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Editorial

Interferon beta babies

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Many women with multiple sclerosis (MS) ask about the risks of pregnancy before starting (or while on) disease-modifying therapies (DMTs). At least two-thirds of patients with MS are women, and the majority are in their childbearing years at the time of clinical onset and diagnosis. DMTs taken during pregnancy could have direct or indirect toxicity (through immunomodulating properties) on pregnancy outcome. High doses of interferon beta (IFNβ) are abortifacient in monkeys, but studies of teratogenicity in animals are limited by the rapid appearance of antibodies to human IFNβ (product information). Therefore, pregnancy outcome after in utero exposure to DMTs is important, particularly because DMTs are increasingly initiated early in the course of MS. In this issue of *Neurology*, two articles provide data on pregnancy outcome after in utero exposure to IFNβ.[1,2]

Sandberg-Wollheim et al.[1] provide the first systematic and comprehensive analysis of pregnancy frequency and outcome, combining data from several randomized clinical trials of IFNβ-1a. Because allocation of treatment (IFNβ-1a at any dose vs placebo) was done randomly, there should be little bias introduced by patient assignment to treatment vs placebo groups for specific factors that could affect pregnancy outcome. Based on their study, there do not appear to be fertility issues for women exposed to IFNβ: The number of pregnancies is similar (or even slightly higher) in the IFNβ groups vs placebo. Furthermore, compared with patients exposed to placebo, immediate pregnancy outcomes (focusing on pregnancy loss and congenital malformations) were not different after in utero exposure to IFNβ-1a or after having discontinued IFNβ-1a at least 2 weeks before becoming pregnant vs placebo. However, the rate of spontaneous abortions in IFNβ-treated women was at the upper limit of the expected range for normal subjects. The data are reassuring and similar to data derived from patients exposed to glatiramer acetate.[3]

One concern is that the study groups in the article are a special subset of women (i.e., those on clinical trials) and may not be representative of the general population now given DMTs as part of "routine" MS management. Moreover, when assessing pregnancy outcome in relation to a maternal disease or teratogenic exposure, it is essential to control for factors such as maternal age, weeks of gestation at recognition of pregnancy, previous pregnancy history, and family history. One must therefore be careful in assigning relationships between treatment and outcome.

Thus, the Sandberg-Wollheim et al.[1] article is good news but has the limitations of relatively small sample size and the fact that all subjects were enrolled in clinical trials. In addition, there are no longitudinal data on live births. Finally, although spontaneous abortions were reported only in patients receiving IFNβ-1a at the time of conception (or within 2 weeks of discontinuing), this rate remains within expected range for subjects.

Also in this issue of *Neurology* is a small prospective study by Boskovic et al.[2] In this study, pregnancy outcomes were compared in three groups: patients (mostly with MS) who conceived while on IFNβ; patients (mostly with MS) who conceived after discontinuing IFNβ; and healthy control subjects. All subjects contacted "Motherisk help-lines," a service that provides counseling to the public and to health professionals regarding the reproductive safety of drugs during pregnancy and lactation. After the expected date of confinement, interviewers follow up on pregnancy outcome. In this cohort, no woman elected to discontinue her pregnancy. There was an increased risk of spontaneous abortion in patients conceiving while on IFNβ and smaller birth weights in exposed infants. There was no difference for fetal death or prematurity. There was also a suggestion that IFNβ exposure during pregnancy may increase the risk of malformations. These findings remain after controlling for potential confounders such as age and cigarette smoking. It is impossible to be certain that the differences reported relate only to IFNβ exposure as the groups were not randomized and not all potential confounders were considered.

As with the study by Sandberg-Wollheim et al.,[1] patients with MS in the study by Boskovic et al.[2]

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were already pregnant when ascertained through "Motherisk." Here again, these women cannot be assumed to be representative of the general population given DMTs for MS. In addition, the data presented on spontaneous abortions are not truly comparable.[2] There are many differences between spontaneous abortions in the first trimester and a loss at 22 weeks (no information was provided on this abortus). In assessing potential teratogens, one cannot ignore the possibility that the parental disease itself affects reproductive outcome (e.g., organ transplant recipients[4] and as suggested by table 1 of the Boskovic et al. article).[2]

In summary, there is still limited information on pregnancy outcome for babies exposed to DMTs in utero because of maternal MS.[3,5] Prudence suggests that discontinuation of IFNβ-1a (and any DMT) prior to initiating pregnancy should remain the rule whenever possible. However, there is no hypothesis or data-driven argument to support aborting pregnancies conceived during IFNβ use.

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