



MALE-MEDIATED DEVELOPMENTAL TOXICITY AND MYCOPHENOLATE EXPOSURE: INFORMATION FOR THE TRANSPLANT PROFESSIONAL

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WHAT IS KNOWN ON THIS TOPIC

Mycophenolate Reproductive Risks: Clinical Data

1. Exposure of female patients to mycophenolate in early pregnancy is associated with increased rates of spontaneous abortion and congenital malformations^{1,2}. Under the former U.S. Food and Drug Administration (FDA) pregnancy category rating system, mycophenolate is rated as category D, defined as “Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.”³
2. **Data from 3 published registry studies evaluating pregnancy outcomes with paternal exposure to mycophenolate have not identified an increased risk of adverse fetal outcomes.**
 - Jones et al. reported outcomes of 208 pregnancies fathered by 152 male transplant recipients receiving mycophenolate and enrolled in the U.S. National Transplantation Pregnancy Registry (NTPR). Outcomes were similar to the general population including rate of spontaneous abortion (6.8% vs. 17.1%), prematurity (10.8% vs. 12.18%) and birth defects (3.1% vs. 3.0%) for mycophenolate-treated patients vs. the general population, respectively⁴.
 - In a report of 54 births fathered by 53 male kidney transplant recipients in China, no birth defects or developmental issues were identified. The proportion of patients receiving mycophenolate was not reported⁵.
 - An earlier publication from the NTPR reported pregnancy outcomes with paternal exposure to mycophenolate to be similar to the general population⁶.

Putative Mechanisms for Male-Mediated Developmental Toxicity

The FDA recently issued a draft guidance document for industry on assessing the effects of pharmaceutical products on male-mediated developmental toxicity⁷. Exposure of male patients to drugs before conception may have the potential to affect the outcome of subsequent progeny and/or male fertility^{7,8}. Mechanisms of male-mediated developmental toxicity may include:

- Genotoxic effects of the drug on the male germ cell and/or sperm cell before conception (i.e., gene mutation or other chromosomal abnormality, altered gene expression)
- Reproductive effects including effects on sperm quality, implantation and the early embryo
- Direct exposure of the conceptus to the drug following seminal transfer and vaginal uptake in a pregnant partner

Mycophenolate Non-Clinical Toxicology Data

1. Mycophenolate sodium was found to be genotoxic in 3 out of 5 assays – the mouse lymphoma/thymidine kinase assay, the micronucleus test in V79 Chinese hamster cells and the *in vivo* mouse micronucleus assay. Mycophenolate sodium was not genotoxic in the bacterial mutation assay or the chromosomal aberration assay in human lymphocytes. The lowest dose level showing genotoxic effects in a mouse bone marrow micronucleus was approximately 3 times the usual clinical exposure of 1440 mg mycophenolate sodium per day⁹. MMF was not found to be genotoxic, with or without metabolic activation, in several assays: the bacterial mutation assay, the yeast mitotic gene conversion assay, the mouse micronucleus aberration assay, or the Chinese hamster ovary cell chromosomal aberration assay¹⁰.
2. Mycophenolate sodium had no effect on fertility of male rats at oral doses up to 40 mg/kg/day, which is approximately 9 times the usual clinical exposure of 1440 mg per day⁹. No treatment-related effects occurred in a 6-month toxicity study of male rat fertility and reproduction with MMF doses up to 20 mg/kg/day¹⁰.
3. No published data regarding levels of mycophenolate in human seminal fluid ejaculate and/or potential fetal exposure via this mechanism were identified.

WHAT IS HAPPENING NOW

In June 2015, the FDA instituted changes to prescription drug labeling requirements pertaining to pregnancy and lactation (not specific to mycophenolate)¹¹. The former product letter categories (A, B, C, D and X) used to classify the risks of prescription drug use during pregnancy have been replaced with three detailed subsections, including **Pregnancy, Lactation, and Females and Males of Reproductive Potential**. Further to this, the FDA issued a draft guidance document for industry on assessing the effects of pharmaceutical products (not specific to mycophenolate) on male-mediated developmental toxicity⁷.

At the same time and in-line with these new U.S. requirements, Hoffman-La Roche Ltd. and Novartis Pharmaceuticals have been working with Health Canada to modify the labeling and Canadian product monographs for *CellCept (mycophenolate mofetil)* and *MYFORTIC (mycophenolate sodium)*, respectively. This includes the following new precautions for men receiving mycophenolate:

Sexually active men should be informed to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomized men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. Men should be informed not to donate sperm/semens during therapy or for at least 90 days following discontinuation of mycophenolate. In addition, female partners of male patients should be informed to use highly effective contraception during treatment and for a total of 90 days after the last dose of any mycophenolate containing product.

This information was detailed in a Health Canada-issued advisory from Hoffman-La Roche Ltd. and Novartis Pharmaceuticals on January 18, 2016 entitled: *Serious Risk of Teratogenicity in Mycophenolate-Containing Products* (available here: <http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/56690a-eng.php>).

Of note, the Myfortic product monograph⁹ has always carried the following warning (which to-date has not been included in the CellCept product monograph¹⁰):

Male Patients: Sexually active men are recommended to use condoms during treatment and for a total of 13 weeks after their last dose of MYFORTIC®. In addition, female partners of the male patients are recommended to use highly effective contraception during treatment and for a total of 13 weeks after the last dose of MYFORTIC®.

CONCLUSION

Available published clinical data does not support an increased risk of adverse pregnancy outcomes with paternal mycophenolate exposure above what is encountered in the general population. Non-clinical data suggests potential genotoxic effects with mycophenolate at doses exceeding typical clinical exposure. **The potential risk of adverse pregnancy outcomes must be balanced against the real risks inherent in altering an immunosuppressant regimen.** Clinicians are encouraged to educate both male and female transplant candidates and recipients accordingly, and discuss options and risks in light of the available data in those planning to conceive.

REFERENCES

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