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

AUTHORS

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Introduction

- Multiple sclerosis (MS) is a chronic demyelinating and neurodegenerative disorder that is much more common in women than in men[1]
  - Diagnosis frequently occurs when patients are in their 20s or 30s; consequently, women of child-bearing age constitute a considerable portion of all patients with MS[1]
- The safety of disease-modifying therapies, such as interferon beta-1b, during pregnancy is a major concern given this typical patient profile
- Although animal studies have suggested an abortifacient activity of interferon beta-1b, data on human exposure during pregnancy are limited, and patients are advised to discontinue treatment if they become pregnant or plan to become pregnant[2]
  - Interferon beta-1b has been given a pregnancy category C rating, which indicates that there is insufficient evidence from human studies to determine if there are teratogenic or abortifacient effects of the drug.[2] However, in some situations, the medication may be more beneficial than harmful[2]

Objective

- To compare pregnancy outcomes in women exposed to interferon beta-1b at conception or during pregnancy with general population comparators

Methods

Population

- 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 from the first day of their last menstrual periods (LMPs) or during pregnancy (but before any prenatal screening) were prospectively enrolled
  - Women with similar exposure who had undergone some prenatal testing and were without abnormal findings that would indicate the need for increased monitoring were also enrolled
  - Retrospective cases (ie, pregnancies submitted after the birth of the infant or in which prenatal testing identified an abnormality prior to registry contact) were excluded

Outcomes measures

- Primary outcome measure was prevalence of major congenital malformations in women exposed to interferon beta-1b during pregnancy (defined as any time after the first day of her LMP)
- Secondary outcome measures included prevalence of spontaneous abortion (SAB), elective abortion, stillbirth, ectopic pregnancy, neonatal death, and maternal death
- Maternal follow-up lasted from enrollment through pregnancy outcome, and infant follow-up continued through the 4-month pediatric visit
- Primary pregnancy outcomes included live birth, SAB, elective abortion, and fetal death/stillbirth
  - A live birth was defined as any delivery resulting in a viable neonate after ≥24 weeks of gestation regardless of length of survival

Methods (cont)

  - The spontaneous loss of a fetus due to natural causes at <20 weeks of gestation was classified as an SAB
  - Any fetus delivered dead after ≥20 weeks of gestation or weighing ≥500 g was classified as a stillbirth
  - Elective abortion included any induced or voluntary fetal loss ending the pregnancy before the age of viability
- 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 secondary or "conditional" abnormalities that would not have been classified as birth defects by MACDP
- Infant size was classified as "small," "appropriate," or "large" for gestational age based on healthcare provider (HCP) assessment

Statistical procedures

- Risk for birth defects was compared with that reported by MACDP, a population-based, birth defect surveillance system that includes all infants born in the metropolitan Atlanta, Georgia area
  - From 1999 to 2003, the MACDP reported 2.78 birth defects per 100 live births[3,4]
- Consistent with the methodology used by the MACDP, prevalence of birth defects was calculated using the number of live births as the denominator, and 95% exact confidence intervals (CIs) were calculated for point estimates
- Risk of SAB was compared with estimates for the general population of the United States (US) from the National Survey of Family Growth (NSFG), which was conducted by the National Center for Health Statistics[5]

Results

Patient disposition

- A total of 99 pregnant women were prospectively enrolled in the Betaseron Pregnancy Registry between April 24, 2006 and July 31, 2011
  - Follow-up of pregnant women and their live-born infants continued through July 16, 2012
  - Outcomes were reported for 96 exposed pregnancies, with 3 pregnancies lost to follow-up
- Initial exposure to interferon beta-1b occurred in the first trimester for 95 patients and in the third trimester for 1 patient
- A total of 74 patients had pediatric follow-up lasting for ≥3 months, of which 59 had follow-up data at 4 months
  - For the remaining 22 patients, follow-up continued only until birth
- Patient demographic data are shown in Table 1
- Prenatal testing prior to enrollment was reported in 33 (34.4%) cases

Pregnancy outcomes

- There were a total of 99 birth outcomes available, including 3 sets of twins (Table 2)
  - These outcomes included 86 live births, 2 stillbirths, and 11 SABs
  - Both stillbirths occurred in black women with a history of prior SAB and other comorbidities that may have affected birth outcomes

Table 1. Maternal demographics

	Analysis population
N	95[a]
Age at enrollment (years)	
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 or unknown	2 (2.1)

[a] One pregnancy lost to follow-up.
[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.
SD, standard deviation.

Table 2. Pregnancy outcomes in the Betaseron Pregnancy Registry

Outcomes, n (%, 95% CI)	Interferon beta-1b–exposed pregnancies	Relative risk (95% CI)
Live births (N=96)	83 (86.4)	-
Birth defects (N=86)[a]	5 (5.8, 1.9–13.0)	2.1 (0.9–4.9) p=0.092[b]
SAB (N=96)	11 (11.5, 5.9–19.6)	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; Fischer's exact test based on binomial distribution for exposures.[3,4]
[c] Relative risk compared with 16.0% rate of SAB reported by NSFG; Fischer's exact test.[5]

  - The first case 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 SAB was 11.5% (95% CI 5.9–19.6)
  - Relative risk of SAB was not significantly different from the 16% estimate for the general population of the US based on NSFG data (p=0.86)
- No elective abortions or maternal deaths were observed, and there were no abnormalities in rate of prematurity or birth weight

Results (cont)

- Infant assessments were made at birth for 86 infants, within 3 months of birth for 74 babies, and at 4 months for 59 babies (Table 3)
  - HCPs assessed infant size as appropriate for gestational age at birth for 67 (77.9%) cases
  - 4-month follow-up did not identify any consistent pattern of developmental abnormalities

Table 3. Infant assessments at birth and at 4 months

	At birth	At 4-month follow-up
Number of infants	86	59
Sex		
Female, n (%)	40 (46.5)	26 (44.1)
Male, n (%)	46 (53.5)	33 (55.9)
Infant weight, g[a]		
Mean (SD)	3155.2 (768.6)	6689.3 (845.2)
Median	3346.8	6747.0
Range	470.0–4593.0	4763.0–8902.0
Infant size, n (%)[b]		
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)[c]		
Mean (SD)	49.1 (4.9)	62.8 (3.5)
Median	50.8	63.5
Range	30.5–55.9	53.3–69.3
Infant head circumference (cm)		
Mean (SD)	34.1 (1.9)	41.6 (1.5)
Median	34.3	41.9
Range	29.5–38.1	37.0–44.5
Gestational age at birth (weeks)		
Mean (SD)	38.0 (2.6)	-
Median	39.0	-
Range	24.0–41.0	-

[a] Mean birth weight in the US is approximately 3200–3600 g.[6]
[b] Infant size relative to gestational age at birth and age at 4 months (±4 weeks), respectively.
[c] Mean birth length in the US is approximately 49–50 cm.[6]
[d] Mean head circumference in the US is approximately 34.8–35.8 cm.[6]

- Birth defects were identified in 5 cases (Table 4) for a prevalence of 5.8% (95% CI 1.9–13.0)
  - 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

Table 4. 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. Chromosom al anomaly	1. Cannot rule out a possible association
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. Cannot rule out a possible association 3. Cannot rule out a possible association 4. Cannot rule out a possible association
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.

Results (cont)

  - All cases reporting birth defects were exposed to interferon beta-1b 250 µg/qod during the first trimester of gestation
  - Relative risk calculation suggested that the birth defect prevalence was not significantly different from that reported by MACDP (2.78%, p=0.092)
  - No defects were found in any of the spontaneous pregnancy losses or stillbirths

Discussion

- The Betaseron Pregnancy Registry reported 99 outcomes in 96 evaluable pregnancies including 86 live births (includes 3 twin pregnancies), 2 stillbirths, and 11 SABs; there were 5 cases with birth defects
  - Risk of birth defects or SAB was not significantly different from comparator populations. However, the small sample size may have contributed to the lack of statistically significant differences in rates of SAB
  - These data represent the largest cohort of patients exposed to interferon beta-1b during pregnancy reported to date; however, the sample size was still smaller than necessary to have sufficient statistical power to draw definitive conclusions
- The findings of the Betaseron Pregnancy Registry contrast with some earlier studies that found lower birth weight,[7] shorter gestational period,[8] or higher SAB rates[9] in interferon beta–exposed pregnancies
  - Most other studies combined subjects exposed to either interferon beta-1a or -1b into a single group, resulting in low numbers of patients exposed to interferon beta-1b and limited statistical power to draw conclusions
  - In addition, some of these studies analyzed retrospectively enrolled patients[8,10]
- Similar to other studies that included infant assessments,[8,11] the Betaseron Pregnancy Registry did not find any developmental deficits in exposed infants after follow-up of up to 4 months
- The results reported here for interferon beta-1b are generally similar to those reported in a sample of intramuscular interferon beta-1a–exposed pregnancies,[12] suggesting that beta interferon exposure may not be associated with increased risk of negative pregnancy outcomes
- Limitations of this study include
  - Underreporting because not every report of exposure was obtained
  - Differential reporting because there may have been reasons why some reports may have been provided to the registry and others may not have been provided
  - Underascertainment of birth defects because not every birth defect may have been identified
  - Early pregnancy losses were not captured in the registry population
  - Data on infant outcomes were only collected for up to 4 months, reducing the ability of this registry to measure developmental progress
  - High variability in SAB data may have contributed to the lack of statistical significance in the comparison with NSFG
  - Lower than expected recruitment limited the statistical power to draw conclusions

Conclusions

- Definitive conclusions are not possible due to the smaller than expected sample size
- However, there was no pattern to suggest increased birth defects or low birth weight/size in exposed infants, or increased rate of SAB or preterm delivery in exposed pregnant women
- Continued monitoring through routine postmarketing pharmacovigilance activities will continue

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