Mycophenolate mofetil/mycophenolate sodium and congenital malformation.

The FDA has issued an alert regarding mycophenolate mofetil (MFM, CellCept®) and mycophenolate sodium (Myfortic®) following reports on outcomes of pregnancies suggesting an increased risk of pregnancy loss and congenital malformation in association with maternal use of these drugs during pregnancy. Mycophenolate mofetil and mycophenolate sodium must be considered as associated with an increased risk of pregnancy loss and congenital malformation with regards to attitudes of prescription and information to patients.

Mycophenolate mofetil and mycophenolate sodium are considered contra-indicated during pregnancy. Grounds for this attitude lie on their mechanism of action (inhibition of purine synthesis), as well as animal data (rat, rabbit) showing a teratogenic effect at levels of exposure comparable, or inferior, to those prescribed in humans after an organ transplant (dose/m2).

The FDA has issued an alert regarding mycophenolate mofetil (MFM, CellCept®) and mycophenolate sodium (Myfortic®) following reports on outcomes of pregnancies suggesting an increased risk of pregnancy loss and congenital malformation in association with maternal use of these drugs during pregnancy. Malformations concern principally external/mid ear and facial anomalies (cleft lip/palate), but distal limb (hypoplastic nails, shortened fifth finger), esophagus, kidney (ectopic location) and heart anomalies were reported. Of approximately one hundred registered exposures, pregnancy loss rate was between 30 and 42%, and the rate of structural malformations/ polymalformations was between 18 and 22%. Anomalies of the ear were noted in two thirds to three quarters of these cases.

Summary of data:

- *United States National Transplant Pregnancy Registry [réf. 1]:*

26 exposed pregnancies
11 spontaneous abortions (42%)
4 cases of structural anomalies among 18 live born infants (22%), comprising 3 cases with ear anomaly, and 2 cases of cleft lip/palate

- *Post-marketing registry held by Roche (1995-2007)* [DHP Letter Oct. 07]:

77 exposed pregnancies
25 spontaneous abortions (32%)

14 cases of structural anomalies (18%), among which 6 cases with ear anomaly

- *Approximately 5 isolated published cases [réf. 2-6], including malformation of the ear in 4 cases.*

The gathering of these observations, generally retrospective, does not allow for an estimation of the incidence of malformations (preferential reporting of pathological outcomes, recall bias, etc.). Nevertheless, the recurrence of similar patterns of malformation speaks in favor of a causal relation to maternal drug use of mycophenolate mofetil/ mycophenolate sodium, and supports the attitude up to now based on measure of caution and experimental data suggesting a potential risk. Mycophenolate mofetil and mycophenolate sodium must be considered as associated with an increased risk of pregnancy loss and congenital malformation with regards to attitudes of prescription and information to patients.

Practically, these data will mean little or no change to current attitudes, but the increased risk can be enhanced:

Prescribing mycophenolate mofetil to women of child-baring potential: Rule out an ongoing pregnancy, highly recommend contraception, inform the patient regarding potential risks.

If a pregnancy is planned: Give preference to another immunosuppressant, whenever possible, at least during the first trimester of pregnancy. If no alternative can be considered and treatment is mandatory, inform the patient regarding potential risks and ensure an adapted follow-up (see below).

Pregnancy occurring during treatment: Inform the patient regarding potential risks and assess whether continuation of mycophenolate mofetil is mandatory (especially during the first trimester of pregnancy).
If exposure occurred during the first trimester, prenatal screening centered on the described malformations should be carried out (high level ultrasound in a specialized unit). Other than risk of spontaneous abortion and malformations, an increased risk of infections should be taken into account with these treatments. Pediatricians in charge for the child should be advised of maternal exposure to these drugs.

All serious or unexpected adverse effects must be reported to a pharmacovigilance center (such as spontaneous abortion, malformation, premature birth). Recording of exposures and their prospective follow-up should be carried out, as is gathering of uneventful outcomes of fortuitously exposed pregnancies, in order to add to our knowledge regarding these substances, and to minimize bias in the interpretation of exposure data (contact for the Swiss Teratology Information Service: 021 314 42 67).

References:

1. Sifontis NM, Coscia LA, Constantinescu S, Lavelanet AF, Moritz MJ, Armenti VT. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation 2006;82:1698–702.

2. Schoner K, Steinhard J, Figiel J, Rehder H. Severe Facial Clefts in Acrofacial Dysostosis: A Consequence of Prenatal Exposure to Mycophenolate Mofetil? Obstet Gynecol. 2008 Feb;111(2):483-486

3. Velinov M, Zellers N. The fetal mycophenolate mofetil syndrome. Clin Dysmorphol 2008;17:77–8.

4. Tjeertes IF, Bastiaans DE, van Ganzewinkel CJ, Zegers SH. Neonatal anemia and hydrops fetalis after maternal mycophenolate mofetil use. J Perinatol 2007;27:62–4.

5. Perez-Aytes A, Ledo A, Boso V, Sàenz P, Roma E, Poveda JL, Vento M. In utero exposure to mycophenolate mofetil: a characteristic phenotype? Am J Med Genet A. 2008 Jan 1;146(1):1-7

6. Le Ray C, Coulomb A, Elefant E, Frydman R, Audibert F. Mycophenolate Mofetil in Pregnancy after renal transplantation: a case of major fetal malformations. Obstet Gynecol 2004;103:1091–4.

Laura Rothuizen, Françoise Livio, Jérôme Biollaz 21.02.2008