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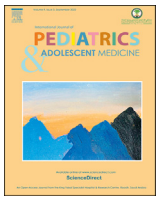

Case Report

# Fetal malformations associated with exposure to mycophenolic acid during the first trimester

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ABSTRACT

Mycophenolic acid [MPA] is a powerful inhibitor of lymphocyte proliferation. Although this drug has been used across the globe for various maternal comorbidities, multiple concerns have been raised regarding its teratogenic effects. The Food and Drug Administration has changed its category to drug category D (evidence of fetal risk) in 2007. A wide range of congenital malformations in infants born to a mother using this medication have been described in the literature, but there is no specific set pattern of these malformations. We report a case of a female infant who had exposure to mycophenolate by maternal use during the initial phase of 1st trimester of her pregnancy and ended up having multiple congenital malformations. She was managed with multidisciplinary approach and was finally discharged home on respiratory support, after two months of hospital stay. The fact that our patient shared a pattern of congenital malformations with other reported cases who were exposed to mycophenolate in utero strongly suggests that mycophenolate had a causal role and that there might be an emerging fetal mycophenolate mofetil syndrome (FMMS).



## 1. Introduction

Mycophenolic acid (MPA) is a powerful inhibitor of lymphocyte proliferation. It has immunosuppressive property which was first described in 1969 [1]. The safety profile, clinical efficacy, pharmacodynamics and pharmacokinetic properties of mycophenolate have led to its use as a standard of care in solid organ transplantation and lupus nephritis [2,3]. Mycophenolate is often used as a glucocorticoid-sparing agent in management of various connective tissue disorders like systemic lupus erythematosus, rheumatic diseases, systemic sclerosis, inflammatory myopathies, and some systemic vasculidities [4,5]. In general, antenatal exposure of mothers to MPA during pregnancy is not merely associated with miscarriages but also an increased likelihood of phenotypic malformations in some infants who survive till delivery [6]. There are numerous developmental malformations seen in some of the foetuses with maternal exposure to MPA products but specific patterns of malformations such as hypertelorism, cleft lip and cleft palate, micrognathia and atresia of external auditory canal with or without microtia have been postulated in the literature after the exposure of mothers to MPA in the first trimester of their pregnancy [7].

## 2. Case report

In our case report, we present a 2-month old female infant, delivered by C-section to a 39 year old, Gravida 9 Para 8 + 1 mother, at 34 weeks of gestation. Her mother was a known case of SLE, secondary Sjögren syndrome, lupus nephritis, carditis and hypertension. She also developed gestational diabetes during this pregnancy. She underwent six cycles of IV cyclophosphamide with the last dose taken 12 months prior to this pregnancy and then maintained on Perindopril, Prednisolone, Hydroxychloroquine, bisoprolol and 1g of Mycophenolate BID. She was informed about the

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teratogenic effects of Mycophenolate upon prescription by the primary physician in her previous hospital. Previous pregnancies were significant for a second trimester abortion in the second pregnancy, neonatal death in the fourth pregnancy with no known reason, preterm delivery in the sixth pregnancy due to placental abruption at 32 weeks gestation and resulted in neonatal death, and gestational diabetes in the seventh pregnancy.

In our case, the baby was born with multiple congenital anomalies including depressed nasal bridge, hypertelorism, microtia, micrognathia, complete cleft lip and palate, upper eye lid coloboma and renal malformations, which were hypothesized to be due to teratogenic effects of Mycophenolate. As mentioned, the mother was on Mycophenolate and she was compliant with her medications. Since it was an unplanned pregnancy, neither the mother nor the primary physician were aware of the pregnancy so she continued her medications during pregnancy in first trimester until the 8th week of gestation when she found out that she was pregnant and mycophenolate was discontinued. She was referred to our hospital on the 15th week of gestation. Prenatally, the ultrasound showed polyhydramnios with congenital malformations in the form of cleft lip and palate. Mother was offered Amniocentesis at 18 weeks of gestation but she refused initially. However, it was done at 21 weeks of gestation and samples were taken for single nucleotide polymorphism (SNP) analysis and whole-exome sequencing (WES), both of which turned out to be unremarkable.

The baby was delivered flat at birth with a low heart rate and poor respiratory efforts, resuscitation was carried out as per the NRP guidelines and the baby was shifted to NICU on CPAP with acceptable saturation and heart rate. Apgar scores were five, seven, and nine at one, five, and 10 min after birth, respectively. Birth weight was 1.69 kg. Later in NICU, she started to have episodes of bradycardia and desaturation. Hence intubation was carried out by the most senior physician in the unit keeping in view the difficulty of her airway.

Upon examination she had dysmorphic facies, coloboma of eyelid, systolic grade 2 murmur along the left lower parasternal border. Normal female genitalia. She had workup done as follow: Head US & brain MRI were normal. Echocardiography showed small VSD & PDA. She did not require treatment for PDA and it was closed spontaneously. Abdominal ultrasound showed bilateral low grade hydronephrosis. During the NICU stay she required respiratory support from the day of admission until discharge and was sent home on respiratory support via tracheal mask. Different subspecialties were involved in the management of this patient, including Medical Genetics, Audiology, Ophthalmology, Pediatric ENT, Pediatric Surgery, Pediatric Cardiology, Pediatric Pulmonology, Pediatric Urology, and dietitian. The baby was given follow up appointments in the respective clinics after discharge.

The patient was initially placed on ventilatory support through the tracheal mask which was gradually weaned to flow of 4 L/min, FiO2 21%. Patient was not gaining weight optimally so formula was gradually shifted from regular to infatrini and dietitian was involved. Mother was called upon to the hospital frequently over the last few weeks before discharge, in order to get her trained for tracheostomy and gastrostomy care. She was given CPR teaching and baby was discharged on respiratory support after the mother was confident and comfortable taking care of her daughter at home.

## 3. Discussion

In our case, the baby was born with multiple congenital malformations in form of depressed nasal bridge, hypertelorism, microtia, micrognathia, renal malformation, cleft lip and palate and upper eye lid coloboma, which were hypothesized to be due to teratogenic effects of Mycophenolate taken by the mother for her comorbidities. MPA is a precursor of mycophenolic acid, which itself is an immunosuppressive agent and inhibits inosine monophosphate dehydrogenase thereby blocking the de-novo guanosine synthesis, both in T and B lymphocytes.

Susceptibility towards drug-induced malformations depends on several factors such as the dose, timing and duration when the drug exposure occurs, whether the drug is being absorbed by the developing fetal tissue and whether there is teratogenicity in animal studies [8,9]. Since the pattern of malformations is not uniform in all the children born to mothers who took MPA during the initial phase of their pregnancy or even throughout pregnancy so the answer remains unclear, whether the risks to the developing fetus are dose-related, time-related, associated with maternal comorbidities, pharmacogenetic factors, and/or the result of drug interactions [10].

Keeping in view above-mentioned concerns, FDA has changed the category for all MPA products from category C (fetal risk cannot be ruled out) to category D (evidence of fetal risk) in 2007 and also to include a black box warning to be added to the prescribing information that this medication increases the risk of first trimester pregnancy loss and congenital malformations in pregnancies [10]. Furthermore, the warning also mentions that females of reproductive age taking MPA must be counselled and reassured [10]. Although in certain cases, the risks of discontinuing MPA treatment may outweigh the risks to the pregnancy however it is recommended that MPA should be avoided not only 6 weeks prior to conception but also during pregnancy and these recommendations are published in patient and prescribing guidelines [10].

Several in-vitro studies have shown number of single clinical observation however a recent study from a group of various European teratogen information services have published data that supports the existence of a specific mycophenolate mofetil (MMF) embryopathy [11]. The typical pattern of such embryopathy includes external ear anomalies {ranging from hypoplastic pinna (microtia) to complete absence of the pinna (anotia)}; ocular anomalies (Coloboma of iris or retina and anophthalmia/microphthalmia) and cleft lip with or without cleft palate. Congenital heart defects, oesophageal atresia, vertebral malformations, diaphragmatic hernia, distal limb anomalies, renal and central nervous system anomalies are seen less frequently. Although neurological deficits have been documented, neurodevelopmental outcome seems favourable only in small number of patients where information about this issue is available [11].

Hydroxychloroquine (HCQ) is an antimalarial drug frequently used in the treatment of autoimmune disorders. Its use is not only considered to be safe during pregnancy but continuation of HCQ during pregnancy is to improve disease management and pregnancy outcomes [12–14].

Data regarding the safety of HCQ for autoimmune disorders in pregnancy do not suggest an increase in adverse obstetrical outcomes, such as spontaneous abortion, prematurity [15–17]. However, data regarding major congenital malformations associated with early pregnancy exposure is scarce, largest published cohort study including fewer than 200 exposed pregnancies [18].

Furthermore, interruption of therapy can induce a flare of maternal disease and increase the risk of unfavourable pregnancy outcome [19–21]. HCQ can reduce maternal requirement and fetal exposure to corticosteroids and other immunosuppressing drugs during gestation. Keeping the published data in view, it is highly unlikely that these adverse effects have been resulted from maternal HCQ use during pregnancy.

## 4. Conclusion

Our case shared multiple congenital malformations with other

reported cases who were exposed antenatally to Mycophenolate, this suggests that Mycophenolate could have a causal role in this presentation and that there might be an emerging fetal mycophenolate mofetil syndrome (FMMS).

## Ethical considerations

This is a retrospective study which will utilize existing information, with no additional blood test or any other procedure used for purpose of the study.

The following other ethical considerations were taken.

1) All data needed for research already exist and were obtained through routine clinical care.
2) All data will be stored in Pediatric Research Unit, accessed only by the Principal Investigator and the assigned Assistant Clinical Research Coordinators.
3) The entire patient's information will be kept strictly confidential. Each patient will be given a study number, and all patient data will be entered in to the designated data sheet (EXCEL) without any patient's identifiers.
4) Waiver of informed consent is submitted with justification.
5) The Declaration of Helsinki and GCP guidelines will be followed.

Our approval from Office of Research Affairs (ORA): Case report.

## Declaration of competing interest

The presentation of the information that the authors are involved with promotes quality and improvement in health care and will not promote any specific business interest. The authors have declared that there is no existing conflict of interest.

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