DMT Use During Pregnancy

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Some DMTs are Safe During Pregnancy

Multiple sclerosis (MS) commonly occurs in women of childbearing age. Although MS itself has not been shown to increase the risk of spontaneous abortion or congenital defects, the use of disease-modifying therapy (DMT) during pregnancy is controversial. Because studies cannot be conducted to evaluate the risk to the fetus, regulatory authorities have restricted the use of DMT during pregnancy. Magnhild Sandberg, MD, PhD, University of Lund, Lund, Sweden, presented data to support the hypothesis that some DMTs are safe during pregnancy.

The US Food and Drug Administration (FDA) has labeled glatiramer acetate (GA) as a Category B substance and interferon beta, natalizumab, and fingolimod as Category C substances (Table 1). Exposure to drugs in utero is calculated from the date of conception, but it is not clear how to properly calculate exposure for agents with a long half-life or biological effect. Information on DMT use during pregnancy has been collected from pregnancies that have accidentally occurred during treatment trials, post-marketing surveillance, and various registries. Because of recall bias, only prospective data should be considered.

Table 1. FDA Pregnancy Categories.

Category A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimester).
Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Category C	Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Category D	There is no 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.
Category X	Studies in animals or humans have demonstrated fetal abnormalities, and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience; and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Analysis of pregnancy outcomes from trials and post-marketing surveillance on subcutaneous interferon beta-1a (IFNB-1a) showed that out of 425 exposed pregnancies with known outcomes, there were 324 live births (76.2%), 49 (11.5%) spontaneous abortions, 39 (9.2%) elective terminations, 4 (0.9%) stillbirths, 5 (1.2%) ectopic pregnancies, and 7 birth defects [Sandberg-Wollheim M. *Mult Scler J* 2011]. Pregnancy outcomes from a registry of intramuscular IFNB-1a revealed 226 pregnancies with 193 (85.4%) live births, 28 (12.4%) spontaneous abortions, 4 (1.8%) elective terminations, 1 (0.4%) stillbirth, and 15 birth defects [Abstract P894. ECTRIMS 2010]. In an Italian cohort of 88 pregnancies exposed to IFNB compared with 318 unexposed MS-pregnancies, there were 75 (85.2%) live births in the exposed group versus 295 (92.8%) in the unexposed group. Among the live births, there were 5 (5.7%) birth defects in the exposed group versus 22 (6.9%) in the unexposed group [Amato MP et al. *Neurology* 2010].

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In a German multi-center cohort of GA exposure during pregnancy, there were 25/31 live births (1 birth defect) in the exposed group, 57/64 (5 birth defects) in unexposed MS patients, and 1405/1556 (86 birth defects) in non-MS controls. Spontaneous abortions occurred in 1 exposed pregnancy, 6 unexposed MS pregnancies, and 138 unexposed non-MS pregnancies [Weber-Schoendorfer C. *Mult Scler J* 2009]. An Italian poster of GA exposure reported 16/17 live births (0 birth defects) in the exposed group and 295/318 live births (unknown birth defects) in the unexposed group, with 1 spontaneous abortion in the exposed group and 20 spontaneous abortions in the unexposed group [Abstract P689. ECTRIMS 2011]. After counseling, a group of 25 women chose to remain on GA throughout their pregnancies, which resulted in 19 live births (one infant born with a minor anomaly), three spontaneous abortions, two elective terminations (both because of trisomy 21), and one ectopic pregnancy [Abstract P06.177. AAN 2010].

In a registry of natalizumab-exposed pregnancies (n=277), there were 234 (84.5%) live births with 23 (8.3%) birth defects, 31 spontaneous abortions, and 12 elective terminations [Abstract P1005. ECTRIMS 2011]. From a German database, there were 35 natalizumab-exposed pregnancies with 29 live births, 1 birth defect, and 5 spontaneous abortions versus 23 unexposed pregnancies with 21 live births, 1 birth defect, 1 spontaneous abortion, and 1 stillbirth [Hellwig et al *Mult Scler J* 2011]. Fingolimod has only recently received market authorization and pregnancy data are limited and inconclusive [Abstract P07.184. AAN 2011].

Data from available sources showed that as long as therapy was discontinued as soon as pregnancy was recognized, fetal exposure to IFNB-1a did not increase the rate of spontaneous abortions relative to the general population, the majority of pregnancies were associated with normal live births, and most congenital anomalies occurred singly. For GA, reported exposed pregnancies are fewer, and results are, therefore, less conclusive. For natalizumab, the list of birth defects includes several major birth defects, and the final results of the registry should be awaited.

Avoid DMT in Pregnancy

Laura Airas, MD, PhD, Turku University Hospital, Turku, Finland, argued that insufficient evidence is available to recommend DMT use during pregnancy. The low MS relapse rate during pregnancy makes the use of DMT questionable. Currently, women with MS may be counseled to stop taking DMT one month before stopping contraception to protect the early developing embryo from potential adverse effects, but if the pregnancy is delayed, the total time without DMT can be prolonged. The other option is for women to stop DMT when they have a positive pregnancy test, so there is no gap in treatment prior to pregnancy. However, the early embryo may be exposed to harmful effects, or early spontaneous abortions may occur (which are not reported in pregnancy registries).

Women are also told not to take DMT while breastfeeding but MS relapses can be frequent in the postpartum period. Most women do not have major problems even without postpartum DMT. Those with active disease before or during pregnancy or with high disability are at greatest risk for postpartum relapses.

Although the data are insufficient to recommend DMT during pregnancy and breastfeeding, the available information can be used to assess the risk-benefit ratio. The Finnish database, www.medbase.fi, provides information on DMT use during pregnancy and lactation. Data on IFNB show abortions in animal studies, no teratogenicity in animals or humans, and increased miscarriage risk. Current clinical experience shows no clear basis for a washout period before a planned pregnancy. IFNB can be discontinued when pregnancy is confirmed. IFNB is not secreted into breast milk and may be safe during lactation.

GA has demonstrated no increased pregnancy risk in animal studies. Information collected by the manufacturer includes around 150 live born infants with no indication of increased risk of adverse pregnancy outcomes [reviewed in Salminen HJ et al. *J Neurol* 2010]. Hence, a washout period before pregnancy is not necessary. GA secretion into breast milk is not known, but it probably is safe to use while breastfeeding. In animal studies, natalizumab is absorbed by the placenta and causes bone malformations, and abortions. Natalizumab may induce abortions in humans but is not a significant teratogen. It is safest to discontinue natalizumab 1 to 3 months before stopping contraception, but in selected cases continuation can be considered until the time of a positive pregnancy test, to minimize the time without MS-treatment. Natalizumab is secreted into human milk, and its effects on infants are unknown.

Animal studies have shown miscarriages and malformations of the heart and vasculature with fingolimod use. Contraception should be used during treatment and during a two-month washout period prior to conception. Fingolimod is secreted into breast milk; its effects on infants are unknown, and it should be avoided.

Available data are insufficient to give evidence-based recommendations about the use of DMT during pregnancy and breastfeeding, but can be used to evaluate risk-benefit ratios, which should be discussed with the patient.