Pregnancy outcomes from the global pharmacovigilance database on interferon beta-1b exposure

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Abstract

Background: The goal of the present cohort study was to review outcomes of patients exposed to interferon beta-1b during pregnancy.

Methods: Pregnancy cases with exposure to interferon beta-1b reported to Bayer’s pharmacovigilance (PV) database from worldwide sources from January 1995 through February 2018 were retrieved for evaluation. Only cases where pregnancy outcomes were unknown at the time of reporting (i.e. prospective cases) were included in the analysis of this retrospective cohort study.

Results: As of February 2018, 2581 prospective pregnancies exposed to interferon beta-1b were retrieved from the database; 1348 pregnancies had documented outcomes. The majority of outcomes [1106 cases (82.0%)] were live births. Health status was known for 981 live births (no known health status for 125). Most of the prospective pregnancies with known outcomes corresponded to live births with no congenital anomalies [896 cases (91.3%)]. Spontaneous abortion occurred in 160 cases (11.9%). Congenital birth defects were observed in 14/981 live births with known health status [1.4%, 95% confidence interval (CI) 0.78–2.38]. No consistent pattern in the type of birth defect was identified. Rates of both spontaneous abortion and birth defects were not higher than the general population.

Conclusions: These PV data, the largest sample of interferon beta-1b-exposed patients reported to date, suggest no increase in risk of spontaneous abortion or congenital anomalies in women exposed during pregnancy.

Keywords: incidence studies, multiple sclerosis, neonatal, observational study

Introduction

Multiple sclerosis (MS), a chronic demyelinating disease, more common in women than in men, is frequently diagnosed in young patients during their peak reproductive years.1 Although MS has not been shown to increase the rate of adverse pregnancy outcomes,2 information regarding the risk associated with exposure to disease-modifying therapies (DMTs) has been limited. Animal data suggested an increased risk of early pregnancy losses. Studies in humans had sample sizes too small to draw firm conclusions; therefore, we aim to use a pharmacovigilance (PV) database as an alternative source of information on exposure during pregnancy, which is crucial for guiding decision-making during this time period.
MS, which could result in accumulated neurological disability. Concerns also arise when patients have an unplanned pregnancy during treatment.5

Interferon beta-1b (Betaferon®/Betaseron®, Bayer AG; Extavia, Novartis Pharmaceuticals Corporation) demonstrated a favorable safety and efficacy profile in patients with clinically isolated syndrome suggestive of MS, relapsing MS, and secondary progressive MS.6–13 Some preliminary evidence on the effects of exposure during pregnancy has been reported, suggesting a relatively low risk of abnormal outcomes.14,15 In the present study, we aimed to strengthen the data regarding interferon beta-1b exposure during pregnancy by analyzing a large sample size from a PV database.

Methods

Pregnancy cases with exposure to interferon beta-1b reported to Bayer from worldwide sources up to February 2018 were retrieved from Bayer’s global PV database for this retrospective cohort study. All cases were assessed for medical confirmation (confirmed versus unconfirmed), as the medically confirmed cases would present to be more reliable sources of information than patient-reported cases. However, all cases received the same level of surveillance with similar follow-up processes. The database contains data on more than 3800 pregnancies with exposure to interferon beta-1b collected over more than 20 years since January 1995, making it the largest dataset available on interferon beta-1b exposure to date, and the source of many cases that can be assessed for patterns of outcomes.

In order to limit the potential for recall bias in the dataset, only prospective cases (patients who have been exposed to interferon beta-1b but whose data were entered into the database prior to the knowledge of the pregnancy outcome or prior to the detection of a congenital malformation)16,17 were included in the present analysis as retrospective pregnancy cases (data acquired after the outcome of the pregnancy is known or after the detection of a congenital malformation) have an inherent reporting bias toward adverse outcomes as normal outcomes are less likely to be reported.16,17 This may lead to a higher proportion of abnormal outcomes that does not reflect the ‘true’ prevalence rate.16 All considered cases were consistent with the European Medicines Agency guidelines on exposure to medicinal products during pregnancy.16 The database included pregnancies that were reported spontaneously, during clinical trials, in registries, or through patient support programs, where patients were supervised by nursing staff when the pregnancies were confirmed. Outcomes and follow-up information were collected from patients and their health care providers. Institutional Review Board (IRB) approval was not required for the analysis of these PV data.

The calculations of rates for pregnancy losses were based on the total number of known pregnancies and the rates of outcomes after birth were based among the total number of cases with known live birth outcomes. Calculations of outcomes were conducted using the following formulas:

(1) Rate of live births = (total live births/total number known pregnancy outcomes) × 100

(2) Rate of spontaneous abortions = (total number of spontaneous abortions/total number of known pregnancy outcomes) × 100

(3) Rate of congenital anomalies = (total pregnancies with congenital anomaly/total number of live births with known outcomes) × 100

For these calculations, live births included those classified as a healthy child, nonhealthy child, congenital anomaly, and live birth with missing information on health status. The congenital anomalies were registered in the safety database and described as reported, and were classified as per ICD-10 exclusively for this study by the authors with the intention to facilitate and group the terms. Pregnancy losses included ectopic pregnancies, spontaneous abortions, stillbirth/fetal death. We defined spontaneous abortions as pregnancy losses occurring at less than 22 weeks gestation without elective medical or surgical intervention, which includes the subdivision of threatened abortions, incomplete abortions, inevitable abortions, missed abortions, septic abortions, complete abortions, and recurrent spontaneous abortions.16,18 After 22 weeks, live births, or stillbirths, were defined as the complete expulsion or extraction of products of conception at any point during gestation.16

Spontaneous abortions were compared with reference rates of abnormal pregnancy outcomes
Rates of pregnancies resulting in congenital disorders in the database were compared with rates from the general population using the EUROCAT database, a European network of population-based registries for the epidemiologic surveillance of congenital anomalies (2012–2016), and the Metropolitan Atlanta Congenital Defects Program (MACDP) database, a US population-based system that records birth defects (1978–2005). Approximately 80% of the case reports came from the United States and Europe, and, therefore, these American and European databases were considered appropriate for comparison. The exact Clopper Pearson method was used to calculate 95% confidence intervals (95% CIs). The standardized incidence ratio (SIR) for birth defects was calculated as the ratio of observed to expected events, with 95% CI calculated using the exact Poisson method by Owen. Any SIR smaller than 1.00 indicated a lower than expected number of birth defects.

Results
As of February 2018, there were a total of 3884 pregnancy cases in the database, of which 2581 prospective pregnancies exposed to interferon beta-1b were retrieved from 2548 individual case safety reports (Figure 1). A total of 1348 pregnancies had documented outcomes and were included in the data analyses regardless of gestational age. The majority of cases came from North America (43%, including 37% from the US) and Europe (41%, including 22% from Europe).
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Most of the cases (83%) were solicited from observational studies and Patient Support Programs. From the remaining spontaneous reports (17%), 62% were medically confirmed. Most exposures (59.6%) occurred during the first trimester (Table 1).

A total of 896 cases [91.3% (95% CI 89.40, 93.02)] were live births of healthy children with no congenital anomalies.

Spontaneous abortion occurred in 160 cases [11.9% (95% CI 10.19, 13.72)]. Patient age at abortion varied from 16 to 48 years (median of 31 years). Gestational age information was available in 43% (69/190) of the spontaneous abortions. The majority of the outcomes [1106/1348, 82.0% (95% CI 79.89, 84.06)] were live births (Figure 3).

### Table 1. Timing of interferon beta-1b exposure.

| Time of exposure, n (%) | Before conception n=6 | First trimester n=909 | Second trimester n=38 | Third trimester n=9 | Timing unknown n=386 | Total n=1348 |
|------------------------|------------------------|-----------------------|-----------------------|---------------------|----------------------|--------------|
| Total live births      | 4 (66.7)               | 745 (82.0)            | 36 (94.7)             | 9 (100)             | 312 (80.8)           | 1106         |
| Total live birth with known health statusa | 3 (50.0)               | 675 (74.3)            | 32 (84.2)             | 8 (88.9)            | 263 (68.1)           | 981          |
| Live birth, missing information for health status | 1 (16.7)               | 70 (0.08)             | 4 (10.5)              | 1 (11.1)            | 49 (12.7)            | 125          |
| Total known pregnancy outcomesb | 6 (17.1)               | 909 (61.9)            | 38 (52.8)             | 9 (52.9)            | 386 (39.1)           | 1348         |
| Pregnancy loss         | 2 (33.3)               | 164 (18.0)            | 2 (5.3)               | 0 (0.0)             | 74 (19.2)            | 242          |
| Ectopic pregnancies    | 0 (0.0)                | 3 (0.003)             | 0 (0.0)               | 0 (0.0)             | 4 (1.0)              | 7            |
| Spontaneous abortion   | 2 (33.3)               | 110 (12.1)            | 1 (2.6)               | 0 (0.0)             | 47 (12.2)            | 160          |
| Elective abortion      | 0 (0.0)                | 26 (2.9)              | 0 (0.0)               | 0 (0.0)             | 16 (4.1)             | 42           |
| Therapeutic abortion   | 0 (0.0)                | 10 (1.1)              | 0 (0.0)               | 0 (0.0)             | 3 (0.8)              | 13           |
| Stillbirth/fetal death | 0 (0.0)                | 15 (1.7)              | 1 (2.6)               | 0 (0.0)             | 4 (1.0)              | 20           |
| Live birth, child healthy | 3 (100.0)              | 607 (89.9)            | 30 (93.8)             | 8 (100.0)           | 248 (94.3)           | 896          |
| Live birth, child not healthy | 0 (0.0)                | 57 (8.4)              | 2 (6.3)               | 0 (0.0)             | 12 (4.6)             | 71           |
| Live birth with congenital anomaly | 0 (0.0)                | 11 (1.6)              | 0 (0.0)               | 0 (0.0)             | 3 (1.1)              | 14           |
| Pregnancy outcome unknown | 29 (82.9)              | 560 (38.1)            | 34 (47.2)             | 8 (47.1)            | 602 (60.9)           | 1233         |
| Total cases            | 35 (1.4)               | 1469 (56.9)           | 72 (2.8)              | 17 (0.7)            | 988 (38.3)           | 2581         |

aThis total was used to calculate the percentage of live birth events. 
bThis total was used to calculate the percentage of pregnancy losses.
CI, confidence interval.
abortions prospectively reported, which varied from 3 to 18 weeks (median of 8 weeks). Six patients reported history of previous spontaneous abortion and two had previous elective abortions. Alternative explanations were available for six cases, and included car accident, thyroid disease, myoma, metabolic, and cardiac disorder. Four patients reported to be taking several concomitant drugs at the time of the abortion, including bupropion, venlafaxine, solumedrol, clonazepam, trazodone, lioresal, and antiepileptics.

One fetal death at the second trimester of gestation was related to chromosomal anomaly (Trisomy 21), and three patients opted for therapeutic/elective abortion due to congenital anomalies of the fetus: spina bifida and diaphragmatic hernia, gastrochisis, and anencephaly. For most of the spontaneous, elective, and therapeutic abortions, information about congenital anomalies was either not observed or not reported.

Congenital anomalies (Table 2) were observed in 14 of 981 live births with known health status [1.4% (95% CI 0.78, 2.38)]. Maternal age at birth varied from 23 to 38 years (median 31 years). This rate of birth defects (1.4%) was comparable to both the MACDP database reference rate of major congenital anomalies in the US population (2.8%) and to the EUROCAT database (2.4%) (Table 3).19,20 The SIR for birth defects was 0.61 (95% CI 0.31, 0.94). No consistent pattern in the type of birth defect was identified. Six patients reported pregnancy history of prematurity and spontaneous or elective abortions. A congenital heart defect was observed in one neonate of a gemellar gestation, with the other neonate healthy.

A separate analysis was conducted to assess the potential for bias in retrospectively reported cases within the database. A total of 1303 cases were retrospectively reported to the database (i.e. after pregnancy outcome was already known). Within the retrospective subset, 1219 cases (93.6%) included known pregnancy outcomes, compared with 47.8% of prospective cases. Timing of interferon beta-1b exposure was unknown in 58.8% of retrospective cases. The percentage of live births in the retrospective subset was 69.2% (compared with 82.0% in the prospective subset). Negative pregnancy outcomes were reported more frequently in the retrospective cohort than in the prospective cohort, including spontaneous abortions (21.2% versus 11.9%) and congenital anomalies (5.6% versus 1.4%).

**Discussion**

In this study containing the largest worldwide sample of patients exposed to interferon beta-1b during pregnancy reported in the global PV database, we did not find an increase in the rate of abnormal pregnancy outcomes. Rates of spontaneous abortion and major or minor birth defects were not higher than background estimates from the general population. Therefore, our data provide important information showing that first-trimester exposure to interferon beta-1b did not increase the risk of adverse pregnancy outcomes.

It is important to note that the rates of birth defects in the present analysis were lower than those reported in population data, and the SIR suggested a lower than expected rate of birth defects. However, the 95% CIs for these calculations were relatively wide and the upper limits
Table 2. Congenital anomalies from live birth outcomes with known health status.

| Age | Medical history | Concomitant drugs                                      | Pregnancy history | Gestational age at drug exposure | Gestational age at delivery | Child information                               | Classification by ICD 10 system |
|-----|----------------|--------------------------------------------------------|-------------------|---------------------------------|-----------------------------|-----------------------------------------------|----------------------------------|
| 24  | HPV            | Ethinylestradiol, etonogestrel, oxycocet               | G3P3. Premature newborn death 3 weeks postpartum  | 7 weeks                     | 36 weeks                     | Plagiocephaly/Plagiocephaly                  | Congenital musculoskeletal deformities of head, face, spine and chest [Q67] |
| 31  | N/A            | Zolpidem, tretinoin, benzoyl peroxide with clindamycin, prednisone, temazepam, acyclovir, baclofen, ibuprofen, naproxen | G2P1 A1. Previous spontaneous abortion | First trimester              | N/A                          | Congenital knee dislocation/Congenital knee dislocation | Other congenital musculoskeletal deformities [Q68] |
| 25  | N/A            | N/A                                                    | G2P2              | First trimester                 | N/A                         | Right hand 6th digit/Polydactyly             | Polydactyly [Q69] |
| 31  | N/A            | N/A                                                    | N/A               | 6 weeks                        | 39 weeks, 4 days            | 2 hamartomas in left ear/Hamartoma          | Phakomatoses, not elsewhere classified [Q85] |
| 34  | N/A            | Oxycocet                                               | N/A               | N/A                            | 38 weeks                    | Double outlet ventricle anomaly/Double outlet right ventricle | Congenital malformations of cardiac chambers and connections [Q20] |
| 38  | N/A            | Heparin-fraction, progesterone in oil                  | G3P3. Cervical incompetence | N/A                            | 34 weeks                    | Down’s syndrome/Trisomy 21                  | Down syndrome [Q90] |
| 35  | N/A            | N/A                                                    | N/A               | N/A                            | 35 weeks, 4 days            | Trisomy 21 and duodenal atresia/Trisomy 21, Duodenal atresia | Down syndrome [Q90]/Congenital absence, atresia and stenosis of small intestine [Q41] |
| 36  | N/A            | Immunoglobulin                                         | N/A               | First trimester                 | 38 weeks, 3 days           | Renal dysgenesis/Renal aplasia              | Renal agenesis and other reduction defects of kidney [Q60] |

(Continued)
| Age | Medical history | Concomitant drugs | Pregnancy history | Gestational age at drug exposure | Gestational age at delivery | Congenital anomaly as reported/MedDRA PT | Classification by ICD 10 system |
|-----|----------------|--------------------|-------------------|-------------------------------|---------------------------|------------------------------------------|--------------------------------|
| 31  | N/A            | Acetylsalicylic acid, Wobenzyme® | N/A              | 6weeks                        | N/A                       | Renal reflux II and left auricular dysplasia/Congenital vesicoureteric reflux, ear malformation | Congenital obstructive defects of renal pelvis and congenital malformations of ureter [Q62]/Other congenital malformations of ear [Q17] |
| N/A | MS exacerbation, UTI during pregnancy | Macrobid and recreational marijuana | G4P1 with 3 elective abortions due to MS | 1week                        | N/A                       | Right renal pyelectasis/Pyelocaliectasis | Congenital obstructive defects of renal pelvis and congenital malformations of ureter [Q62] |
| 34  | N/A            | N/A                | N/A               | First trimester              | N/A                       | Cleft palate/Cleft palate              | Cleft palate [Q35] |
| 29  | Obesity, HTN   | Nifedipine         | N/A               | First trimester              | N/A                       | Spina bifida/Spina bifida              | Spina bifida [Q05] |
| 23  | HTN during pregnancy | Sertraline     | G1P1              | 5weeks                       | 38weeks                    | Ventriculoseptal defect, patent ductus arteriosus, patent foramen ovale, hip dysplasia/Ventricular septal defect, Patent ductus arteriosus, developmental hip dysplasia, Atrial septal defect | Congenital malformations of cardiac septa [Q21]/Congenital malformations of great arteries [Q25]/Congenital malformations of cardiac septa [Q21]/Congenital deformities of hip [Q65] |
| 32  | HTN, previous conisation | Ferrous sulfate | N/A               | 4weeks                       | 38weeks                    | Ventricular septal defect/Ventricular septal defect | Congenital malformations of cardiac septa [Q21] |

*aWobenzyme is a blend of pancreatin, protease, chymotrypsin, bromelaine, papain, and rutosid. GPA, gravida, para, abortus; HTN, hypertension; MS, multiple sclerosis; N/A, not available; UTI, urinary tract infection.*
were close to the expected population range, suggesting that there is no meaningful difference between the present study and the MADCP or EUROCAT data. While these wide CIs were likely driven by the relatively small number of congenital anomalies, this study still captured the largest sample of interferon beta-1b-exposed patients to date, and, therefore, had the highest statistical power to measure these outcomes.

Only prospective cases were used to estimate prevalence rates of abnormal pregnancy outcomes. A strength of using prospective cases is that it allows for the calculation of an estimated risk, as the occurrence of adverse events and total number of exposure pregnancies are known.17 Retrospective pregnancy cases have an inherent reporting bias because they may be influenced by the outcome itself, distorting the actual rates of these adverse outcomes, and may lead to unfounded fears among pregnant women who could benefit from the continuation of the treatment.17,21–23 Indeed this potential bias is shown in the higher rates of spontaneous abortion and congenital anomalies in retrospectively reported cases relative to the prospectively reported cases in the interferon beta-1b PV database. Consequently, this prospective sample, the largest sample of patients with exposure to interferon beta-1b during pregnancy reported to date, more accurately reflects the effects of interferon beta-1b on pregnancy outcomes.

Results similar to this study have been reported in other analyses of beta interferon exposure during pregnancy. The 99 interferon beta-1b-exposed pregnancies captured in the prospective US Betaseron Pregnancy Registry resulted in 83 (86.4%) live births, 11 (11.5%) spontaneous abortions, and 5 (5.8%) cases with birth defects.14 An additional registry that collected data from patients in Italy exposed to interferon beta during pregnancy found that only 7 of 88 pregnancies (8%) resulted in spontaneous abortion, and no significant fetal complications were observed in live births.24 Recent registries with interferon beta in pregnancy have shown rates for congenital anomalies that vary from 1.8% to 3.08%.25,26 A study using 445 pregnancies (251 exposed interferon beta, 194 unexposed to DMTs) data from the German Multiple Sclerosis Pregnancy Registry observed that the congenital anomaly rates in live births from interferon beta exposed patients versus patients without DMT exposure to be 3.08% (7/226) versus 5.52% (10/179) (p=0.197), respectively.25 Additionally, data regarding pregnancy outcomes from interferon beta exposure collected from population-based registers in Finland and Sweden demonstrated that interferon beta exposure during pregnancy was associated with 1.8% [12/683, 95% CI 0.91–3.05] of live births with congenital anomalies, and 3.3% [49/1506, 95% CI 2.42–4.28] in the unexposed cohort.26

In the past decade, the shift toward preventing disease activity as a goal of treatment has renewed the interest of patients in family planning because patients with MS may face a future with reduced disease-related neurological disability. In fact,

| Table 3. Congenital anomalies in the interferon beta-1b sample versus the MACDP and EUROCAT databases. |
|-------------------------------------------------|
| **Interferon beta-1b database sample** | **MACDP database** | **EUROCAT database** |
| Rate of congenital anomalies | Rate of major congenital anomalies | Expected number of cases |
| 1.4%a | 2.8%b | 25d |

*aProportion of sample from prospective cases of pregnancies with exposure to interferon beta-1b. 
*bNumber of infants and fetuses with a major birth defect that were delivered during a specified period divided by the number of live births during that period. 
*cNumber of pregnancies with congenital anomalies in the sample from prospective cases of pregnancies with exposure to interferon beta-1b. 
*dCalculated per the EUROCAT reference prevalence rate of congenital anomalies (2012–2016): 2558.2/100,000 births. Rate calculated as the number of cases with congenital anomalies, divided by the number of cases resulting in birth (live birth, fetal death/stillbirth, and termination of pregnancy for fetal anomaly after prenatal diagnosis). 
EUROCAT, European network of population-based registries for the epidemiologic surveillance of congenital anomalies; MACDP, Metropolitan Atlanta Congenital Defects Program.
pregnancy rates in women with MS have increased over the past several years, in contrast to the trend in the general population of North America of decreasing pregnancy rates.27 Available data suggest that the rate of relapses may decrease during pregnancy; however, natural history studies showed that relapse rates increase after birth.28 There is also evidence to suggest that the risk of postpartum relapses and disability is higher in women with more disease activity before and during pregnancy.29,30

The findings from these studies examining relapse and disability before, during, and after pregnancy underline the importance of controlling disease activity with DMTs until pregnancy starts. Therefore, it is crucial to assess which DMTs for MS can be considered as having a positive benefit–risk ratio when used during conception, pregnancy, and/or breastfeeding.31,32 The results of the present database analysis suggest that the rates of abnormal pregnancy outcomes in women exposed to interferon beta-1b until conception, and during the first trimester of pregnancy, did not exceed those of the general population. This information is important when a patient plans a pregnancy, taking into consideration the balance between the potential harms that may arise from discontinuation of treatment with interferon beta-1b against the benefit of continuing the treatment until pregnancy is confirmed.

The characteristics of the interferon beta-1b molecule may limit the possibility of harmful effects during pregnancy. For example, the relatively large size of the molecule may prevent it from crossing the placental barrier.33,34 In addition, the half-life may be relatively short, such that it limits the opportunities for interferon beta-1b molecules to come in contact with the developing fetus.

Limitations of the present study include generally known limitations inherent in data from PV databases, namely the lack of a direct comparator group, the potential for underreporting,35 or for inaccurate or incomplete records, as records are based partly on voluntary reporting from health care professionals and patients. Consequently, the data depend on the individual quality of reports, which is a well-known limitation of spontaneous reporting.17 The data included in our study are ‘as reported,’ and, therefore, rely on the reporters’ accuracy. Furthermore, we cannot disregard the fact that some patients may have been exposed to numerous medications, and the possibility of incorrectly making the association of the pregnancy outcome with the other various treatments the patients were taking. Although spontaneous abortions are commonly said to occur in 15–20% of pregnancies, total spontaneous abortions could be much higher if losses that occur prior to clinical recognition are taken into consideration.36 Patient records in this analysis also primarily reflect exposure to interferon beta-1b during the first trimester of pregnancy; data on exposure during the second and third trimesters were collected from a limited number of patients. However, the first 22 weeks are those most critical with the highest risk of congenital anomalies as well as the most likely clinical scenario for patients on interferon beta-1b. Comparisons to unexposed patients with MS, and/or non-MS controls, would have been helpful, and such comparisons are difficult when working with PV data. Consequently, analyses of PV with comparisons to population data have been implemented successfully in the past.37,38 Furthermore, the comparison with population data should take into consideration that PV data represents reporting rates while SIR uses incidence rates.

This PV data review is the largest interferon beta-1b dataset evaluated for pregnancy exposure. The data presented here provide evidence that interferon beta-1b exposure during pregnancy did not lead to a pattern of negative pregnancy outcomes. The results of this analysis should add to the body of knowledge to help physicians and patients in their benefit–risk evaluation, and to make a more informed decision on treatment when planning pregnancy.

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References

1. Coyle PK, Christie S, Fodor P, et al. Multiple sclerosis gender issues: clinical practices of women neurologists. Mult Scler 2004; 10: 582–588.

2. Vaughn C, Bushra A, Kolb C, et al. An update on the use of disease-modifying therapy in pregnant patients with multiple sclerosis. CNS Drugs 2018; 32: 161–178.

3. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler 2018; 24: 96–120.

4. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline: disease-modifying therapies for adults with multiple sclerosis. Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology, https://download.lww.com/wolterskluwer_vitalstream_com/PermaLink/WNL/A/WNL_2018_04_19_RAEGRANT_NEUROLOGY201835181R1_SDC3.pdf. (2018, accessed 7 December 2018).

5. Fragoso YD, Boggild M, Macias-Islas MA, et al. The effects of long-term exposure to disease-modifying drugs during pregnancy in multiple sclerosis. Clin Neurol Neurosurg 2013; 115: 154–159.

6. Kappos L, Edan G, Freedman MS, et al. The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. Neurology 2016; 87: 978–987.

7. Edan G, Kappos L, Montalban X, et al. Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT. J Neurol Neurosurg Psychiatry 2014; 85: 1183–1189.

8. Kappos L, Freedman MS, Polman CH, et al. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. Lancet 2007; 370: 389–397.

9. Kappos L, Freedman MS, Polman CH, et al. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. Lancet Neurol 2009; 8: 987–997.

10. Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 2006; 67: 1242–1249.

11. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993; 43: 655–661.

12. The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. Neurology 1995; 45: 1277–1285.

13. MS ESGoib-bisp. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. Lancet 1998; 352: 1491–1497.

14. Coyle PK, Sinclair SM, Scheuerle AE, et al. Final results from the Betaseron (interferon beta-1b) pregnancy registry: a prospective observational study of birth defects and pregnancy-related adverse events. BMJ Open 2014; 4: e004536.

15. Romero RS, Lunzmann C and Bugge JP. Pregnancy outcomes in patients exposed to interferon beta-1b. J Neurol Neurosurg Psychiatry 2015; 86: 587–589.

16. European Medicines Agency. Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data, https://www.ema.europa.eu/documents/regulatory-procedural-guideline/guideline-exposure-medicinal-products-during-pregnancy-need-post-authorisation-data_en.pdf. (accessed 15 January 2019).

17. Kennedy DL, Uhl K and Kweder SL. Pregnancy exposure registries. Drug Saf 2004; 27: 215–228.

18. Griebel CP, Halvorsen J, Golemon TB, et al. Management of spontaneous abortion. Am Fam Physician 2005; 72: 1243–1250.

19. EUROCAT. Prevalence tables, http://www.eurocat-network.eu/accessprevalencedata/prevalencetables. (accessed 7 December 2018).

20. US Centers for Disease Control. Update on overall prevalence of major birth defects - Atlanta, Georgia, 1978–2005, https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm. (accessed 7 December 2018).

21. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics.
Evaluation and Research. FDA guidance for industry: postapproval pregnancy safety studies, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry (accessed 25 February 2020).

22. Bar-Oz B, Moretti ME, Mareels G, et al. Reporting bias in retrospective ascertainment of drug-induced embryopathy. *Lancet* 1999; 354: 1700–1701.

23. Koren G and Nickel S. Sources of bias in signals of pharmaceutical safety in pregnancy. *Clin Invest Med* 2010; 33: E349–E355.

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

25. Thiel S, Langer-Gould A, Rockhoff M, et al. Interferon-beta exposure during first trimester is safe in women with multiple sclerosis-A prospective cohort study from the German Multiple Sclerosis and Pregnancy Registry. *Mult Scler* 2016; 22: 801–809.

26. Hellwig K, Geissbuhler Y, Sabido M, et al. Pregnancy and infant outcomes with interferon-beta exposure: data from the European Interferon Beta Pregnancy Registry and population based registries in Finland and Sweden. Poster presented at the Annual Meeting of the European Committee for Treatment and Research in Multiple Sclerosis. 10–12 October 2018, Berlin, Germany.

27. Houtchens MK, Edwards NC, Schneider G, et al. Pregnancy rates and outcomes in women with and without MS in the United States. *Neurology* 2018; 91: e1559–e1569.

28. Confavreux C, Hutchinson M, Hours MM, et al. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. *N Engl J Med* 1998; 339: 285–291.

29. Hughes SE, Spelman T, Gray OM, et al. Predictors and dynamics of postpartum relapses in women with multiple sclerosis. *Mult Scler* 2014; 20: 739–746.

30. Portaccio E, Ghezzi A, Hakiki B, et al. Postpartum relapses increase the risk of disability progression in multiple sclerosis: the role of disease modifying drugs. *J Neurol Neurosurg Psychiatry* 2014; 85: 845–850.

31. Fragoso YD, Adoni T, Brooks JBB, et al. Practical evidence-based recommendations for patients with multiple sclerosis who want to have children. *Neuro Ther* 2018; 7: 207–232.

32. Vukusic S and Marignier R. Multiple sclerosis and pregnancy in the ‘treatment era’. *Nat Rev Neurol* 2015; 11: 280–289.

33. Chalier JC, Guerre-Millo M, Nandakumaran M, et al. Clearance of compounds of different molecular size in the human placenta in vitro. *Biol Neonate* 1985; 48: 143–148.

34. Waysbort A, Giroux M, Mansat V, et al. Experimental study of transplacental passage of alpha interferon by two assay techniques. *Antimicrob Agents Chemother* 1993; 37: 1232–1237.

35. Lopez-Gonzalez E, Herdeiro MT and Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. *Drug Saf* 2009; 32: 19–31.

36. Brown S. Miscarriage and its associations. *Semin Reprod Med* 2008; 26: 391–400.

37. Geissbuhler Y, Vile J, Koren G, et al. Evaluation of pregnancy outcomes in patients with multiple sclerosis after fingolimod exposure. *Ther Adv Neurol Disord* 2018; 11: 1–9.

38. Sandberg-Wollheim M, Alteri E, Moraga MS, et al. Pregnancy outcomes in multiple sclerosis following subcutaneous interferon beta-1a therapy. *Mult Scler* 2011; 17: 423–430.