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Multiple sclerosis, immunomodulators, and pregnancy outcome: a prospective observational study

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Background There is still uncertainty about the management of pregnant women exposed to immunomodulatory therapy for treatment of multiple sclerosis (MS) in pregnancy.
Objective To assess the safety of interferon (IFN)-β1a, IFN-β1b, and glatiramer acetate (GA) for treatment of MS during pregnancy.
Methods A prospective observational cohort study was performed with patients enrolled through a drug risk assessment by the Teratology Information Service (TIS), Berlin, from 1996 to 2007. Pregnancy outcomes for four groups of women were compared: two exposed groups (IFN, $n = 69$; GA, $n = 31$), MS patients without exposure to IFN or GA ($n = 64$) and a healthy comparative group ($n = 1556$).
Results Spontaneous abortion rates were in normal range for all groups except the small subgroup of IFN-β1b exposed ($n = 21$), where 28% aborted spontaneously. There were two major birth defects in the GA group (club feet and atrioventricular canal) and none in the IFN cohort. Preterm delivery was not significantly different between exposed cohorts and healthy controls. The adjusted mean birth weight was in normal range in all groups (>3200 g), but newborns exposed to IFN had a significantly lower birth weight.
Conclusion Our findings suggest that neither GA nor IFN constitutes a major risk for prenatal developmental toxicity. *Multiple Sclerosis* 2009; **15**: 1037–1042. http://msj.sagepub.com

Key words: abnormalities; drug-induced; cohort study; glatiramer acetate; interferon beta; multiple sclerosis; pregnancy; pregnancy outcome

Introduction

Multiple sclerosis (MS) is one of the most common neurological diseases affecting young adults, with a disproportional increase in incidence in young women [1]. Currently, start of basic disease-modifying therapies (DMTs) for MS is recommended early in the course of the disease [2,3]. Because of the lack of experience with drug safety, it is suggested that either treatment be suspended when a pregnancy is planned [4] or a critical assessment of the pros and cons of ceasing therapy should be performed (product information, Avonex, Rebif, and Betaferon). Nevertheless, inadvertent pregnancies occur. Although disease activity and relapse rates usually improve during pregnancy, especially in the third trimester, higher relapse rates are observed postpartum [5,6].

Interferon (IFN)-β1a, IFN-β1b, and glatiramer acetate (GA) belong to the basic DMT in MS. IFNs are a group of naturally-occurring macromolecules with antiviral, antiproliferative, and immunomodulatory properties. Genetic engineering techniques have made specific IFNs available. The precise mechanism of action in MS is still under investigation. No animal teratogenicity is described in IFNs. According to the manufacturer, increased abortion rates were observed in rhesus monkeys at IFN-β1b doses 2.8–40 times those used clinically. However, maternal toxicity was also noted in the monkeys at these drug levels.

Glatiramer acetate (Copolymer 1, Copaxone) is a mixture of synthetic polypeptides composed of four amino acids. Given subcutaneously GA is readily absorbed, and most of a dose is quickly degraded into smaller fragments in the subcutaneous department. GA is believed to induce the regulatory cells

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