

more common in women than in men.¹ Given this typical patient profile, many patients with MS are women in their reproductive years. None of the currently approved disease-modifying therapies (DMTs) for patients with MS are recommended for use during pregnancy. Furthermore, all of these medications have been given a pregnancy category B, C, D or X by the US Food and Drug Administration, indicating that in the best case (category B), animal studies have failed to identify potential harmful effects of the medication but long-term safety data in humans are not available or, in the worst case (category X), studies in human patients or animals have identified risks of negative birth outcomes associated with exposure during pregnancy and the medication should not be used by patients who are or may become pregnant.¹

Patients should be informed of the potential hazards of medication use during pregnancy, and discontinuation should be considered if patients become pregnant during treatment. However there are few recommendations about when to stop medication before becoming pregnant. Thus, some patients may be taking a DMT when they become pregnant, thereby leading to fetal exposure. In addition, unplanned pregnancies can occur during treatment with DMTs, increasing the chance of accidental exposure to the fetus. Given these potential challenges, counselling patients about the possible risks of DMT use during pregnancy is an important part of disease management for patients with MS.

Reliable data on the effects of DMTs on pregnancy outcomes are difficult to obtain. Randomised, controlled trials of the potential teratogenic effects of DMT exposure during pregnancy are unlikely to be conducted given the ethical concerns of such a trial. In addition, prospective observational studies or registries require many years to reach a sample size that affords the statistical power to detect a difference in the relevant risk compared with the general population or untreated patients. Consequently, an analysis of prospective cases from existing pharmacovigilance databases may be an appropriate alternative to help guide decision-making in this population.

METHODS

The objective of the present analysis was to review pregnancy outcomes in patients who were exposed to interferon beta-1b (Betaferon/Betaseron; Bayer HealthCare Pharmaceuticals) during pregnancy. Worldwide pregnancy cases reported to

Pregnancy outcomes in patients exposed to interferon beta-1b

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system that is usually diagnosed in a patient's 20s or 30s and is

Table 1 Birth defects reported in pharmacovigilance database

Case	Event	Approximate trimester exposure	Infant sex	Maternal age, years	Comments
1	Ventriculoseptal defect, patent ductus arteriosus and foramen ovale, hip dysplasia	1	Female	23	Concomitant medication (first trimester): sertraline
2	Congenital hernia in the groin	1	Male	31	Interferon beta-1b stopped during first trimester. The patient was treated with glatiramer acetate during pregnancy. Born at 39 gestational weeks. Weight was 2.45 kg (5 lbs 6 oz—considered “low weight”) and 49 cm (19.3 inch) The physician attributes hernia to the fact that the child was born “by his foot” and was pulled out during the delivery
3	Ectopic kidney, agenesis, renal dysgenesis, obstructive congenital abnormalities to the renal pelvis and ureter	1	Male	36	Term delivery
4	Spina bifida, hydrocephalus and clubfeet	1	Male	29	The patient was primiparous. Concurrent medical conditions included body mass index of 40.8 (weight: 260 lbs, height: 5 feet 7 inch) and hypertension. Concomitant medications included nifedipine, ascorbic acid, thiamine, cyanocobalamin, retinol, riboflavin and calcium (prenatal). The patient’s second child was healthy
5	Capillary haemangioma (parietal area and left third toe. Both measured 0.5 cm in size)	1	Male	27	Urinary tract infection during pregnancy treated with 2 capsules of nitrofurantoin
6	Right eye has line from iris noted, at fourth month: no birth defects	1	Male	26	Concomitant conditions included depression and bipolar disorder (diagnosed preconception). Concomitant medication was given. Previous pregnancies (3) resulted in spontaneous abortions
7	Pilonidal dimple without sinus	1	Male	30	Previous pregnancies resulted in 1 spontaneous abortion and 1 male infant with ambiguous genitalia
8	Polydactyilia (postaxial digit, contains only soft tissue without a nail and measured approximately 1 cm)	1	Male	25	Pregnancy history included 1 live birth with no history of birth defects or maternal complications. Concomitant medications included prenatal vitamins for pregnancy At-term delivery

Bayer HealthCare’s global pharmacovigilance database were retrieved and assessed for teratogenicity. To avoid reporting bias, only prospective cases (those who were pregnant at the time of reporting) were included in this analysis. Pregnancies reported spontaneously, during clinical trials, in registries or by patient support programmes were included. Outcomes and follow-up information were collected from patients and their healthcare providers.

RESULTS

As of July 2013, the cumulative postmarketing exposure since interferon beta-1b became available in 1993 was estimated to be 1 367 697 patient-years. As of April 2013, 1045 prospective pregnancies with exposure to interferon beta-1b were retrieved. A total of 423 pregnancies had documented outcomes, with 113 reporting an abnormal outcome. The majority of the cases with abnormal outcomes were reported in the USA (73); with 15 in Brazil; 3 each in Canada, Germany and Turkey; 2 each in Belgium, Italy, Poland, Portugal and Russia; and 1 each in Australia, Hungary, Ireland, Serbia, Spain and the UK. Maternal age data were available from 105 of the cases reporting an

abnormal outcome. Median age at exposure was 30 years (range 10–48 years, mean 31.2 years).

The majority of outcomes were normal live births (308 of 423 (72.8%)). Spontaneous abortions occurred in 61 (14.4%) of the 423 prospective pregnancy cases. This rate is consistent with the rate reported in the general population (12–15%)² and specifically in the population of the USA (15–16%).³ Induced abortions were reported in 3 (<1%) cases. In addition, there were 2 (<1%) ectopic pregnancies and 11 (3%) cases of fetal death, 1 of which was possibly accompanied by unspecified malformations. Thirty cases (7%) reported other outcomes, including preterm delivery (n=10), premature labour and delivery (n=2), infant large for gestational age (n=3), infant small for gestational age (n=1), transient problems during delivery (n=4), caesarean section (n=8), lethargy (n=1) and hypotonia at 4 months of age (n=1). Cumulatively, major and minor birth defects were observed in 8 of 423 pregnancy outcomes (1.9%), similar to the 3% rate reported in the USA⁴ and the 2% rate reported in the European Union.⁵ There was no specific pattern of birth defects (table 1) and no pattern with maternal age at exposure could be identified.

DISCUSSION

This cohort represents the largest number of interferon beta-1b-exposed pregnancies to be reported to date. Importantly, the rates of spontaneous abortions and birth defects did not differ from available population estimates. In addition, no pattern of specific birth defects was observed. Other studies that examined pregnancies exposed to interferon beta have found, evidence of low birth weight or prematurity in infants born after exposure to interferon beta.¹ However, these studies contained much smaller sample sizes (N=16–88 with interferon beta exposure) and often did not distinguish between interferon beta-1b and beta-1a exposure.

Despite the relative size of the population in this analysis, the number of cases is still too small to make a final assessment of the safety of interferon beta-1b during pregnancy. Rather, these data are meant to provide a descriptive overview of the safety profile of interferon beta-1b during pregnancy.

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