very preterm (28 to < 32 weeks) and moderate to late preterm (32 to < 37 weeks) in line with World Health Organisation's definitions [15]. Congenital malformations were classified according to the European Surveillance of Congenital Anomalies (EUROCAT) definitions [16].

Descriptive statistics were used to summarise the data. Categorical variables were displayed as a number (n) and frequencies (%). Continuous variables were presented as median (minimum–maximum).

Results

We identified ten pregnancies that were assumed to be completed by the time of the data collection period. Outcomes of nine pregnancies were available and included in our analysis.

Median age, median body-mass index and median gestational age at first consultation were detected as 32 (26–42), 23.0 (19.2–31.5) and 5w4d (5w0d–16w4d), respectively. Maternal characteristics at first consultation are presented in Table 1 and detailed information regarding exposures during pregnancy is shown in Table 2. None of the cases had a history of consanguineous marriage.

Favipiravir exposure

All cases received at least a full course of favipiravir treatment consisting of a loading dose of 1600 mg twice daily followed by a maintenance dose of 600 mg with 12-h intervals during the next 4 days. Case 2 received two consecutive full courses, Case 6 received one full course and one without a loading dose at separate times and Case 8 received two separate full courses of favipiravir treatment. Case 4 received one full course of treatment during the preconceptional period and Case 8 was exposed to favipiravir at both the preconceptional period and at the first week of the first trimester. The rest of the cases were exposed to the drug during the first trimester (Table 2).

Other drug exposures

Case 7 did not have any other exposures except favipiravir. The median number of exposed comedications was 5.5 (1–15) in eight cases.

Case 6 had a higher number of exposures with 15 active ingredients and followed by Case 5 and 1 with exposure to 10 and 9 active ingredients, respectively. Except Case 7 and 9, all cases used analgesic drugs such as paracetamol and nonsteroid anti-inflammatory drugs. Five cases (Case 2, 3, 5, 6 and 8) had exposures to vitamins, minerals, and other nutritional products; mainly consisting of vitamin D3, vitamin C and zinc. Detailed information regarding comedication exposures is presented in Tables 2 and 3.

Non-drug exposures

Case 2, 4, 5 and 6 were exposed to ionizing radiation due to mandible radiograph, posterior-anterior chest X-ray and/or thorax CT scan (Table 2). It was noted that Case 1 continued smoking throughout the pregnancy, Case 5 stopped at the fourth gestational week and the other cases were non-smokers. Exposures to alcohol, caffeine and herbal products are summarized in Table 2.

Pregnancy outcome

Case 2 resulted in spontaneous abortion, while Case 3 and 5 had elective termination. Case 4 resulted in extreme preterm birth and the rest of the cases resulted in live term deliveries (Table 2).

The median birth weight of six live infants was 2992 g (550–3200 g) and the median length was 50 cm (44–52 cm). Characteristics of the infants are presented in Table 1.

Infant 4, the extremely premature newborn, was reported dead on the 5th day of NICU admission. Infant 7 had mild transient neonatal jaundice and Infant 8 experienced transient respiratory distress with a good response to neonatal resuscitation. Both cases did not require any further interventions. Infant 9 was suspected to have mild pelviectasis in the left kidney based on the findings of mild central calyceal dilatation with a renal pelvis diameter of 7.5 mm detected on antenatal renal ultrasonography at 38w3d of gestation. A pediatric nephrology follow-up every three months was recommended for this case. It was noted that the diameter of renal pelvis was measured within the normal range at postnatal third month visit without any intervention.

Discussion

Outcomes of nine pregnancies with favipiravir use during the periconceptional period and/or during the first trimester were presented in this study. One spontaneous abortion, two elective terminations, one extreme preterm live delivery and five term live deliveries were observed. The extremely preterm live infant died during NICU admission. None of the infants had congenital malformation.

Preclinical data indicate an increased risk of fetal loss and malformation in rodents and monkeys [11]. Nevertheless, there are no well-controlled clinical studies evaluating the influence of favipiravir use during pregnancy on the human fetus. The existing body of knowledge regarding this matter is scarce and mainly consists of case-based evaluations. The first published report regarding the use of favipiravir during pregnancy is about a 25-year-old mother and her baby who used favipiravir during prepartum 4 days in addition to other treatments for Ebola virus infection. The case report indicates that the baby was born alive with Ebola-virus infection, but the mother died due to postpartum hemorrhage [17].

This study presents the outcomes of nine pregnancies consisting of one case with exposure during the preconceptional period, one case with both preconceptional period and first trimester exposure and seven cases of first trimester exposures. The women were unaware of the pregnancy when they were exposed to favipiravir. The details and extend of favipiravir exposures, comorbidities, comedications and non-drug exposures were also analyzed.

Two third of the cases resulted in live deliveries, one being extreme preterm and the others being term. It was noteworthy that the time of favipiravir exposure in the case that resulted in extreme preterm delivery was more than one

Table 1 Maternal and infant characteristics

	Study population	Case numbers
Maternal characteristics ($n=9$)		
Median maternal age, years (min.–max.)	32 (26–42)	
Maternal BMI categories*, *n* (%)		
Underweight	–	–
Normal	6 (66.7%)	1, 3, 6, 7, 8, 9
Overweight	2 (22.2%)	4, 5
Obese	1 (11.1%)	2
Maternal education level, *n* (%)		
Illiterate	–	–
Primary education	1 (11.1%)	8
Secondary education	3 (33.3%)	2, 4, 9
Tertiary education	5 (55.6%)	1, 3, 5, 6, 7
Occupation, *n* (%)		
Unemployed	4 (44.4%)	2, 4, 8, 9
Employed	5 (55.6%)	1, 3, 5, 6, 7
Chronic disease, *n* (%)		
Yes	2 (22.2%)	2, 8
No	7 (77.8%)	1, 3, 4, 5, 6, 7, 9
Gravidity, *n* (%)		
1	5 (55.6%)	1, 3, 5, 6, 7
2	1 (11.1%)	4
≥ 3	3 (33.3%)	2, 8, 9
Parity, *n* (%)		
0	5 (55.6%)	1, 3, 5, 6, 7
1	2 (22.2%)	4, 9
2	2 (22.2%)	2, 8
≥ 3	–	–
Previous miscarriages, *n* (%)		
0	7 (77.8%)	1, 2, 3, 4, 5, 6, 7
1	–	–
2	2 (22.2%)	8, 9
Previous stillbirth, *n* (%)		
Yes	–	–
No	9 (100.0%)	1, 2, 3, 4, 5, 6, 7, 8, 9
Previous children with birth defects, *n* (%)		
Yes	–	–
No	9 (100.0%)	1, 2, 3, 4, 5, 6, 7, 8, 9
Infant characteristics ($n=6$)		
Sex, *n* (%)		
Female	6 (100.0%)	1, 4, 6, 7, 8, 9
Male	–	
Birth weight, *n* (%)		
< 2500 g	2 (33.3%)	4, 8
≥ 2500 g	4 (66.7%)	1, 6, 7, 9
Median birth height, cm (min.–max.)	50 (44–52)	1, 6, 7, 8, 9

min.–max: minimum–maximum, *BMI:* body mass index

*Underweight: < 18.5 kg/m^2, Normal: 18.5–24.9 kg/m^2, Overweight: 25.0–29.9 kg/m^2, Obese: ≥ 30 kg/m^2

Table 2 Exposure patterns and pregnancy outcomes

Case	Maternal age (years)	Chronic disease	Favipiravir exposure			Comedications (Daily dose, exposure period)	Other exposures	Mode of delivery/Gestational age at time of delivery	Pregnancy outcome
			Cumulative dose	Dose regiment	Gestational period				
1	32	–	8000 mg	Loading dose: 2×1600 mg (within 24 h) Maintenance dose: 2×600 mg (4 days)	12w2d–12w6d	Aceclofenac (100 mg/day, 6w2d–7w1d) Azithromycin (500 mg/day, 6w2d–6w4d) Midazolam (2 mg/day, 6w2d) Propofol (100 mg/day, 6w2d) Paracetamol (1500 mg/day, 10w5d–11w2d) Cefixime (800 mg/day, 10w5d–11w2d) Hyoscine butylbromide (10 mg/day, 10w5d–13w4d) Fosfomycin (3000 mg/day, 10w5d) Medroxyprogesterone acetate (10 mg/day, 14w5d–15w3d)	Alcohol: 2 standard units of drink per two weeks during first trimester Smoking: 8 cigarettes per day	VD 40w1d	Healthy newborn weighing 3200 g with no malformation
2	42	Hypo-thyroidism	8000 mg	Loading dose: 2×1600 mg (within 24 h) Maintenance dose: 2×600 mg (4 days)	2w3d–3w1d	Levothyroxine sodium (50 mcg/day throughout the pregnancy) Paracetamol (500 mg/day, 2w3d–2w5d)	X-Ray: Thorax CT scan at 3w1d Herbal products: 3 cups of Oregano tea at 3w6d		Spontaneous abortion at 5th week
			8000 mg	Loading dose: 2×1600 mg (within 24 h) Maintenance dose: 2×600 mg (4 days)	3w2d–3w6d	Vitamin D3 (1500 IU/day, 3w2d–3w4d) Ferrous glycine sulphate (100 mg/day, 2w3d–3w3d) Folic acid (500 mcg/day, 2w3d–3w3d) Vitamin B12 (2.5 mcg/day 2w3d–3w3d)	Caffeine: 10 cups of black tea and 1 cup of coffee consumption per day		
3	29	–	8000 mg	Loading dose: 2×1600 mg (within 24 h) Maintenance dose: 2×600 mg (4 days)	5w3d–6w1d	Vitamin C (100 mg/day, 5w3d–6w1d) Zinc (10 mg/day, 5w3d–6w1d) Propolis (8 mg/day, 5w3d–6w1d) Vitamin D3 (500 IU/day, 5w3d–6w1d) Enoxaparin (4000 IU/day, 5w3d–6w1d)			Elective termination at 8th week
4	35	–	8000 mg	Loading dose: 2×1600 mg (within 24 h) Maintenance dose: 2×600 mg (4 days)	Preconceptional 48 days to 44 days	Ornidazole (1000 mg/day, 3w5d–4w4d) Diclofenac sodium (50 mg/day, 4w5d–5w0d)	X-Ray: Mandible X-Ray at 5w0d	C/S 26w0d	Premature newborn weighing 550 g with no malformation. Death on 5th day of NICU admission

Table 2 (continued)

Case	Maternal age (years)	Chronic disease	Favipiravir exposure			Comedications (Daily dose, exposure period)	Other exposures	Mode of delivery/Gestational age at time of delivery	Pregnancy outcome
			Cumulative dose	Dose regiment	Gestational period				
5	27	–	8000 mg	Loading dose: 2 × 1600 mg (within 24 h) Maintenance dose: 2 × 600 mg (4 days)	2w0d–2w5d	Paracetamol (500 mg/day irregular use during 2w0d–2w5d) Vitamin C (1000 mg/day irregular use during 2w0d–3w0d) Zinc (50 mg/day irregular use within 2w0d–3w0d and 5 mg/day starting at 4w0d during pregnancy) Vitamin D3 (2000 IU/day irregular use within 2w0d–3w0d and 5 mg/day starting at 4w0d during pregnancy) Acetylsalicylic acid (100 mg/day 2w0d–3w1d) Enoxaparin (4000 IU/day 2w0d–2w1d and 3w1d–6w4d) Folic acid (400 mcg/day starting at 4w0d during pregnancy) Iodine (150 mcg/day starting at 4w0d during pregnancy) Vitamin B12 (12 mcg/day starting at 4w0d during pregnancy) Vitamin B6 (10 mg/day starting at 4w0d during pregnancy)	X-Ray: Posterior–anterior Chest X-Ray at 4w0d Herbal products: Oregano tea, Hibiscus tea, Licorice tea consumption during 5 days within first two weeks of pregnancy Smoking: 8 cigarettes per day until 4w0d of pregnancy	–	Elective termination at 9th week

Table 2 (continued)

Case	Maternal age (years)	Chronic disease	Favipiravir exposure			Comedications (Daily dose, exposure period)	Other exposures	Mode of delivery/Gestational age at time of delivery	Pregnancy outcome
			Cumulative dose	Dose regiment	Gestational period				
6	28	–	8000 mg	Loading dose: 2 × 1600 mg (within 24 h) Maintenance dose: 2 × 600 mg (4 days)	2w2d–2w6d	Ibuprofen (200 mg/day, 2w0d–2w1d) Pseudoephedrine HCl (30 mg/day, 2w0d–2w1d) Acetylsalicylic acid (100 mg/day, 2w1d–5w5d) Famotidine (40 mg/day, 2w2d–4w2d) Paracetamol (500 mg/day, 2w1d–3w2d) Methylprednisolone (60 mg/day, 3w4d) Ipratropium bromide (160 mcg/day, at 3w4d and 4w1d–4w3d) Pantoprazole (40 mg/day, 3w4d) Deflazacort (30 mg/day, 3w4d–4w3d) Budesonide (0.5 mg/day, 3w4d–4w0d) Salbutamol (800 mcg/day, 4w1d–4w3d) Levodropropizine (180 mg/day, 4w1d–4w3d) Magnesium (300 mg/day, 4w1d–4w3d) Zinc (30 mg/day, 4w1d–4w3d) Vitamin D3 (1500 IU/day during 2w2d–4w0d and 2000 IU/day during 4w1d–4w5d)	X-Ray: Posterior–anterior Chest X-Rays at 2w1d and 4w1d Thorax CT scan at 3w4d	VD 40w2d	Healthy newborn weighing 2980 g with no malformation
			7200 mg	Loading dose: – Maintenance dose: 2 × 600 mg (6 days)	3w4d–4w2d				
7	34	–	8000 mg	Loading dose: 2 × 1600 mg (within 24 h) Maintenance dose: 2 × 600 mg (4 days)	1w6d–2w3d	–		VD 40w0d	Healthy newborn with mild transient neonatal jaundice weighing 3004 g with no malformation Spontaneous remission within 4 days

Table 2 (continued)

Case	Maternal age (years)	Chronic disease	Favipiravir exposure			Comedications (Daily dose, exposure period)	Other exposures	Mode of delivery/Gestational age at time of delivery	Pregnancy outcome
			Cumulative dose	Dose regiment	Gestational period				
8	38	Asthma Chronic bronchitis Gestational diabetes mellitus	8000 mg	Loading dose: 2 × 1600 mg (within 24 h) Maintenance dose: 2 × 600 mg (4 days)	Preconceptional 15th days to 11th days	Acetylsalicylic acid (100 mg/day, 0w6d–3w6d) Dexketoprofen(25 mg/day, 1w1d–2w1d) Ibuprofen (600 mg/day, 1w1d–2w1d) Pseudoephedrine HCl (90 mg/day 1w1d–2w1d) Vitamin C (900 mg/day, 1w1d–2w1d)	–	C/S 37w0d	Newborn with transient respiratory distress weighing 2188 g with no malformation. Good response to neonatal resuscitation. No additional intervention required
			8000 mg	Loading dose: 2 × 1600 mg (within 24 h) Maintenance dose: 2 × 600 mg (4 days)	0w6d–1w3d				
9	26	–	8000 mg	Loading dose: 2 × 1600 mg (within 24 h) Maintenance dose: 2 × 600 mg (4 days)	0w3d–1w0d	Ondansetron (8 mg/day, irregular use starting at 8w5d during unspecified period)	–	C/S 38w4d	Antenatal mild pelviectasis in left kidney. No intervention required. Healthy newborn weighing 3150 g

VD vaginal delivery, *C/S* caesarean section

month prior to conception. Elimination half-life of favipiravir is reported as 2 to 5.5 h and the drug does not accumulate or sequester in the body [2, 18]. Considering the short elimination half-life, the exposure and the outcome were unlikely to have a causal relationship. The infant did not have a congenital malformation and died on the 5th day of NICU admission. In a retrospective analysis of the effects of antenatal favipiravir exposure, two preterm deliveries were reported among 29 pregnancies. One of the pregnancies was reported to result in twin birth at 32nd gestational week and the other was a singleton. No congenital abnormalities related to favipiravir exposure were observed in either of the preterm infants [13].

Two of the term infants were healthy and no postnatal health problems were detected up until the second month. Both infants had in utero exposures to multiple drugs, which have the potential to impose risk to fetus. The cumulative maternal favipiravir exposure in one of these pregnancies was 8000 mg for 5 days at the end of the first trimester, while it was 15,200 mg for 11 days during the first 4 weeks of the first trimester in the other. It was concluded that the mother of the latter mentioned infant had a symptomatic disease course, because during treatment she was exposed to favipiravir for longer than recommended and she underwent two consecutive chest X-rays and one thorax CT-scan. In the rest of the term infants, one infant had mild transient neonatal jaundice, one infant had transient respiratory distress and the other had an antenatal diagnosis of mild pelviectasis in the left kidney.

In the infant with mild neonatal jaundice who was delivered at 40w2d, jaundice was reported to become evident within the postnatal first week and resolved spontaneously. It is known that 60% of term infants and 80% of preterm infants may develop neonatal jaundice. In physiological jaundice, bilirubin levels increase starting from postnatal third or fourth day and decrease mostly following days returning to normal levels by the end of the postnatal second week [19]. In our case, no structural abnormality that may cause jaundice was reported. The infant had no other in utero exposures. The causal relationship between transient neonatal jaundice and favipiravir exposure at the second week of gestation was evaluated as unlikely.

Infant 8, who experienced transient respiratory distress with good response to neonatal resuscitation and positive pressure ventilation, had a maternal history of asthma, chronic bronchitis, and gestational diabetes. Cumulative favipiravir exposure was a total of 16,000 mg for 10 days during both the preconceptional period and the first gestational week. The mother has an absolute indication for caesarean section due to placenta previa totalis. The caesarean delivery was reported to be followed by hysterectomy due to placenta increta and atonic uterus. Respiratory distress occurs in 7% of the term newborns [20]. Elective caesarean

Table 3 Pharmacological groups of the exposed comedications

Pharmacological Group	Case numbers
Analgesics	1, 2, 3, 4, 5, 6, 8
Antibacterial drugs	1, 3, 4
Anesthetics	1
Systemic hormonal drugs and hormone regulators	1, 2
Urinary antispasmodics	1
Urinary anti-infectives	1
Vitamins, minerals and other nutritional products	2, 3, 5, 6, 8
Antithrombotic drugs/anticoagulants	3, 5, 6, 8
Nasal decongestants	6, 8
Drugs used in ulcer treatment	6
Corticosteroids (Glucocorticoids)	6
Drugs used in reactive and obstructive respiratory diseases	6
Cough and cold medicines	6
Antiemetics and drugs used against nausea	9

delivery prior to full term increases the risk of respiratory morbidities [21, 22]. Risk factors for transient neonatal distress are elective caesarean, preterm delivery, male sex, low birth weight and maternal conditions such as asthma and gestational diabetes [20, 23–25]. The risk factors in our case, except male sex, coincided with the outcome.

The infant with antenatal mild pelviectasis diagnosis in left kidney based on the finding of mild central calyceal dilatation was reported to have an anterior–posterior renal pelvic diameter of 7.1 mm, 6.1 mm, 6.3 mm, and 7.5 mm at 22nd, 26th, 30th and 38th weeks of gestation, respectively. Based on these findings, the infant was diagnosed with grade 1 pelviectasis according to The Urinary Tract Dilation Classification System [26]. A pediatric nephrology follow-up every three months was recommended for the infant. Antenatal hydronephrosis is observed in approximately 1–5% of pregnancies and is usually detected in fetal ultrasonography during the third trimester. Most of the mild pelviectasies detected in antenatal period usually resolves spontaneously at the early postnatal period [27]. In our case, it was noted that the diameter of the renal pelvis was measured within the normal range at postnatal third month visit without any intervention and the infant did not have any records of abnormalities. The cumulative maternal exposure to favipiravir was 8000 mg for five days during the first week of gestation. Furthermore, we could not locate any study that directly associates ondansetron, the comedication that the mother had been exposed for an unspecified period within the first trimester, with congenital renal malformations. In a preliminary report of a prospective observation of 20 pregnancies with favipiravir exposure conducted by Ozen et al., one case of bilateral renal pelvicalyceal dilation detected in both prenatal and postnatal ultrasonographies was reported. It was also noted that the case is on a cardiology follow up programme due to an unspecified cardiac malformation, but the extend and timing of favipiravir exposure and the information regarding the follow-up of renal malformation were lacking. On the other hand, the preliminary report includes 7 pregnancies with a known outcome and the study is yet to be completed [14].

Spontaneous abortion at the fifth week of gestation was noted in a case (Case 2) with cumulative 16,000 mg favipiravir exposure for 10 days within the time of four weeks following her last menstrual period. The case had a history of paracetamol, vitamin D3, vitamin B12, ferrous glycine sulphate, folic acid use at therapeutic doses; caffeine consumption at nontoxic doses; oregano tea consumption for a short period and exposure to thorax CT scan. Advanced maternal age of the case was an independent risk factor for spontaneous abortion [28]. The case also took levothyroxine for thyroid hormone replacement. It is reported that the required dose of levothyroxine during pregnancy may increase up to 23–30% and thyroid functions should be monitored by serum TSH levels. Untreated hypothyroidism may cause fetal loss up to 60% in cases with severe maternal hypothyroidism [29]. In our case, the mother used thyroid hormone replacement at a dose of 50 mcg/day. Yet, we could not locate any medical records that indicate a dose adjustment up until the fifth week of the pregnancy. It is noteworthy that characteristics of favipiravir use, and other exposures of the case were alike those of Case 6, who gave birth to a healthy term infant, except advanced maternal age and hypothyroidism (Table 2). No spontaneous abortions were reported among 29 pregnancies in Tirmikcioglu Z.'s study which was conducted on a similar population [13].

In the cases of transient neonatal jaundice, antenatal renal pelviectasis, spontaneous abortion and transient neonatal respiratory distress, exposure to favipiravir took place within the 4 weeks following the last menstrual period. A second exposure during the preconceptional period was also

described in the case with respiratory distress. It is a known fact that the influence of teratogen and mutagen agents on the fetus depends on the dosage and the timing of the exposure. "All-or-none" phenomenon, one of the tenets of teratology, refers to the theory that the exposure that occurs before organogenesis gives rise to either no adverse fetal outcome or in embryonic death. Yet, exposure to mutagens that cause chromosomal breakage, translocation, deletion, or single nucleotide mutation on germ cells is an exception to this doctrine, even when the exposure takes place before the fertilization [30]. Preclinical studies of favipiravir suggest a low risk of genotoxicity [11]. Yet, the data regarding long term use of favipiravir in humans are quite limited.

In terms of the fetal risks of exposed comedications among our cases, medroxyprogesterone acetate was the only agent that was categorized as contraindicated during pregnancy. Due to their uterine relaxant properties that are known to cause delay the spontaneous abortion of a defective fetus, the use of progesterone derivatives during the first four months of gestation is not recommended. Although it is classified as contraindicated, there is no concrete evidence suggesting that therapeutic doses of medroxyprogesterone acetate use during early pregnancy is associated with an increase in non-genital malformations. The evidence on whether hypospadias is associated with its use is also conflicting [31]. The women (Case 1) who was exposed to this agent during 14w5d–15w3d delivered a term and healthy baby with no malformation.

Nonsteroidal anti-inflammatory agents were another group of drugs with evidence of fetal risk among our population. Case 1, 4, 6 and 8 had a history of nonsteroidal anti-inflammatory drug use during the first trimester. It is reported that exposure to nonsteroids significantly increases the risk of spontaneous abortion. The risk is reported to be even higher when the exposure course is longer and takes place around the periconceptional period [32]. Despite the history of high-risk drug exposures, none of those pregnancies resulted in spontaneous abortion.

The size of the study population was small and on the ground of retrospective data collection, the data that we got was restricted to the information on medical records. Evaluating solely the fetal effects of favipiravir was not possible, as, except in one case, the women were exposed to multiple comedications, x-ray, tobacco smoke and herbal products. On the other hand, the true extent of exposure to favipiravir could not be assessed via measuring the plasma concentration of the drug and its major metabolite. Thus, the real magnitude of fetal exposure was not known. Furthermore, favipiravir is also reported to be distributed into sperm. Hence, effective contraception during favipiravir use and seven days after the last dose is recommended for both men and women of reproductive age [2, 11]. As the records we retrospectively evaluated did not have information regarding paternal favipiravir exposure, no evaluation was made regarding this aspect.

The data from the small population we evaluated indicate that favipiravir is not likely to be a major teratogen for a human fetus. None of the cases has resulted in congenital malformations. Yet, it is not possible to draw a definite conclusion due to the small sample size and methodological limitations. Favipiravir exposures during pregnancy should be followed up closely and the outcomes should be reported consistently.

Acknowledgements The authors would like to thank Dr. Y. Cem Kaplan (Professor of Pharmacology) for his insightful suggestions and careful reading of the manuscript.

Author contributions OE: project conceptualization and development, data collection, data analysis and interpretation, manuscript writing and editing. OG: project conceptualization and development, data collection, data analysis, manuscript writing. CI: project conceptualization and development, data collection, data analysis, manuscript writing. SK: project conceptualization, data analysis, manuscript editing. AG: project conceptualization and development, data collection, data analysis and interpretation, manuscript editing and revision. All authors read and approved the final manuscript.

Funding The authors declare that no funds, grants, or other support were received during the study and preparation of this manuscript.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Ethics approval Approval was granted by the Dokuz Eylul University Ethics Committee for Non-Interventional Studies. This study was conducted in line with the principles of the Declaration of Helsinki and Good Clinical Practices. During the data analysis, patients were anonymized, and no data was shared with other parties except the researchers. The records regarding patients' identities were protected in compliance with the relevant national and international legislations and registrations.

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