

Mycophenolate Mofetil Use For Lupus Nephritis During Pregnancy: Report Of A Case Of Fetal Malformations And Literature Update

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Abstract

Mycophenolate mofetil (MMF) is an immunosuppressive drug used to avoid rejection after solid organ transplantation and in the management of autoimmune diseases. There are few works describing its teratogenic effects when a woman becomes pregnant while taking MMF, but currently the recommendation is to avoid its use during pregnancy (classified category D by FDA). A case of major fetal malformations (cleft palate and micrognathia) is presented related to the use of MMF during pregnancy; the mother was affected by severe lupus nephritis and was taking MMF from before and throughout the pregnancy. All the cases of fetal malformations attributed to MMF are updated and review.

INTRODUCTION

The management of autoimmune diseases has improved during recent decades because of a better understanding of their physiopathology. When these treatments are used in pregnant women, their consequences on fetuses must be thoroughly evaluated. Some drugs, as cyclosporine A, azathioprine, prednisone or tacrolimus, have established well-known, studied and published fetal effects ¹; although there are some concerns about their use in pregnancy, no increased incidence of major fetal malformations has been proven ². However, there are very few works about mycophenolate mofetil (MMF); it is a relatively new immunosuppressive drug which use has spread quickly.

In pregnant rats and rabbits treatment with MMF during the organogenesis period resulted in severe birth defects ¹. There is not enough information about MMF effects on human fetuses, but currently most authors recommend avoiding its use from 6 weeks before conception ³.

Here we present a case in which a woman with severe lupus nephritis became pregnant while she was taking MMF. The fetus was born prematurely and had severe congenital malformations in her jaw and palate, but her long-term outcome has been positive.

CASE

The patient was a 31-year-old primiparous Caucasian woman who was affected by systemic lupus erythematosus (SLE) with severe lupus nephritis for several years. Her immunosuppressive treatment included MMF (1500 mg/day) and deflazacort (90 mg/day), and she was also receiving acetylsalicylic acid, nifedipine and furosemide. The pregnancy was diagnosed at 8 weeks of gestation, and her physicians decided not to modify her treatment, given the severity of her renal disease. No fetal malformations were detected prenatally and fetal caryotype was normal 46 XX. In the 27th week of gestation the patient was admitted to hospital because of preeclampsia, that couldn't be kept under control. The gestation was electively terminated by caesarean section at 31^{5/7} weeks.

A female lifeborn infant was born, with birth weight 1035 g (<3rd percentile), length 39 cm (20th percentile) and head circumference 27.5 cm (10th percentile). She presented severe microretrognathia and complete cleft palate (figure); her upper gum and lip were normal, as was the rest of her physical examination. She needed endotracheal intubation for 48 hours because of several life-threatening obstructive apnoea episodes. She was electively extubated and remained on spontaneous breathing later on. She required oxygen therapy intermittently and presented some mild and self-limited apnoea-bradycardia episodes.

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While she was admitted in our centre, many complementary examinations were done. She presented with severe glosoptosis but oropharynx, epiglottis, glottis, and subglottic space were morphologically normal. Normal results were obtained from the following exams: cerebral MRI at 46 weeks of postconceptional age, humoral and cellular immunity, abdominal, cerebral and cardiac ultrasound scans, and eye examination.

The infant was admitted till the fourth month of life (48 weeks of corrected age), since she presented two episodes of bronchiolitis and swallowing problems to be fed by bottle. Oro/nasogastric tube couldn't be removed until the age of 9 months (7 months of corrected age). She presented persistent growth retardation, with her weight curve under the 3rd percentile; length and head circumference were always within normal limits. She is currently two years old and her neurodevelopmental examination is normal. Her weight remains under the 3rd percentile (8100 g) and her height is normal (86 cm, 50th percentile).

Figure 1

Table 1. Mechanisms of action of mycophenolate mofetil

| | |
|------------------------------|---|
| On T lymphocytes | <ul style="list-style-type: none"> Inhibits proliferation by depletion of dGTP and suppression of DNA synthesis Does not inhibit production of interleukin-2 |
| On B lymphocytes | <ul style="list-style-type: none"> Inhibits proliferation and differentiation, leading to decrease of antibody and autoantibody production |
| On monocytes and macrophages | <ul style="list-style-type: none"> Reduces the recruitment of mononuclear cells into sites of inflammation Decreases IL-1β and TNF-α production |
| On dendritic cells | <ul style="list-style-type: none"> Inhibits maturation process |
| On endothelial cells | <ul style="list-style-type: none"> Reduces leukocyte adhesion by decreasing exposure of endothelial cells to TNF-α |
| Other effects | <ul style="list-style-type: none"> Decreases production of cytokine-induced nitric oxide Does not induce expression of transforming growth factor-β, thus is not fibrogenic May decrease high density lipoprotein oxidation and thereby lower atherosclerosis risk Increases the activity of ganciclovir against cytomegalovirus Does not cause bone loss |

Figure 2

Table 2. Reported effects on human fetuses after mycophenolate mofetil use during pregnancy

| Author Year | Transplant or SLE* | Life-born | Cleft lip/palate | Micrognathia | Microtia | EAC** atresia | Hypertelorism | Other signs | Long-term outcome |
|-------------------------------|--------------------|-----------|------------------|--------------|----------|---------------|---------------|---|---|
| Pérgola 2001 ¹² | Transplant | Yes | - | - | - | - | - | Shortened fifth finger, hypoplastic fingers and toenails, aberrant blood vessel | Good |
| Le Ray 2004 ² | Transplant | No | + | + | + | + | + | Corpus callosum agenesis, ectopic kidney | - |
| Armenti 2004 ³ | Transplant | Yes | + | - | + | - | - | - | Hearing aid needed |
| Sifontis 2006 ⁵ | Transplant | Yes | + | - | + | - | - | Congenital diaphragmatic hernia, congenital heart disease | Died at 24 h of age |
| Sifontis 2006 ⁶ | Transplant | Yes | - | - | + | - | - | - | NA |
| Tjeertes 2007 ⁷ | Transplant | Yes | - | - | + | + | - | Hydrops fetalis | NA |
| Ei Sebaaly 2007 ⁴ | SLE | No | - | - | + | + | + | Polydactyly, nail hypoplasia, ventricular septal defect, anterior position of aorta | - |
| Pérez-Ayres 2008 ⁹ | Transplant | Yes | + | + | + | + | + | Bilateral conorectal coloboma | Hearing aid needed. Normal neurodevelopment |
| Huang 2008 ⁸ | SLE | No | - | + | + | + | + | Bifid nasal tip | - |
| Vainov 2008 ¹⁰ | SLE | Yes | + | + | + | + | + | Epicardic folds, brachydactyly, trichomalacia, arching eyebrows, thick everted lower lip | Mild motor delay, severe speech delay |
| Schoner 2008 ¹¹ | SLE | No | + | - | + | + | + | Multiple facial clefts, coloboma, corpus callosum agenesis, hydrocephalus, timus hypoplasia, lung hypoplasia, truncus arteriosus, esophageal atresia, single umbilical artery, unilateral kidney agenesis, syndactyly | - |
| Present case | SLE | Yes | + | + | - | - | - | - | Good neurodevelopment |

*SLE: systemic lupus erythematosus; **EAC: external auditory canal, NA: non available

Figure 3

Figure 1. Front image showing cleft palate and lateral facial profile demonstrating micrognathia.



COMMENT

We present a case of major congenital malformations in the newborn of a woman who was taking MMF since before and throughout the gestation. The malformations are similar to those described in animal models that were administered MMF during their organogenesis period¹.

Mycophenolate mofetil is an immunosuppressive drug used since its approval in 1999 by the FDA. Actually, it is a prodrug that has to be hydrolyzed in the intestine and blood to form its active metabolite, mycophenolic acid. All the described effects of MMF on different cell types are summarized in table 1⁴; however, the mechanism of action of its potential teratogenic effect remains unknown.

In case of SLE, MMF use is indicated if lupus nephritis or severe SLE resistant to other drugs are present. In these cases, MMF has proved to be generally effective and slightly less toxic than other immunosuppressive drugs, as it is widely reviewed in an excellent very recent paper⁵.

There are limited works in the literature describing cases of women who became pregnant while they were on treatment with MMF. Most of them were women who had undergone solid organ transplants. According to the last data from the US National Transplantation Registry⁶, from 26 pregnancies with those characteristics, 11 of them resulted in spontaneous abortion; of the other 15, four cases of congenital malformations at birth were reported.

A more recent paper is focused in a review of all the reported cases of fetal malformations supposedly associated to MMF use⁷. They describe 10 cases, 7 of them after renal transplantation and 3 in which MMF was taken by pregnant women affected by corticoid resistant lupus nephritis. After analysing the different cases reported, Pérez-Aytes et al. describe what they call a characteristic phenotype for fetuses/newborns after in utero exposure to MMF⁸. The six main features are the following: cleft palate, cleft lip, microtia, atresia of external auditory canal, micrognathia, and hypertelorism. They qualify the long-term development as probably favourable, but more data are needed. The table 2 summarizes all the malformations described in these children (updated to October 2008).

The increasing number of cases reporting malformations in fetuses from pregnancies developed during treatment with MMF has been the reason why FDA has changed this drug from Pregnancy Category C to Category D, which means “Positive evidence of fetal risk”⁹.

The aim of our case is to contribute more information to the possible –and likely– teratogenic effects of MMF. It is phenotypically coherent with other cases reported by the most important sources on the subject, and it is the fifth case reported from a non transplanted pregnant woman. Moreover, it adds some extra data such as the patient good long-term neurodevelopment. In conclusion we believe that this case should be taken into consideration and that pregnancies developed while on treatment with MMF must be qualified as high-risk pregnancies and they require a particularly accurate follow-up.

TRANSPARENCY DECLARATION

None of the authors of the report have got any conflict of interest about mycophenolate mofetil manufacturers. The results presented in this paper have not been published previously in whole or part.

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