The pill times 2

What every woman with multiple sclerosis should know

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Until fingolimod came along, the first US Food and Drug Administration–approved pill for relapsing-remitting multiple sclerosis (RRMS), teratogenicity of multiple sclerosis (MS) drugs had not been a big issue. Strange, for a disease that affects primarily women of childbearing age. Why? Because previously approved MS drugs were all large recombinant protein molecules. Large molecules cross the placenta by active transport, an issue for natalizumab (a monoclonal antibody), but only after the first trimester, during which the critical periods for organogenesis have been completed. The most commonly used self-injectables (β-interferons and glatiramer acetate) are barely detectable in the circulation and have no known active transport mechanisms. Then came fingolimod, a pill that requires that women who want children take an oral contraceptive or use an otherwise reliable form of contraception.

In this issue of *Neurology*®, Karlsson et al.[1] report the outcomes of women with unplanned pregnancies while enrolled in fingolimod clinical trials. Sixty-six of these occurred, of which 20 patients had elective abortions and 41 attempted to carry their babies to term. Of these 41 women, 26 (63%) had healthy-appearing newborns, 9 (22%) had spontaneous first-trimester abortions, 4 pregnancies (10%) were terminated due to fetal abnormalities, and 2 (5%) babies were born with major malformations. The in utero–detected abnormalities that led to termination were consistent with malformations seen in animal studies and included tetralogy of Fallot, failure of fetal development, and intrauterine death, including a baby who died from acrania, a severe neural tube defect. The combined frequency of pregnancies with poor fetal outcomes (n = 6, 14.6%) far exceeds the expected congenital malformation rate of 3%.[2]

These findings highlight the challenges in choosing among the increasing number of MS drugs for women of childbearing potential, illustrate the need for pregnancy registries, and serve as a reminder that counseling about reliable methods of birth control is essential.

Rarely are there any human teratogenicity data available for new drugs, including MS drugs, during the first several years on the market. Thus the benefit to the woman needs to be weighed against the risk of exposure to the fetus based largely on inferences from pharmacokinetic and animal studies. Important considerations that can increase a drug's potential for teratogenicity include small molecular size (less than 600 Da), slow clearance, higher doses, high albumin binding, or high tissue level exposures.[3]

Unplanned pregnancies are common, even apparently in women reporting use of 2 forms of contraception while participating in MS clinical trials.[1] This is concerning because the first trimester is the period of greatest susceptibility to teratogenesis of all organ systems, particularly to small molecules.

The new oral medications for RRMS (fingolimod, teriflunomide, and dimethyl fumarate [DMF]) are all small molecules that readily diffuse across the placenta. The estimated clearance of fingolimod is 6–8 weeks and 2 years for teriflunomide in nonpregnant patients. Reduction in plasma albumin during pregnancy increases the volume of distribution of albumin-bound drugs. Since fingolimod and teriflunomide are albumin-bound, this mechanism could also contribute to prolonged fetal exposure and increased risk of teratogenicity. Thus, it is recommended that women stop fingolimod 2 months prior[4] and teriflunomide 2 years prior to conception.[5] It is perhaps not surprising that the infant with acrania was exposed to high-dose fingolimod.

The half-life for DMF is short and it is not albumin-bound. But radiolabeled-DMF animal studies demonstrated high tissue exposure in the kidneys, liver, pancreas, and brain, which could increase the risk of teratogenicity in these organs.[6]

In contrast, monoclonal antibodies (e.g., natalizumab) are large molecules that are actively transported across the placenta but not in substantial quantity until the second trimester.[7] The injectable MS medications—β-interferons and glatiramer acetate—are large molecules that are barely detectable in the circulation, without active transport mechanisms, and therefore extremely unlikely to cross the placenta in meaningful amounts. Accidental first-trimester

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exposure to these agents has not yet been associated with an increased risk of teratogenicity[8,9] despite a larger number of exposed women and longer time in use than the results reported by Karlsson et al.[1]

All of the MS medications discussed herein, with the exception of glatiramer acetate, have been associated with increased rates of spontaneous abortions in animal studies, although usually at doses based on body surface area higher than those recommended in humans.[4–6] However, the small molecules have a much stronger abortefactive potential in animals, particularly fingolimod and teriflunomide, than the large molecule drugs.

Teratogenic effects of fingolimod and teriflunomide have been described in animal studies. In contrast, the large molecule drugs did not increase the risk of major malformations in animals. The main teratogenic effects of fingolimod (which modulates a receptor involved in vascular formation during embryogenesis) were cardiac malformations, in addition to increased fetal loss.[4] Teriflunomide increases teratogenesis across many organ systems, most commonly craniofacial and skeletal defects at doses based on body surface area lower than those recommended in humans.[5] The newest MS pill, DMF, increased the risk of delayed development, including small birth size, and delayed ossification with first-trimester exposure.[6]

The US Food and Drug Administration should be commended for requiring pregnancy registries for new MS medications, as should Novartis for providing high-quality data and appropriately circumspect conclusions. Unlike many other voluntary pregnancy registries, a substantial amount of information on other potential confounding factors is reported for the cases with major malformations. The quality of postmarketing data will require continued commitment from the manufacturers and cooperation from treating physicians.

The higher-than-normal rate of teratogenicity associated with accidental pregnancy exposure to fingolimod is concerning. It serves as a reminder to women who desire children that oral MS agents may pose a substantial risk to the unborn child and should be used simultaneously with a reliable form of birth control.

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