Update on the Teratogenicity of Maternal Mycophenolate Mofetil

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Abstract

Mycophenolic acid (MPA) products, namely mycophenolate mofetil and mycophenolate sodium, are immunosuppressive medications used to prevent rejection in solid organ transplant recipients and to treat various autoimmune disorders. Mycophenolate therapy is considered to be teratogenic based on observational studies of pregnancies exposed to MPA, which demonstrated an increased incidence of miscarriages in pregnancies exposed to MPA during their first trimester and a pattern of birth defects in the offspring of some pregnancies exposed to MPA. Herein, we have detailed case and series reports in a comprehensive literature review summarizing what is known to date regarding fetal exposure to MPA. Based on evidence from the literature, results of postmarketing surveillance, and information from registries such as the National Transplantation Pregnancy Registry in the United States, it is advised that pregnancy be avoided by women taking MPA. Preconception planning offers the opportunity to explore the alternatives to protect the mother, her transplanted organ, and minimize fetal risk. How to proceed in cases of unplanned pregnancies exposed to MPA in transplant recipients is a complex issue. Research involving large epidemiological studies is expected to be sparse as women heed the warnings about becoming pregnant on MPA. Published recommendations for managing MPA in women of childbearing potential include discontinuing the medication prior to conception, switching the MPA to another medication, or discontinuing the MPA when the pregnancy is discovered.

Keywords
- mycophenolate mofetil
- mycophenolic acid
- mycophenolate sodium
- fetus
- immunosuppression
- teratogen
- birth defect
- transplantation
- pregnancy

Introduction

The history of mycophenolic acid (MPA) began with its discovery in 1893.1 Its immunosuppressive property was first described in 1969.2 After years of drug development, two oral forms are now available—the mofetil ester, that is, mycophenolate mofetil (MMF) and the enteric-coated mycophenolate sodium (EC-MPS), which may lower gastrointestinal adverse events associated with MMF.3 MMF was launched in the United States under the brand name CellCept by Roche

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Laboratories (Basel, Switzerland) in 1995 for the prevention of rejection in solid organ transplantation. From the 2012 annual report of the Scientific Registry of Transplant Recipients, the majority of initial immunosuppressive regimens for transplant recipients in the United States included MPA: kidney (81%), lung (80%), liver (80%), pancreas (90%), and heart (91%). MPA products have also been used to reduce inflammation in autoimmune conditions, including lupus nephritis, vasculitis, psoriasis, erythema multiforme, rheumatoid arthritis, refractory autoimmune hepatitis, myasthenia gravis, and hyperimmunoglobulinemia D. The treatment of autoimmune conditions with MPA products is considered off-label use in the United States. EC-MPS was approved in 2004 and marketed in the United States under the brand name Myfortic by Novartis Pharmaceuticals (Basel, Switzerland). Generic formulations of both medications are now available in the United States. Both the MPA products are also marketed generically worldwide and under various brand names.

**Mechanism of Action**

Active metabolite MPA is formed when the prodrug MMF undergoes hepatic ester hydrolysis. MPA is a noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase and blocks de novo purine synthesis on which T- and B-lymphocytes are dependent. MPA also has a range of immunosuppressant activities and anti-inflammatory properties. The primary toxicities of MPA are gastrointestinal side effects and bone marrow suppression. For prevention of transplant rejection, MPA products are typically used in combination with a calcineurin inhibitor, cyclosporine or tacrolimus with or without prednisone. In adults, the oral dosage range for MMF is 500 to 2,000 mg/day in two divided doses, and for EC-MPS, the oral dosage range is 360 to 1,440 mg/day. MPA undergoes enterohepatic recirculation and the inactive metabolite, mycophenolic glucuronide is primarily excreted in the urine. MMF has a plasma half-life of 16 to 18 hours and EC-MPS has a half-life of approximately 12 hours after oral administration. MPA is highly bound to albumin, and plasma levels may be increased by drugs with high protein-binding capacity and by conditions affecting plasma protein levels. Unlike calcineurin inhibitors, MPA blood trough levels only weakly correlate with efficacy and do not correlate with toxicity.

**Animal and Human Evidence of Teratogenicity**

Animal studies showed evidence of malformations, intrauterine death, or intrauterine growth retardation at MMF doses which appear to be within recommended clinical doses based on body surface area. In rabbits, MMF caused ectopia cordis, ectopic kidney, umbilical hernia, and diaphragmatic hernia, whereas, in rats, the anomalies reported included anophthalmia, agnathia, and hydrocephaly. There have been many case and series reports regarding human exposures during pregnancy, which are presented herein. In those cases, where adverse fetal outcomes were noted, several reports measured normal karyotypes. In general, maternal exposure to MPA during pregnancy is associated with miscarriages and a likely phenotype of malformations in a percentage of infants who survive to delivery. There is a wide variety of developmental malformations seen in some fetuses exposed to MPA products, several of which are common to other teratogens or genetic syndromes, but a specific pattern of malformations has been repeatedly described in the literature as the result of exposure to MPA in the first trimester. This constellation includes isolated and conglomerate occurrences and various gradations of microtia, orofacial clefts, coloboma, hypertelorism, micrognathia, congenital heart defects, agenesis of the corpus callosum, esophageal atresia, and digital hypoplasia. In some cases, the anomalies are associated with miscarriage, stillbirth, or neonatal death, while in some, the conditions can be ameliorated with treatment after birth.

**Teratogenicity Risk Assessment and Clinical Studies**

Susceptibility to drug-induced malformations depends on many variables including the dose of the drug, when the drug exposure occurs, if the drug is absorbed by the developing fetal tissues, and whether there is teratogenicity in animal studies. As the pattern of malformations is not seen in all children born to mothers who took MPA during the first trimester of pregnancy or even throughout pregnancy, questions remain unanswered such as whether the risks to the fetus are timing related, dose related, associated with maternal comorbidities, pharmacogenetic factors, and/or the result of drug interactions. As the number of fetal exposures has declined because MPA has been found to be a likely human teratogen, it is less likely that sufficient epidemiological analysis will be conducted to answer these questions. While most potential mothers on MPA products will be advised to either reconsider pregnancy based on health considerations, discontinue the medication, or switch to an alternative medication prior to a planned pregnancy, best practice guidelines for what to do in the setting of an unplanned pregnancy continue to develop. When MPA was introduced in 1995, there was speculation that there may be risks associated with its use during pregnancy based on the results of animal reproductive studies. However, the original package labeling cautioned that there were no adequate human studies and that the potential benefits might have warranted the use of the drug in pregnant women despite potential risks seen in animal studies. To reflect this warning, the U.S. Food and Drug Administration (FDA) initially gave MPA a category C pregnancy designation, where fetal risk could not be ruled out. It was not until 2006 that the National Transplantation Pregnancy Registry (NTPR) reported a pattern of malformations and an association with miscarriages in transplant recipients taking MPA compared with those who did not. The pattern of malformations was noted to be microtia, including cleft lip and palate. Since the NTPR’s initial report, there have been numerous case reports.
and series further delineating this pattern of birth defects among the offspring of those treated with MPA during early pregnancy.\textsuperscript{6,12,21,29–32,36–68} In 2007, the FDA changed the pregnancy category for all MPA products from category C (fetal risk cannot be ruled out) to category D (evidence of fetal risk). Although the FDA pregnancy categorical system is expected to be changed soon, at the time of this review, clinicians still rely on the present FDA pregnancy categories.

The case and series reports to date are summarized in \textit{Tables 1} and \textit{2}. The rate of birth defects in the general U. S. population is approximately 3 to 5\%\textsuperscript{33} The NTPR analysis revealed that the incidence of birth defects in children born to transplant recipients, not including those recipients exposed to MPA, is estimated to be 4 to 5\%.\textsuperscript{54} Additionally, in a NTPR analysis, the birth defect rate was 14\% in the newborn of kidney recipients with MPA exposure during early pregnancy, as compared with 6\% in the offspring of kidney recipients when MPA was discontinued prior to pregnancy.\textsuperscript{55} Data in \textit{Tables 3} show the cumulative number of pregnancy outcomes with exposure to MPA reported in the literature to date. The frequencies of individual birth defects in these reports are described in \textit{Table 4}. From this information, the phenotypical presentation of MPA-mediated developmental anomalies appears to include microtia-external auditory canal atresia, facial clefts, cardiac, skeletal, eye, tracheoesophageal, and facial anomalies. Usually these defects occur in combinations. Several authors have described the improbability that this combination of defects could be the result of any other exposure or genetic predisposition.\textsuperscript{43,44,56}

Although early miscarriage rates are difficult to quantify, the miscarriage rate in the general population is estimated to be 8 to 20\%\textsuperscript{61} Studies have shown miscarriage rates without MPA exposure in transplant patients to be approximately 13 to 22\%\textsuperscript{55,62} and in systemic lupus erythematosus (SLE) patients, the rate is 7 to 20\%\textsuperscript{53,64} Series reports of pregnancy outcomes with MPA exposure show miscarriage rates between 28 and 64\%\textsuperscript{12,28,51,55} two to three times higher than nonexposed groups. According to the NTPR, the miscarriage rate for kidney transplant recipients exposed to MPA was 52\%, which was significantly higher than the 19\% of female kidney recipients who miscarried after discontinuing MPA preconception \((p < 0.001)\).\textsuperscript{55}

In 2007, along with changing the pregnancy category for all MPA products, the FDA required a black box warning be added to the prescribing information regarding an increased risk of first trimester pregnancy loss and congenital malformations in pregnancies exposed to MPA. The warning also states that females of reproductive potential taking MPA must be counseled regarding pregnancy prevention and planning.\textsuperscript{25,26} Although, in some cases, the risks to the mother of discontinuing MPA treatment may outweigh the risks to the pregnancy, it is recommended that MPA be avoided in the 6 weeks prior to conception and during pregnancy. Worldwide, these recommendations are publicized in patient and prescribing guidelines.\textsuperscript{25,26,65–67} The recommendations for taking MPA have been reinforced in the United States by an FDA-mandated Risk Evaluation and Mitigation Strategy (REMS) which was launched in 2013 for all MPA products. The FDA-mandated REMS for MPA products includes a medication guide and elements to assure safe use. The elements to assure safe use ask prescribers to complete online training, obtain patient signatures on the patient prescriber acknowledgment form, and to voluntarily report MPA pregnancy exposures to the MPA pregnancy registry. This registry collects data on pregnancies exposed to MPA within 6 weeks of conception or during pregnancy for both transplant and nontransplant indications.\textsuperscript{68} In contrast, the NTPR is a condition-based registry; thus, the data collected by the NTPR are confined to exposure in transplant recipients. The NTPR’s unique long-term follow-up, and established internal comparison groups of MPA-unexposed patients, demonstrates the value of reporting all posttransplant pregnancies to the NTPR (NTPRRegistry.org) in addition to reporting the subset of MPA exposures to the MPA REMS pregnancy registry (www.mycophenolate.rems.com).

\section*{Dose–Effect Relationship}

Studies to date have been inconclusive in determining if there is a dose–effect relationship between MPA and adverse pregnancy outcomes. An accepted teratological principle is that there is a dose–effect relationship with developmental toxicity, where there is a threshold dose below which there are no adverse fetal effects and above which there is an increase in frequency of adverse fetal effects.\textsuperscript{35} In published reports, there has been a wide range of dosages of MPA taken by mothers during pregnancy. The adult dose range for MMF is wide and adverse events have been reported when women were taking as little as 250 mg daily.\textsuperscript{65} Blood trough levels do not correlate well with drug effectiveness or toxicity; thus, blood levels of MPA are infrequently measured. The NTPR conducted an analysis of those pregnancies with exposure to MPA products based on available dosing information.\textsuperscript{69} This analysis included 105 pregnancies with 106 outcomes in 71 solid organ recipients (kidney, kidney–pancreas, liver, heart, and lung). Daily doses ranged from 250 to 3,000 mg. There were 46 live births and 14 of the 46 (30.4\%) had a variety of birth defects reported. There were 58 spontaneous abortions (miscarriages) and two stillbirths. Weekly MPA doses were analyzed comparing viable outcomes (live births with birth defects and live births without birth defects) to nonviable outcomes (stillbirths and spontaneous abortions). Mean weekly doses were 7,768 \pm 4,317 mg for viable outcomes versus 8,847 \pm 3,905 mg for nonviable outcomes. Overall, higher MPA doses were seen in those pregnancies with nonviable outcomes. For the viable outcomes, there was no significant difference between the mean weekly MPA doses when comparing live births with and without birth defects.\textsuperscript{69}

Hoeltzenbein et al\textsuperscript{12}'s review of 57 prospective pregnancies from the collaborative study of European Teratology Information Services also did not reveal differences in the dosages of mothers of healthy newborn compared with the offspring who were born with MPA-related abnormalities. This was the largest prospective study regarding pregnancy exposure to MPA, and confirmed the increase in miscarriage, a phenotypical pattern, and an increased incidence of birth.
| Reference                  | Age and Indication | MPA product exposure | Concomitant immunosuppression | Other concomitant medications | Pregnancy outcomes | Birth defects                                                                                     |
|----------------------------|--------------------|----------------------|--------------------------------|-------------------------------|-------------------|-----------------------------------------------------------------------------------------------|
| Pérgola et al (2001)³⁶      | 33 y kidney transplant | 1,000 BID; from 6–7 wk to 26 wk 500 mg BID until delivery | Tacrolimus 7 BID adjusted per trough level, prednisone 25 daily | Nifedipine until wk 10; trimethoprim/sulfamethoxazole, acyclovir until wk 26; famotidine, erythropoietin | LB 34 wk 2,250 g | Hypoplastic nails, shortened 5th fingers, “aberrant blood vessel between trachea and esophagus” |
| Le Ray et al (2004)³⁷      | 27 y kidney transplant | 500 daily until 13 wk | Tacrolimus 9 daily, prednisone 15 daily, azathioprine 50 daily (13 wk until delivery) | None reported | TOPº 22 wk | Microtia and external auditory duct atresia, cleft lip/palate, micrognathia, ocular hypertelorism, left pelvic ectopic kidney, agenesis corpus callosum |
| Källén et al (2005)³⁸      | 22 y liver transplant | “Early exposure”; dose not specified | Tacrolimus, prednisone | Ursodeoxycholic acid | LB | Esophageal atresia and complex cardiac defect, iris anomaly |
| El Sebaaly et al (2007)³⁹  | SLE                | 1,000 BID           | Prednisone                      | Hydroxychloroquine, perindopril | TOPº 25 wk | Bilateral anotia, external auditory duct atresia, polydactyly, nail hypoplasia, anterior positioning of the aorta, interventricular communication, kidney asymmetry |
| Perez-Aytes et al (2007)³⁹ | 25 y kidney transplant | 500 daily until 10 wk | Tacrolimus 12 daily | None reported | LBº 41 wk 3,050 g | Cleft lip and palate, bilateral microtia, bilateral absence of external ear canals, severe micrognathia, ocular hypertelorism and ptosis, bilateral chorionetal coloboma |
| Tjeertes et al (2007)²¹    | 36 y kidney transplant | Dose not specified | Tacrolimus, prednisone | Olanzapine, nitrazepam, and haloperidol from mo 4, darbepoetin-a and methyldopa during last trimester | LBº 35 wk 2,330 g | Microtia, nonimmune hydrops fetalis |
| Anderka et al (2008)³⁰      | 19 y SLE            | 1,000 BID until 11–12 wk | Prednisone                      | Lisinopril, hydroxychloroquine in 1st trimester; acetaminophen | LBº 31 wk 980 g | Bilateral microtia, right small pinna and preauricular pit, left malformed pinna and no external auditory canal (bilateral conductive deafness) |

(Continued)
| Reference                          | Age and Indication                  | MPA product exposurea | Concomitant immunosuppression | Other concomitant medications | Pregnancy outcomes | Birth defects                                                                 |
|-----------------------------------|-------------------------------------|-----------------------|-------------------------------|-------------------------------|--------------------|-----------------------------------------------------------------------------|
| Andrade Vila et al (2008)          | 35 y heart transplant               | 500 BID until 5 wk; 250 BID until delivery | Tacrolimus 3 BID, prednisone 5 daily | Pravastatin, diltiazem, carbamazepine | LB (weight not reported) | Left eye microphthalmia, complete bilateral atresia of the auditory conduit and middle ear, malformation of the auricular pavilion, palatine gap, mild pulmonary stenosis |
| Ang et al (2008)                   | 32 y erythema multiforme (two pregnancies) | 500 TID until 5 wk | Unknown | Unknown | M 7 wk | Bilateral microtia and external ear canal atresia (conductive hearing loss), right inferonasal iris and chorioretinal coloboma |
| Velinov and Zellers (2008)         | SLE (age not reported)              | 500 BID until 8 wk | Adalimumab 40 QOW | None reported | LB 32 wk, 4,442 g | Arched eyebrows, bilateral microtia with aural atresia, cleft palate, hypertelorism, epicanthic folds, everted lower lip, severe tracheomalacia, micrognathia, brachydactyly |
| Ruiz-Campillo et al (2008)         | 31 y SLE                            | 1,500 daily          | Deflazacort                   | Acetylsalicylic acid, nifedipine, furosemide | LB³ 31 wk, 1,035 g | Severe microretrognathia, complete cleft palate |
| Schoner et al (2008)               | SLE (age not reported)              | 750 BID until wk 8   | Azathioprine 50 daily wk 8 to termination | None reported | TOP³ 17 wk | Macrostomia with bilateral cleft lip and palate, downward slanting palpebral fissures, eyelid colobomas, small anophthalmic eyeballs with multiple malformations, microretrognathia, atretic auditory canals, syndactyly, thymus and lung hypoplasia, heart defects, esophageal atresia with tracheoesophageal fistula, left renal agenesis, agenesis corpus callosum |
| Huang et al (2008)                 | 36 y SLE                            | 1,000 BID until 12 wk | Prednisone 30 daily           | Irbesartan from 12 wk to delivery, hydroxychloroquine, felodipine | TOP³ 22 wk | Ocular hypertelorism, bilateral microtia and external auditory canal atresia, and bifold nasal tip |
| Dei Malatesta et al (2009)         | 35 y kidney transplant              | 500 daily            | Tacrolimus 4 daily, prednisone 5 QOD | None reported | LB³ 37 wk, 2,850 g | Right eye choroidal coloboma involving the optic disc (type 1) |
| Reference                | Age and Indication | MPA product exposure | Concomitant immunosuppression | Other concomitant medications | Pregnancy outcomes | Birth defects                                                                                                                                 |
|-------------------------|--------------------|----------------------|-------------------------------|-----------------------------|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Jackson et al (2009)<sup>b,48</sup> | 20 y liver transplant | 1,000 BID until 17 wk; 500 BID from 17 wk to delivery | Tacrolimus 5 BID, prednisone 2.5 BID | Trimethoprim/sulfamethoxazole, acyclovir begun between 17 and 27 wk | LB<sup>c</sup> 35 wk, child death at 125 d of cardiorespiratory failure | Bilateral cleft lip and palate, multiple cardiac defects, cataracts, left microphthalmia with ocular hypertelorism, microtia with external ear canal atresia, intestinal malrotation, overlapping fingers and skeletal anomalies of the ribs and vertebrae, immature white matter development, bilateral coloboma |
| Parisi et al (2009)<sup>b,32</sup> | 36 y kidney transplant | 250 BID | Tacrolimus 5 daily, prednisone 5 daily | amlodipine, metoprolol, furosemide, erythropoetin, acyclovir (1<sup>st</sup> month) | LB<sup>c</sup> 35 wk; 2163 g; Neonatal death on day 2 | Congenital diaphragmatic hernia, cleft palate, ocular hypertelorism, retrognathia, microtia with no external auditory canals, short webbed neck, esophageal atresia with tracheoesophageal fistula, bifid thoracic vertebra, short thumbs and fifth fingers with hypoplastic toenails |
| Zahra et al (2009)<sup>58</sup> | 34 y liver transplant | 1,000 daily to 12 wk | Cyclosporine 300 mg | None reported | LB 38 wk, 2,480 g | None reported |
| Koshy et al (2010)<sup>59</sup> | 37 y kidney transplant | 250 BID | Tacrolimus 2 BID, prednisone 5 daily | Labetalol 200 BID | LB 32 wk | Microtia, bilateral atresia of the auditory canals (intact inner ear function), downward slanting palpebral fissures, mild retrognathia, bifid uvula |
| Lin et al (2011)<sup>31</sup> | 22 y kidney transplant | 1,000 daily until month 3; entire bottle at about month 2 of pregnancy (attempted suicide) | Tacrolimus 6 daily, prednisone 5 daily | Omeprazole, ferrous sulfate | LB<sup>c</sup> 40 wk, 2,064 g | Prenatal ultrasound: multiple congenital heart defects; additional postnatal findings: bilateral microtia and absent external auditory canals, preauricular skin tags, microphthalmia, inferior iris coloboma, micrognathia, hypoplasia of lower face, hard and soft cleft palate, short webbed neck, hypoplastic scapulae, mild rhizomelic shortening, bilateral cryptorchidism |
defects with MPA exposure. The authors also stressed that MPA exposure past week 7 resulted in an increased risk for birth defects. The lack of definitive results in these small group analyses leaves open the question of whether the teratogenicity of MPA is dose related. Only one author reported the blood level of MPA in an infant born with microtia to a mother taking MPA during her pregnancy. Tjeertes et al found a blood level of 3.1 mg/L in the newborn, which dropped to 0.6 mg/L after 10 days. The authors were not able to correlate the infants’ blood level with maternal blood level as it was not tested, nor was the maternal dose during pregnancy reported.

Strategies to Reduce Maternal MPA Exposure

Ghafari and Sanadgol reported the outcome of 61 pregnancies in 53 kidney recipients, among them 38 recipients had pregnancies with exposure to MMF. Neither the number of live births with MMF exposure was reported nor the exposure to MMF in the newborn with birth defects were mentioned (clubfoot and two infants with large facial hemangiomas). The authors concluded that MMF may be as safe as azathioprine (AZA) in pregnancy, by comparing the MMF outcomes to 15 recipients with AZA exposure as there were no differences between the outcomes.

Klieger-Grossmann et al also postulate that the incidence of malformations with exposure to MPA may be lower than the 27% that was originally reported. In their prospective study of 10 pregnancies on MPA for varying reasons, there were five live births (no malformations), four miscarriages, and one termination. They identified one retrospective case of MPA exposure where the baby exhibited microtia and severe hearing loss. The authors did recommend diagnostic imaging in the case of MPA exposure to ascertain whether the phenotypic malformations are visualized.

It has become common practice during prepregnancy planning for clinicians to either discontinue MPA or switch MPA to another medication that is considered safe to take during pregnancy. This approach is not effective for unplanned pregnancies or if the mother’s treated condition is not responsive to other medications. The NTPR compared 114 pregnancies conceived on MPA to 163 pregnancies where MPA was discontinued prior to conception in kidney recipients. The women who discontinued MPA had significantly longer transplant-to-conception intervals and lower peripartum serum creatinine levels, as well as a significantly higher rate of live births and a lower incidence of birth defects, as previously discussed. Rejection rates during pregnancy and graft loss within 2 years of delivery were similar between the groups. Thus, for the short term, discontinuing MPA did not adversely affect graft function and resulted in more favorable pregnancy outcomes.

MPA Alternatives

For transplant recipients, the common alternative agent used when switching from MPA is AZA, which historically is

| Reference | Age and indication | MPA product exposure | Other concomitant medications | Pregnancy outcomes | Concomitant immunosuppression | Other concomitant medications | Birth defects |
|-----------|--------------------|----------------------|-------------------------------|-------------------|-----------------------------|-----------------------------|---------------|
| Perales-Puchalt et al (2012) | 25 y kidney transplant | Dose not specified | None reported | LB (gestational age and birth weight not specified) | None reported | None reported | Cleft palate |

Abbreviations: BID, mg twice a day; LB, live birth; M, miscarriage; MPA, mycophenolic acid; QOD, mg every other day; QOW, mg every other week; S, stillbirth; SLE, systemic lupus erythematosus; TID, mg three times a day; TOP, termination of pregnancy.

Note: Unless noted, medication was continued throughout pregnancy.

This table (continued)
### Table 2  Series reports with exposure to mycophenolate

| Reference and cases reported in the reference | Age and Indication | MPA product exposurea | Concomitant immunosuppression | Concomitant medications | Pregnancy outcome | Birth defects |
|-----------------------------------------------|--------------------|-----------------------|-------------------------------|-------------------------|------------------|--------------|
| Ortiz et al (2009)60                          | 5 mothers 5 pregn- | Mean daily dose 1.5 daily | Prednisone (5) | Hydroxychloroquine (4), alendronate (3), benazepril (1) | 3 LB 2 M | None |
| Klieger-Grossmann et al (2010)50             | 10 mothers 11 preg- | 750 daily             | Not reported                  | Not reported            | 4 M (36%) 6 LB 1 TOP | 1 (17%) |
| 1                                             | 42 y kidney trans- | 250 BID wk 8–13       | Not reported                  | Not reported            | LB 37 wk 2,850 g | None |
| 2                                             | 36 y SLE           | 500 daily              | Not reported                  | Not reported            | M 8 wk          | None |
| 3                                             | 29 y SLE           | 500 daily until wk 5   | Not reported                  | Not reported            | TOP 12 wk       | None |
| 4                                             | 27 y SLE           | 500 BID                | Not reported                  | Not reported            | M 8 wk          | None |
| 5                                             | 24 y SLE           | 500 BID                | Not reported                  | Not reported            | M 12 wk         | None |
| 6                                             | 34 y kidney trans- | 500 BID until wk 6     | Not reported                  | Not reported            | LB 36 wk 2,900 g | None |
| 7                                             | 32 y autoimmune   | 500 BID until wk 12    | Not reported                  | Not reported            | M 13 wk         | None |
| 8                                             | 39 y kidney trans- | 500 BID until wk 6     | Not reported                  | Not reported            | LB 37 wk 2,375 g | None |
| 9                                             | 26 y rheumatoid ar- | 500 daily until wk 7   | Not reported                  | Not reported            | LB 42 wk 2,960 g | None |
| 10                                            | Unknown           | 500 BID until wk 12    | Not reported                  | Not reported            | LB              | Microtia with hearing loss |
| Hoeltzenbein et al (2012)12                    | 57 pregnancies    | 1,000 BID              | Prednisone                    | Hydroxychloroquine, perindopril | 16 M (28%) 29 LB 12 TOP | 8 malformations 6 LB (21%) 2 TOP due to malformations |
| 1                                             | SLE               | 750 daily until wk 8   | Prednisone, azathioprine      | Enalapril, hydroxy-    | TOP 25 wk       | See ► Table 1 (case report by El Sebaaly et al)39 |
| 2                                             | SLE               | 500 daily              | Prednisone                    | Hydroxychloroquine,    | TOP 23 wk       | Microtia, external ear canal atresia, colobomal cyst, olfactory nerve agenesis, hypertelorism, malar hypoplasia, brachycephaly, microretrognathia, esophageal atresia type III, retroesophageal right subclavian artery, campito-/clindactyly |

(Continued)
| Reference and cases reported in the reference | Age and indication of pregnancy | MPA product exposure | Concomitant medications | Concomitant immunosuppression | Birth defects |
|------------------------------------------------|--------------------------------|----------------------|-------------------------|----------------------------|---------------|
| 3 Kidney transplant | 500 daily until 10 wk | Unknown dose until 8 wk | Tacrolimus, prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 4 SLE | 500 daily until 8 wk | 1,000 daily until 18 wk | Tacrolimus, azathioprine, prednisone | Cyclosporine, prednisone | Large left sided deft lip and palate and bilateral auditory canal atresia |
| 5 Kidney transplant | Unknown dose until 8 wk | Various doses in early pregnancy | Cyclosporine, prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 6 Liver transplant | 1,440 daily (EC-MPS) until 5 wk | Various doses in early pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 7 Hyper IgD syndrome | 1,280 daily (CARTA) until 5 wk | Various doses in early pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 8 Unknown | Unknown dose until 8 wk | Various doses in early pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 9L B | Unknown dose until 8 wk | Various doses in early pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 10 Unknown dose until 8 wk | Various doses in early pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 114 Kidney transplant: 114 recipients, 113 pregnancies outcomes | 1,400 BID until 16 wk | Various doses in early pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 125 BD until 11 wk | Various doses in early pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 13 500 BD switched to sirolimus at 24 wk | Various doses in early pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 14 Case 1 |1,000 BID until 16 wk | Dose unknown throughout pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 15 Case 2 |1,000 BID until 16 wk | Dose unknown throughout pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 16 Case 3 |1,000 BID until 16 wk | Dose unknown throughout pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 17 Case 4 |1,000 BID until 16 wk | Dose unknown throughout pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 18 Case 5 |1,000 BID until 16 wk | Dose unknown throughout pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |
| 19 Case 6 |1,000 BID until 16 wk | Dose unknown throughout pregnancy | Tacrolimus and prednisone | Most on a calcineurin inhibitor | Microtia, external auditory canal atresia, begin cystic kidney |

NTPR (2013)^

NTPR (2013)^

Case report by Parisi et al^

Case report by Parisi et al^

Case report by Parisi et al^

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*Not reported in Table 1*

**Continued**
considered safe for use during pregnancy.\textsuperscript{75–79} The NTPR analyzed 56 recipients (46 kidney, 7 pancreas–kidney, 2 heart, 1 lung) who conceived 58 pregnancies after switching from MPA to AZA more than 6 weeks prior to conception.\textsuperscript{79} Pregnancy outcomes included 51 live births (88%), 4 spontaneous abortions (7%), 2 stillbirths, and 1 therapeutic abortion. The stillbirths were associated with placenta previa and tetraploidy. Birth defects reported were familial clubfoot (two) and hypospadias (two). Half of the recipients resumed MPA postpartum. At last maternal follow-up, 2 (4%) kidney recipients reported graft loss within 2 years of delivery (remained on AZA), 1 pancreas–kidney recipient lost pancreatic function during pregnancy, and the remaining 53 recipients reported adequate transplant function. From this study, it was concluded that switching from MPA to AZA more than 6 weeks prior to conception can result in successful pregnancy outcomes without an increased incidence of graft loss within 2 years of delivery. In this study group, 4% of kidney recipients lost their graft, whereas the NTPR reported a graft loss of 6 to 8% within 2 years of delivery in kidney recipients. This group also did not exhibit the increased miscarriage rate or pattern of birth defects found in pregnancies conceived while taking MPA during pregnancy.

Al Maimouni et al.\textsuperscript{72} reported on seven SLE patients who switched from MPA to AZA in anticipation of pregnancy. Although pregnancy outcomes were not reported, there was no increased disease activity in the 6 months following the switch.\textsuperscript{72} In another study of 23 SLE patients who switched from MPA to AZA in anticipation of pregnancy, 18 patients delivered 18 live births. Although three of the patients had to restart MPA due to renal flares and another had a renal flare postpartum, the authors concluded that patients with stable lupus nephritis in remission could safely switch from MPA to AZA in anticipation of pregnancy.\textsuperscript{71} A similar study of eight SLE females, which assessed the rate of renal flares associated with switching from MMF to AZA in anticipation for pregnancy, showed that three out of the eight patients had renal flares following the switch. Of the three patients who had renal flares, two became pregnant, and both developed preeclampsia leading to a cesarean delivery in one at 35 weeks and birth by induction at 37 weeks in the other. Those who experience renal flares had significantly higher urine protein creatinine ratios, anti-dsDNA titers, and abnormal C3 at the time of switching medications, suggesting that these variables may be possible predictors of adverse outcomes in SLE patients who switch medications prior to pregnancy.\textsuperscript{73}

### Paternal MPA Exposure

Owing to the risks in female patients with exposure to MPA during pregnancy, questions have arisen regarding fathering pregnancies while taking MPA. Overall, the outcomes of pregnancies fathered by male transplant recipients appear similar to those of the general population and the MPA embryopathies have not been noted in those pregnancies fathered by transplant recipients; thus, MPA is considered safe for male patients to take at the time of conception. This is

### Table 2 (Continued)

| Reference and cases reported in the reference | Age and indication of pregnancy | MPA product exposure | Concomitant immunosuppression | Concomitant medications | Pregnancy outcome | Birth defects |
|-----------------------------------------------|--------------------------------|----------------------|------------------------------|-------------------------|------------------|-------------|
| Mohamed-Ahmed et al (2014)\textsuperscript{53} | Liver transplant: 7 pregnancies; heart transplant: 2 pregnancies | 500 mg qd until 4 wk | Tacrolimus and prednisone | Labetalol, Coumadin switch to enoxaparin sodium | LB 34 wk 1,758 g | Ventricular septal defect | Not reported |
| | | | | | | "Good fetal outcome" (2) | "Poor fetal outcome" (7) |

Abbreviations: BID, mg twice a day; LB, live birth; M, miscarriage; MPA, mycophenolic acid; QOD, every other day; S, stillbirth; SLE, systemic lupus erythematosus; TID, three times a day; TOP, termination of pregnancy.

Note: Unless noted, medication was continued throughout pregnancy.

a Denotes gestational age in weeks.

b May overlap with NTPR.

c Poor fetal outcome defined as stillbirth, miscarriage, very low birth weight (<1,500 g), small for gestational age (<10th%), congenital anomaly, admission to neonatal unit, very preterm.

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1. Coscia et al. Teratogenicity of Maternal Mycophenolate Mofetil. Journal of Pediatric Genetics Vol. 4 No. 2/2015

Paternal MPA Exposure

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supported by an NTPR study of 152 male recipients with exposure to MPA who fathered 205 pregnancies (208 outcomes, including three pairs of twins). Pregnancy outcomes included 194 (93%) live births and 14 (7%) spontaneous abortions. Among live births, there were six malformations reported, for an incidence of 3.1%. No specific pattern of malformations was identified.

**Limitations of Clinical Studies**

It has been suggested that the rate of birth defects in MPA-exposed pregnancy outcomes is inflated owing to the potential bias in reporting retrospective analyses versus prospectively ascertained cases. There is some variability in the data in these reports, as some of the cases were reviewed retrospectively. Do retrospective analyses over- or underreport adverse outcomes? If you take a snapshot of reporting, it is possible that adverse outcomes are reported more frequently. However, with longer-term studies, two factors may counteract: (1) consistency in rates of adverse outcomes reporting over time equilibrate and (2) women with successive pregnancies blend retrospective and prospective data.

**Practical Approach and Recommendations**

There are several strategies that seem prudent when prescribing MPA. Prior to initiation of MPA in a woman of reproductive potential, there should be extensive counseling, stressing the importance of appropriate contraception and a discussion regarding the potential risks if the woman were to become pregnant, that is, increased rate of miscarriage and the possibility that the infant could exhibit a certain pattern of malformations. The FDA-mandated medication guide that accompanies MPA products includes the warnings that there should be a negative pregnancy test within 1 week of starting MPA and that two different types of effective birth control should be used simultaneously for 4 weeks before starting MPA, throughout MPA therapy, and for the 6 weeks following any discontinuation of MPA, and that the effectiveness of oral contraceptives may be affected by MPA. These same cautions are also in prescribing information published outside of the United States.

When a patient plans a pregnancy, it is recommended that the patient discuss with her health care provider her health considerations should she discontinue MPA and the alternatives, given the patient’s specific issues. In many cases, it is reasonable to switch MPA to a medication that is safer to use during pregnancy, such as temporarily replacing MPA with AZA in conjunction with adding or increasing prednisone, in an attempt to balance the risks. Ideally, MPA should be discontinued at least 6 weeks prior to conception. There are several reports supporting this strategy. No doubt there are uncommon situations where the potential immunosuppressive benefit of taking MPA while pregnant would outweigh the potential risk to the fetus, considering the alternative medications and the reports of the high miscarriage rates and the incidence of birth defects.

The more challenging situation is when a patient has an unplanned pregnancy resulting in MPA exposure during organogenesis. In the published series and case reports,
different strategies were used with varying results. MPA was decreased when pregnancy was discovered,\textsuperscript{36,48} MPA was switched to another agent\textsuperscript{41,79} or MPA was discontinued.\textsuperscript{29,30} In other cases, pregnancy termination was recommended based on potential risks or the results of diagnostic testing.\textsuperscript{37,39} Although not all pregnancies exposed to MPA beyond organogenesis have resulted in adverse outcomes, the treatment decision is complex as it takes into account the fetal risks as well as the health of the mother and transplanted organ. The obstetrician and neonatal and transplant teams should be prepared for the delivery of a newborn that may have defects if there was MPA exposure.

Huang et al\textsuperscript{42} suggest that further discussion with the patient in the form of genetic counseling should take place regarding the possibility of fetal malformations in the event of MPA exposure during the first trimester. Repeat fetal sonography is advisable to attempt prenatal diagnosis of any MPA embryopathy focusing on the potential craniofacial abnormalities. Echocardiography at 23 weeks to rule out cardiac defects. This will allow for the appropriate staff and timely interventions after delivery.\textsuperscript{84}

After the pregnancy, there is a question of when to resume MPA. The postpartum period is a fragile time for patients from both health and lifestyle standpoints. Abrupt pharmacokinetic changes follow delivery. Maternal immune reconstitution poses a threat. Postpartum depression also threatens medication adherence. Careful monitoring during the postpartum period is recommended. Some transplant patients risk rejection if they stay off MPA for too long, whereas other patients can tolerate a MPA-free regimen. If the patient desires subsequent pregnancies, the question arises whether she should remain off MPA until she conceives again or if she should resume MPA until conception is planned.

Breastfeeding

Special consideration should also be given to the patient who wishes to breastfeed. Because it is expected that MPA is secreted in human breast milk, the product labeling advises against breastfeeding while taking MPA. In animal studies, MPA was found in breast milk and there is no published information about the measurement of MPA in human breast milk. Patients who have discontinued MPA prior to or during their pregnancy are frequently taking other medications for which breastfeeding has historically been discouraged. Breastfeeding and the use of human milk confer unique nutritional and nonnutritional benefits to the infant and the mother\textsuperscript{88} and detecting the presence of a drug in human milk does not always imply a risk to the infant. One hundred four transplant recipients participating in the NTPR reported breastfeeding their infants; among them seven children born between 2002 and 2008 (five kidney, two heart) were breastfed while their mothers were maintained on MPA. To date none have reported adverse effects due to breastfeeding.\textsuperscript{89}

Continued long-term follow-up of MPA-exposed offspring is warranted as they mature into adulthood, to identify any subtle, lasting effects of immunosuppression exposure. All transplant centers are encouraged to continue to report all pregnancies in transplant recipients to the NTPR.

In Memoriam

This article is dedicated to Vincent T. Armenti, MD, PhD (1952–2014), the founder and principal investigator of the NTPR. His guidance and leadership allowed the NTPR to flourish and provide countless transplant recipients with scientific information on which to base their family planning decisions.

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