BMJ open

Final results from the Betaseron® (interferon beta-1b) Pregnancy Registry

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004536
Article Type:	Research
Date Submitted by the Author:	22-Nov-2013
Complete List of Authors:	Coyle, Patricia; Stony Brook University and MS Comprehensive Care Center, Roberts, Susan; University of North Carolina Wilmington, Clinical Research Program Scheuerle, Angela; Tesserae Genetics, Medical Genetics Thorp, John; University of North Carolina Schools of Medicine and Public Health, Department of Obstetrics and Gynecology Albano, Jessica; INC Research LLC, Post Approval and Strategic Services Rametta, Mark; Bayer HealthCare Pharmaceuticals,
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Obstetrics and gynaecology, Pharmacology and therapeutics, Reproductive medicine
Keywords:	Multiple sclerosis < NEUROLOGY, interferon beta-1b, pediatrics, pregnancy, congenital abnormalities

Final results from the Betaseron® (interferon beta-1b) Pregnancy Registry

Authors: PK Coyle, MD;[1] S Sinclair Roberts, PhD, MPH, RN;[2] AE Scheuerle, MD;[3] JM Thorp Jr, MD;[4] JD Albano, PhD, MPH;[5] MJ Rametta, DO[6]

[1]Stony Brook University Department of Neurology and MS Comprehensive Care Center, Stony Brook, NY

[2]University of North Carolina Wilmington, Clinical Research Program, Wilmington, NC

[3]Tesserae Genetics, Medical Genetics, Dallas, TX

[4]University of North Carolina Schools of Medicine and Public Health, Department of Obstetrics and Gynecology, Chapel Hill, NC

[5]INC Research LLC, Post Approval and Strategic Services, Raleigh, NC

[6]Bayer HealthCare Pharmaceuticals, US Medical Affairs, Neurology, Whippany, NJ

Correspondence to:

Name: Patricia Coyle

Affiliation: Stony Brook University and MS Comprehensive Care Center

Address: HSC T12-020; SUNY at Stony Brook, Stony Brook, NY 11794-8121

Telephone number: 631-444-8188

Fax number: 631-444-1474

Email address: patricia.coyle@stonybrookmedicine.edu

Search terms: multiple sclerosis, interferon beta-1b, pediatrics, pregnancy, congenital abnormalities

Word count: 2,391 words

ABSTRACT

Objectives: Women with multiple sclerosis are often diagnosed and treated during their reproductive years. Limited data are available on the safety of treatment during pregnancy. The Betaseron® Pregnancy Registry prospectively monitored women exposed to interferon beta-1b (IFNB-1b) during pregnancy to estimate the rates of birth defects, spontaneous abortions (SABs), and other negative outcomes in this population.

Design: From 2006-2011, this observational registry enrolled women exposed prior to conception or during pregnancy (but prior to or without abnormalities on prenatal screening). Follow-up continued from enrollment through the 4-month pediatric visit.

Setting: Patients in the United States who met these criteria were enrolled in the registry.

Results: The registry enrolled 99 pregnant women; 4 were lost to follow up. The earliest exposure to IFNB-1b occurred during the first trimester for 95 pregnancies and the third trimester for 1 pregnancy. There were 99 birth outcomes (3 twins), including 86 (86.9%) live births, 11 (11.1%) SABs, and 2 (2.0%) stillbirths. Birth defects were reported in 5 (5.1%) cases. Rates of birth defects and SAB were not significantly different from population comparators. No developmental concerns were identified at the 4 month pediatric visit.

Conclusions: The small sample size limits the ability to draw definitive conclusions; however, there was no pattern to suggest increased negative outcomes with IFNB-1b.

ARTICLE SUMMARY

Strengths and limitations of this study

- The Betaseron Pregnancy Registry contains the largest sample of interferon beta-1b-exposed pregnancies collected to date
- The smaller than expected sample size limits the ability to draw definitive conclusions; however, there was no pattern to suggest increased negative outcomes with interferon beta-1b
- Limitations of the Betaseron Pregnancy Registry include the potential for underreporting or differential reporting of outcomes due to the exclusion of retrospective patients
- Birth defect ascertainment was limited relative to population-based public health programs
- Data on infant outcomes were only collected for up to 4 months, reducing the ability of the registry to measure developmental progress

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating and neurodegenerative disorder that affects over 400,000 people in the United States.[1,2] MS is much more common in women than men, and diagnosis frequently occurs when patients are in their 20s and 30s.[3,4] Consequently, women of child-bearing age constitute a considerable portion of all patients with MS. Furthermore, up to 10% have disease onset during pregnancy.[1]

The approved disease-modifying treatments (DMTs) for patients with MS have been given pregnancy category ratings of B, C, D, or X by the US Food and Drug Administration based on clinical experience and/or preclinical data (see Table 1 for pregnancy categorizations of currently-approved DMTs and a definition of different pregnancy classifications).[5-14] The safety of these agents during pregnancy is a major concern given the patient profile outlined above. However, data on pregnancy outcomes in DMT-exposed patients is limited. Among the beta interferons, this is particularly true for interferon beta-1b (Betaseron®/Betaferon®; Bayer HealthCare Pharmaceuticals; Whippany, NJ).

Table 1. Pregnancy classifications of disease modifying treatments (DMTs) approved for use by patients with MS.

Disease-modifying therapy	Pregnancy category
Glatiramer acetate (Copaxone®)[9]	B
Interferon beta-1b (Betaseron®/Betaferon®; Extavia®)[5,14]	C
Intramuscular interferon beta-1a (Avonex®)[7]	C
Subcutaneous interferon beta-1a (Rebif®)[11]	C

Fingolimod (Gilenya®)[8]	C
Dimethyl fumarate (Tecfidera®)[13]	C
Natalizumab (Tysabri®)[6]	C
Mitoxantrone[6,10]	D
Teriflunomide (Aubagio®)[6,10,12]	X

FDA pregnancy categories[15]

- Category A: No evidence of adverse effects in studies of pregnant humans
- Category B: No studies from humans, but no evidence of adverse effects in studies of pregnant animals; or negative effects observed in animal models but no evidence of adverse effects in humans
- Category C: Insufficient evidence from human studies, but research with pregnant animals identified some medication-related negative outcomes; in some situations, the medication may be more beneficial than harmful
- Category D: Medication-related negative outcomes in human studies but medication may be needed in some situations
- Category X: Medication-related negative outcomes in human or animal studies; there are no situations in which the medicine should be used

No teratogenic effects were seen in studies of pregnant rhesus monkeys exposed to interferon beta-1b. However, dose-related abortifacient activity was seen at doses from 0.028 mg/kg/d to 0.42 mg/kg/d, which is 2.8 to 4.0 times the recommended human dose based on surface area comparison.[5] Although data on human exposure during pregnancy are limited, patients are advised to discontinue treatment with interferon beta-1b if they become pregnant or plan to become pregnant.[5] The goal of the Betaseron Pregnancy Registry was to compare pregnancy outcomes in women

exposed to interferon beta-1b at conception or during pregnancy relative to general population comparators. This is the largest observational study reported to date for interferon beta-1b.

METHODS

Population and outcome measures

The Betaseron Pregnancy Registry was a voluntary, prospective, observational, exposure-registration and follow-up study. Women with an existing pregnancy who had been exposed to interferon beta-1b at any time after the first day of the last menstrual period (LMP), or during pregnancy but before any prenatal screening (eg, ultrasound, amniocentesis), were prospectively enrolled in the registry. Women with similar exposure who had undergone some prenatal testing and were without abnormal findings suggestive of fetal abnormalities were also enrolled. Because retrospective cases (ie, pregnancies submitted after the birth of the infant) can be biased toward reporting of unusual or severe outcomes, these cases and those in which an abnormality was identified prior to registry contact were excluded.

The primary outcome measure was the prevalence of major congenital malformations in infants exposed to interferon beta-1b during gestation, defined as any time after the first day of the mother's LMP. Secondary outcome measures included the prevalence of spontaneous abortion and other negative pregnancy outcomes in exposed women. Prevalence of elective abortion, stillbirth, ectopic pregnancy, neonatal death, and maternal death was assessed. Reporting was conducted by health care providers

(HCPs), patients, or representatives of the study sponsor. Maternal follow-up lasted from enrollment through pregnancy outcome. Infant follow-up continued through the 4-month pediatric visit in most cases.

Pregnancy outcomes were classified as live birth, spontaneous abortion, elective abortion, or fetal death/stillbirth. A live birth was defined as any delivery resulting in a viable neonate ≥24 weeks of gestation. The spontaneous loss of a fetus at <20 weeks of gestation was classified as a spontaneous abortion. Any fetus delivered dead ≥20 weeks of gestation, or weighing ≥500 g regardless of gestational age, was classified as a stillbirth. Fetal death occurring >20 weeks but <28 weeks was classified as early fetal loss while death occurring ≥28 weeks was considered late fetal loss. Elective abortions encompassed any induced or voluntary ending of the pregnancy. Other pregnancy outcomes included ectopic pregnancies, maternal death, and neonatal death. Infant size was classified as “small,” “appropriate,” or “large” for gestational age based on HCP assessment.

Birth defects were defined as any significant structural or chromosomal defect diagnosed with signs/symptoms using the Metropolitan Atlanta Congenital Defects Program (MACDP) classification of birth defects, or any case with 2 or more secondary or “conditional” abnormalities that would not have been classified as primary birth defects by MACDP. Birth defects were coded using a version of the coding system of the British Pediatric Association (BPA) in which the BPA code list was modified to increase the possibility of detecting a potential signal by grouping similar defect or defects with similar etiology together.[16] All codes were sorted into the appropriate organ system classes[16] by an expert in dysmorphology (AES) who evaluated the potential

temporal relationship with exposure to interferon beta-1b. Defects were classified as "Defect with a known cause, temporality may be irrelevant;" "No temporal association;" or "Unable to assess temporality."

Conduct of the registry was overseen by an independent review board. The Western Institutional Review Board (WIRB) reviewed and approved the protocol, which included a waiver of documentation of informed consent. The Betaseron Pregnancy Registry was listed in the public trials registry (www.clinicaltrials.gov) under NCT00317564.

Statistical procedures

Analyses were conducted on all prospective evaluable cases (ie, enrolled pregnancies, not lost to follow-up, with known outcome and birth defect status). Prevalence of birth defects was calculated using the number of live births as the denominator and 95% exact confidence intervals (CI) were calculated for point estimates. Outcome data were stratified by the earliest trimester of exposure to interferon beta-1b. Comparator populations were used for 2 outcomes. Risk of negative spontaneous abortions was compared with estimates for the general population of the United States from the National Survey of Family Growth (NSFG), which was conducted by the National Center for Health Statistics,[17] using Fisher's exact test based on binomial distribution for exposures. Risk for birth defects was compared with that reported by the MACDP.[18,19] This population-based birth defect surveillance system includes all infants born in the metropolitan area of Atlanta, Georgia. From 1999 to 2003, the MACDP estimated the birth defect prevalence to be 2.78 birth defects per 100 live births in its database.[18,19]

Role of the funding source

The study was jointly designed by members of the data safety monitoring board and the study sponsor. The authors had access to all the data, participated in analysis and interpretation, and were members of the publication committee. The decision to submit the article for publication was made jointly by the members of the steering committee.

RESULTS

Patient disposition

Between April 24, 2006 and July 31, 2011, 99 pregnant women were prospectively enrolled in the Betaseron Pregnancy Registry. Follow-up of pregnant women and their live-born infants continued through July 16, 2012. Pregnancy outcomes were reported for 96 exposed pregnancies, with 3 pregnancies lost to follow-up (Table 2). Initial exposure to interferon beta-1b occurred in the first trimester for 95 patients, and in the third trimester for 1 patient. Seventy-four patients had pediatric follow up. For the remaining 22 patients, follow-up continued only until birth. Prenatal testing prior to enrollment was reported in 33 cases (34.4%).

Table 2. Maternal demographics.

	Analysis population (N=96)
Age at enrollment (years)	
n	95
Mean (SD)	30.9 (5.29)

Median (range)	31.0 (19-44)
Age category, n (%)	
≤19 years	1 (1.0)
20-34 years	69 (71.9)
≥35 years	25 (26.0)
Missing	1 (1.0)
Race/ethnicity, n (%)	
White	62 (64.6)
Black	25 (26.0)
Hispanic	2 (2.1)
Asian	0 (0)
Other	6 (6.3)
Missing	1 (1.0)
MS duration at enrollment, n (%)	
<1 year	23 (24.0)
1-5 years	51 (53.1)
6-10 years	11 (11.5)
>10 years	6 (6.3)
Missing	5 (5.2)
Earliest trimester of exposure,[a] n (%)	
First	95 (99.0)
Second	0 (0)
Third	1 (1.0)
Prenatal tests, n (%)	
Prenatal test(s) after enrollment	53 (55.2)
Prenatal test(s) prior to enrollment	33 (34.4)
Date of prenatal test(s) not provided	1 (1.0)
No prenatal tests	7 (7.3)
Missing/unknown	2 (2.1)

[a] First trimester exposure was initial exposure occurring from the first day of the LMP through 13 weeks gestation; third trimester exposure was initial exposure occurring in the 28th week through the end of the pregnancy.

The majority of the sample was white (62 patients [64.6%]); 25 patients (26.0%) were black. In addition, 2 patients (2.1%) were Hispanic while 6 patients were of other races/ethnicities (6.3%) and race/ethnicity data were missing for 1 patient (1.0%). Note that the distribution of race/ethnicity in the Betaseron Pregnancy Registry was different from population norms in the United States (72.4% white, 12.6% black, 16.3% Hispanic).[20]

Pregnancy outcomes

There were a total of 99 birth outcomes available, including 3 sets of twins. These outcomes included 86 live births, 2 stillbirths, and 11 spontaneous abortions (Table 3). Both stillbirths occurred in black women with a history of prior spontaneous abortion and other comorbidities that may have affected birth outcomes. The first case, ending in stillbirth, reported hypertension, obesity (post gastric bypass), and oligohydramnios. The second reported antiphospholipid antibody syndrome, maternal human papillomavirus infection, early rupture of membranes attributed to vaginal bacterial infection, and preterm labor and delivery attributed to incompetent cervix. The prevalence of spontaneous abortion in the Betaseron Pregnancy Registry (11.5% [95% CI 5.9–19.6]) was not significantly different from the 16% estimate for the general population of the

United States based on NSFG data (relative risk 0.7 [95% CI 0.4–1.2], P=.86, Fisher's exact test based on binomial distribution for exposures).

Table 3. Pregnancy outcomes in the Betaseron Pregnancy Registry.

Outcomes, n (%, 95% CI)	Interferon beta-1b–exposed pregnancies	Relative risk (RR) (95% CI)
Live births (N=96)	83 (86.4%)	-
Birth defects (N=86)[a]	5 (5.8%, 1.9–13.0)	RR (95% CI) 2.1 (0.9-4.9), P=0.092[b]
Spontaneous abortions (N=96)	11 (11.5%, 5.9–19.6)	RR (95% CI) 0.7 (0.4–1.2) P=0.8603[c]
Stillbirth (N=96)	2 (2.1)	-
Maternal deaths	0 (0)	-
Infant deaths	0 (0)	-
Ectopic pregnancies	0 (0)	-

[a] Excludes spontaneous and elective abortions <20 weeks gestation with reported birth defects per MACDP convention. The denominator is restricted to live births.

[b] Relative risk compared with 2.78% reported by MACDP; Fisher's exact test based on binomial distribution for exposures.[18,19]

[c] Relative risk compared with 16.0% rate of SAB reported by NSFG; Fisher's exact test.[21]

Infant assessments were made at birth for 86 babies, up to 3 months of age for 74 babies, and at 4 months for 59 babies (Table 4). HCPs assessed infant size as appropriate for gestational age at birth for 67 cases (77.9%). Four-month follow-up did not identify any consistent pattern of developmental abnormalities. Birth defects were identified in 5 cases (Table 5), resulting in a relative risk of 2.1 (95% CI 0.9–4.9). The

reported birth defects occurred in several different organ systems, including the musculoskeletal, cardiovascular, and circulatory systems, with no pattern to the organ systems affected. For all cases reporting birth defects, the earliest exposure to interferon beta-1b 250 micrograms dosed every other day occurred during the first trimester of gestation. No birth defects were reported among the spontaneous pregnancy losses or stillbirths. The birth defect prevalence estimated by the Betaseron Pregnancy Registry (5.8% [95% CI 1.9–13.0]) was not significantly different (note the overlapping confidence intervals in data from the Betaseron Pregnancy Registry) from that reported by MACDP (2.78%, *P*=.092, Fisher's exact test).

Table 4. Infant assessments at birth and at 4 months.

	At birth	**At 4-month follow-up**	**Approximate median in US population at birth[22]**
Number of infants	86	59	
Sex, n (%)			
Female	40 (46.5)	26 (44.1)	
Male	46 (53.5)	33 (55.9)	
Infant weight, g			
Median	3346.8	6747.0	3200-3600
Range	470.0-4593.0	4763.0-8902.0	
Infant size, n (%)[a]			
Small	7 (8.1)	3 (5.1)	
Appropriate	67 (77.9)	48 (81.4)	
Large	7 (8.1)	6 (10.2)	
Missing	5 (5.8)	2 (3.4)	

Infant length (cm)			
Median	50.8	63.5	49-50
Range	30.5-55.9	53.3-69.3	
Infant head circumference (cm)			
Median	34.3	41.9	34.8-35.8
Range	29.5-38.1	37.0-44.5	
Gestational age at birth (weeks)			
Median	39.0	NA	
Range	24.0-41.0	NA	

[a] Infant size relative to gestational age at birth and age at 4 months (±4 weeks), respectively.

Table 5. Summary of birth defect cases

Case	Description of the reported birth defects	Organ system	Temporality assessment
1	Live infant, male, 34 weeks gestation 1. Trisomy 21 (Down syndrome)[a]	1. Chromosome anomaly	1. Defect with known cause, temporality may be irrelevant
2	Live infant, male, 40 weeks gestation 1. Hemangioma (capillary hemangioma parietal area and left 3rd toe)	1. Circulatory system	1. Unable to assess temporality
3	Live infant, female, 39 weeks gestation 1. Hip dysplasia (defect) 2. Patent foramen ovale (conditional defect) 3. Patent ductus arteriosus (conditional defect) 4. Ventriculoseptal defect (defect)	1. Other musculoskeletal defects 2. Heart 3. Circulatory system 4. Heart	1. Unable to assess temporality 2. Defect with known cause, temporality may be irrelevant 3. Defect with known cause, temporality may be irrelevant 4. Defect with known cause, temporality may be irrelevant
4	Live infant, male, 36 weeks gestation 1. Abnormal shape of the head without craniosynostosis	1. Musculoskeletal defects	1. No temporal association
5	Live infant, male, 38 weeks gestation 1. Polydactyly	1. Limb reduction/ addition defects	1. No temporal association

[a] The mother of this infant was older than 35 years of age.

Because of the relatively high percentage of black patients in the Betaseron Pregnancy Registry, a subanalysis of pregnancy outcome data was conducted to compare black and non-black patients. No significant differences were seen between these two populations in prevalence of birth defects or rates of spontaneous abortion. However, small sample sizes in this subanalysis limit the conclusions that can be drawn from these data.

DISCUSSION

This Betaseron Pregnancy Registry reported 99 outcomes in 96 evaluable pregnancies (including 3 twin pregnancies), consisting of 86 live births, 2 stillbirths, and 11 spontaneous abortions. There were 5 cases with birth defects. The risk of spontaneous abortion or birth defect was not significantly different from comparator populations. In addition, no elective abortions or maternal deaths were observed and there were no abnormalities in rate of prematurity or in birth weight/size. These data represent the largest cohort of interferon beta-1b-exposed patients reported to date; however, the sample size was still smaller than necessary to have sufficient statistical power to draw definitive conclusions.

To date, several publications have discussed the results of exposure to interferon beta formulations during pregnancy. A recent review of this literature suggested that beta interferons may be associated with some negative outcomes,[23] a conclusion that contrasts with the findings presented here. Three studies (N=88, N=69, and N=23) found low birth weight in infants exposed to interferon beta formulations (either

interferon beta-1a or beta-1b) during gestation.[24-26] Another study (N=14) found evidence of prematurity with interferon beta exposure, but birth weight was not significantly lower than unexposed comparators.[27] However, another study (N=63) did not find evidence of low birth weight following interferon beta exposure.[28] Other negative pregnancy outcomes, including a higher rate of spontaneous abortion and shorter mean birth length, have also been associated with exposure to interferon beta formulations.[24,25]

In contrast, the Betaseron Pregnancy Registry did not find any patterns to suggest negative pregnancy outcomes associated with interferon beta-1b exposure. It should be noted that the 5 aforementioned studies combined subjects exposed to either interferon beta-1a or beta-1b into a single group.[24-28] Two of these studies did not provide separate numbers of interferon beta-1a and beta-1b-exposed patients.[24,26] In the 3 studies that divided exposure groups into interferon beta-1a and beta-1b, patients with interferon beta-1b monotherapy exposure numbered only 10–21[25,27,28], thereby limiting the statistical power to draw conclusions about the effects of interferon beta-1b on pregnancy outcomes. The Betaseron Pregnancy Registry data reported here have the advantage of a much larger sample size (99 outcomes).

The Betaseron Pregnancy Registry included pediatric follow-up, which has not been not consistently reported: only 2 other studies have assessed pediatric outcomes. The first (N=14) reported normal development of interferon beta-1a- or beta-1b-exposed infants up to the 12-month milestones (walking and talking).[27] A later study (N=88) found no developmental abnormalities in interferon beta-exposed infants after 2.1 years of follow-up.[24] The Pregnancy Registry's findings are consistent with these previous reports and

reinforce the hypothesis that there are no obvious postnatal effects from in utero interferon beta-1b exposure.

The potential risks associated with interferon beta-1b exposure during pregnancy, which were not found to be significantly different from comparator cohorts in this study, need to be considered along with the risks for patients with MS who remain untreated during pregnancy. Prior research suggested that MS itself was not associated with increased risk for negative pregnancy outcomes.[1] However, risk for relapses is higher after delivery, with 20%–40% of patients experiencing a clinical relapse or worsening of the disease in the first 3 months postpartum.[1]

The results reported here are similar to 2 recent presentations related to intramuscular interferon beta-1a exposure during pregnancy. In the first, no pattern suggestive of increased negative outcomes was found in 306 pregnancies in the Avonex Pregnancy Exposure Registry.[29] Similarly, post marketing surveillance (N=552) found the rate of spontaneous abortion was consistent with the general population, with no evidence of increased rates of birth defects.[30] Together with the Betaseron Pregnancy Registry, the preponderance of data suggest no pattern of increased negative outcomes for women and infants exposed to interferon beta formulations during pregnancy, a finding that was supported by a recent review of the literature related to interferon beta exposure during pregnancy (N=1105).[31]

This is also the first study to report on pregnancy exposure outcomes in black patients with MS. No differences were noted based on race.

Limitations of the Betaseron Pregnancy Registry include the potential for underreporting or differential reporting of outcomes due to the exclusion of retrospective patients. However, it is important to note that data from these patients were captured through post-marketing surveillance efforts. In addition, birth defect ascertainment was limited relative to population-based public health programs. Lastly, data on infant outcomes were only collected for up to 4 months, reducing the ability of the registry to measure developmental progress.

Due to restricted sample size, definitive conclusions cannot be drawn from the Betaseron Pregnancy Registry data. However, there was no pattern to suggest an increased risk of birth defects in infants or an increased rate of spontaneous abortions and preterm delivery in women after exposure to interferon beta-1b during pregnancy. Birth weight also did not differ from population estimates and the 4 month infant follow-up did not identify any developmental concerns. Continued monitoring through routine post-marketing surveillance activities is recommended.

ACKNOWLEDGMENTS

We are grateful to the patients and their healthcare providers for their contributions to the study. Additionally, we thank Robert C. Ristuccia, PhD (Precept Medical Communications), for assistance with preparation of the manuscript (funded by Bayer HealthCare Pharmaceuticals).

COMPETING INTERESTS

- PK Coyle has received compensation for consulting/educational activities from Aconda, Accordant, Bayer, Biogen Idec, Genentech/Roche, Genzyme/Sanofi Aventis, Merck-Serono, Mylan, Novartis, and Teva Neurosciences. She has received research funding from Actelion, Novartis, and Opexa.
- S Sinclair Roberts has received compensation for consulting activities from Bayer, Lilly, and INC Research.
- AE Scheuerle has received compensation for consulting activities from Abbott, Amylin, Bayer, Biogen Idec, INC Research, Genentech, Novartis, PPD, TAP Pharma, Roche, Teva, and UCB Pharma.
- JM Thorp has received compensation for consulting from Bayer, GlaxoSmithKline, and PPD.
- JD Albano is an employee of INC Research, the coordinating center for the Betaseron Pregnancy Registry.
- MJ Rametta is a salaried employee of Bayer HealthCare.

AUTHOR CONTRIBUTIONS

- PK Coyle: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- S Sinclair Roberts: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- AE Scheuerle: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board

- JM Thorp: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- J Albano: Provided oversight for the conduct of the study, including the statistical analysis, interpreted data, and actively contributed to the writing and reviewing of the manuscript
- MJ Rametta: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Sponsor's responsible clinician for registry

This study was funded by Bayer HealthCare Pharmaceuticals, Inc.

REFERENCES

1. Bennett KA. Pregnancy and multiple sclerosis. *Clin Obstet Gynecol.* 2005;48(1):38-47.
2. Vlahiotis A, Sedjo R, Cox ER, et al. Gender differences in self-reported symptom awareness and perceived ability to manage therapy with disease-modifying medication among commercially insured multiple sclerosis patients. *J Manag Care Pharm.* 2010;16(3):206-216.
3. Compston A, Coles A. Multiple sclerosis. *Lancet.* 2002;359(9313):1221-1231.
4. Coyle PK, Christie S, Fodor P, et al. Multiple sclerosis gender issues: clinical practices of women neurologists. *Mult Scler.* 2004;10(5):582-588.
5. Betaseron [package insert]. Montville, NJ: Bayer HealthCare Pharmaceuticals; 2010.
6. Tysabri [package insert]. Cambridge, MA: Biogen Idec Inc; 2012.
7. Avonex [package insert]. Cambridge, MA: Biogen Idec Inc; 2012.
8. Gilenya [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.
9. Copaxone [package insert]. Kansas City, MO: TEVA Neuroscience; 2012.
10. Mitoxantrone [package insert]. Kansas City, MO: TEVA Neurosciences; 2012.

11. Rebif [package insert]. Rockland, MA: EMD Serono; 2012.

12. Aubagio [package insert]. Cambridge, MA: Genzyme Corporation; 2012.

13. Tecfidera [package insert]. Cambridge, MA: Biogen Idec Inc; 2013.

14. Extavia [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.

15. US Department of Health and Human Services OoWH. Pregnancy and Medicines. Available at http://www.womenshealth.gov/publications/our-publications/fact-sheet/pregnancy-medicines.pdf. (accessed December 21, 2012).

16. Scheuerle A, Tilson H. Birth defect classification by organ system: a novel approach to heighten teratogenic signalling in a pregnancy registry. *Pharmacoepidemiol Drug Saf.* 2002;11(6):465-475.

17. Jones RK, Kost K. Underreporting of induced and spontaneous abortion in the United States: an analysis of the 2002 National Survey of Family Growth. *Stud Fam Plann.* 2007;38(3):187-197.

18. Correa A, Cragan J, Kucik J, et al. Metropolitan Atlanta Congenital Defects Program 40th anniversary edition surveillance report: reporting birth defects surveillance data. *Birth Defects Research (Part A).* 2007;79:65-93.

19. Correa A, Cragan J, Kucik J, et al. Errata. *Birth Defects Research (Part A).* 2008;82(1):41-62.

20. U.S.Census Bureau. Overview of race and Hispanic origin: 2010. http://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf. (accessed April 2013).

21. Jones CA, Pohar SL, Warren S, et al. The burden of multiple sclerosis: a community health survey. *Health Qual Life Outcomes.* 2008;6:1.

22. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data.* 2000;(314):1-27.

23. Lu E, Wang BW, Guimond C, et al. Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review. *Neurology.* 2012;79(11):1130-1135.

24. Amato MP, Portaccio E, Ghezzi A, et al. Pregnancy and fetal outcomes after interferon-beta exposure in multiple sclerosis. *Neurology.* 2010;75(20):1794-1802.

25. Boskovic R, Wide R, Wolpin J, et al. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology.* 2005;65(6):807-811.

26. Weber-Schoendorfer C, Schaefer C. Multiple sclerosis, immunomodulators, and pregnancy outcome: a prospective observational study. *Mult Scler.* 2009;15(9):1037-1042.

27. Patti F, Cavallaro T, Lo FS, et al. Is in utero early-exposure to interferon beta a risk factor for pregnancy outcomes in multiple sclerosis? *J Neurol.* 2008;255(8):1250-1253.

28. Hellwig K, Haghikia A, Rockhoff M, Gold R. Multiple sclerosis and pregnancy: experience from a nationwide database in Germany. *Ther Adv Neurol Disord.* 2012;5(5):247-253.

29. Tomczyk S, Richman S, Wallace K, et al. Final results from the AVONEX (intramuscular-beta-1a) pregnancy exposure registry. Presented at the Annual Meeting of the European Society for Research and Treatment in Multiple Sclerosis. Lyon, France. October 10-13. 2012.

30. Tomczyk S, Sperling B. Post-marketing pregnancy outcomes in patients exposed to intramuscular-interferon-beta-1a. Presented at the Annual Meeting of the European Committee for Treatment and Research in Multiple Sclerosis. Lyon, France. October 10-13. 2012.

31. Hughes S, Spelman T, Gray O, et al. Exposure to interferon-beta therapy in early pregnancy: a literature review of pregnancy outcomes in women with multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2012;83:Supple 2 A17.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Title includes the word "registry."
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found - complete
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Paragraph 1 on page 4
Objectives	3	State specific objectives, including any prespecified hypotheses Paragraph on page 5
Methods		
Study design	4	Present key elements of study design early in the paper Pages 6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Paragraph 2 on page 6; paragraph 1 on page 9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Paragraph 2-3, page 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Paragraph 2, page 6; paragraph 1-2 on page 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Paragraph 2, page 6
Bias	9	Describe any efforts to address potential sources of bias Paragraph 3, page 7
Study size	10	Explain how the study size was arrived at Paragraph 2, page 9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Paragraph 2, page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Paragraph 2, page 8
		(*b*) Describe any methods used to examine subgroups and interactions Paragraph 2, page 8

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Paragraph 2, page 9
		(b) Give reasons for non-participation at each stage Paragraph 2, page 9
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Paragraph 2, page 9; paragraph 1 page 10; Table 2
		(b) Indicate number of participants with missing data for each variable of interest Paragraph 2, page 9; Table 2
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time Pages 11-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - NA
		(*b*) Report category boundaries when continuous variables were categorized - NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period - NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Paragraph 1, page 16
Discussion		
Key results	18	Summarise key results with reference to study objectives Paragraph 2, page 16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Paragraph 1, page 16; paragraph 1, page 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Paragraph 2, page 18
Generalisability	21	Discuss the generalisability (external validity) of the study results Paragraph 2, page 18
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Paragraph 1, page 8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Final results from the Betaseron® (interferon beta-1b) Pregnancy Registry: a prospective observational study of birth defects and pregnancy-related adverse events

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004536.R1
Article Type:	Research
Date Submitted by the Author:	21-Feb-2014
Complete List of Authors:	Coyle, Patricia; Stony Brook University and MS Comprehensive Care Center, Roberts, Susan; University of North Carolina Wilmington, Clinical Research Program Scheuerle, Angela; Tesserae Genetics, Medical Genetics Thorp, John; University of North Carolina Schools of Medicine and Public Health, Department of Obstetrics and Gynecology Albano, Jessica; INC Research LLC, Post Approval and Strategic Services Rametta, Mark; Bayer HealthCare Pharmaceuticals,
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Obstetrics and gynaecology, Pharmacology and therapeutics, Reproductive medicine
Keywords:	Multiple sclerosis < NEUROLOGY, interferon beta-1b, pediatrics, pregnancy, congenital abnormalities

Final results from the Betaseron® (interferon beta-1b) Pregnancy Registry: a prospective observational study of birth defects and pregnancy-related adverse events

Authors: PK Coyle, MD;[1] SM Sinclair, PhD, MPH, RN;[2] AE Scheuerle, MD;[3] JM Thorp Jr, MD;[4] JD Albano, PhD, MPH;[5] MJ Rametta, DO[6]

[1]Stony Brook University Department of Neurology and MS Comprehensive Care Center, Stony Brook, NY
[2]University of North Carolina Wilmington, Clinical Research Program, Wilmington, NC
[3]Tesserae Genetics, Medical Genetics, Dallas, TX
[4]University of North Carolina Schools of Medicine and Public Health, Department of Obstetrics and Gynecology, Chapel Hill, NC
[5]INC Research LLC, Post Approval and Strategic Services, Raleigh, NC
[6]Bayer HealthCare Pharmaceuticals, US Medical Affairs, Neurology, Whippany, NJ

Correspondence to:
Name: Patricia Coyle
Affiliation: Stony Brook University and MS Comprehensive Care Center
Address: HSC T12-020; SUNY at Stony Brook, Stony Brook, NY 11794-8121
Telephone number: 631-444-8188
Fax number: 631-444-1474
Email address: patricia.coyle@stonybrookmedicine.edu

Search terms: multiple sclerosis, interferon beta-1b, pediatrics, pregnancy, congenital abnormalities

Word count: 2,784 words

ABSTRACT

Objectives: Women with multiple sclerosis are often diagnosed and treated during their reproductive years. Limited data are available on the safety of treatment during pregnancy. The Betaseron® Pregnancy Registry prospectively monitored women exposed to interferon beta-1b (IFNB-1b) during pregnancy to estimate the rates of birth defects, spontaneous abortions (SABs), and other negative outcomes in this population.

Design: From 2006-2011, this observational registry enrolled women exposed prior to conception or during pregnancy (but prior to or without abnormalities on prenatal screening). Follow-up continued from enrollment through the 4-month pediatric visit.

Setting: Patients in the United States who met these criteria were enrolled in the registry.

Results: The registry enrolled 99 pregnant women; 3 were lost to follow up. The earliest exposure to IFNB-1b occurred during the first trimester for 95 pregnancies and the third trimester for 1 pregnancy. There were 99 birth outcomes (3 twins), including 86 (86.9%) live births, 11 (11.1%) SABs, and 2 (2.0%) stillbirths. Birth defects were reported in 5 (5.1%) cases. Rates of birth defects and SAB were not significantly different from population comparators. No developmental concerns were identified at the 4 month pediatric visit.

Conclusions: The small sample size limits the ability to draw definitive conclusions; however, there was no pattern to suggest increased negative outcomes with IFNB-1b.

ARTICLE SUMMARY

Strengths and limitations of this study

- The Betaseron Pregnancy Registry contains the largest sample of interferon beta-1b-exposed pregnancies collected to date
- The relatively small sample size limits the ability to draw definitive conclusions; however, there was no pattern to suggest increased negative outcomes with interferon beta-1b
- Limitations of the Betaseron Pregnancy Registry include the potential for underreporting or differential reporting of outcomes due to the exclusion of retrospective patients and the voluntary nature of participation
- Birth defect ascertainment was limited to data obtained from reporting health care providers; infants were not examined directly as part of the registry
- Data on infant outcomes were only collected for up to 4 months, reducing the ability of the registry to measure developmental progress, defects diagnosed beyond 4 months of age, and resolution of suspected defects reported in early infancy

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating and neurodegenerative disorder that affects over 400,000 people in the United States.[1,2] MS is much more common in women than men, and diagnosis frequently occurs when patients are in their 20s and 30s.[3,4] Consequently, women of child-bearing age constitute a considerable portion of all patients with MS. Furthermore, up to 10% have disease onset during pregnancy.[1]

The approved disease-modifying treatments (DMTs) for patients with MS have been given pregnancy category ratings of B, C, D, or X by the US Food and Drug Administration based on clinical experience and/or preclinical data (see Table 1 for pregnancy categorizations of currently-approved DMTs and a definition of different pregnancy classifications).[5-14] The safety of these agents during pregnancy is a major concern given the patient profile outlined above. However, data on pregnancy outcomes in DMT-exposed patients is limited. Among the beta interferons, this is particularly true for interferon beta-1b (Betaseron®/Betaferon®; Bayer HealthCare Pharmaceuticals; Whippany, NJ).

Table 1. Pregnancy classifications of disease modifying treatments (DMTs) approved for use by patients with MS.

Disease-modifying therapy	Pregnancy category
Glatiramer acetate (Copaxone®)[9]	B
Interferon beta-1b (Betaseron®/Betaferon®; Extavia®)[5,14]	C
Intramuscular interferon beta-1a (Avonex®)[7]	C
Subcutaneous interferon beta-1a (Rebif®)[11]	C

Fingolimod (Gilenya®)[8]	C
Dimethyl fumarate (Tecfidera®)[13]	C
Natalizumab (Tysabri®)[6]	C
Mitoxantrone[6,10]	D
Teriflunomide (Aubagio®)[6,10,12]	X

FDA pregnancy categories[15]

- Category A: No evidence of adverse effects in studies of pregnant humans
- Category B: No studies from humans, but no evidence of adverse effects in studies of pregnant animals; or negative effects observed in animal models but no evidence of adverse effects in humans
- Category C: Insufficient evidence from human studies, but research with pregnant animals identified some medication-related negative outcomes; in some situations, the medication may be more beneficial than harmful
- Category D: Medication-related negative outcomes in human studies but medication may be needed in some situations
- Category X: Medication-related negative outcomes in human or animal studies; there are no situations in which the medicine should be used

No teratogenic effects were seen in studies of pregnant rhesus monkeys exposed to interferon beta-1b. However, dose-related abortifacient activity was seen at doses from 0.028 mg/kg/d to 0.42 mg/kg/d, which is 2.8 to 4.0 times the recommended human dose based on surface area comparison.[5] Although data on human exposure during pregnancy are limited, patients are advised to discontinue treatment with interferon beta-1b if they become pregnant or plan to become pregnant.[5] The goal of the Betaseron Pregnancy Registry was to compare pregnancy outcomes in women

exposed to interferon beta-1b at conception or during pregnancy relative to general population comparators. This is the largest observational study reported to date for interferon beta-1b.

METHODS

Population and outcome measures

The Betaseron Pregnancy Registry was a voluntary, prospective, observational, exposure-registration and follow-up study. Women with an existing pregnancy who had been exposed to interferon beta-1b at any time after the first day of the last menstrual period (LMP), or during pregnancy but before any prenatal screening (eg, ultrasound, amniocentesis), were prospectively enrolled in the registry. Women with similar exposure who had undergone some prenatal testing and were without abnormal findings suggestive of fetal abnormalities were also enrolled. Given the widespread use of early prenatal testing, restricting enrollment to women without prenatal testing would have dramatically reduced the available population, hindering the success of the registry.[16,17] Because retrospective cases (ie, pregnancies submitted after the birth of the infant or after evidence suggestive of an abnormality on prenatal tests) can be biased toward reporting of unusual or severe outcomes, these cases and those in which an abnormality was identified prior to registry contact were excluded.

The primary outcome measure was the rate of major congenital malformations in infants exposed to interferon beta-1b during gestation, defined as any time after the first day of the mother's LMP. Secondary outcome measures included the prevalence of

spontaneous abortion and other negative pregnancy outcomes in exposed women. Prevalence of elective abortion, stillbirth, ectopic pregnancy, neonatal death, and maternal death was assessed. Reporting was conducted by health care providers (HCPs), patients, or representatives of the study sponsor. Maternal follow-up lasted from enrollment through pregnancy outcome. Infant follow-up continued through the 4-month pediatric visit in most cases.

Pregnancy outcomes were classified as live birth, spontaneous abortion, elective abortion, or fetal death/stillbirth. A live birth was defined as any delivery resulting in a viable neonate ≥24 weeks of gestation. The spontaneous loss of a fetus at <20 weeks of gestation was classified as a spontaneous abortion. Any fetus delivered dead ≥20 weeks of gestation, or weighing ≥500 g regardless of gestational age, was classified as a stillbirth. Fetal death occurring >20 weeks but <28 weeks was classified as early fetal loss while death occurring ≥28 weeks was considered late fetal loss. Elective abortions encompassed any induced or voluntary ending of the pregnancy. Other pregnancy outcomes included ectopic pregnancies, maternal death, and neonatal death. Infant size was classified as “small,” “appropriate,” or “large” for gestational age based on HCP assessment.

Birth defects were defined as any significant structural or chromosomal defect diagnosed with signs/symptoms using the Metropolitan Atlanta Congenital Defects Program (MACDP) classification of birth defects, or any case with 2 or more secondary or “conditional” abnormalities that would not have been classified as primary birth defects by MACDP. Conditional abnormalities, some of which were also referred to as “minor birth defects”, were included if present in a cluster of 2 or more to increase the

sensitivity of monitoring and to avoid missing a potential signal. Birth defects were coded using an organ system classification to increase the possibility of detecting a potential signal by grouping together similar defects or defects with similar etiology.[18] All cases were coded in accordance with both the MACDP code book and the organ system classification by an expert in dysmorphology (AES) who evaluated the potential temporal relationship between the exposure to interferon beta-1b and the etiology of the defect, considering other potential confounders (eg, exposure to other therapies received during the pregnancy, maternal or paternal history of defects, underlying disease).[18] Further follow-up for birth defect cases was conducted if additional information was needed by the dysmorphologist or the data safety monitoring board (DSMB). Defects were classified as “Defect with a known cause, temporality may be irrelevant;” “No temporal association;” or “Unable to assess temporality.” Available data for each defect case were reviewed individually for potential confounders and relevant information was evaluated and recorded.

Conduct of the registry was overseen by an independent DSMB. The Western Institutional Review Board (WIRB) reviewed and approved the protocol, which included a waiver of documentation of informed consent. The Betaseron Pregnancy Registry was listed in the public trials registry (www.clinicaltrials.gov) under NCT00317564.

Statistical procedures

Analyses were conducted on all prospective evaluable cases (ie, enrolled pregnancies, not lost to follow-up, with known outcome and birth defect status). The birth defect rate was calculated by dividing the number of cases with birth defects among all live births

and fetal losses >20 weeks gestation (numerator) by the number of live births (denominator). This approach increased the sensitivity of monitoring and may have overestimated the true rate; however it erred on the side of caution. Since the presence or absence of birth defects is difficult to ascertain among fetal losses, including fetal losses in the denominator would have biased the birth defect rate downwards. Ninety-five percent exact confidence intervals (CI) were calculated for birth defect rate and other point estimates. Outcome data were stratified by the earliest trimester of exposure to interferon beta-1b.

Population-based external comparator groups were used to evaluate the rates of spontaneous abortion and birth defects in the registry. Risk of spontaneous abortions was compared with estimates for the general population of the United States from the National Survey of Family Growth (NSFG), which was conducted by the National Center for Health Statistics,[19] using Fisher's exact test based on binomial distribution for exposures. Risk of birth defects was compared with that reported by the MACDP.[20,21] This population-based birth defect surveillance system includes all infants born in the metropolitan area of Atlanta, Georgia. From 1999 to 2003, the MACDP estimated the population birth defect rate to be 2.78 birth defects per 100 live births in its database.[20,21]

When the Registry was designed and launched, it aimed to enroll approximately 420 pregnant women to reach the goal of 210 live births to evaluate the primary endpoint (risk of birth defects). This sample size was estimated to be sufficient to rule out a 2.2-fold increase in birth defects compared to the MACDP rate of 2.78[20,21] with 80% power (assuming a 5% level of significance). The sample size goal of 420 pregnancies was

expected to result in only 210 live births because of losses to follow up, enrollment failures, and a live birth rate of 62%.[17]. After approximately 5 years of operation, Registry enrollment resulted in only 99 live births.

Role of the funding source

The study was jointly designed by members of the DSMB and the study sponsor. The authors, which included both the DSMB and representatives of the sponsor, had access to all the data, participated in analysis and interpretation, and were members of the publication committee. The decision to submit the article for publication was made jointly by the members of the steering committee and the sponsor.

RESULTS

Patient disposition

Between April 24, 2006 and July 31, 2011, 99 pregnant women were prospectively enrolled in the Betaseron Pregnancy Registry. Follow-up of pregnant women and their live-born infants continued through July 16, 2012. Pregnancy outcomes were reported for 96 exposed pregnancies, with 3 pregnancies lost to follow-up (Table 2). Initial exposure to interferon beta-1b occurred in the first trimester for 95 patients, and in the third trimester for 1 patient. Seventy-four patients had pediatric follow up. For the remaining 22 patients, follow-up continued only until birth. Prenatal testing prior to enrollment was reported in 33 cases (34.4%).

Table 2. Maternal demographics.

	Analysis population (N=96)
Age at enrollment (years)	
n	95[a]
Mean (SD)	30.9 (5.29)
Median (range)	31.0 (19-44)
Age category, n (%)	
≤19 years	1 (1.0)
20-34 years	69 (71.9)
≥35 years	25 (26.0)
Missing	1 (1.0)
Race/ethnicity, n (%)	
White	62 (64.6)
Black	25 (26.0)
Hispanic	2 (2.1)
Asian	0 (0)
Other	6 (6.3)
Missing	1 (1.0)
MS duration at enrollment, n (%)	
<1 year	23 (24.0)
1-5 years	51 (53.1)
6-10 years	11 (11.5)
>10 years	6 (6.3)
Missing	5 (5.2)
Earliest trimester of exposure,[b] n (%)	
First	95 (99.0)
Second	0 (0)
Third	1 (1.0)
Prenatal tests, n (%)	

Prenatal test(s) after enrollment	53 (55.2)
Prenatal test(s) prior to enrollment	33 (34.4)
Date of prenatal test(s) not provided	1 (1.0)
No prenatal tests	7 (7.3)
Missing/unknown	2 (2.1)

[a] Age data were missing for 1 case.

[b] First trimester exposure was initial exposure occurring from the first day of the LMP through 13 weeks gestation; third trimester exposure was initial exposure occurring in the 28th week through the end of the pregnancy.

The majority of the sample was white (62 patients [64.6%]); 25 patients (26.0%) were black. In addition, 2 patients (2.1%) were Hispanic while 6 patients were of other races/ethnicities (6.3%) and race/ethnicity data were missing for 1 patient (1.0%). Note that the distribution of race/ethnicity in the Betaseron Pregnancy Registry was different from population norms in the United States (72.4% white, 12.6% black, 16.3% Hispanic).[22]

Pregnancy outcomes

From the 96 evaluable pregnancies, there was a total of 99 birth outcomes available, including 3 sets of twins. These outcomes included 86 live births, 2 stillbirths, and 11 spontaneous abortions (Table 3). Both stillbirths occurred in black women with a history of prior spontaneous abortion and other comorbidities that may have affected birth outcomes. The first case, ending in stillbirth, reported hypertension, obesity (post gastric bypass), and oligohydramnios. The second reported antiphospholipid antibody syndrome, maternal human papillomavirus infection, early rupture of membranes attributed to vaginal bacterial infection, and preterm labor and delivery attributed to

incompetent cervix. The prevalence of spontaneous abortion in the Betaseron Pregnancy Registry (11.5% [95% CI 5.9–19.6]) was not significantly different from the 16% estimate for the general population of the United States based on NSFG data (relative risk 0.7 [95% CI 0.4–1.2], P=.86, Fisher's exact test based on binomial distribution for exposures).

Table 3. Pregnancy outcomes in the Betaseron Pregnancy Registry.

Outcomes, n (%, 95% CI)	**Interferon beta-1b–exposed pregnancies**	**Relative risk (RR) (95% CI)**
Live births (N=96)	83 (86.4%)	-
Birth defects (N=86)[a]	5 (5.8%, 1.9–13.0)	RR (95% CI) 2.1 (0.9-4.9), P=0.092[b]
Spontaneous abortions (N=96)	11 (11.5%, 5.9–19.6)	RR (95% CI) 0.7 (0.4–1.2) P=0.8603[c]
Stillbirth (N=96)	2 (2.1)	-
Maternal deaths	0 (0)	-
Infant deaths	0 (0)	-
Ectopic pregnancies	0 (0)	-

[a] Excludes spontaneous and elective abortions <20 weeks gestation with reported birth defects per MACDP convention. The denominator is restricted to live births.

[b] Relative risk compared with 2.78% reported by MACDP; Fisher's exact test based on binomial distribution for exposures.[20,21]

[c] Relative risk compared with 16.0% rate of SAB reported by NSFG; Fisher's exact test.[23]

Infant assessments were made at birth for 86 babies, up to 3 months of age for 74 babies, and at 4 months for 59 babies (Table 4). HCPs assessed infant size as

appropriate for gestational age at birth for 67 cases (77.9%). Four-month follow-up did not identify any consistent pattern of developmental abnormalities. Birth defects were identified in 5 cases (Table 5), resulting in a relative risk of 2.1 (95% CI 0.9–4.9). The reported birth defects occurred in several different organ systems, including the musculoskeletal, cardiovascular, and circulatory systems, with no pattern to the organ systems affected. For all cases reporting birth defects, the earliest exposure to interferon beta-1b 250 micrograms dosed every other day occurred during the first trimester of gestation. No birth defects were reported among the spontaneous pregnancy losses or stillbirths. The birth defect rate estimated by the Betaseron Pregnancy Registry (5.8% [95% CI 1.9–13.0]) was not significantly different from that reported by MACDP (2.78%, *P*=.092, Fisher's exact test). The relatively wide confidence intervals, which include the MACDP rate, reflect the small sample size and suggest no difference between the birth defect rate from the Betaseron Pregnancy Registry and the MACPD.

Table 4. Infant assessments at birth and at 4 months.

	At birth	**At 4-month follow-up**	**Approximate median in US population at birth[24]**
Number of infants	86	59	
Sex, n (%)			
Female	40 (46.5)	26 (44.1)	
Male	46 (53.5)	33 (55.9)	
Infant weight, g			
Median	3346.8	6747.0	3200-3600

Range	470.0-4593.0	4763.0-8902.0	
Infant size, n (%)[a]			
Small	7 (8.1)	3 (5.1)	
Appropriate	67 (77.9)	48 (81.4)	
Large	7 (8.1)	6 (10.2)	
Missing	5 (5.8)	2 (3.4)	
Infant length (cm)			
Median	50.8	63.5	49-50
Range	30.5-55.9	53.3-69.3	
Infant head circumference (cm)			
Median	34.3	41.9	34.8-35.8
Range	29.5-38.1	37.0-44.5	
Gestational age at birth (weeks)			
Median	39.0	NA	
Range	24.0-41.0	NA	

[a] Infant size relative to gestational age at birth and age at 4 months (±4 weeks), respectively.

Table 5. Summary of birth defect cases

Case	Description of the reported birth defects[a]	Organ system	Temporality assessment
1	Live infant, male, 34 weeks gestation 1. Trisomy 21 (Down syndrome)[b]	1. Chromosome anomaly	1. Defect with known cause, temporality may be irrelevant
2	Live infant, male, 40 weeks gestation 1. Hemangioma (capillary hemangioma parietal area and left 3rd toe)	1. Circulatory system	1. Unable to assess temporality
3	Live infant, female, 39 weeks gestation 1. Hip dysplasia (defect) 2. Patent foramen ovale (conditional defect) 3. Patent ductus arteriosus (conditional defect) 4. Ventriculoseptal defect (defect)	1. Other musculoskeletal defects 2. Heart 3. Circulatory system 4. Heart	1. Unable to assess temporality 2. Defect with known cause, temporality may be irrelevant 3. Defect with known cause, temporality may be irrelevant 4. Defect with known cause, temporality may be irrelevant
4	Live infant, male, 36 weeks gestation 1. Abnormal shape of the head without craniosynostosis	1. Musculoskeletal defects	1. No temporal association
5	Live infant, male, 38 weeks gestation 1. Polydactyly	1. Limb reduction/ addition defects	1. No temporal association

[a] Gestational age data are birth ages, not age at exposure.

[b] The mother of this infant was older than 35 years of age.

Because of the relatively high percentage of black patients in the Betaseron Pregnancy Registry, a subanalysis of pregnancy outcome data was conducted to compare black and non-black patients. No significant differences were seen between these two populations in the rates of birth defects or rates of spontaneous abortion. However, small sample sizes in this subanalysis limit the conclusions that can be drawn from these data.

DISCUSSION

This Betaseron Pregnancy Registry reported 99 outcomes in 96 evaluable pregnancies (including 3 twin pregnancies), consisting of 86 live births, 2 stillbirths, and 11 spontaneous abortions. There were 5 cases with birth defects. Among these 5 cases were a variety of birth defects which were not clustered around a single type of defect or effected organ system. In addition, 2 of these cases had defects that were not temporally related to interferon beta-1b exposure (ie, the timing of the exposure was not consistent with the development of the defect) and 1 had a chromosomal abnormality potentially related to advanced maternal age that was classified as having no temporal association to exposure. This lack of a consistent pattern suggests that there was no signal for birth defects due to interferon beta-1b exposure. The risk of spontaneous abortion or birth defect was not significantly different from comparator populations. In addition, no elective abortions or maternal deaths were observed and there were no abnormalities in rate of prematurity or in birth weight/size. These data represent the largest cohort of interferon beta-1b-exposed patients reported to date; however, the

sample size was still smaller than necessary to have sufficient statistical power to draw definitive conclusions.

To date, several publications have discussed the results of exposure to interferon beta formulations during pregnancy; however none have exclusively examined interferon beta-1b exposure. A recent review of this literature suggested that beta interferons may be associated with some negative outcomes,[25] a conclusion that contrasts with the findings presented here. Three studies, also with small sample sizes, (N=88, N=69, and N=23) found low birth weight in infants exposed to interferon beta formulations (either interferon beta-1a or beta-1b) during gestation.[26-28] Another study (N=14) found evidence of prematurity with interferon beta exposure, but birth weight was not significantly lower than unexposed comparators.[29] However, another study (N=63) did not find evidence of low birth weight following interferon beta exposure.[30] Other negative pregnancy outcomes, including a higher rate of spontaneous abortion and shorter mean birth length, have also been associated with exposure to interferon beta formulations.[26,27]

In contrast, the Betaseron Pregnancy Registry did not find any patterns to suggest negative pregnancy outcomes associated with interferon beta-1b exposure. It should be noted that the 5 aforementioned studies combined subjects exposed to either interferon beta-1a or beta-1b into a single group.[26-30] Two of these studies did not provide separate numbers of interferon beta-1a and beta-1b-exposed patients.[26,28] In the 3 studies that divided exposure groups into interferon beta-1a and beta-1b, patients with interferon beta-1b monotherapy exposure numbered only 10–21[27,29,30], thereby limiting the statistical power to draw conclusions about the effects of interferon beta-1b on

pregnancy outcomes. The Betaseron Pregnancy Registry data reported here have the advantage of a much larger sample size (99 outcomes), albeit much lower than planned when the registry was designed.

The Betaseron Pregnancy Registry included pediatric follow-up, which has not been not consistently reported in other studies: only 2 other studies have assessed pediatric outcomes.[26,29] The first (N=14) reported normal development of interferon beta-1a- or beta-1b-exposed infants up to the 12-month milestones (walking and talking).[29] A later study (N=88) found no developmental abnormalities in interferon beta-exposed infants after 2.1 years of follow-up.[26] The Betaseron Pregnancy Registry's findings are consistent with these previous reports and reinforce the hypothesis that there are no obvious postnatal effects from in utero interferon beta-1b exposure.

The potential risks associated with interferon beta-1b exposure during pregnancy, which were not found to be significantly different from comparator cohorts in this study, need to be considered along with the risks for patients with MS who remain untreated during pregnancy. Prior research suggested that MS itself was not associated with increased risk for negative pregnancy outcomes.[1] However, risk for relapses is higher after delivery, with 20%–40% of patients experiencing a clinical relapse or worsening of the disease in the first 3 months postpartum.[1]

The results reported here are similar to 2 recent presentations related to intramuscular interferon beta-1a exposure during pregnancy. In the first, no pattern suggestive of increased negative outcomes was found in 306 pregnancies in the Avonex Pregnancy Exposure Registry.[31] Similarly, post marketing surveillance (N=552) found the rate of

spontaneous abortion was consistent with the general population, with no evidence of increased birth defect rates.[32] Together with the Betaseron Pregnancy Registry, the preponderance of data suggest no pattern of increased negative outcomes for women and infants exposed to interferon beta formulations during pregnancy, a finding that was supported by a recent review of the literature related to interferon beta exposure during pregnancy (N=1105).[33]

This is also the first study to report on pregnancy exposure outcomes in black patients with MS. No differences were noted based on race.

Limitations of the Betaseron Pregnancy Registry include the potential for underreporting or differential reporting of outcomes due to the exclusion of retrospective patients. However, it is important to note that data from these retrospective patients were captured through post-marketing surveillance efforts. In addition, birth defect ascertainment was limited to voluntary reports from health care providers (not unlike population-based public health surveillance programs), which potentially limited the level of detail needed to fully characterize a birth defect case and rule out missed or misdiagnoses. Lastly, data on infant outcomes were only collected for up to 4 months, reducing the ability of the registry to measure developmental progress.

Due to low sample size, definitive conclusions cannot be drawn from the Betaseron Pregnancy Registry data. However, there was no pattern to suggest an increased risk of birth defects in infants or an increased rate of spontaneous abortions in women after exposure to interferon beta-1b during pregnancy. Infant assessments, such as birth weight, birth length, and head circumference, also did not differ from population

estimates and the 4 month infant follow-up did not identify any developmental concerns. Continued monitoring through routine post-marketing surveillance activities is recommended.

ACKNOWLEDGMENTS

We are grateful to the patients and their healthcare providers for their contributions to the study. Additionally, we thank Robert C. Ristuccia, PhD (Precept Medical Communications), for assistance with preparation of the manuscript (funded by Bayer HealthCare Pharmaceuticals).

AUTHOR CONTRIBUTIONS

- PK Coyle: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- SM Sinclair: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- AE Scheuerle: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- JM Thorp: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- J Albano: Provided oversight for the conduct of the study, including the statistical analysis, interpreted data, and actively contributed to the writing and reviewing of the manuscript
- MJ Rametta: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Sponsor's responsible clinician for registry

FUNDING

This study was funded by Bayer HealthCare Pharmaceuticals, Inc.

COMPETING INTERESTS

- PK Coyle has received compensation for consulting/educational activities from Aconda, Accordant, Bayer, Biogen Idec, Genentech/Roche, Genzyme/Sanofi Aventis, Merck-Serono, Mylan, Novartis, and Teva Neurosciences. She has received research funding from Actelion, Novartis, and Opexa.
- S Sinclair Roberts has received compensation for consulting activities from Bayer, Lilly, and INC Research.
- AE Scheuerle has received compensation for consulting activities from Abbott, Amylin, Bayer, Biogen Idec, INC Research, Genentech, Novartis, PPD, TAP Pharma, Roche, Teva, and UCB Pharma.
- JM Thorp has received compensation for consulting from Bayer, GlaxoSmithKline, and PPD.
- JD Albano is an employee of INC Research, the coordinating center for the Betaseron Pregnancy Registry.
- MJ Rametta is a salaried employee of Bayer HealthCare.

DATA SHARING STATEMENT

Some unpublished data remain in the final clinical study report. The data safety monitoring board of the registry (the authors of this paper) decided these data were not necessary for publication.

References

1. Bennett KA. Pregnancy and multiple sclerosis. *Clin Obstet Gynecol.* 2005;48(1):38-47.
2. Vlahiotis A, Sedjo R, Cox ER, et al. Gender differences in self-reported symptom awareness and perceived ability to manage therapy with disease-modifying medication among commercially insured multiple sclerosis patients. *J Manag Care Pharm.* 2010;16(3):206-216.
3. Compston A, Coles A. Multiple sclerosis. *Lancet.* 2002;359(9313):1221-1231.
4. Coyle PK, Christie S, Fodor P, et al. Multiple sclerosis gender issues: clinical practices of women neurologists. *Mult Scler.* 2004;10(5):582-588.
5. Betaseron [package insert]. Montville, NJ: Bayer HealthCare Pharmaceuticals; 2010.
6. Tysabri [package insert]. Cambridge, MA: Biogen Idec Inc; 2012.
7. Avonex [package insert]. Cambridge, MA: Biogen Idec Inc; 2012.
8. Gilenya [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.
9. Copaxone [package insert]. Kansas City, MO: TEVA Neuroscience; 2012.
10. Mitoxantrone [package insert]. Kansas City, MO: TEVA Neurosciences; 2012.
11. Rebif [package insert]. Rockland, MA: EMD Serono; 2012.
12. Aubagio [package insert]. Cambridge, MA: Genzyme Corporation; 2012.
13. Tecfidera [package insert]. Cambridge, MA: Biogen Idec Inc; 2013.
14. Extavia [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.
15. US Department of Health and Human Services OoWH. Pregnancy and Medicines. Available at http://www.womenshealth.gov/publications/our-publications/fact-sheet/pregnancy-medicines.pdf. Accessed December 21, 2012.
16. Covington D, Roberts S, McKain L. Impact of prenatal testing on birth defect prevalence in pregnancy exposure registries. *Pharmacoepidemiol Drug Saf.* 2008;17(Supplement 1):S13.

17. US Food and Drug Administration. Guidance for industry establishing pregnancy exposure registries. Available at http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133332.pdf. Accessed February 2014.

18. Scheuerle A, Tilson H. Birth defect classification by organ system: a novel approach to heighten teratogenic signalling in a pregnancy registry. *Pharmacoepidemiol Drug Saf.* 2002;11(6):465-475.

19. Jones RK, Kost K. Underreporting of induced and spontaneous abortion in the United States: an analysis of the 2002 National Survey of Family Growth. *Stud Fam Plann.* 2007;38(3):187-197.

20. Correa A, Cragan J, Kucik J. Metropolitan Atlanta Congenital Defects Program 40th anniversary edition surveillance report: reporting birth defects surveillance data. *Birth Defects Research (Part A).* 2007;79:65-93.

21. Correa A, Cragan J, Kucik J, et al. Errata. *Birth Defects Research (Part A).* 2008;82(1):41-62.

22. U.S.Census Bureau. Overview of race and Hispanic origin: 2010. http://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf. Accessed April 2013.

23. Jones CA, Pohar SL, Warren S, et al. The burden of multiple sclerosis: a community health survey. *Health Qual Life Outcomes.* 2008;6:1.

24. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data.* 2000;(314):1-27.

25. Lu E, Wang BW, Guimond C, et al. Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review. *Neurology.* 2012;79(11):1130-1135.

26. Amato MP, Portaccio E, Ghezzi A, et al. Pregnancy and fetal outcomes after interferon-beta exposure in multiple sclerosis. *Neurology.* 2010;75(20):1794-1802.

27. Boskovic R, Wide R, Wolpin J, et al. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology.* 2005;65(6):807-811.

28. Weber-Schoendorfer C, Schaefer C. Multiple sclerosis, immunomodulators, and pregnancy outcome: a prospective observational study. *Mult Scler.* 2009;15(9):1037-1042.

29. Patti F, Cavallaro T, Lo FS, et al. Is in utero early-exposure to interferon beta a risk factor for pregnancy outcomes in multiple sclerosis? *J Neurol.* 2008;255(8):1250-1253.

30. Hellwig K, Haghikia A, Rockhoff M, et al. Multiple sclerosis and pregnancy: experience from a nationwide database in Germany. *Ther Adv Neurol Disord.* 2012;5(5):247-253.

31. Tomczyk S, Richman S, Wallace K,. Final results from the AVONEX (intramuscular-beta-1a) pregnancy exposure registry. Presented at the Annual Meeting of the European Society for Research and Treatment in Multiple Sclerosis. Lyon, France. October 10-13. 2012.

32. Tomczyk S, Sperling B. Post-marketing pregnancy outcomes in patients exposed to intramuscular-interferon-beta-1a. Presented at the Annual Meeting of the European Committee for Treatment and Research in Multiple Sclerosis. Lyon, France. October 10-13. 2012.

33. Hughes S, Spelman T, Gray O, et al. Exposure to interferon-beta therapy in early pregnancy: a literature review of pregnancy outcomes in women with multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2012;83:Supple 2 A17.

Final results from the Betaseron® (interferon beta-1b) Pregnancy Registry: a prospective observational study of birth defects and pregnancy-related adverse events

~~Final results from the Betaseron® (interferon beta-1b) Pregnancy Registry~~

Authors: PK Coyle, MD;[1] SM Sinclair ~~Roberts~~, PhD, MPH, RN;[2] AE Scheuerle, MD;[3] JM Thorp Jr, MD;[4] JD Albano, PhD, MPH;[5] MJ Rametta, DO[6]

[1]Stony Brook University Department of Neurology and MS Comprehensive Care Center, Stony Brook, NY

[2]University of North Carolina Wilmington, Clinical Research Program, Wilmington, NC

[3]Tesserae Genetics, Medical Genetics, Dallas, TX

[4]University of North Carolina Schools of Medicine and Public Health, Department of Obstetrics and Gynecology, Chapel Hill, NC

[5]INC Research LLC, Post Approval and Strategic Services, Raleigh, NC

[6]Bayer HealthCare Pharmaceuticals, US Medical Affairs, Neurology, Whippany, NJ

Correspondence to:

Name: Patricia Coyle

Affiliation: Stony Brook University and MS Comprehensive Care Center

Address: HSC T12-020; SUNY at Stony Brook, Stony Brook, NY 11794-8121

Telephone number: 631-444-8188

Fax number: 631-444-1474

Email address: patricia.coyle@stonybrookmedicine.edu

Search terms: multiple sclerosis, interferon beta-1b, pediatrics, pregnancy, congenital abnormalities

Word count: 2,~~391~~ 784 words

ABSTRACT

Objectives: Women with multiple sclerosis are often diagnosed and treated during their reproductive years. Limited data are available on the safety of treatment during pregnancy. The Betaseron® Pregnancy Registry prospectively monitored women exposed to interferon beta-1b (IFNB-1b) during pregnancy to estimate the rates of birth defects, spontaneous abortions (SABs), and other negative outcomes in this population.

Design: From 2006-2011, this observational registry enrolled women exposed prior to conception or during pregnancy (but prior to or without abnormalities on prenatal screening). Follow-up continued from enrollment through the 4-month pediatric visit.

Setting: Patients in the United States who met these criteria were enrolled in the registry.

Results: The registry enrolled 99 pregnant women; ~~4~~ 3 were lost to follow up. The earliest exposure to IFNB-1b occurred during the first trimester for 95 pregnancies and the third trimester for 1 pregnancy. There were 99 birth outcomes (3 twins), including 86 (86.9%) live births, 11 (11.1%) SABs, and 2 (2.0%) stillbirths. Birth defects were reported in 5 (5.1%) cases. Rates of birth defects and SAB were not significantly different from population comparators. No developmental concerns were identified at the 4 month pediatric visit.

Conclusions: The small sample size limits the ability to draw definitive conclusions; however, there was no pattern to suggest increased negative outcomes with IFNB-1b.

ARTICLE SUMMARY

Strengths and limitations of this study

- The Betaseron Pregnancy Registry contains the largest sample of interferon beta-1b-exposed pregnancies collected to date
- The ~~smaller than expected~~relatively small sample size limits the ability to draw definitive conclusions; however, there was no pattern to suggest increased negative outcomes with interferon beta-1b
- Limitations of the Betaseron Pregnancy Registry include the potential for underreporting or differential reporting of outcomes due to the exclusion of retrospective patients and the voluntary nature of participation
- Birth defect ascertainment was limited ~~relative to population-based public health programs~~to data obtained from reporting health care providers; infants were not examined directly as part of the registry
- Data on infant outcomes were only collected for up to 4 months, reducing the ability of the registry to measure developmental progress, defects diagnosed beyond 4 months of age, and resolution of suspected defects reported in early infancy

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating and neurodegenerative disorder that affects over 400,000 people in the United States.[1,2] MS is much more common in women than men, and diagnosis frequently occurs when patients are in their 20s and 30s.[3,4] Consequently, women of child-bearing age constitute a considerable portion of all patients with MS. Furthermore, up to 10% have disease onset during pregnancy.[1]

The approved disease-modifying treatments (DMTs) for patients with MS have been given pregnancy category ratings of B, C, D, or X by the US Food and Drug Administration based on clinical experience and/or preclinical data (see Table 1 for pregnancy categorizations of currently-approved DMTs and a definition of different pregnancy classifications).[5-14] The safety of these agents during pregnancy is a major concern given the patient profile outlined above. However, data on pregnancy outcomes in DMT-exposed patients is limited. Among the beta interferons, this is particularly true for interferon beta-1b (Betaseron®/Betaferon®; Bayer HealthCare Pharmaceuticals; Whippany, NJ).

Table 1. Pregnancy classifications of disease modifying treatments (DMTs) approved for use by patients with MS.

Disease-modifying therapy	Pregnancy category
Glatiramer acetate (Copaxone®)[9]	B
Interferon beta-1b (Betaseron®/Betaferon®; Extavia®)[5,14]	C
Intramuscular interferon beta-1a (Avonex®)[7]	C
Subcutaneous interferon beta-1a (Rebif®)[11]	C

Fingolimod (Gilenya®)[8]	C
Dimethyl fumarate (Tecfidera®)[13]	C
Natalizumab (Tysabri®)[6]	C
Mitoxantrone[6,10]	D
Teriflunomide (Aubagio®)[6,10,12]	X

FDA pregnancy categories[15]

- Category A: No evidence of adverse effects in studies of pregnant humans
- Category B: No studies from humans, but no evidence of adverse effects in studies of pregnant animals; or negative effects observed in animal models but no evidence of adverse effects in humans
- Category C: Insufficient evidence from human studies, but research with pregnant animals identified some medication-related negative outcomes; in some situations, the medication may be more beneficial than harmful
- Category D: Medication-related negative outcomes in human studies but medication may be needed in some situations
- Category X: Medication-related negative outcomes in human or animal studies; there are no situations in which the medicine should be used

No teratogenic effects were seen in studies of pregnant rhesus monkeys exposed to interferon beta-1b. However, dose-related abortifacient activity was seen at doses from 0.028 mg/kg/d to 0.42 mg/kg/d, which is 2.8 to 4.0 times the recommended human dose based on surface area comparison.[5] Although data on human exposure during pregnancy are limited, patients are advised to discontinue treatment with interferon beta-1b if they become pregnant or plan to become pregnant.[5] The goal of the Betaseron Pregnancy Registry was to compare pregnancy outcomes in women

exposed to interferon beta-1b at conception or during pregnancy relative to general population comparators. This is the largest observational study reported to date for interferon beta-1b.

METHODS

Population and outcome measures

The Betaseron Pregnancy Registry was a voluntary, prospective, observational, exposure-registration and follow-up study. Women with an existing pregnancy who had been exposed to interferon beta-1b at any time after the first day of the last menstrual period (LMP), or during pregnancy but before any prenatal screening (eg, ultrasound, amniocentesis), were prospectively enrolled in the registry. Women with similar exposure who had undergone some prenatal testing and were without abnormal findings suggestive of fetal abnormalities were also enrolled. Given the widespread use of early prenatal testing, restricting enrollment to women without prenatal testing would have dramatically reduced the available population, hindering the success of the registry.[16,17] Because retrospective cases (ie, pregnancies submitted after the birth of the infant or after evidence suggestive of an abnormality on prenatal tests) can be biased toward reporting of unusual or severe outcomes, these cases and those in which an abnormality was identified prior to registry contact were excluded.

The primary outcome measure was the ~~prevalence~~ rate of major congenital malformations in infants exposed to interferon beta-1b during gestation, defined as any time after the first day of the mother's LMP. Secondary outcome measures included the

prevalence of spontaneous abortion and other negative pregnancy outcomes in exposed women. Prevalence of elective abortion, stillbirth, ectopic pregnancy, neonatal death, and maternal death was assessed. Reporting was conducted by health care providers (HCPs), patients, or representatives of the study sponsor. Maternal follow-up lasted from enrollment through pregnancy outcome. Infant follow-up continued through the 4-month pediatric visit in most cases.

Pregnancy outcomes were classified as live birth, spontaneous abortion, elective abortion, or fetal death/stillbirth. A live birth was defined as any delivery resulting in a viable neonate ≥24 weeks of gestation. The spontaneous loss of a fetus at <20 weeks of gestation was classified as a spontaneous abortion. Any fetus delivered dead ≥20 weeks of gestation, or weighing ≥500 g regardless of gestational age, was classified as a stillbirth. Fetal death occurring >20 weeks but <28 weeks was classified as early fetal loss while death occurring ≥28 weeks was considered late fetal loss. Elective abortions encompassed any induced or voluntary ending of the pregnancy. Other pregnancy outcomes included ectopic pregnancies, maternal death, and neonatal death. Infant size was classified as “small,” “appropriate,” or “large” for gestational age based on HCP assessment.

Birth defects were defined as any significant structural or chromosomal defect diagnosed with signs/symptoms using the Metropolitan Atlanta Congenital Defects Program (MACDP) classification of birth defects, or any case with 2 or more secondary or “conditional” abnormalities that would not have been classified as primary birth defects by MACDP. Conditional abnormalities, some of which were also referred to as “minor birth defects”, were included if present in a cluster of 2 or more to increase the

sensitivity of monitoring and to avoid missing a potential signal. Birth defects were coded using ~~a version of the coding system of the British Pediatric Association (BPA) in which the BPA code list was modified~~an organ system classification to increase the possibility of detecting a potential signal by grouping together similar defects or defects with similar etiology ~~together~~.[18] All ~~codes were sorted into the appropriate organ system classes~~ cases were coded in accordance with both the MACDP code book and the organ system classification by an expert in dysmorphology (AES) who evaluated the potential temporal relationship ~~with~~between the exposure to interferon beta-1b and the etiology of the defect, considering other potential confounders (eg, exposure to other therapies received during the pregnancy, maternal or paternal history of defects, underlying disease).[18] Further follow-up for birth defect cases was conducted if additional information was needed by the dysmorphologist or the data safety monitoring board (DSMB). Defects were classified as "Defect with a known cause, temporality may be irrelevant;" "No temporal association;" or "Unable to assess temporality." Available data for each defect case were reviewed individually for potential confounders and relevant information was evaluated and recorded.

Conduct of the registry was overseen by an independent DSMB~~review board~~. The Western Institutional Review Board (WIRB) reviewed and approved the protocol, which included a waiver of documentation of informed consent. The Betaseron Pregnancy Registry was listed in the public trials registry (www.clinicaltrials.gov) under NCT00317564.

Statistical procedures

Analyses were conducted on all prospective evaluable cases (ie, enrolled pregnancies, not lost to follow-up, with known outcome and birth defect status). ~~Prevalence of~~The birth defect rate~~s~~ was calculated by dividing the number of cases with birth defects among all live births and fetal losses >20 weeks gestation (numerator) by ~~using~~ the number of live births (~~as the~~ denominator). This approach increased the sensitivity of monitoring and may have overestimated the true rate; however it erred on the side of caution. Since the presence or absence of birth defects is difficult to ascertain among fetal losses, including fetal losses in the denominator would have biased the birth defect rate downwards. ~~and 95%~~Ninety-five percent exact confidence intervals (CI) were calculated for birth defect rate and other point estimates. Outcome data were stratified by the earliest trimester of exposure to interferon beta-1b.

Population-based external ~~C~~comparator ~~populations~~ groups were used ~~for 2 outcomes~~to evaluate the rates of spontaneous abortion and birth defects in the registry. Risk of ~~negative~~ spontaneous abortions was compared with estimates for the general population of the United States from the National Survey of Family Growth (NSFG), which was conducted by the National Center for Health Statistics,[19] using Fisher's exact test based on binomial distribution for exposures. Risk ~~for~~ of birth defects was compared with that reported by the MACDP.[20,21] This population-based birth defect surveillance system includes all infants born in the metropolitan area of Atlanta, Georgia. From 1999 to 2003, the MACDP estimated the population birth defect ~~prevalence~~ rate to be 2.78 birth defects per 100 live births in its database.[20,21]

When the Registry was designed and launched, it aimed to enroll approximately 420 pregnant women to reach the goal of 210 live births to evaluate the primary endpoint

(risk of birth defects). This sample size was estimated to be sufficient to rule out a 2.2-fold increase in birth defects compared to the MACDP rate of 2.78[20,21] with 80% power (assuming a 5% level of significance). The sample size goal of 420 pregnancies was expected to result in only 210 live births because of losses to follow up, enrollment failures, and a live birth rate of 62%.[17]. After approximately 5 years of operation, Registry enrollment resulted in only 99 live births.

Role of the funding source

The study was jointly designed by members of the ~~data safety monitoring board~~ DSMB and the study sponsor. The authors, which included both the DSMB and representatives of the sponsor, had access to all the data, participated in analysis and interpretation, and were members of the publication committee. The decision to submit the article for publication was made jointly by the members of the steering committee and the sponsor.

RESULTS

Patient disposition

Between April 24, 2006 and July 31, 2011, 99 pregnant women were prospectively enrolled in the Betaseron Pregnancy Registry. Follow-up of pregnant women and their live-born infants continued through July 16, 2012. Pregnancy outcomes were reported for 96 exposed pregnancies, with 3 pregnancies lost to follow-up (Table 2). Initial exposure to interferon beta-1b occurred in the first trimester for 95 patients, and in the

third trimester for 1 patient. Seventy-four patients had pediatric follow up. For the remaining 22 patients, follow-up continued only until birth. Prenatal testing prior to enrollment was reported in 33 cases (34.4%).

Table 2. Maternal demographics.

	Analysis population (N=96)
Age at enrollment (years)	
n	95[a]
Mean (SD)	30.9 (5.29)
Median (range)	31.0 (19-44)
Age category, n (%)	
≤19 years	1 (1.0)
20-34 years	69 (71.9)
≥35 years	25 (26.0)
Missing	1 (1.0)
Race/ethnicity, n (%)	
White	62 (64.6)
Black	25 (26.0)
Hispanic	2 (2.1)
Asian	0 (0)
Other	6 (6.3)
Missing	1 (1.0)
MS duration at enrollment, n (%)	
<1 year	23 (24.0)
1-5 years	51 (53.1)
6-10 years	11 (11.5)
>10 years	6 (6.3)

Missing	5 (5.2)
Earliest trimester of exposure,[a] [b] n (%)	
First	95 (99.0)
Second	0 (0)
Third	1 (1.0)
Prenatal tests, n (%)	
Prenatal test(s) after enrollment	53 (55.2)
Prenatal test(s) prior to enrollment	33 (34.4)
Date of prenatal test(s) not provided	1 (1.0)
No prenatal tests	7 (7.3)
Missing/unknown	2 (2.1)

[a] Age data were missing for 1 case.

[b] First trimester exposure was initial exposure occurring from the first day of the LMP through 13 weeks gestation; third trimester exposure was initial exposure occurring in the 28th week through the end of the pregnancy.

The majority of the sample was white (62 patients [64.6%]); 25 patients (26.0%) were black. In addition, 2 patients (2.1%) were Hispanic while 6 patients were of other races/ethnicities (6.3%) and race/ethnicity data were missing for 1 patient (1.0%). Note that the distribution of race/ethnicity in the Betaseron Pregnancy Registry was different from population norms in the United States (72.4% white, 12.6% black, 16.3% Hispanic).[22]

Pregnancy outcomes

From the 96 evaluable pregnancies, t~~T~~here was a total of 99 birth outcomes available, including 3 sets of twins. These outcomes included 86 live births, 2 stillbirths, and 11 spontaneous abortions (Table 3). Both stillbirths occurred in black women with a history

of prior spontaneous abortion and other comorbidities that may have affected birth outcomes. The first case, ending in stillbirth, reported hypertension, obesity (post gastric bypass), and oligohydramnios. The second reported antiphospholipid antibody syndrome, maternal human papillomavirus infection, early rupture of membranes attributed to vaginal bacterial infection, and preterm labor and delivery attributed to incompetent cervix. The prevalence of spontaneous abortion in the Betaseron Pregnancy Registry (11.5% [95% CI 5.9–19.6]) was not significantly different from the 16% estimate for the general population of the United States based on NSFG data (relative risk 0.7 [95% CI 0.4–1.2], P=.86, Fisher's exact test based on binomial distribution for exposures).

Table 3. Pregnancy outcomes in the Betaseron Pregnancy Registry.

Outcomes, n (%, 95% CI)	**Interferon beta-1b–exposed pregnancies**	**Relative risk (RR) (95% CI)**
Live births (N=96)	83 (86.4%)	-
Birth defects (N=86)[a]	5 (5.8%, 1.9–13.0)	RR (95% CI) 2.1 (0.9-4.9), P=0.092[b]
Spontaneous abortions (N=96)	11 (11.5%, 5.9–19.6)	RR (95% CI) 0.7 (0.4–1.2) P=0.8603[c]
Stillbirth (N=96)	2 (2.1)	-
Maternal deaths	0 (0)	-
Infant deaths	0 (0)	-
Ectopic pregnancies	0 (0)	-

[a] Excludes spontaneous and elective abortions <20 weeks gestation with reported birth defects per MACDP convention. The denominator is restricted to live births.

[b] Relative risk compared with 2.78% reported by MACDP; Fisher's exact test based on binomial distribution for exposures.[20,21]

[c] Relative risk compared with 16.0% rate of SAB reported by NSFG; Fisher's exact test.[23]

Infant assessments were made at birth for 86 babies, up to 3 months of age for 74 babies, and at 4 months for 59 babies (Table 4). HCPs assessed infant size as appropriate for gestational age at birth for 67 cases (77.9%). Four-month follow-up did not identify any consistent pattern of developmental abnormalities. Birth defects were identified in 5 cases (Table 5), resulting in a relative risk of 2.1 (95% CI 0.9–4.9). The reported birth defects occurred in several different organ systems, including the musculoskeletal, cardiovascular, and circulatory systems, with no pattern to the organ systems affected. For all cases reporting birth defects, the earliest exposure to interferon beta-1b 250 micrograms dosed every other day occurred during the first trimester of gestation. No birth defects were reported among the spontaneous pregnancy losses or stillbirths. The birth defect ~~prevalence~~ rate estimated by the Betaseron Pregnancy Registry (5.8% [95% CI 1.9–13.0]) was not significantly different ~~(note the overlapping confidence intervals in data from the Betaseron Pregnancy Registry)~~ from that reported by MACDP (2.78%, *P*=.092, Fisher's exact test). The relatively wide confidence intervals, which include the MACDP rate, reflect the small sample size and suggest no difference between the birth defect rate from the Betaseron Pregnancy Registry and the MACPD.

Table 4. Infant assessments at birth and at 4 months.

	At birth	At 4-month	Approximate

		follow-up	median in US population at birth[24]
Number of infants	86	59	
Sex, n (%)			
Female	40 (46.5)	26 (44.1)	
Male	46 (53.5)	33 (55.9)	
Infant weight, g			
Median	3346.8	6747.0	3200-3600
Range	470.0-4593.0	4763.0-8902.0	
Infant size, n (%)[a]			
Small	7 (8.1)	3 (5.1)	
Appropriate	67 (77.9)	48 (81.4)	
Large	7 (8.1)	6 (10.2)	
Missing	5 (5.8)	2 (3.4)	
Infant length (cm)			
Median	50.8	63.5	49-50
Range	30.5-55.9	53.3-69.3	
Infant head circumference (cm)			
Median	34.3	41.9	34.8-35.8
Range	29.5-38.1	37.0-44.5	
Gestational age at birth (weeks)			
Median	39.0	NA	
Range	24.0-41.0	NA	

[a] Infant size relative to gestational age at birth and age at 4 months (±4 weeks), respectively.

Table 5. Summary of birth defect cases

Case	Description of the reported birth defects[a]	Organ system	Temporality assessment
1	Live infant, male, 34 weeks gestation 1. Trisomy 21 (Down syndrome)[ab]	1. Chromosome anomaly	1. Defect with known cause, temporality may be irrelevant
2	Live infant, male, 40 weeks gestation 1. Hemangioma (capillary hemangioma parietal area and left 3rd toe)	1. Circulatory system	1. Unable to assess temporality
3	Live infant, female, 39 weeks gestation 1. Hip dysplasia (defect) 2. Patent foramen ovale (conditional defect) 3. Patent ductus arteriosus (conditional defect) 4. Ventriculoseptal defect (defect)	1. Other musculoskeletal defects 2. Heart 3. Circulatory system 4. Heart	1. Unable to assess temporality 2. Defect with known cause, temporality may be irrelevant 3. Defect with known cause, temporality may be irrelevant 4. Defect with known cause, temporality may be irrelevant
4	Live infant, male, 36 weeks gestation 1. Abnormal shape of the head without craniosynostosis	1. Musculoskeletal defects	1. No temporal association
5	Live infant, male, 38 weeks gestation 1. Polydactyly	1. Limb reduction/ addition defects	1. No temporal association

[a] Gestational age data are birth ages, not age at exposure.

[b] The mother of this infant was older than 35 years of age.

Because of the relatively high percentage of black patients in the Betaseron Pregnancy Registry, a subanalysis of pregnancy outcome data was conducted to compare black and non-black patients. No significant differences were seen between these two populations in ~~prevalence~~ the rates of birth defects or rates of spontaneous abortion. However, small sample sizes in this subanalysis limit the conclusions that can be drawn from these data.

DISCUSSION

This Betaseron Pregnancy Registry reported 99 outcomes in 96 evaluable pregnancies (including 3 twin pregnancies), consisting of 86 live births, 2 stillbirths, and 11 spontaneous abortions. There were 5 cases with birth defects. Among these 5 cases were a variety of birth defects which were not clustered around a single type of defect or effected organ system. In addition, 2 of these cases had defects that were not temporally related to interferon beta-1b exposure (ie, the timing of the exposure was not consistent with the development of the defect) and 1 had a chromosomal abnormality potentially related to advanced maternal age that was classified as having no temporal association to exposure. This lack of a consistent pattern suggests that there was no signal for birth defects due to interferon beta-1b exposure. The risk of spontaneous abortion or birth defect was not significantly different from comparator populations. In addition, no elective abortions or maternal deaths were observed and there were no abnormalities in rate of prematurity or in birth weight/size. These data represent the largest cohort of interferon beta-1b-exposed patients reported to date; however, the

sample size was still smaller than necessary to have sufficient statistical power to draw definitive conclusions.

To date, several publications have discussed the results of exposure to interferon beta formulations during pregnancy; however none have exclusively examined interferon beta-1b exposure. A recent review of this literature suggested that beta interferons may be associated with some negative outcomes,[25] a conclusion that contrasts with the findings presented here. Three studies, also with small sample sizes, (N=88, N=69, and N=23) found low birth weight in infants exposed to interferon beta formulations (either interferon beta-1a or beta-1b) during gestation.[26-28] Another study (N=14) found evidence of prematurity with interferon beta exposure, but birth weight was not significantly lower than unexposed comparators.[29] However, another study (N=63) did not find evidence of low birth weight following interferon beta exposure.[30] Other negative pregnancy outcomes, including a higher rate of spontaneous abortion and shorter mean birth length, have also been associated with exposure to interferon beta formulations.[26,27]

In contrast, the Betaseron Pregnancy Registry did not find any patterns to suggest negative pregnancy outcomes associated with interferon beta-1b exposure. It should be noted that the 5 aforementioned studies combined subjects exposed to either interferon beta-1a or beta-1b into a single group.[26-30] Two of these studies did not provide separate numbers of interferon beta-1a and beta-1b-exposed patients.[26,28] In the 3 studies that divided exposure groups into interferon beta-1a and beta-1b, patients with interferon beta-1b monotherapy exposure numbered only 10–21[27,29,30], thereby limiting the statistical power to draw conclusions about the effects of interferon beta-1b on

pregnancy outcomes. The Betaseron Pregnancy Registry data reported here have the advantage of a much larger sample size (99 outcomes), albeit much lower than planned when the registry was designed.

The Betaseron Pregnancy Registry included pediatric follow-up, which has not been not consistently reported in other studies: only 2 other studies have assessed pediatric outcomes.[26,29] The first (N=14) reported normal development of interferon beta-1a- or beta-1b-exposed infants up to the 12-month milestones (walking and talking).[29] A later study (N=88) found no developmental abnormalities in interferon beta-exposed infants after 2.1 years of follow-up.[26] The Betaseron Pregnancy Registry's findings are consistent with these previous reports and reinforce the hypothesis that there are no obvious postnatal effects from in utero interferon beta-1b exposure.

The potential risks associated with interferon beta-1b exposure during pregnancy, which were not found to be significantly different from comparator cohorts in this study, need to be considered along with the risks for patients with MS who remain untreated during pregnancy. Prior research suggested that MS itself was not associated with increased risk for negative pregnancy outcomes.[1] However, risk for relapses is higher after delivery, with 20%–40% of patients experiencing a clinical relapse or worsening of the disease in the first 3 months postpartum.[1]

The results reported here are similar to 2 recent presentations related to intramuscular interferon beta-1a exposure during pregnancy. In the first, no pattern suggestive of increased negative outcomes was found in 306 pregnancies in the Avonex Pregnancy Exposure Registry.[31] Similarly, post marketing surveillance (N=552) found the rate of

spontaneous abortion was consistent with the general population, with no evidence of increased ~~rates of~~ birth defect ~~s~~rates.[32] Together with the Betaseron Pregnancy Registry, the preponderance of data suggest no pattern of increased negative outcomes for women and infants exposed to interferon beta formulations during pregnancy, a finding that was supported by a recent review of the literature related to interferon beta exposure during pregnancy (N=1105).[33]

This is also the first study to report on pregnancy exposure outcomes in black patients with MS. No differences were noted based on race.

Limitations of the Betaseron Pregnancy Registry include the potential for underreporting or differential reporting of outcomes due to the exclusion of retrospective patients. However, it is important to note that data from these retrospective patients were captured through post-marketing surveillance efforts. In addition, birth defect ascertainment was limited to voluntary reports from health care providers (not unlike ~~relative to~~ population-based public health surveillance programs), which potentially limited the level of detail needed to fully characterize a birth defect case and rule out missed or misdiagnoses. Lastly, data on infant outcomes were only collected for up to 4 months, reducing the ability of the registry to measure developmental progress.

Due to ~~restricted~~ low sample size, definitive conclusions cannot be drawn from the Betaseron Pregnancy Registry data. However, there was no pattern to suggest an increased risk of birth defects in infants or an increased rate of spontaneous abortions ~~and preterm delivery~~ in women after exposure to interferon beta-1b during pregnancy. Infant assessments, such as ~~B~~birth weight, birth length, and head circumference, also

did not differ from population estimates and the 4 month infant follow-up did not identify any developmental concerns. Continued monitoring through routine post-marketing surveillance activities is recommended.

ACKNOWLEDGMENTS

We are grateful to the patients and their healthcare providers for their contributions to the study. Additionally, we thank Robert C. Ristuccia, PhD (Precept Medical Communications), for assistance with preparation of the manuscript (funded by Bayer HealthCare Pharmaceuticals).

COMPETING INTERESTS

- PK Coyle has received compensation for consulting/educational activities from Aconda, Accordant, Bayer, Biogen Idec, Genentech/Roche, Genzyme/Sanofi Aventis, Merck-Serono, Mylan, Novartis, and Teva Neurosciences. She has received research funding from Actelion, Novartis, and Opexa.
- S Sinclair Roberts has received compensation for consulting activities from Bayer, Lilly, and INC Research.
- AE Scheuerle has received compensation for consulting activities from Abbott, Amylin, Bayer, Biogen Idec, INC Research, Genentech, Novartis, PPD, TAP Pharma, Roche, Teva, and UCB Pharma.
- JM Thorp has received compensation for consulting from Bayer, GlaxoSmithKline, and PPD.

- JD Albano is an employee of INC Research, the coordinating center for the Betaseron Pregnancy Registry.
- MJ Rametta is a salaried employee of Bayer HealthCare.

AUTHOR CONTRIBUTIONS

- PK Coyle: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- SM Sinclair ~~Roberts~~: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- AE Scheuerle: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- JM Thorp: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- J Albano: Provided oversight for the conduct of the study, including the statistical analysis, interpreted data, and actively contributed to the writing and reviewing of the manuscript
- MJ Rametta: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Sponsor's responsible clinician for registry

This study was funded by Bayer HealthCare Pharmaceuticals, Inc.

References

1. Bennett KA. Pregnancy and multiple sclerosis. *Clin Obstet Gynecol.* 2005;48(1):38-47.

2. Vlahiotis A, Sedjo R, Cox ER, Burroughs TE, Rauchway A, Lich R. Gender differences in self-reported symptom awareness and perceived ability to manage therapy with disease-modifying medication among commercially insured multiple sclerosis patients. *J Manag Care Pharm.* 2010;16(3):206-216.

3. Compston A, Coles A. Multiple sclerosis. *Lancet.* 2002;359(9313):1221-1231.

4. Coyle PK, Christie S, Fodor P, et al. Multiple sclerosis gender issues: clinical practices of women neurologists. *Mult Scler.* 2004;10(5):582-588.

5. Betaseron [package insert]. Montville, NJ: Bayer HealthCare Pharmaceuticals; 2010.

6. Tysabri [package insert]. Cambridge, MA: Biogen Idec Inc; 2012.

7. Avonex [package insert]. Cambridge, MA: Biogen Idec Inc; 2012.

8. Gilenya [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.

9. Copaxone [package insert]. Kansas City, MO: TEVA Neuroscience; 2012.

10. Mitoxantrone [package insert]. Kansas City, MO: TEVA Neurosciences; 2012.

11. Rebif [package insert]. Rockland, MA: EMD Serono; 2012.

12. Aubagio [package insert]. Cambridge, MA: Genzyme Corporation; 2012.

13. Tecfidera [package insert]. Cambridge, MA: Biogen Idec Inc; 2013.

14. Extavia [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.

15. US Department of Health and Human Services OoWH. Pregnancy and Medicines. Available at http://www.womenshealth.gov/publications/our-publications/fact-sheet/pregnancy-medicines.pdf. Accessed December 21, 2012.

16. Covington D, Roberts S, McKain L. Impact of prenatal testing on birth defect prevalence in pregnancy exposure registries. *Pharmacoepidemiol Drug Saf.* 2008;17(Supplement 1):S13.

17. US Food and Drug Administration. Guidance for industry establishing pregnancy exposure registries. Available at http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133332.pdf. Accessed February 2014.

18. Scheuerle A, Tilson H. Birth defect classification by organ system: a novel approach to heighten teratogenic signalling in a pregnancy registry. *Pharmacoepidemiol Drug Saf.* 2002;11(6):465-475.

19. Jones RK, Kost K. Underreporting of induced and spontaneous abortion in the United States: an analysis of the 2002 National Survey of Family Growth. *Stud Fam Plann.* 2007;38(3):187-197.

20. Correa A, Cragan J, Kucik J. Metropolitan Atlanta Congenital Defects Program 40th anniversary edition surveillance report: reporting birth defects surveillance data. *Birth Defects Research (Part A).* 2007;79:65-93.

21. Correa A, Cragan J, Kucik J, et al. Errata. *Birth Defects Research (Part A).* 2008;82(1):41-62.

22. U.S.Census Bureau. Overview of race and Hispanic origin: 2010. http://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf. Accessed April 2013.

23. Jones CA, Pohar SL, Warren S, Turpin KV, Warren KG. The burden of multiple sclerosis: a community health survey. *Health Qual Life Outcomes.* 2008;6:1.

24. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data.* 2000;(314):1-27.

25. Lu E, Wang BW, Guimond C, Synnes A, Sadovnick D, Tremlett H. Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review. *Neurology.* 2012;79(11):1130-1135.

26. Amato MP, Portaccio E, Ghezzi A, et al. Pregnancy and fetal outcomes after interferon-beta exposure in multiple sclerosis. *Neurology.* 2010;75(20):1794-1802.

27. Boskovic R, Wide R, Wolpin J, Bauer DJ, Koren G. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology.* 2005;65(6):807-811.

28. Weber-Schoendorfer C, Schaefer C. Multiple sclerosis, immunomodulators, and pregnancy outcome: a prospective observational study. *Mult Scler.* 2009;15(9):1037-1042.

29. Patti F, Cavallaro T, Lo FS, et al. Is in utero early-exposure to interferon beta a risk factor for pregnancy outcomes in multiple sclerosis? *J Neurol.* 2008;255(8):1250-1253.

30. Hellwig K, Haghikia A, Rockhoff M, Gold R. Multiple sclerosis and pregnancy: experience from a nationwide database in Germany. *Ther Adv Neurol Disord.* 2012;5(5):247-253.

31. Tomczyk S, Richman S, Wallace K, Liu S, Sperling B. Final results from the AVONEX (intramuscular-beta-1a) pregnancy exposure registry. Presented at the Annual Meeting of the European Society for Research and Treatment in Multiple Sclerosis. Lyon, France. October 10-13. 2012.

32. Tomczyk S, Sperling B. Post-marketing pregnancy outcomes in patients exposed to intramuscular-interferon-beta-1a. Presented at the Annual Meeting of the European Committee for Treatment and Research in Multiple Sclerosis. Lyon, France. October 10-13. 2012.

33. Hughes S, Spelman T, Gray O, et al. Exposure to interferon-beta therapy in early pregnancy: a literature review of pregnancy outcomes in women with multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2012;83:Supple 2 A17.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Title includes the word "registry."
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found - complete
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Paragraph 1 on page 4
Objectives	3	State specific objectives, including any prespecified hypotheses Paragraph on page 5
Methods		
Study design	4	Present key elements of study design early in the paper Pages 6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Paragraph 2 on page 6; paragraph 1 on page 9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Paragraph 2-3, page 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Paragraph 2, page 6; paragraph 1-2 on page 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Paragraph 2, page 6
Bias	9	Describe any efforts to address potential sources of bias Paragraph 3, page 7
Study size	10	Explain how the study size was arrived at Paragraph 2, page 9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Paragraph 2, page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Paragraph 2, page 8
		(*b*) Describe any methods used to examine subgroups and interactions Paragraph 2, page 8

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Paragraph 2, page 9
		(b) Give reasons for non-participation at each stage Paragraph 2, page 9
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Paragraph 2, page 9; paragraph 1 page 10; Table 2
		(b) Indicate number of participants with missing data for each variable of interest Paragraph 2, page 9; Table 2
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time Pages 11-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - NA
		(*b*) Report category boundaries when continuous variables were categorized - NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period - NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Paragraph 1, page 16
Discussion		
Key results	18	Summarise key results with reference to study objectives Paragraph 2, page 16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Paragraph 1, page 16; paragraph 1, page 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Paragraph 2, page 18
Generalisability	21	Discuss the generalisability (external validity) of the study results Paragraph 2, page 18
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Paragraph 1, page 8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Final results from the Betaseron® (interferon beta-1b) Pregnancy Registry: a prospective observational study of birth defects and pregnancy-related adverse events

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004536.R2
Article Type:	Research
Date Submitted by the Author:	04-Apr-2014
Complete List of Authors:	Coyle, Patricia; Stony Brook University and MS Comprehensive Care Center, Roberts, Susan; University of North Carolina Wilmington, Clinical Research Program Scheuerle, Angela; Tesserae Genetics, Medical Genetics Thorp, John; University of North Carolina Schools of Medicine and Public Health, Department of Obstetrics and Gynecology Albano, Jessica; INC Research LLC, Post Approval and Strategic Services Rametta, Mark; Bayer HealthCare Pharmaceuticals,
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology, Obstetrics and gynaecology, Pharmacology and therapeutics, Reproductive medicine
Keywords:	Multiple sclerosis < NEUROLOGY, interferon beta-1b, pediatrics, pregnancy, congenital abnormalities

Final results from the Betaseron® (interferon beta-1b) Pregnancy Registry: a prospective observational study of birth defects and pregnancy-related adverse events

Authors: PK Coyle, MD;[1] SM Sinclair, PhD, MPH, RN;[2] AE Scheuerle, MD;[3] JM Thorp Jr, MD;[4] JD Albano, PhD, MPH;[5] MJ Rametta, DO[6]

[1]Stony Brook University Department of Neurology and MS Comprehensive Care Center, Stony Brook, NY
[2]University of North Carolina Wilmington, Clinical Research Program, Wilmington, NC
[3]Tesserae Genetics, Medical Genetics, Dallas, TX
[4]University of North Carolina Schools of Medicine and Public Health, Department of Obstetrics and Gynecology, Chapel Hill, NC
[5]INC Research LLC, Post Approval and Strategic Services, Raleigh, NC
[6]Bayer HealthCare Pharmaceuticals, US Medical Affairs, Neurology, Whippany, NJ

Correspondence to:
Name: Patricia Coyle
Affiliation: Stony Brook University and MS Comprehensive Care Center
Address: HSC T12-020; SUNY at Stony Brook, Stony Brook, NY 11794-8121
Telephone number: 631-444-8188
Fax number: 631-444-1474
Email address: patricia.coyle@stonybrookmedicine.edu

Search terms: multiple sclerosis, interferon beta-1b, pediatrics, pregnancy, congenital abnormalities

Word count: 2,784 words

ABSTRACT

Objectives: Women with multiple sclerosis are often diagnosed and treated during their reproductive years. Limited data are available on the safety of treatment during pregnancy. The Betaseron® Pregnancy Registry prospectively monitored women exposed to interferon beta-1b (IFNB-1b) during pregnancy to estimate the rates of birth defects, spontaneous abortions (SABs), and other negative outcomes in this population.

Design: From 2006-2011, this observational registry enrolled women exposed prior to conception or during pregnancy (but prior to or without abnormalities on prenatal screening). Follow-up continued from enrollment through the 4-month pediatric visit.

Setting: Patients in the United States who met these criteria were enrolled in the registry.

Results: The registry enrolled 99 pregnant women; 3 were lost to follow up. The earliest exposure to IFNB-1b occurred during the first trimester for 95 pregnancies and the third trimester for 1 pregnancy. There were 99 birth outcomes (3 twins), including 86 (86.9%) live births, 11 (11.1%) SABs, and 2 (2.0%) stillbirths. Birth defects were reported in 5 (5.1%) cases. Rates of birth defects and SAB were not significantly different from population comparators. No developmental concerns were identified at the 4 month pediatric visit.

Conclusions: The small sample size limits the ability to draw definitive conclusions; however, there was no pattern to suggest increased negative outcomes with IFNB-1b.

ARTICLE SUMMARY

Strengths and limitations of this study

- The Betaseron Pregnancy Registry contains the largest sample of interferon beta-1b-exposed pregnancies collected to date
- The relatively small sample size limits the ability to draw definitive conclusions; however, there was no pattern to suggest increased negative outcomes with interferon beta-1b
- Limitations of the Betaseron Pregnancy Registry include the potential for underreporting or differential reporting of outcomes due to the exclusion of retrospective patients and the voluntary nature of participation
- Birth defect ascertainment was limited to data obtained from reporting health care providers; infants were not examined directly as part of the registry
- Data on infant outcomes were only collected for up to 4 months, reducing the ability of the registry to measure developmental progress, defects diagnosed beyond 4 months of age, and resolution of suspected defects reported in early infancy

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating and neurodegenerative disorder that affects over 400,000 people in the United States.[1,2] MS is much more common in women than men, and diagnosis frequently occurs when patients are in their 20s and 30s.[3,4] Consequently, women of child-bearing age constitute a considerable portion of all patients with MS. Furthermore, up to 10% have disease onset during pregnancy.[1]

The approved disease-modifying treatments (DMTs) for patients with MS have been given pregnancy category ratings of B, C, D, or X by the US Food and Drug Administration based on clinical experience and/or preclinical data (see Table 1 for pregnancy categorizations of currently-approved DMTs and a definition of different pregnancy classifications).[5-14] The safety of these agents during pregnancy is a major concern given the patient profile outlined above. However, data on pregnancy outcomes in DMT-exposed patients is limited. Among the beta interferons, this is particularly true for interferon beta-1b (Betaseron®/Betaferon®; Bayer HealthCare Pharmaceuticals; Whippany, NJ).

Table 1. Pregnancy classifications of disease modifying treatments (DMTs) approved for use by patients with MS.

Disease-modifying therapy	Pregnancy category
Glatiramer acetate (Copaxone®)[9]	B
Interferon beta-1b (Betaseron®/Betaferon®; Extavia®)[5,14]	C
Intramuscular interferon beta-1a (Avonex®)[7]	C

Subcutaneous interferon beta-1a (Rebif®)[11]	C
Fingolimod (Gilenya®)[8]	C
Dimethyl fumarate (Tecfidera®)[13]	C
Natalizumab (Tysabri®)[6]	C
Mitoxantrone[6,10]	D
Teriflunomide (Aubagio®)[6,10,12]	X

FDA pregnancy categories[15]

- Category A: No evidence of adverse effects in studies of pregnant humans
- Category B: No studies from humans, but no evidence of adverse effects in studies of pregnant animals; or negative effects observed in animal models but no evidence of adverse effects in humans
- Category C: Insufficient evidence from human studies, but research with pregnant animals identified some medication-related negative outcomes; in some situations, the medication may be more beneficial than harmful
- Category D: Medication-related negative outcomes in human studies but medication may be needed in some situations
- Category X: Medication-related negative outcomes in human or animal studies; there are no situations in which the medicine should be used

No teratogenic effects were seen in studies of pregnant rhesus monkeys exposed to interferon beta-1b. However, dose-related abortifacient activity was seen at doses from 0.028 mg/kg/d to 0.42 mg/kg/d, which is 2.8 to 4.0 times the recommended human dose based on surface area comparison.[5] Although data on human exposure during pregnancy are limited, patients are advised to discontinue treatment with interferon beta-1b if they become pregnant or plan to become pregnant.[5] The goal of the

Betaseron Pregnancy Registry was to compare pregnancy outcomes in women exposed to interferon beta-1b at conception or during pregnancy relative to general population comparators. This is the largest observational study reported to date for interferon beta-1b.

METHODS

Population and outcome measures

The Betaseron Pregnancy Registry was a voluntary, prospective, observational, exposure-registration and follow-up study. Women with an existing pregnancy who had been exposed to interferon beta-1b at any time after the first day of the last menstrual period (LMP), or during pregnancy but before any prenatal screening (eg, ultrasound, amniocentesis), were prospectively enrolled in the registry. Women with similar exposure who had undergone some prenatal testing and were without abnormal findings suggestive of fetal abnormalities were also enrolled. Given the widespread use of early prenatal testing, restricting enrollment to women without prenatal testing would have dramatically reduced the available population, hindering the success of the registry.[16,17] Because retrospective cases (ie, pregnancies submitted after the birth of the infant or after evidence suggestive of an abnormality on prenatal tests) can be biased toward reporting of unusual or severe outcomes, these cases and those in which an abnormality was identified prior to registry contact were excluded.

The primary outcome measure was the rate of major congenital malformations in infants exposed to interferon beta-1b during gestation, defined as any time after the first day of

the mother's LMP. Secondary outcome measures included the prevalence of spontaneous abortion and other negative pregnancy outcomes in exposed women. Prevalence of elective abortion, stillbirth, ectopic pregnancy, neonatal death, and maternal death was assessed. Reporting was conducted by health care providers (HCPs), patients, or representatives of the study sponsor. Maternal follow-up lasted from enrollment through pregnancy outcome. Infant follow-up continued through the 4-month pediatric visit in most cases.

Pregnancy outcomes were classified as live birth, spontaneous abortion, elective abortion, or fetal death/stillbirth. A live birth was defined as any delivery resulting in a viable neonate ≥24 weeks of gestation. The spontaneous loss of a fetus at <20 weeks of gestation was classified as a spontaneous abortion. Any fetus delivered dead ≥20 weeks of gestation, or weighing ≥500 g regardless of gestational age, was classified as a stillbirth. Fetal death occurring >20 weeks but <28 weeks was classified as early fetal loss while death occurring ≥28 weeks was considered late fetal loss. Elective abortions encompassed any induced or voluntary ending of the pregnancy. Other pregnancy outcomes included ectopic pregnancies, maternal death, and neonatal death. Infant size was classified as "small," "appropriate," or "large" for gestational age based on HCP assessment.

Birth defects were defined as any significant structural or chromosomal defect diagnosed with signs/symptoms using the Metropolitan Atlanta Congenital Defects Program (MACDP) classification of birth defects, or any case with 2 or more secondary or "conditional" abnormalities that would not have been classified as primary birth defects by MACDP. Conditional abnormalities, some of which were also referred to as

"minor birth defects", were included if present in a cluster of 2 or more to increase the sensitivity of monitoring and to avoid missing a potential signal. Birth defects were coded using an organ system classification to increase the possibility of detecting a potential signal by grouping together similar defects or defects with similar etiology.[18] All cases were coded in accordance with both the MACDP code book and the organ system classification by an expert in dysmorphology (AES) who evaluated the potential temporal relationship between the exposure to interferon beta-1b and the etiology of the defect, considering other potential confounders (eg, exposure to other therapies received during the pregnancy, maternal or paternal history of defects, underlying disease).[18] Further follow-up for birth defect cases was conducted if additional information was needed by the dysmorphologist or the data safety monitoring board (DSMB). Defects were classified as "Defect with a known cause, temporality may be irrelevant;" "No temporal association;" or "Unable to assess temporality." Available data for each defect case were reviewed individually for potential confounders and relevant information was evaluated and recorded.

Conduct of the registry was overseen by an independent DSMB. The Western Institutional Review Board (WIRB) reviewed and approved the protocol, which included a waiver of documentation of informed consent. The Betaseron Pregnancy Registry was listed in the public trials registry (www.clinicaltrials.gov) under NCT00317564.

Statistical procedures

Analyses were conducted on all prospective evaluable cases (ie, enrolled pregnancies, not lost to follow-up, with known outcome and birth defect status). The birth defect rate

was calculated by dividing the number of cases with birth defects among all live births and fetal losses >20 weeks gestation (numerator) by the number of live births (denominator). This approach increased the sensitivity of monitoring and may have overestimated the true rate; however it erred on the side of caution. Since the presence or absence of birth defects is difficult to ascertain among fetal losses, including fetal losses in the denominator would have biased the birth defect rate downwards. Ninety-five percent exact confidence intervals (CI) were calculated for birth defect rate and other point estimates. Outcome data were stratified by the earliest trimester of exposure to interferon beta-1b.

Population-based external comparator groups were used to evaluate the rates of spontaneous abortion and birth defects in the registry. Risk of spontaneous abortions was compared with estimates for the general population of the United States from the National Survey of Family Growth (NSFG), which was conducted by the National Center for Health Statistics,[19] using Fisher's exact test based on binomial distribution for exposures. Risk of birth defects was compared with that reported by the MACDP.[20,21] This population-based birth defect surveillance system includes all infants born in the metropolitan area of Atlanta, Georgia. From 1999 to 2003, the MACDP estimated the population birth defect rate to be 2.78 birth defects per 100 live births in its database.[20,21]

When the Registry was designed and launched, it aimed to enroll approximately 420 pregnant women to reach the goal of 210 live births to evaluate the primary endpoint (risk of birth defects). This sample size was estimated to be sufficient to rule out a 2.2-fold increase in birth defects compared to the MACDP rate of 2.78[20,21] with 80% power

(assuming a 5% level of significance). The sample size goal of 420 pregnancies was expected to result in only 210 live births because of losses to follow up, enrollment failures, and a live birth rate of 62%.[17]. After approximately 5 years of operation, Registry enrollment resulted in only 99 live births.

Role of the funding source

The study was jointly designed by members of the DSMB and the study sponsor. The authors, which included both the DSMB and representatives of the sponsor, had access to all the data, participated in analysis and interpretation, and were members of the publication committee. The decision to submit the article for publication was made jointly by the members of the steering committee and the sponsor.

RESULTS

Patient disposition

Between April 24, 2006 and July 31, 2011, 99 pregnant women were prospectively enrolled in the Betaseron Pregnancy Registry. Follow-up of pregnant women and their live-born infants continued through July 16, 2012. Pregnancy outcomes were reported for 96 exposed pregnancies, with 3 pregnancies lost to follow-up (Table 2). Initial exposure to interferon beta-1b occurred in the first trimester for 95 patients, and in the third trimester for 1 patient. Seventy-four patients had pediatric follow up. For the remaining 22 patients, follow-up continued only until birth. Prenatal testing prior to enrollment was reported in 33 cases (34.4%).

Table 2. Maternal demographics.

	Analysis population (N=96)
Age at enrollment (years)	
n	95[a]
Mean (SD)	30.9 (5.29)
Median (range)	31.0 (19-44)
Age category, n (%)	
≤19 years	1 (1.0)
20-34 years	69 (71.9)
≥35 years	25 (26.0)
Missing	1 (1.0)
Race/ethnicity, n (%)	
White	62 (64.6)
Black	25 (26.0)
Hispanic	2 (2.1)
Asian	0 (0)
Other	6 (6.3)
Missing	1 (1.0)
MS duration at enrollment, n (%)	
<1 year	23 (24.0)
1-5 years	51 (53.1)
6-10 years	11 (11.5)
>10 years	6 (6.3)
Missing	5 (5.2)
Earliest trimester of exposure,[b] n (%)	
First	95 (99.0)
Second	0 (0)

Third	1 (1.0)
Prenatal tests, n (%)	
Prenatal test(s) after enrollment	53 (55.2)
Prenatal test(s) prior to enrollment	33 (34.4)
Date of prenatal test(s) not provided	1 (1.0)
No prenatal tests	7 (7.3)
Missing/unknown	2 (2.1)

[a] Age data were missing for 1 case.

[b] First trimester exposure was initial exposure occurring from the first day of the LMP through 13 weeks gestation; third trimester exposure was initial exposure occurring in the 28th week through the end of the pregnancy.

The majority of the sample was white (62 patients [64.6%]); 25 patients (26.0%) were black. In addition, 2 patients (2.1%) were Hispanic while 6 patients were of other races/ethnicities (6.3%) and race/ethnicity data were missing for 1 patient (1.0%). Note that the distribution of race/ethnicity in the Betaseron Pregnancy Registry was different from population norms in the United States (72.4% white, 12.6% black, 16.3% Hispanic).[22]

Pregnancy outcomes

From the 96 evaluable pregnancies, there was a total of 99 birth outcomes available, including 3 sets of twins. These outcomes included 86 live births, 2 stillbirths, and 11 spontaneous abortions (Table 3). Both stillbirths occurred in black women with a history of prior spontaneous abortion and other comorbidities that may have affected birth outcomes. The first case, ending in stillbirth, reported hypertension, obesity (post gastric bypass), and oligohydramnios. The second reported antiphospholipid antibody

syndrome, maternal human papillomavirus infection, early rupture of membranes attributed to vaginal bacterial infection, and preterm labor and delivery attributed to incompetent cervix. The prevalence of spontaneous abortion in the Betaseron Pregnancy Registry (11.5% [95% CI 5.9–19.6]) was not significantly different from the 16% estimate for the general population of the United States based on NSFG data (relative risk 0.7 [95% CI 0.4–1.2], P=.86, Fisher's exact test based on binomial distribution for exposures).

Table 3. Pregnancy outcomes in the Betaseron Pregnancy Registry.

Outcomes, n (%, 95% CI)	**Interferon beta-1b–exposed pregnancies**	**Relative risk (RR) (95% CI)**
Live births (N=96)	83 (86.4%)	-
Birth defects (N=86)[a]	5 (5.8%, 1.9–13.0)	RR (95% CI) 2.1 (0.9-4.9), P=0.092[b]
Spontaneous abortions (N=96)	11 (11.5%, 5.9–19.6)	RR (95% CI) 0.7 (0.4–1.2) P=0.8603[c]
Stillbirth (N=96)	2 (2.1)	-
Maternal deaths	0 (0)	-
Infant deaths	0 (0)	-
Ectopic pregnancies	0 (0)	-

[a] Excludes spontaneous and elective abortions <20 weeks gestation with reported birth defects per MACDP convention. The denominator is restricted to live births.

[b] Relative risk compared with 2.78% reported by MACDP; Fisher's exact test based on binomial distribution for exposures.[20,21]

[c] Relative risk compared with 16.0% rate of SAB reported by NSFG; Fisher's exact test.[23]

Infant assessments were made at birth for 86 babies, up to 3 months of age for 74 babies, and at 4 months for 59 babies (Table 4). HCPs assessed infant size as appropriate for gestational age at birth for 67 cases (77.9%). Four-month follow-up did not identify any consistent pattern of developmental abnormalities. Birth defects were identified in 5 cases (Table 5), resulting in a relative risk of 2.1 (95% CI 0.9–4.9). The reported birth defects occurred in several different organ systems, including the musculoskeletal, cardiovascular, and circulatory systems, with no pattern to the organ systems affected. For all cases reporting birth defects, the earliest exposure to interferon beta-1b 250 micrograms dosed every other day occurred during the first trimester of gestation. No birth defects were reported among the spontaneous pregnancy losses or stillbirths. The birth defect rate estimated by the Betaseron Pregnancy Registry (5.8% [95% CI 1.9–13.0]) was not significantly different from that reported by MACDP (2.78%, *P*=.092, Fisher's exact test). The relatively wide confidence intervals, which include the MACDP rate, reflect the small sample size and suggest no difference between the birth defect rate from the Betaseron Pregnancy Registry and the MACPD.

Table 4. Infant assessments at birth and at 4 months.

	At birth	**At 4-month follow-up**	**Approximate median in US population at birth[24]**
Number of infants	86	59	
Sex, n (%)			
Female	40 (46.5)	26 (44.1)	

Male	46 (53.5)	33 (55.9)	
Infant weight, g			
Median	3346.8	6747.0	3200-3600
Range	470.0-4593.0	4763.0-8902.0	
Infant size, n (%)[a]			
Small	7 (8.1)	3 (5.1)	
Appropriate	67 (77.9)	48 (81.4)	
Large	7 (8.1)	6 (10.2)	
Missing	5 (5.8)	2 (3.4)	
Infant length (cm)			
Median	50.8	63.5	49-50
Range	30.5-55.9	53.3-69.3	
Infant head circumference (cm)			
Median	34.3	41.9	34.8-35.8
Range	29.5-38.1	37.0-44.5	
Gestational age at birth (weeks)			
Median	39.0	NA	
Range	24.0-41.0	NA	
Gestational age at birth, n (%)[b,c]			
Preterm	8 (10.0)	NA	9.9%
Term	72 (90.0)	NA	

[a] Infant size relative to gestational age at birth and age at 4 months (±4 weeks), respectively.

[b] Gestational age at birth calculated as [(280-(corrected estimated due date – outcome date))/7]; estimated due date (EDD) was used when corrected EDD was not available. Preterm births were defined as any baby born before the end of the 36th gestational week and term births were defined as those born after ≥37 weeks, 0 days gestation.[25]

[c] Among singleton live births; excludes 3 twin pregnancies (6 live births) with outcomes at 24 weeks, 5 days; 36 weeks, 3 days; and 36 weeks, 5 days.

Table 5. Summary of birth defect cases

Case	Description of the reported birth defects[a]	Organ system	Temporality assessment
1	Live infant, male, 34 weeks gestation 1. Trisomy 21 (Down syndrome)[b]	1. Chromosome anomaly	1. Defect with known cause, temporality may be irrelevant
2	Live infant, male, 40 weeks gestation 1. Hemangioma (capillary hemangioma parietal area and left 3rd toe)	1. Circulatory system	1. Unable to assess temporality
3	Live infant, female, 39 weeks gestation 1. Hip dysplasia (defect) 2. Patent foramen ovale (conditional defect) 3. Patent ductus arteriosus (conditional defect) 4. Ventriculoseptal defect (defect)	1. Other musculoskeletal defects 2. Heart 3. Circulatory system 4. Heart	1. Unable to assess temporality 2. Defect with known cause, temporality may be irrelevant 3. Defect with known cause, temporality may be irrelevant 4. Defect with known cause, temporality may be irrelevant
4	Live infant, male, 36 weeks gestation 1. Abnormal shape of the head without craniosynostosis	1. Musculoskeletal defects	1. No temporal association
5	Live infant, male, 38 weeks gestation 1. Polydactyly	1. Limb reduction/ addition defects	1. No temporal association

[a] Gestational age data are birth ages, not age at exposure.

[b] The mother of this infant was older than 35 years of age.

Because of the relatively high percentage of black patients in the Betaseron Pregnancy Registry, a subanalysis of pregnancy outcome data was conducted to compare black and non-black patients. No significant differences were seen between these two populations in the rates of birth defects or rates of spontaneous abortion. However, small sample sizes in this subanalysis limit the conclusions that can be drawn from these data.

DISCUSSION

This Betaseron Pregnancy Registry reported 99 outcomes in 96 evaluable pregnancies (including 3 twin pregnancies), consisting of 86 live births, 2 stillbirths, and 11 spontaneous abortions. There were 5 cases with birth defects. Among these 5 cases were a variety of birth defects which were not clustered around a single type of defect or effected organ system. In addition, 2 of these cases had defects that were not temporally related to interferon beta-1b exposure (ie, the timing of the exposure was not consistent with the development of the defect) and 1 had a chromosomal abnormality potentially related to advanced maternal age that was classified as having no temporal association to exposure. This lack of a consistent pattern suggests that there was no signal for birth defects due to interferon beta-1b exposure. The risk of spontaneous abortion or birth defect was not significantly different from comparator populations. In addition, no elective abortions or maternal deaths were observed and there were no abnormalities in rate of prematurity or in birth weight/size. These data represent the largest cohort of interferon beta-1b-exposed patients reported to date; however, the

sample size was still smaller than necessary to have sufficient statistical power to draw definitive conclusions.

To date, several publications have discussed the results of exposure to interferon beta formulations during pregnancy; however none have exclusively examined interferon beta-1b exposure. A recent review of this literature suggested that beta interferons may be associated with some negative outcomes,[26] a conclusion that contrasts with the findings presented here. Three studies, also with small sample sizes, (N=88, N=69, and N=23) found low birth weight in infants exposed to interferon beta formulations (either interferon beta-1a or beta-1b) during gestation.[27-29] Another study (N=14) found evidence of prematurity with interferon beta exposure, but birth weight was not significantly lower than unexposed comparators.[30] However, another study (N=63) did not find evidence of low birth weight following interferon beta exposure.[31] Other negative pregnancy outcomes, including a higher rate of spontaneous abortion and shorter mean birth length, have also been associated with exposure to interferon beta formulations.[27,28]

In contrast, the Betaseron Pregnancy Registry did not find any patterns to suggest negative pregnancy outcomes associated with interferon beta-1b exposure. It should be noted that the 5 aforementioned studies combined subjects exposed to either interferon beta-1a or beta-1b into a single group.[27-31] Two of these studies did not provide separate numbers of interferon beta-1a and beta-1b-exposed patients.[27,29] In the 3 studies that divided exposure groups into interferon beta-1a and beta-1b, patients with interferon beta-1b monotherapy exposure numbered only 10–21[28,30,31], thereby limiting the statistical power to draw conclusions about the effects of interferon beta-1b on

pregnancy outcomes. The Betaseron Pregnancy Registry data reported here have the advantage of a much larger sample size (99 outcomes), albeit much lower than planned when the registry was designed.

The Betaseron Pregnancy Registry included pediatric follow-up, which has not been not consistently reported in other studies: only 2 other studies have assessed pediatric outcomes.[27,30] The first (N=14) reported normal development of interferon beta-1a- or beta-1b-exposed infants up to the 12-month milestones (walking and talking).[30] A later study (N=88) found no developmental abnormalities in interferon beta-exposed infants after 2.1 years of follow-up.[27] The Betaseron Pregnancy Registry's findings are consistent with these previous reports and reinforce the hypothesis that there are no obvious postnatal effects from in utero interferon beta-1b exposure.

The potential risks associated with interferon beta-1b exposure during pregnancy, which were not found to be significantly different from comparator cohorts in this study, need to be considered along with the risks for patients with MS who remain untreated during pregnancy. Prior research suggested that MS itself was not associated with increased risk for negative pregnancy outcomes.[1] However, risk for relapses is higher after delivery, with 20%–40% of patients experiencing a clinical relapse or worsening of the disease in the first 3 months postpartum.[1]

The results reported here are similar to 2 recent presentations related to intramuscular interferon beta-1a exposure during pregnancy. In the first, no pattern suggestive of increased negative outcomes was found in 306 pregnancies in the Avonex Pregnancy Exposure Registry.[32] Similarly, post marketing surveillance (N=552) found the rate of

spontaneous abortion was consistent with the general population, with no evidence of increased birth defect rates.[33] Together with the Betaseron Pregnancy Registry, the preponderance of data suggest no pattern of increased negative outcomes for women and infants exposed to interferon beta formulations during pregnancy, a finding that was supported by a recent review of the literature related to interferon beta exposure during pregnancy (N=1105).[34]

This is also the first study to report on pregnancy exposure outcomes in black patients with MS. No differences were noted based on race.

Limitations of the Betaseron Pregnancy Registry include the potential for underreporting or differential reporting of outcomes due to the exclusion of retrospective patients. However, it is important to note that data from these retrospective patients were captured through post-marketing surveillance efforts. In addition, birth defect ascertainment was limited to voluntary reports from health care providers (not unlike population-based public health surveillance programs), which potentially limited the level of detail needed to fully characterize a birth defect case and rule out missed or misdiagnoses. Lastly, data on infant outcomes were only collected for up to 4 months, reducing the ability of the registry to measure developmental progress.

Due to low sample size, definitive conclusions cannot be drawn from the Betaseron Pregnancy Registry data. However, there was no pattern to suggest an increased risk of birth defects in infants or an increased rate of spontaneous abortions in women after exposure to interferon beta-1b during pregnancy. Infant assessments, such as birth weight, birth length, and head circumference, also did not differ from population

estimates and the 4 month infant follow-up did not identify any developmental concerns. Continued monitoring through routine post-marketing surveillance activities is recommended.

ACKNOWLEDGMENTS

We are grateful to the patients and their healthcare providers for their contributions to the study. Additionally, we thank Robert C. Ristuccia, PhD (Precept Medical Communications), for assistance with preparation of the manuscript (funded by Bayer HealthCare Pharmaceuticals).

FUNDING

This study was funded by Bayer HealthCare Pharmaceuticals, Inc.

AUTHOR CONTRIBUTIONS

- PK Coyle: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- SM Sinclair: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- AE Scheuerle: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- JM Thorp: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- JD Albano: Provided oversight for the conduct of the study, including the statistical analysis, interpreted data, and actively contributed to the writing and reviewing of the manuscript
- MJ Rametta: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Sponsor's responsible clinician for registry

COMPETING INTERESTS

- PK Coyle has received compensation for consulting/educational activities from Aconda, Accordant, Bayer, Biogen Idec, Genentech/Roche, Genzyme/Sanofi Aventis, Merck-Serono, Mylan, Novartis, and Teva Neurosciences. She has received research funding from Actelion, Novartis, and Opexa.
- S Sinclair Roberts has received compensation for consulting activities from Bayer, Lilly, and INC Research.
- AE Scheuerle has received compensation for consulting activities from Abbott, Amylin, Bayer, Biogen Idec, INC Research, Genentech, Novartis, PPD, TAP Pharma, Roche, Teva, and UCB Pharma.
- JM Thorp has received compensation for consulting from Bayer, GlaxoSmithKline, and PPD.
- JD Albano is an employee of INC Research, the coordinating center for the Betaseron Pregnancy Registry.
- MJ Rametta is a salaried employee of Bayer HealthCare.

DATA SHARING STATEMENT

Some unpublished data remain in the final clinical study report. The data safety monitoring board of the registry (the authors of this paper) decided these data were not necessary for publication.

References

1. Bennett KA. Pregnancy and multiple sclerosis. *Clin Obstet Gynecol.* 2005;48(1):38-47.
2. Vlahiotis A, Sedjo R, Cox ER, et al. Gender differences in self-reported symptom awareness and perceived ability to manage therapy with disease-modifying medication among commercially insured multiple sclerosis patients. *J Manag Care Pharm.* 2010;16(3):206-216.
3. Compston A, Coles A. Multiple sclerosis. *Lancet.* 2002;359(9313):1221-1231.
4. Coyle PK, Christie S, Fodor P, et al. Multiple sclerosis gender issues: clinical practices of women neurologists. *Mult Scler.* 2004;10(5):582-588.
5. Betaseron [package insert]. Montville, NJ: Bayer HealthCare Pharmaceuticals; 2010.
6. Tysabri [package insert]. Cambridge, MA: Biogen Idec Inc; 2012.
7. Avonex [package insert]. Cambridge, MA: Biogen Idec Inc; 2012.
8. Gilenya [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.
9. Copaxone [package insert]. Kansas City, MO: TEVA Neuroscience; 2012.
10. Mitoxantrone [package insert]. Kansas City, MO: TEVA Neurosciences; 2012.
11. Rebif [package insert]. Rockland, MA: EMD Serono; 2012.
12. Aubagio [package insert]. Cambridge, MA: Genzyme Corporation; 2012.
13. Tecfidera [package insert]. Cambridge, MA: Biogen Idec Inc; 2013.
14. Extavia [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.
15. US Department of Health and Human Services OoWH. Pregnancy and Medicines. Available at http://www.womenshealth.gov/publications/our-publications/fact-sheet/pregnancy-medicines.pdf. Accessed December 21, 2012.
16. Covington D, Roberts S, McKain L. Impact of prenatal testing on birth defect prevalence in pregnancy exposure registries. *Pharmacoepidemiol Drug Saf.* 2008;17(Supplement 1):S13.
17. US Food and Drug Administration. Guidance for industry establishing pregnancy exposure registries. Available at

http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133332.pdf. Accessed February 2014.

18. Scheuerle A, Tilson H. Birth defect classification by organ system: a novel approach to heighten teratogenic signalling in a pregnancy registry. *Pharmacoepidemiol Drug Saf.* 2002;11(6):465-475.

19. Jones RK, Kost K. Underreporting of induced and spontaneous abortion in the United States: an analysis of the 2002 National Survey of Family Growth. *Stud Fam Plann.* 2007;38(3):187-197.

20. Correa A, Cragan J, Kucik J. Metropolitan Atlanta Congenital Defects Program 40th anniversary edition surveillance report: reporting birth defects surveillance data. *Birth Defects Research (Part A).* 2007;79:65-93.

21. Correa A, Cragan J, Kucik J, et al. Errata. *Birth Defects Research (Part A).* 2008;82(1):41-62.

22. U.S.Census Bureau. Overview of race and Hispanic origin: 2010. http://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf. Accessed April 2013.

23. Jones CA, Pohar SL, Warren S, et al. The burden of multiple sclerosis: a community health survey. *Health Qual Life Outcomes.* 2008;6:1.

24. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data.* 2000;(314):1-27.

25. ACOG Committee Opinion No 579: Definition of term pregnancy. *Obstet Gynecol.* 2013;122(5):1139-1140.

26. Lu E, Wang BW, Guimond C, et al. Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review. *Neurology.* 2012;79(11):1130-1135.

27. Amato MP, Portaccio E, Ghezzi A, et al. Pregnancy and fetal outcomes after interferon-beta exposure in multiple sclerosis. *Neurology.* 2010;75(20):1794-1802.

28. Boskovic R, Wide R, Wolpin J, et al. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology.* 2005;65(6):807-811.

29. Weber-Schoendorfer C, Schaefer C. Multiple sclerosis, immunomodulators, and pregnancy outcome: a prospective observational study. *Mult Scler.* 2009;15(9):1037-1042.

30. Patti F, Cavallaro T, Lo FS, et al. Is in utero early-exposure to interferon beta a risk factor for pregnancy outcomes in multiple sclerosis? *J Neurol.* 2008;255(8):1250-1253.

31. Hellwig K, Haghikia A, Rockhoff M, et al. Multiple sclerosis and pregnancy: experience from a nationwide database in Germany. *Ther Adv Neurol Disord.* 2012;5(5):247-253.

32. Tomczyk S, Richman S, Wallace K, et al. Final results from the AVONEX (intramuscular-beta-1a) pregnancy exposure registry. Presented at the Annual Meeting of the European Society for Research and Treatment in Multiple Sclerosis. Lyon, France. October 10-13. 2012.

33. Tomczyk S, Sperling B. Post-marketing pregnancy outcomes in patients exposed to intramuscular-interferon-beta-1a. Presented at the Annual Meeting of the European Committee for Treatment and Research in Multiple Sclerosis. Lyon, France. October 10-13. 2012.

34. Hughes S, Spelman T, Gray O, et al. Exposure to interferon-beta therapy in early pregnancy: a literature review of pregnancy outcomes in women with multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2012;83:Supple 2 A17.

Final results from the Betaseron® (interferon beta-1b) Pregnancy Registry: a prospective observational study of birth defects and pregnancy-related adverse events

Authors: PK Coyle, MD;[1] SM Sinclair, PhD, MPH, RN;[2] AE Scheuerle, MD;[3] JM Thorp Jr, MD;[4] JD Albano, PhD, MPH;[5] MJ Rametta, DO[6]

[1]Stony Brook University Department of Neurology and MS Comprehensive Care Center, Stony Brook, NY
[2]University of North Carolina Wilmington, Clinical Research Program, Wilmington, NC
[3]Tesserae Genetics, Medical Genetics, Dallas, TX
[4]University of North Carolina Schools of Medicine and Public Health, Department of Obstetrics and Gynecology, Chapel Hill, NC
[5]INC Research LLC, Post Approval and Strategic Services, Raleigh, NC
[6]Bayer HealthCare Pharmaceuticals, US Medical Affairs, Neurology, Whippany, NJ

Correspondence to:
Name: Patricia Coyle
Affiliation: Stony Brook University and MS Comprehensive Care Center
Address: HSC T12-020; SUNY at Stony Brook, Stony Brook, NY 11794-8121
Telephone number: 631-444-8188
Fax number: 631-444-1474
Email address: patricia.coyle@stonybrookmedicine.edu

Search terms: multiple sclerosis, interferon beta-1b, pediatrics, pregnancy, congenital abnormalities

Word count: 2,784 words

ABSTRACT

Objectives: Women with multiple sclerosis are often diagnosed and treated during their reproductive years. Limited data are available on the safety of treatment during pregnancy. The Betaseron® Pregnancy Registry prospectively monitored women exposed to interferon beta-1b (IFNB-1b) during pregnancy to estimate the rates of birth defects, spontaneous abortions (SABs), and other negative outcomes in this population.

Design: From 2006-2011, this observational registry enrolled women exposed prior to conception or during pregnancy (but prior to or without abnormalities on prenatal screening). Follow-up continued from enrollment through the 4-month pediatric visit.

Setting: Patients in the United States who met these criteria were enrolled in the registry.

Results: The registry enrolled 99 pregnant women; 3 were lost to follow up. The earliest exposure to IFNB-1b occurred during the first trimester for 95 pregnancies and the third trimester for 1 pregnancy. There were 99 birth outcomes (3 twins), including 86 (86.9%) live births, 11 (11.1%) SABs, and 2 (2.0%) stillbirths. Birth defects were reported in 5 (5.1%) cases. Rates of birth defects and SAB were not significantly different from population comparators. No developmental concerns were identified at the 4 month pediatric visit.

Conclusions: The small sample size limits the ability to draw definitive conclusions; however, there was no pattern to suggest increased negative outcomes with IFNB-1b.

ARTICLE SUMMARY

Strengths and limitations of this study

- The Betaseron Pregnancy Registry contains the largest sample of interferon beta-1b-exposed pregnancies collected to date
- The relatively small sample size limits the ability to draw definitive conclusions; however, there was no pattern to suggest increased negative outcomes with interferon beta-1b
- Limitations of the Betaseron Pregnancy Registry include the potential for underreporting or differential reporting of outcomes due to the exclusion of retrospective patients and the voluntary nature of participation
- Birth defect ascertainment was limited to data obtained from reporting health care providers; infants were not examined directly as part of the registry
- Data on infant outcomes were only collected for up to 4 months, reducing the ability of the registry to measure developmental progress, defects diagnosed beyond 4 months of age, and resolution of suspected defects reported in early infancy

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating and neurodegenerative disorder that affects over 400,000 people in the United States.[1,2] MS is much more common in women than men, and diagnosis frequently occurs when patients are in their 20s and 30s.[3,4] Consequently, women of child-bearing age constitute a considerable portion of all patients with MS. Furthermore, up to 10% have disease onset during pregnancy.[1]

The approved disease-modifying treatments (DMTs) for patients with MS have been given pregnancy category ratings of B, C, D, or X by the US Food and Drug Administration based on clinical experience and/or preclinical data (see Table 1 for pregnancy categorizations of currently-approved DMTs and a definition of different pregnancy classifications).[5-14] The safety of these agents during pregnancy is a major concern given the patient profile outlined above. However, data on pregnancy outcomes in DMT-exposed patients is limited. Among the beta interferons, this is particularly true for interferon beta-1b (Betaseron®/Betaferon®; Bayer HealthCare Pharmaceuticals; Whippany, NJ).

Table 1. Pregnancy classifications of disease modifying treatments (DMTs) approved for use by patients with MS.

Disease-modifying therapy	Pregnancy category
Glatiramer acetate (Copaxone®)[9]	B
Interferon beta-1b (Betaseron®/Betaferon®; Extavia®)[5,14]	C
Intramuscular interferon beta-1a (Avonex®)[7]	C

Subcutaneous interferon beta-1a (Rebif®)[11]	C
Fingolimod (Gilenya®)[8]	C
Dimethyl fumarate (Tecfidera®)[13]	C
Natalizumab (Tysabri®)[6]	C
Mitoxantrone[6,10]	D
Teriflunomide (Aubagio®)[6,10,12]	X

FDA pregnancy categories[15]

- Category A: No evidence of adverse effects in studies of pregnant humans
- Category B: No studies from humans, but no evidence of adverse effects in studies of pregnant animals; or negative effects observed in animal models but no evidence of adverse effects in humans
- Category C: Insufficient evidence from human studies, but research with pregnant animals identified some medication-related negative outcomes; in some situations, the medication may be more beneficial than harmful
- Category D: Medication-related negative outcomes in human studies but medication may be needed in some situations
- Category X: Medication-related negative outcomes in human or animal studies; there are no situations in which the medicine should be used

No teratogenic effects were seen in studies of pregnant rhesus monkeys exposed to interferon beta-1b. However, dose-related abortifacient activity was seen at doses from 0.028 mg/kg/d to 0.42 mg/kg/d, which is 2.8 to 4.0 times the recommended human dose based on surface area comparison.[5] Although data on human exposure during pregnancy are limited, patients are advised to discontinue treatment with interferon beta-1b if they become pregnant or plan to become pregnant.[5] The goal of the

Betaseron Pregnancy Registry was to compare pregnancy outcomes in women exposed to interferon beta-1b at conception or during pregnancy relative to general population comparators. This is the largest observational study reported to date for interferon beta-1b.

METHODS

Population and outcome measures

The Betaseron Pregnancy Registry was a voluntary, prospective, observational, exposure-registration and follow-up study. Women with an existing pregnancy who had been exposed to interferon beta-1b at any time after the first day of the last menstrual period (LMP), or during pregnancy but before any prenatal screening (eg, ultrasound, amniocentesis), were prospectively enrolled in the registry. Women with similar exposure who had undergone some prenatal testing and were without abnormal findings suggestive of fetal abnormalities were also enrolled. Given the widespread use of early prenatal testing, restricting enrollment to women without prenatal testing would have dramatically reduced the available population, hindering the success of the registry.[16,17] Because retrospective cases (ie, pregnancies submitted after the birth of the infant or after evidence suggestive of an abnormality on prenatal tests) can be biased toward reporting of unusual or severe outcomes, these cases and those in which an abnormality was identified prior to registry contact were excluded.

The primary outcome measure was the rate of major congenital malformations in infants exposed to interferon beta-1b during gestation, defined as any time after the first day of

the mother's LMP. Secondary outcome measures included the prevalence of spontaneous abortion and other negative pregnancy outcomes in exposed women. Prevalence of elective abortion, stillbirth, ectopic pregnancy, neonatal death, and maternal death was assessed. Reporting was conducted by health care providers (HCPs), patients, or representatives of the study sponsor. Maternal follow-up lasted from enrollment through pregnancy outcome. Infant follow-up continued through the 4-month pediatric visit in most cases.

Pregnancy outcomes were classified as live birth, spontaneous abortion, elective abortion, or fetal death/stillbirth. A live birth was defined as any delivery resulting in a viable neonate ≥24 weeks of gestation. The spontaneous loss of a fetus at <20 weeks of gestation was classified as a spontaneous abortion. Any fetus delivered dead ≥20 weeks of gestation, or weighing ≥500 g regardless of gestational age, was classified as a stillbirth. Fetal death occurring >20 weeks but <28 weeks was classified as early fetal loss while death occurring ≥28 weeks was considered late fetal loss. Elective abortions encompassed any induced or voluntary ending of the pregnancy. Other pregnancy outcomes included ectopic pregnancies, maternal death, and neonatal death. Infant size was classified as "small," "appropriate," or "large" for gestational age based on HCP assessment.

Birth defects were defined as any significant structural or chromosomal defect diagnosed with signs/symptoms using the Metropolitan Atlanta Congenital Defects Program (MACDP) classification of birth defects, or any case with 2 or more secondary or "conditional" abnormalities that would not have been classified as primary birth defects by MACDP. Conditional abnormalities, some of which were also referred to as

"minor birth defects", were included if present in a cluster of 2 or more to increase the sensitivity of monitoring and to avoid missing a potential signal. Birth defects were coded using an organ system classification to increase the possibility of detecting a potential signal by grouping together similar defects or defects with similar etiology.[18] All cases were coded in accordance with both the MACDP code book and the organ system classification by an expert in dysmorphology (AES) who evaluated the potential temporal relationship between the exposure to interferon beta-1b and the etiology of the defect, considering other potential confounders (eg, exposure to other therapies received during the pregnancy, maternal or paternal history of defects, underlying disease).[18] Further follow-up for birth defect cases was conducted if additional information was needed by the dysmorphologist or the data safety monitoring board (DSMB). Defects were classified as "Defect with a known cause, temporality may be irrelevant;" "No temporal association;" or "Unable to assess temporality." Available data for each defect case were reviewed individually for potential confounders and relevant information was evaluated and recorded.

Conduct of the registry was overseen by an independent DSMB. The Western Institutional Review Board (WIRB) reviewed and approved the protocol, which included a waiver of documentation of informed consent. The Betaseron Pregnancy Registry was listed in the public trials registry (www.clinicaltrials.gov) under NCT00317564.

Statistical procedures

Analyses were conducted on all prospective evaluable cases (ie, enrolled pregnancies, not lost to follow-up, with known outcome and birth defect status). The birth defect rate

was calculated by dividing the number of cases with birth defects among all live births and fetal losses >20 weeks gestation (numerator) by the number of live births (denominator). This approach increased the sensitivity of monitoring and may have overestimated the true rate; however it erred on the side of caution. Since the presence or absence of birth defects is difficult to ascertain among fetal losses, including fetal losses in the denominator would have biased the birth defect rate downwards. Ninety-five percent exact confidence intervals (CI) were calculated for birth defect rate and other point estimates. Outcome data were stratified by the earliest trimester of exposure to interferon beta-1b.

Population-based external comparator groups were used to evaluate the rates of spontaneous abortion and birth defects in the registry. Risk of spontaneous abortions was compared with estimates for the general population of the United States from the National Survey of Family Growth (NSFG), which was conducted by the National Center for Health Statistics,[19] using Fisher's exact test based on binomial distribution for exposures. Risk of birth defects was compared with that reported by the MACDP.[20,21] This population-based birth defect surveillance system includes all infants born in the metropolitan area of Atlanta, Georgia. From 1999 to 2003, the MACDP estimated the population birth defect rate to be 2.78 birth defects per 100 live births in its database.[20,21]

When the Registry was designed and launched, it aimed to enroll approximately 420 pregnant women to reach the goal of 210 live births to evaluate the primary endpoint (risk of birth defects). This sample size was estimated to be sufficient to rule out a 2.2-fold increase in birth defects compared to the MACDP rate of 2.78[20,21] with 80% power

(assuming a 5% level of significance). The sample size goal of 420 pregnancies was expected to result in only 210 live births because of losses to follow up, enrollment failures, and a live birth rate of 62%.[17]. After approximately 5 years of operation, Registry enrollment resulted in only 99 live births.

Role of the funding source

The study was jointly designed by members of the DSMB and the study sponsor. The authors, which included both the DSMB and representatives of the sponsor, had access to all the data, participated in analysis and interpretation, and were members of the publication committee. The decision to submit the article for publication was made jointly by the members of the steering committee and the sponsor.

RESULTS

Patient disposition

Between April 24, 2006 and July 31, 2011, 99 pregnant women were prospectively enrolled in the Betaseron Pregnancy Registry. Follow-up of pregnant women and their live-born infants continued through July 16, 2012. Pregnancy outcomes were reported for 96 exposed pregnancies, with 3 pregnancies lost to follow-up (Table 2). Initial exposure to interferon beta-1b occurred in the first trimester for 95 patients, and in the third trimester for 1 patient. Seventy-four patients had pediatric follow up. For the remaining 22 patients, follow-up continued only until birth. Prenatal testing prior to enrollment was reported in 33 cases (34.4%).

Table 2. Maternal demographics.

	Analysis population (N=96)
Age at enrollment (years)	
n	95[a]
Mean (SD)	30.9 (5.29)
Median (range)	31.0 (19-44)
Age category, n (%)	
≤19 years	1 (1.0)
20-34 years	69 (71.9)
≥35 years	25 (26.0)
Missing	1 (1.0)
Race/ethnicity, n (%)	
White	62 (64.6)
Black	25 (26.0)
Hispanic	2 (2.1)
Asian	0 (0)
Other	6 (6.3)
Missing	1 (1.0)
MS duration at enrollment, n (%)	
<1 year	23 (24.0)
1-5 years	51 (53.1)
6-10 years	11 (11.5)
>10 years	6 (6.3)
Missing	5 (5.2)
Earliest trimester of exposure,[b] n (%)	
First	95 (99.0)
Second	0 (0)

Third	1 (1.0)
Prenatal tests, n (%)	
Prenatal test(s) after enrollment	53 (55.2)
Prenatal test(s) prior to enrollment	33 (34.4)
Date of prenatal test(s) not provided	1 (1.0)
No prenatal tests	7 (7.3)
Missing/unknown	2 (2.1)

[a] Age data were missing for 1 case.

[b] First trimester exposure was initial exposure occurring from the first day of the LMP through 13 weeks gestation; third trimester exposure was initial exposure occurring in the 28th week through the end of the pregnancy.

The majority of the sample was white (62 patients [64.6%]); 25 patients (26.0%) were black. In addition, 2 patients (2.1%) were Hispanic while 6 patients were of other races/ethnicities (6.3%) and race/ethnicity data were missing for 1 patient (1.0%). Note that the distribution of race/ethnicity in the Betaseron Pregnancy Registry was different from population norms in the United States (72.4% white, 12.6% black, 16.3% Hispanic).[22]

Pregnancy outcomes

From the 96 evaluable pregnancies, there was a total of 99 birth outcomes available, including 3 sets of twins. These outcomes included 86 live births, 2 stillbirths, and 11 spontaneous abortions (Table 3). Both stillbirths occurred in black women with a history of prior spontaneous abortion and other comorbidities that may have affected birth outcomes. The first case, ending in stillbirth, reported hypertension, obesity (post gastric bypass), and oligohydramnios. The second reported antiphospholipid antibody

syndrome, maternal human papillomavirus infection, early rupture of membranes attributed to vaginal bacterial infection, and preterm labor and delivery attributed to incompetent cervix. The prevalence of spontaneous abortion in the Betaseron Pregnancy Registry (11.5% [95% CI 5.9–19.6]) was not significantly different from the 16% estimate for the general population of the United States based on NSFG data (relative risk 0.7 [95% CI 0.4–1.2], P=.86, Fisher's exact test based on binomial distribution for exposures).

Table 3. Pregnancy outcomes in the Betaseron Pregnancy Registry.

Outcomes, n (%, 95% CI)	**Interferon beta-1b–exposed pregnancies**	**Relative risk (RR) (95% CI)**
Live births (N=96)	83 (86.4%)	-
Birth defects (N=86)[a]	5 (5.8%, 1.9–13.0)	RR (95% CI) 2.1 (0.9-4.9), P=0.092[b]
Spontaneous abortions (N=96)	11 (11.5%, 5.9–19.6)	RR (95% CI) 0.7 (0.4–1.2) P=0.8603[c]
Stillbirth (N=96)	2 (2.1)	-
Maternal deaths	0 (0)	-
Infant deaths	0 (0)	-
Ectopic pregnancies	0 (0)	-

[a] Excludes spontaneous and elective abortions <20 weeks gestation with reported birth defects per MACDP convention. The denominator is restricted to live births.

[b] Relative risk compared with 2.78% reported by MACDP; Fisher's exact test based on binomial distribution for exposures.[20,21]

[c] Relative risk compared with 16.0% rate of SAB reported by NSFG; Fisher's exact test.[23]

Infant assessments were made at birth for 86 babies, up to 3 months of age for 74 babies, and at 4 months for 59 babies (Table 4). HCPs assessed infant size as appropriate for gestational age at birth for 67 cases (77.9%). Four-month follow-up did not identify any consistent pattern of developmental abnormalities. Birth defects were identified in 5 cases (Table 5), resulting in a relative risk of 2.1 (95% CI 0.9–4.9). The reported birth defects occurred in several different organ systems, including the musculoskeletal, cardiovascular, and circulatory systems, with no pattern to the organ systems affected. For all cases reporting birth defects, the earliest exposure to interferon beta-1b 250 micrograms dosed every other day occurred during the first trimester of gestation. No birth defects were reported among the spontaneous pregnancy losses or stillbirths. The birth defect rate estimated by the Betaseron Pregnancy Registry (5.8% [95% CI 1.9–13.0]) was not significantly different from that reported by MACDP (2.78%, *P*=.092, Fisher's exact test). The relatively wide confidence intervals, which include the MACDP rate, reflect the small sample size and suggest no difference between the birth defect rate from the Betaseron Pregnancy Registry and the MACPD.

Table 4. Infant assessments at birth and at 4 months.

	At birth	**At 4-month follow-up**	**Approximate median in US population at birth[24]**
Number of infants	86	59	
Sex, n (%)			
Female	40 (46.5)	26 (44.1)	

Male	46 (53.5)	33 (55.9)	
Infant weight, g			
Median	3346.8	6747.0	3200-3600
Range	470.0-4593.0	4763.0-8902.0	
Infant size, n (%)[a]			
Small	7 (8.1)	3 (5.1)	
Appropriate	67 (77.9)	48 (81.4)	
Large	7 (8.1)	6 (10.2)	
Missing	5 (5.8)	2 (3.4)	
Infant length (cm)			
Median	50.8	63.5	49-50
Range	30.5-55.9	53.3-69.3	
Infant head circumference (cm)			
Median	34.3	41.9	34.8-35.8
Range	29.5-38.1	37.0-44.5	
Gestational age at birth (weeks)			
Median	39.0	NA	
Range	24.0-41.0	NA	
Gestational age at birth, n (%)[b,c]			
Preterm	8 (10.0)	NA	9.9%
Term	72 (90.0)	NA	

[a] Infant size relative to gestational age at birth and age at 4 months (±4 weeks), respectively.

[b] Gestational age at birth calculated as [(280-(corrected estimated due date – outcome date))/7]; estimated due date (EDD) was used when corrected EDD was not available. Preterm births were defined as any baby born before the end of the 36th gestational week and term births were defined as those born after ≥37 weeks, 0 days gestation.[25]

[c] Among singleton live births; excludes 3 twin pregnancies (6 live births) with outcomes at 24 weeks, 5 days; 36 weeks, 3 days; and 36 weeks, 5 days.

Table 5. Summary of birth defect cases

Case	Description of the reported birth defects[a]	Organ system	Temporality assessment
1	Live infant, male, 34 weeks gestation 1. Trisomy 21 (Down syndrome)[b]	1. Chromosome anomaly	1. Defect with known cause, temporality may be irrelevant
2	Live infant, male, 40 weeks gestation 1. Hemangioma (capillary hemangioma parietal area and left 3rd toe)	1. Circulatory system	1. Unable to assess temporality
3	Live infant, female, 39 weeks gestation 1. Hip dysplasia (defect) 2. Patent foramen ovale (conditional defect) 3. Patent ductus arteriosus (conditional defect) 4. Ventriculoseptal defect (defect)	1. Other musculoskeletal defects 2. Heart 3. Circulatory system 4. Heart	1. Unable to assess temporality 2. Defect with known cause, temporality may be irrelevant 3. Defect with known cause, temporality may be irrelevant 4. Defect with known cause, temporality may be irrelevant
4	Live infant, male, 36 weeks gestation 1. Abnormal shape of the head without craniosynostosis	1. Musculoskeletal defects	1. No temporal association
5	Live infant, male, 38 weeks gestation 1. Polydactyly	1. Limb reduction/ addition defects	1. No temporal association

[a] Gestational age data are birth ages, not age at exposure.

[b] The mother of this infant was older than 35 years of age.

Because of the relatively high percentage of black patients in the Betaseron Pregnancy Registry, a subanalysis of pregnancy outcome data was conducted to compare black and non-black patients. No significant differences were seen between these two populations in the rates of birth defects or rates of spontaneous abortion. However, small sample sizes in this subanalysis limit the conclusions that can be drawn from these data.

DISCUSSION

This Betaseron Pregnancy Registry reported 99 outcomes in 96 evaluable pregnancies (including 3 twin pregnancies), consisting of 86 live births, 2 stillbirths, and 11 spontaneous abortions. There were 5 cases with birth defects. Among these 5 cases were a variety of birth defects which were not clustered around a single type of defect or effected organ system. In addition, 2 of these cases had defects that were not temporally related to interferon beta-1b exposure (ie, the timing of the exposure was not consistent with the development of the defect) and 1 had a chromosomal abnormality potentially related to advanced maternal age that was classified as having no temporal association to exposure. This lack of a consistent pattern suggests that there was no signal for birth defects due to interferon beta-1b exposure. The risk of spontaneous abortion or birth defect was not significantly different from comparator populations. In addition, no elective abortions or maternal deaths were observed and there were no abnormalities in rate of prematurity or in birth weight/size. These data represent the largest cohort of interferon beta-1b-exposed patients reported to date; however, the

sample size was still smaller than necessary to have sufficient statistical power to draw definitive conclusions.

To date, several publications have discussed the results of exposure to interferon beta formulations during pregnancy; however none have exclusively examined interferon beta-1b exposure. A recent review of this literature suggested that beta interferons may be associated with some negative outcomes,[26] a conclusion that contrasts with the findings presented here. Three studies, also with small sample sizes, (N=88, N=69, and N=23) found low birth weight in infants exposed to interferon beta formulations (either interferon beta-1a or beta-1b) during gestation.[27-29] Another study (N=14) found evidence of prematurity with interferon beta exposure, but birth weight was not significantly lower than unexposed comparators.[30] However, another study (N=63) did not find evidence of low birth weight following interferon beta exposure.[31] Other negative pregnancy outcomes, including a higher rate of spontaneous abortion and shorter mean birth length, have also been associated with exposure to interferon beta formulations.[27,28]

In contrast, the Betaseron Pregnancy Registry did not find any patterns to suggest negative pregnancy outcomes associated with interferon beta-1b exposure. It should be noted that the 5 aforementioned studies combined subjects exposed to either interferon beta-1a or beta-1b into a single group.[27-31] Two of these studies did not provide separate numbers of interferon beta-1a and beta-1b-exposed patients.[27,29] In the 3 studies that divided exposure groups into interferon beta-1a and beta-1b, patients with interferon beta-1b monotherapy exposure numbered only 10–21[28,30,31], thereby limiting the statistical power to draw conclusions about the effects of interferon beta-1b on

pregnancy outcomes. The Betaseron Pregnancy Registry data reported here have the advantage of a much larger sample size (99 outcomes), albeit much lower than planned when the registry was designed.

The Betaseron Pregnancy Registry included pediatric follow-up, which has not been not consistently reported in other studies: only 2 other studies have assessed pediatric outcomes.[27,30] The first (N=14) reported normal development of interferon beta-1a- or beta-1b-exposed infants up to the 12-month milestones (walking and talking).[30] A later study (N=88) found no developmental abnormalities in interferon beta-exposed infants after 2.1 years of follow-up.[27] The Betaseron Pregnancy Registry's findings are consistent with these previous reports and reinforce the hypothesis that there are no obvious postnatal effects from in utero interferon beta-1b exposure.

The potential risks associated with interferon beta-1b exposure during pregnancy, which were not found to be significantly different from comparator cohorts in this study, need to be considered along with the risks for patients with MS who remain untreated during pregnancy. Prior research suggested that MS itself was not associated with increased risk for negative pregnancy outcomes.[1] However, risk for relapses is higher after delivery, with 20%–40% of patients experiencing a clinical relapse or worsening of the disease in the first 3 months postpartum.[1]

The results reported here are similar to 2 recent presentations related to intramuscular interferon beta-1a exposure during pregnancy. In the first, no pattern suggestive of increased negative outcomes was found in 306 pregnancies in the Avonex Pregnancy Exposure Registry.[32] Similarly, post marketing surveillance (N=552) found the rate of

spontaneous abortion was consistent with the general population, with no evidence of increased birth defect rates.[33] Together with the Betaseron Pregnancy Registry, the preponderance of data suggest no pattern of increased negative outcomes for women and infants exposed to interferon beta formulations during pregnancy, a finding that was supported by a recent review of the literature related to interferon beta exposure during pregnancy (N=1105).[34]

This is also the first study to report on pregnancy exposure outcomes in black patients with MS. No differences were noted based on race.

Limitations of the Betaseron Pregnancy Registry include the potential for underreporting or differential reporting of outcomes due to the exclusion of retrospective patients. However, it is important to note that data from these retrospective patients were captured through post-marketing surveillance efforts. In addition, birth defect ascertainment was limited to voluntary reports from health care providers (not unlike population-based public health surveillance programs), which potentially limited the level of detail needed to fully characterize a birth defect case and rule out missed or misdiagnoses. Lastly, data on infant outcomes were only collected for up to 4 months, reducing the ability of the registry to measure developmental progress.

Due to low sample size, definitive conclusions cannot be drawn from the Betaseron Pregnancy Registry data. However, there was no pattern to suggest an increased risk of birth defects in infants or an increased rate of spontaneous abortions in women after exposure to interferon beta-1b during pregnancy. Infant assessments, such as birth weight, birth length, and head circumference, also did not differ from population

estimates and the 4 month infant follow-up did not identify any developmental concerns. Continued monitoring through routine post-marketing surveillance activities is recommended.

ACKNOWLEDGMENTS

We are grateful to the patients and their healthcare providers for their contributions to the study. Additionally, we thank Robert C. Ristuccia, PhD (Precept Medical Communications), for assistance with preparation of the manuscript (funded by Bayer HealthCare Pharmaceuticals).

COMPETING INTERESTS

- PK Coyle has received compensation for consulting/educational activities from Aconda, Accordant, Bayer, Biogen Idec, Genentech/Roche, Genzyme/Sanofi Aventis, Merck-Serono, Mylan, Novartis, and Teva Neurosciences. She has received research funding from Actelion, Novartis, and Opexa.
- S Sinclair Roberts has received compensation for consulting activities from Bayer, Lilly, and INC Research.
- AE Scheuerle has received compensation for consulting activities from Abbott, Amylin, Bayer, Biogen Idec, INC Research, Genentech, Novartis, PPD, TAP Pharma, Roche, Teva, and UCB Pharma.
- JM Thorp has received compensation for consulting from Bayer, GlaxoSmithKline, and PPD.

- JD Albano is an employee of INC Research, the coordinating center for the Betaseron Pregnancy Registry.
- MJ Rametta is a salaried employee of Bayer HealthCare.

AUTHOR CONTRIBUTIONS

- PK Coyle: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- SM Sinclair: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- AE Scheuerle: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- JM Thorp: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Member of the data safety monitoring board
- JD Albano: Provided oversight for the conduct of the study, including the statistical analysis, interpreted data, and actively contributed to the writing and reviewing of the manuscript
- MJ Rametta: Interpreted data and actively contributed to the writing and reviewing of the submitted manuscript. Sponsor's responsible clinician for registry

This study was funded by Bayer HealthCare Pharmaceuticals, Inc.

References

1. Bennett KA. Pregnancy and multiple sclerosis. *Clin Obstet Gynecol.* 2005;48(1):38-47.

2. Vlahiotis A, Sedjo R, Cox ER, Burroughs TE, Rauchway A, Lich R. Gender differences in self-reported symptom awareness and perceived ability to manage therapy with disease-modifying medication among commercially insured multiple sclerosis patients. *J Manag Care Pharm.* 2010;16(3):206-216.

3. Compston A, Coles A. Multiple sclerosis. *Lancet.* 2002;359(9313):1221-1231.

4. Coyle PK, Christie S, Fodor P, et al. Multiple sclerosis gender issues: clinical practices of women neurologists. *Mult Scler.* 2004;10(5):582-588.

5. Betaseron [package insert]. Montville, NJ: Bayer HealthCare Pharmaceuticals; 2010.

6. Tysabri [package insert]. Cambridge, MA: Biogen Idec Inc; 2012.

7. Avonex [package insert]. Cambridge, MA: Biogen Idec Inc; 2012.

8. Gilenya [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.

9. Copaxone [package insert]. Kansas City, MO: TEVA Neuroscience; 2012.

10. Mitoxantrone [package insert]. Kansas City, MO: TEVA Neurosciences; 2012.

11. Rebif [package insert]. Rockland, MA: EMD Serono; 2012.

12. Aubagio [package insert]. Cambridge, MA: Genzyme Corporation; 2012.

13. Tecfidera [package insert]. Cambridge, MA: Biogen Idec Inc; 2013.

14. Extavia [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.

15. US Department of Health and Human Services OoWH. Pregnancy and Medicines. Available at http://www.womenshealth.gov/publications/our-publications/fact-sheet/pregnancy-medicines.pdf. Accessed December 21, 2012.

16. Covington D, Roberts S, McKain L. Impact of prenatal testing on birth defect prevalence in pregnancy exposure registries. *Pharmacoepidemiol Drug Saf.* 2008;17(Supplement 1):S13.

17. US Food and Drug Administration. Guidance for industry establishing pregnancy exposure registries. Available at http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133332.pdf. Accessed February 2014.

18. Scheuerle A, Tilson H. Birth defect classification by organ system: a novel approach to heighten teratogenic signalling in a pregnancy registry. *Pharmacoepidemiol Drug Saf.* 2002;11(6):465-475.

19. Jones RK, Kost K. Underreporting of induced and spontaneous abortion in the United States: an analysis of the 2002 National Survey of Family Growth. *Stud Fam Plann.* 2007;38(3):187-197.

20. Correa A, Cragan J, Kucik J. Metropolitan Atlanta Congenital Defects Program 40th anniversary edition surveillance report: reporting birth defects surveillance data. *Birth Defects Research (Part A).* 2007;79:65-93.

21. Correa A, Cragan J, Kucik J, et al. Errata. *Birth Defects Research (Part A).* 2008;82(1):41-62.

22. U.S.Census Bureau. Overview of race and Hispanic origin: 2010. http://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf. Accessed April 2013.

23. Jones CA, Pohar SL, Warren S, Turpin KV, Warren KG. The burden of multiple sclerosis: a community health survey. *Health Qual Life Outcomes.* 2008;6:1.

24. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data.* 2000;(314):1-27.

25. ACOG Committee Opinion No 579: Definition of term pregnancy. *Obstet Gynecol.* 2013;122(5):1139-1140.

26. Lu E, Wang BW, Guimond C, Synnes A, Sadovnick D, Tremlett H. Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review. *Neurology.* 2012;79(11):1130-1135.

27. Amato MP, Portaccio E, Ghezzi A, et al. Pregnancy and fetal outcomes after interferon-beta exposure in multiple sclerosis. *Neurology.* 2010;75(20):1794-1802.

28. Boskovic R, Wide R, Wolpin J, Bauer DJ, Koren G. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology.* 2005;65(6):807-811.

29. Weber-Schoendorfer C, Schaefer C. Multiple sclerosis, immunomodulators, and pregnancy outcome: a prospective observational study. *Mult Scler.* 2009;15(9):1037-1042.

30. Patti F, Cavallaro T, Lo FS, et al. Is in utero early-exposure to interferon beta a risk factor for pregnancy outcomes in multiple sclerosis? *J Neurol.* 2008;255(8):1250-1253.

31. Hellwig K, Haghikia A, Rockhoff M, Gold R. Multiple sclerosis and pregnancy: experience from a nationwide database in Germany. *Ther Adv Neurol Disord.* 2012;5(5):247-253.

32. Tomczyk S, Richman S, Wallace K, Liu S, Sperling B. Final results from the AVONEX (intramuscular-beta-1a) pregnancy exposure registry. Presented at the

Annual Meeting of the European Society for Research and Treatment in Multiple Sclerosis. Lyon, France. October 10-13. 2012.

33. Tomczyk S, Sperling B. Post-marketing pregnancy outcomes in patients exposed to intramuscular-interferon-beta-1a. Presented at the Annual Meeting of the European Committee for Treatment and Research in Multiple Sclerosis. Lyon, France. October 10-13. 2012.

34. Hughes S, Spelman T, Gray O, et al. Exposure to interferon-beta therapy in early pregnancy: a literature review of pregnancy outcomes in women with multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2012;83:Supple 2 A17.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Title includes the word "registry."
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found - complete
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Paragraph 1 on page 4
Objectives	3	State specific objectives, including any prespecified hypotheses Paragraph on page 5
Methods		
Study design	4	Present key elements of study design early in the paper Pages 6-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Paragraph 2 on page 6; paragraph 1 on page 9
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Paragraph 2-3, page 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Paragraph 2, page 6; paragraph 1-2 on page 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Paragraph 2, page 6
Bias	9	Describe any efforts to address potential sources of bias Paragraph 3, page 7
Study size	10	Explain how the study size was arrived at Paragraph 2, page 9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Paragraph 2, page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Paragraph 2, page 8
		(*b*) Describe any methods used to examine subgroups and interactions Paragraph 2, page 8

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Paragraph 2, page 9
		(b) Give reasons for non-participation at each stage Paragraph 2, page 9
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Paragraph 2, page 9; paragraph 1 page 10; Table 2
		(b) Indicate number of participants with missing data for each variable of interest Paragraph 2, page 9; Table 2
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time Pages 11-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - NA
		(*b*) Report category boundaries when continuous variables were categorized - NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period - NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Paragraph 1, page 16
Discussion		
Key results	18	Summarise key results with reference to study objectives Paragraph 2, page 16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Paragraph 1, page 16; paragraph 1, page 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Paragraph 2, page 18
Generalisability	21	Discuss the generalisability (external validity) of the study results Paragraph 2, page 18
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Paragraph 1, page 8

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.