Recommendations for men taking mycophenolate derivatives and pregnancy following MHRA recommendations.

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Dear colleagues,

- Recent updates to the Summary of Product Characteristics (SmPC) for proprietary brands of mycophenolate derivatives (CellCept®, Roche¹ and Myfortic®, Novartis²) include new advice that sexually active men exposed to these agents should use condoms during treatment and for 90 days or 13 weeks (respectively) after discontinuation.
- Furthermore, the MHRA state that, ‘Female partners of male patients treated with mycophenolate mofetil or mycophenolic acid should use highly effective contraception during treatment and for 90 days after the last dose’³.

These changes have resulted from draft guidance published by the US Food and Drugs Administration (rather than new clinical evidence) stating that:

- “If the risk of male-mediated developmental toxicity is uncertain ... the male patient should be advised on the type ... and duration of precautions needed to prevent pregnancy.”⁴

There is substantial evidence that maternal exposure to mycophenolate derivatives (mycophenolic acid, mycophenolate mofetil) can lead to teratogenicity in human pregnancies, and treatment with such agents be avoided in women for at least 6 weeks prior to attempted conception.

In principle, paternal exposure to teratogenic agents may adversely affect pregnancy in two ways:

- genetic mutation in spermatozoa, or
- transmission of teratogenic agents in seminal fluid leading to local exposure of the ovum and systemic maternal exposure from maternal absorption.

However:

- Two registry studies of pregnancies affected by paternal exposure to mycophenolate derivatives have not identified an increased incidence of fetal malformations compared to the general population (3.1% vs 3%⁵, 2.1% vs 1.9%⁶).
- Following exposure to seminal fluid from fathers taking mycophenolate derivatives, estimated peak maternal plasma concentration of mycophenolate derivative is approximately 1000 times lower than therapeutic levels⁴⁷.
- For stable male transplant recipients considering fathering children, or those with stable immunological renal disease taking mycophenolate derivatives, conversion to alternative immunosuppressive regimes may confer significant risk of graft rejection or risk re-activation of disease.
We recommend that potential fathers taking mycophenolate derivatives are informed of the theoretical risks of mycophenolate exposure to a fetus and be made aware of the contraceptive advice given by the MHRA and contained in the SmPC. We advise that these theoretical risks should be balanced against the risks of conversion to alternative immunosuppressive regimes on their kidney transplant status in an individualised discussion.

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1 http://www.medicines.org.uk/emc/medicine/1680
2 http://www.medicines.org.uk/emc/medicine/14917
7 Assuming seminal fluid concentration of mycophenolic acid equals plasma concentration, ejaculate volume of 5ml, 100% vaginal uptake and female blood volume of 5000ml