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Pregnancy outcomes after exposure to interferon beta: a register-based cohort study among women with MS in Finland and Sweden

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Katja Marja Hakkarainen, Rosa Juuti, Sarah Burkill, Yvonne Geissbühler, Meritxell Sabidó, Catrinel Popescu, Kiliana Suzart-Woischnik, Jan Hillert, Miia Artama, Auli Verkkoniemi-Ahola, Kjell-Morten Myhr, Juha Mehtälä, Shahram Bahmanyar, Scott Montgomery, Pasi Korhonen, the European Interferon Beta Pregnancy Study Group and the Nordic MS Pregnancy & Interferon Beta study group

Correspondence to:
Katja Marja Hakkarainen
StatFinn & EPID Research, Prästgårdsgatan 28, 431 44 Mölndal, Sweden.
katja.hakkarainen@iqvia.com

Rosa Juuti
StatFinn & EPID Research, Espoo, Finland

Sarah Burkill
Karolinska Institute, Stockholm, Sweden

Yvonne Geissbühler
Novartis Pharma AG, Evidence and Launch Excellence, Basel, Switzerland

Meritxell Sabidó
Merck KGaA, Darmstadt, Germany

Catrinel Popescu
Biogen Idec Ltd, Maidenhead, UK

Kiliana Suzart-Woischnik
Bayer AG, Berlin, Germany

Jan Hillert
Karolinska Institute, Stockholm, Sweden

Miia Artama
University of Helsinki, Helsinki, Finland

Auli Verkkoniemi-Ahola
Clinical Neurosciences, Neurology, University of Helsinki, Helsinki, Finland

Helsinki University Hospital, Helsinki, Finland

Kjell-Morten Myhr
Department of Clinical Medicine, University of Bergen, Bergen, Norway

Department of Neurology, Haukeland University Hospital, Bergen, Norway

Juha Mehtälä
StatFinn & EPID Research, Espoo, Finland

Shahram Bahmanyar
Department of Medicine, Karolinska Institutet, Solna, Stockholm, Sweden

Centre for Psychiatry Research, Karolinska Institutet, Solna, Stockholm, Sweden

Stockholm Health Care Services, Stockholm, Sweden

Abstract

Background Our aim was to estimate and compare the prevalence of adverse pregnancy outcomes among pregnant women with multiple sclerosis (MS) exposed to interferon beta (IFNB) and among women with MS unexposed to any MS disease-modifying drug (MSDMD).

Methods This cohort study used Finnish (1996–2014) and Swedish (2005–2014) national register data. Women with MS having IFNB dispensed 6 months before or during pregnancy as the only medication were considered as IFNB exposed (only IFNB-exposed), whereas women with MS unexposed to any MSDMD were considered unexposed (MSDMD-unexposed). Prevalence was described and compared using log-binomial or logistic regression and adjusted for potential confounders including maternal age and comorbidity.

Results Among 2831 pregnancies, 2.2% of the only IFNB-exposed and 4.0% of the MSDMD-unexposed women had serious adverse pregnancy outcomes [elective termination of pregnancy due to foetal anomaly (TOPFA), major congenital anomaly (MCA) in live, or stillbirth]. After adjustments, the prevalence of serious adverse pregnancy outcomes was lower among the only IFNB-exposed compared with the MSDMD-unexposed [relative risk 0.55, 95% confidence interval (CI) 0.31–0.96]. The prevalence of individual outcomes, including MCA, spontaneous abortions, and stillbirths was not increased with IFNB exposure. Women with MS exposed to IFNB appeared more likely to terminate their pregnancy for reasons other than foetal anomaly, compared with MSDMD-unexposed pregnant MS patients (odds ratio 1.71, 95% CI 1.06–2.78).

Conclusion In this large cohort study, no increase in the prevalence of adverse pregnancy outcomes was observed in women with MS exposed to IFNB compared with MS patients unexposed to any MSDMDs. This study together with other evidence led to a change in the labels of the IFNB products in September 2019 in the European Union, and IFNB use today may be considered during pregnancy, if clinically needed.

Keywords: Adverse effects, epidemiology, interferon-beta, multiple sclerosis, pregnancy, pregnancy complications, registries

Introduction

Multiple sclerosis (MS) is the most common chronic neurological disease causing disability in females of childbearing age (20–45 years).[1] Interferon beta (IFNB), including 1a and 1b preparations, five products,[2–6] and biosimilars, are proven to have favourable benefit–risk profiles and have been widely used during the last

Scott Montgomery
Department of Medicine, Karolinska Institutet, Solna, Stockholm, Sweden
School of Medical Sciences, Clinical Epidemiology and Biostatistics, Örebro University, Sweden
Department of Epidemiology and Public Health, University College London, UK
Pasi Korhonen
StatFinn & EPID Research, Espoo, Finland

20 years.[7,8] Thereafter, other MS disease-modifying drugs (MSDMDs) were approved for MS, including alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, mitoxantrone, natalizumab, ocrelizumab and teriflunomide.[9,10] As MS is common among women in childbearing age,[1] treatment choice when planning pregnancy is crucial.

In recent years, observational studies[11–18] and systematic literature reviews[19–21] have shown no increase in the prevalence of adverse pregnancy outcomes, such as congenital anomaly or spontaneous abortion, among women exposed to IFNB before or during pregnancy. Despite the evidence, women treated with IFNB have been recommended to use appropriate contraceptive measures and to consider discontinuing IFNB therapy when planning pregnancy.[2–6] The previous studies have been limited by a small sample size[11–18] with <500 pregnancies in the largest studies,[11,16] lack of a control group or confounder adjustment,[12–15] or by including only spontaneously reported pregnancies.[11,13,17] This cohort study was requested by the European Medicines Agency (EMA) as a post-authorisation safety study (PASS) to investigate adverse pregnancy outcomes with and without exposure to IFNB, thus allowing the provision of more precise information to patients and treating physicians on the associated risks.

The objective of this large register-based cohort study was to estimate and compare the prevalence of adverse pregnancy outcomes among women with MS exposed to IFNB only (only INFB-exposed) and those unexposed to any MSDMDs (MSDMD-unexposed), with a primary composite outcome *serious adverse pregnancy outcome* which consisted of elective terminations of pregnancy due to foetal anomaly (TOPFA), live births with major congenital anomaly (MCA) and stillbirths.

Methods

The methods of this PASS study, including outcomes and analyses, were planned prior to conducting the study, as described in the full study protocol registered in the European Union PAS Register.[22]

Study design, setting, and participants

This cohort study utilised national registers in Finland and Sweden. Data were extracted on women with MS [International Classification of Diseases 10th revision (ICD-10) code G35] who were pregnant during the study period, with the pregnancy ending in spontaneous abortion, ectopic pregnancy, elective termination, stillbirth or live birth, and with a well-defined drug exposure during the study period. The study period was 1 January 1996–31 December 2014 in Finland and 1 July 2005–31 December 2014 in Sweden. If women had multiple pregnancy events during the study period, all were included. The study was granted a positive opinion by the Helsinki University Hospital Ethics Committee (Finland; 159/13/03/00/2016) and approved by the Regional Ethical Review Board in Stockholm (Sweden; 2016/874-31/2). No informed consent was needed from individuals because it is prohibited by Swedish and Finnish law to backtrack registered individuals in registers.

Data sources and data linkage

Data extracted from the healthcare registers (Table 1) were linked with a unique personal identification number. In Finland, the Care Register for Health Care,[23] Medical Birth Register,[24,25] Register on Induced Abortions,[25,26] Register of Congenital Malformations,[27] National Reimbursement Register,[28] and National Prescription Register,[29] were used and in Sweden the National Patient Register,[30] Medical Birth Register,[25,31] Swedish Prescribed Drug Register,[32,33] and the Swedish MS Registry.[34]

Variables

Exposure. Pregnant women were considered only IFNB-exposed if an IFNB product (with Anatomical Therapeutic Chemical codes L03AB07, L03AB08, L03AB13) had been dispensed from the pharmacy, without any dispensation of another MSDMD (Supplemental Table 1), within 6 months before the last menstrual period (LMP) or during pregnancy. Including dispensations within 6 months before the LMP enabled capturing exposure within 3 months before LMP, as the maximum reimbursable volume was for 3 months per dispensation in Finland and Sweden. Women without a dispensation of an IFNB product or another MSDMD during the same period were considered MSDMD-unexposed, with a prolonged purchase period of 9 months before the LMP for mitoxantrone and cladribine. In complementary analyses, women with MS exposed to

Table 1. Used data sources in Finland and Sweden.

	Finland	Sweden
MS diagnosis	National Reimbursement Register[a] Care Register for Health Care[b]	National Patient Register[c] Swedish MS Registry
Adverse pregnancy outcome		
MCA[d] In live births In live births, stillbirths or elective terminations	Medical Birth Register[b,e] Register of Congenital Malformations[b,e]	Medical Birth Register[c]
Spontaneous abortion	Care Register for Health Care[b]	National Patient Register[c]
Ectopic pregnancy	Care Register for Health Care[b]	National Patient Register[c]
Elective termination TOPFA Other reasons	Medical Birth Register[b,e] Care Register for Health Care[b] Register on Induced Abortions[b,e] Register of Congenital Malformations[b,e]	Not recorded in Sweden
Stillbirth	Medical Birth Register[b,e]	Medical Birth Register[c]
Non-live birth[f]	Medical Birth Register[b,e]	Medical Birth Register[c]
Exposure	National Prescription Register[a,e]	Swedish Prescribed Drug Register[c] Swedish MS Registry

[a]Held by the Social Insurance Institution, Finland.
[b]Held by the National Institute for Health and Welfare, Finland.
[c]Held by the National Board of Health and Welfare, Sweden.
[d]In Finland, the follow-up period for the registration of MCA is 12 months after birth, in Sweden 6 months.
[e]Accessed *via* the Drugs and Pregnancy Project jointly run by the National Institute for Health and Welfare, the Finnish Medicines Agency and the Social Insurance Institution.
[f]Non-live birth, defined as either an elective termination or a stillbirth, was used as an outcome, because the rare disease assumption did not hold for live births, which was as defined in the full study protocol.[22]
MCA, major congenital anomaly; MS, multiple sclerosis; TOPFA, termination of pregnancy due to foetal anomaly.

IFNB only were compared with women unexposed to IFNB regardless of exposure to other MSDMDs (IFNB-unexposed; see statistical analyses).

Outcomes. The primary outcome variable was the composite *serious adverse pregnancy outcome*, defined as either TOPFA, live birth with MCA or stillbirth. Other outcomes were MCA in live births; MCA in live births, stillbirths or TOPFA; spontaneous abortion; ectopic pregnancy; TOPFA; elective termination for other reasons; stillbirth; and non-live birth. MCA was defined as ICD codes (9th revision; ICD-9) 740–759, divided into 25 groups, with minor anomalies excluded according to European Surveillance of Congenital Anomalies, and stillbirths as birth weight of ⩾500 g or ⩾22 completed gestational weeks. For spontaneous abortion (ICD-10: O03) and ectopic pregnancies (ICD-10: O00), consecutive healthcare visits within 3 months from each other were combined into a single event where the first visit defined the event date and the last visit determined the diagnosis, as later diagnoses are considered more accurate. Elective termination was defined as ICD-10 code O04 (information only available in Finland). Non-live birth, defined as either an elective termination or a stillbirth, was used as an outcome, because the rare disease assumption did not hold for live births, which was defined in the full study protocol.[22]

Maternal characteristics. The following maternal characteristics were considered as pre-defined

confounding factors, according to availability [Supplemental Table 2(a)], in the adjusted base model (see the following): country of residence, year of pregnancy outcome, maternal age at LMP, number of previous pregnancies, any chronic diseases [Supplemental Table 2(b)], and exposure to any teratogenic medications [Supplemental Table 2(c)]. Additional maternal characteristics were used in the further adjusted model: time since MS diagnosis, duration of MS treatment, residency region, pre-pregnancy weight, pre-pregnancy body mass index, number of previous abortions, smoking status during pregnancy, and number of foetuses in the pregnancy. The confounders were selected *a priori* within the research group, being similar to those in previous studies.[11,16]

Statistical analyses

The maternal characteristics for all pregnancy events (one woman may have multiple events) were reported with unadjusted descriptive statistics [number, percentage, mean, standard deviation (SD), median, minimum and maximum, interquartile range, as applicable], stratified by exposure cohort. The number and prevalence (%) of the outcomes were described for each cohort, with 95% confidence intervals (CI) using Pearson-Clopper.[35] The unit of analysis in all analyses was pregnancy event, also used as the denominator (Table 2).

A primary comparison of the prevalence of the outcomes between the only IFNB-exposed and the MSDMD-unexposed pregnancies was done. Log-binomial regression was used to analyse relative risks (RRs) with 95% CIs. When log-binomial regression could not be fitted, odds ratios (ORs) were reported instead. The prevalence of the outcomes was considered to differ, with statistical significance between the compared exposure groups if the CI did not include 1. Two multivariate models were used: (a) the base model was adjusted for the maternal characteristics described previously; (b) the further adjusted model was determined through a variable selection procedure (Supplement 3), the variables of the adjusted base model and the additional maternal characteristics being the candidate variables. A missing category was used in the analysis for variables with missing values (Table 3 and Supplemental Table 4). To complement the primary comparison, further analyses were performed with an altering unexposed cohort: the *IFNB-unexposed* were defined as women with MS unexposed to IFNB, instead of MSDMD-unexposed as in the main analysis. The adjusted base model was repeated using the IFNB-unexposed cohort.

In a sensitivity analysis, the adjusted base model for MCA was repeated using restricted exposure definitions for IFNB and other MSDMDs: exposure required a dispensation within 6 months (cladribine and mitoxantrone 9 months) before the LMP or during the first trimester of pregnancy (dispensations during the two last trimesters excluded).

A feasibility study estimated 1671 pregnancies in MS patients to be available for analysis, 18% among the only IFNB-exposed and 76% among the MSDMD-unexposed. With an anticipated background rate of 7.3% for the serious adverse pregnancy outcome, the minimum detectable effect size between the study cohorts only IFNB-exposed *versus* MSDMD-unexposed was 1.72 in terms of RR, with an 80% power and a two-sided 5% significance level.

Results

Participants

The study population consisted of 1983 women with MS who had been pregnant in Finland ($n = 755$) or Sweden ($n = 1228$) during the study period. Among these women, 2831 pregnancy events ended in either live birth, ectopic pregnancy, spontaneous abortion, elective termination, or stillbirth (Figure 1). Of the 2831 pregnancy events, 797 were only IFNB-exposed and 1647 MSDMDs-unexposed (Table 3) and 1975 IFNB-unexposed pregnancies, regardless of exposure other MSDMD (Table 3).

The mean age was 30.6 years for the women with only IFNB-exposed pregnancies and 31.8 years for the MSDMD-unexposed, with women aged 36–40 years at LMP comprising 8.9% of the only IFNB-exposed and 20.4% of the MSDMD-unexposed pregnancies. Other chronic diseases before or during pregnancy were recorded among 35.4% of the only IFNB-exposed and 37.7% of the MSDMD-unexposed. The mean duration of MS treatment at LMP was similar in both groups (3.3 *versus* 3.5 years; Table 3; Supplemental Table 4 for maternal characteristics).

Table 2. Number of pregnancy events considered for the denominators of the study outcomes.

Pregnancy events used as denominator	Number of pregnancies (*n*)[a]			Outcome for which used as denominator
	All pregnancy events, including those exposed to IFNB or any other MSDMDs	Only IFNB-exposed pregnancies	MSDMD-unexposed pregnancies	
All pregnancy events[b]	2831	797	1647	Ectopic pregnancies, spontaneous abortions
Elective terminations, stillbirths and live births[c]	2466	718	1397	Serious adverse pregnancy outcome; elective TOPFA or elective termination for other reasons; stillbirths (with or without foetal defects); non-live births; MCA in live births, stillbirths or elective terminations
Finland only	890	295	474	
Live births[c]	2327	666	1330	MCA in live birth

[a]If women had multiple pregnancies during the study period, all pregnancies were included.
[b]Including elective termination (unavailable in Sweden), spontaneous abortion, ectopic pregnancy, stillbirth or live birth.
[c]Including both pre-term and full-term live birth.
IFNB, interferon beta; MCA, major congenital anomaly; MSDMD, multiple sclerosis disease-modifying drug; TOPFA, termination of pregnancy due to foetal anomaly.

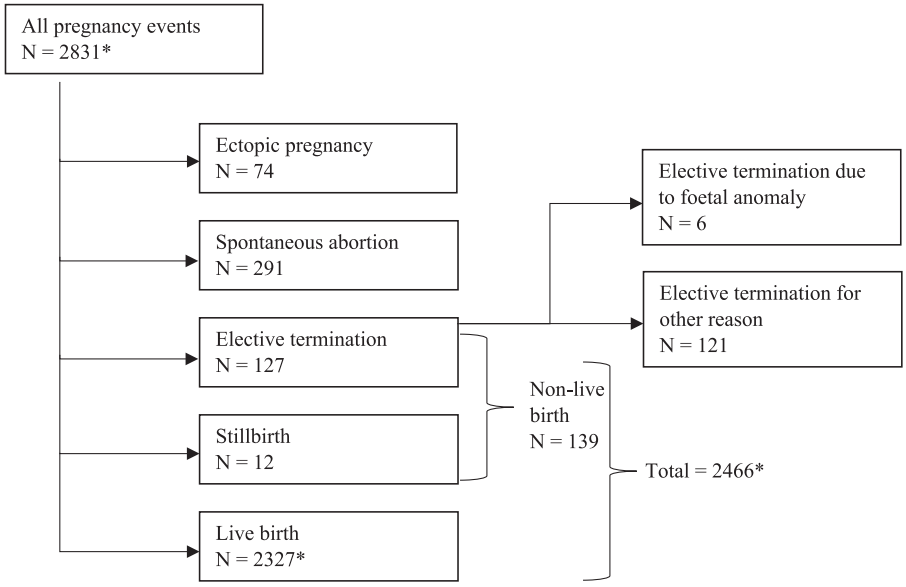

Figure 1. Included pregnancy outcome events.
*Used as a denominator in this study, as described in Table 2.

Serious adverse pregnancy outcome

The prevalence of the composite outcome of *serious adverse pregnancy outcome* was 2.2% (95% CI 1.3–3.6%) for only IFNB-exposed and 4.0% (95% CI 3.0–5.2%) for the MSDMD-unexposed pregnancies (Table 4). When adjusted for the pre-defined covariates in the *base model*, the prevalence of *serious adverse pregnancy outcome* was lower (RR below 1) for the only IFNB-exposed compared with the MSDMD-unexposed pregnancies, RR 0.55, 95% CI 0.31–0.96 [Table 4; Supplemental Table 5(a)]. The result remained in the *further adjusted model* [Table 4; Supplemental Table 5(b)].

Table 3. Maternal characteristics for pregnancy events ($n = 2831$ pregnancy events).

Maternal characteristics	All pregnancy events, including those exposed to IFNB or any other MSDMDs	Exposure groups in main analysis		Alternative exposure (comparator) group in complementary analyses
		Only IFNB-exposed pregnancies	MSDMD-unexposed pregnancies	IFNB-unexposed pregnancies, regardless of exposure other MSDMD
Pregnancy events, *n*	2831[a]	797	1647	1975[b]
Number of women	1983	659	1230	1452
Country of residence				
Finland, *n* (%)	1074 (37.9)	320 (40.2)	614 (37.3)	742 (37.6)
Sweden, *n* (%)	1757 (62.1)	477 (59.8)	1033 (62.7)	1233 (62.4)
Year of pregnancy outcome				
1996–1999, *n* (%)	59 (2.1)	1 (0.1)	58 (3.5)	58 (2.9)
2000–2004, *n* (%)	106 (3.7)	32 (4.0)	70 (4.3)	74 (3.7)
2005–2009, *n* (%)	896 (31.6)	240 (30.1)	538 (32.7)	636 (32.2)
2010–2015, *n* (%)	1770 (62.5)	524 (65.7)	981 (59.6)	1207 (61.1)
Maternal age at LMP				
⩽20 years, *n* (%)	27 (1.0)	8 (1.0)	15 (0.9)	18 (0.9)
21–25 years, *n* (%)	295 (10.4)	100 (12.5)	144 (8.7)	182 (9.2)
26–30 years, *n* (%)	907 (32.0)	273 (34.3)	495 (30.1)	613 (31.0)
31–35 years, *n* (%)	1073 (37.9)	325 (40.8)	613 (37.2)	731 (37.0)
36–40 years, *n* (%)	457 (16.1)	71 (8.9)	336 (20.4)	379 (19.2)
>40 years, *n* (%)	72 (2.5)	20 (2.5)	44 (2.7)	52 (2.6)
Range (min–max)	(17.0–57.0)	(18.0–48.0)	(18.0–57.0)	(17.0–57.0)
Mean (± SD)	31.3 (4.7)	30.6 (4.5)	31.8 (4.7)	31.6 (4.8)
Median (Q1–Q3)	31.0 (28.0–34.0)	31.0 (28.0–33.0)	32.0 (29.0–35.0)	32.0 (29.0–35.0)
Number of previous pregnancies				
0, *n* (%)	1178 (41.6)	347 (43.5)	669 (40.6)	811 (41.1)
1–2, *n* (%)	1406 (49.7)	390 (48.9)	828 (50.3)	983 (49.8)
⩾3, *n* (%)	247 (8.7)	60 (7.5)	150 (9.1)	181 (9.2)
Any chronic disease before or during pregnancy (excluding MS)[c], *n* (%)	1059 (37.4)	282 (35.4)	621 (37.7)	752 (38.1)

(continued)

Table 3. (Continued)

Maternal characteristics	All pregnancy events, including those exposed to IFNB or any other MSDMDs	Exposure groups in main analysis		Alternative exposure (comparator) group in complementary analyses
		Only IFNB-exposed pregnancies	MSDMD-unexposed pregnancies	IFNB-unexposed pregnancies, regardless of exposure other MSDMD
Exposure to any teratogenic medications before[d] or during pregnancy[e]				
Group C, *n* (%)	1626 (57.4)	520 (65.2)	864 (52.5)	907 (45.9)
Group D, *n* (%)	427 (15.1)	149 (18.7)	216 (13.1)	260 (13.2)
Time since MS diagnosis				
⩽2 years, *n* (%)	817 (28.9)	249 (31.2)	471 (28.6)	547 (27.7)
3–5 years, *n* (%)	985 (34.8)	285 (35.8)	560 (34.0)	678 (34.3)
>5 years, *n* (%)	1029 (36.3)	263 (33.0)	616 (37.4)	750 (38.0)
Range, years (min–max)	(–0.8 to 20.5)	(–0.7 to 16.0)	(–0.8 to 20.5)	(–0.8 to 20.5)
Mean, years (± SD)	4.5 (3.6)	4.2 (3.2)	4.6 (3.8)	4.6 (3.8)
Median, years (Q1–Q3)	3.7 (1.7–6.5)	3.4 (1.7–6.1)	3.8 (1.7–6.6)	3.8 (1.6–6.6)
Duration of MS treatment[f]				
⩽2 years, *n* (%)	1025 (36.2)	342 (42.9)	552 (33.5)	654 (33.1)
3–5 years, *n* (%)	795 (28.1)	252 (31.6)	393 (23.9)	526 (26.6)
>5 years, *n* (%)	683 (24.1)	199 (25.0)	378 (23.0)	471 (23.8)
Never (no use), *n* (%)	328 (11.6)	4 (0.5)	324 (19.7)	324 (16.4)
Range, years (min–max)	(0.0–20.1)	(0.0–14.0)	(0.0–18.9)	(0.0–20.1)
Mean, years (± SD)	3.5 (3.2)	3.3 (2.8)	3.5 (3.4)	3.5 (3.4)
Median, years (Q1–Q3)	2.7 (0.8–5.3)	2.5 (1.1–5.0)	2.7 (0.0–5.4)	2.8 (0.5–5.4)

[a]All the 2831 pregnancies included: 797 only IFNB-exposed and 1647 MSDMD-unexposed pregnancies (exposure groups in main analysis); an additional 328 pregnancies exposed exclusively to other MSDMDs excluding IFNB (included in the alternative comparator group in complementary analyses); and an additional 59 pregnancies exposed to both INFB and other MSDMDs (not included in the analyses in this manuscript).
[b]In the alternative comparator group, the 1975 pregnancies included the 1647 MSDMD-unexposed pregnancies plus an additional 328 pregnancies exposed exclusively to other MSDMDs excluding IFNB.
[c]List of chronic diseases (excluding MS) listed in Supplemental Table 2(b).
[d]6 months before LMP.
[e]Teratogenic C and D drugs are based on year 2017 list in Sweden [Supplemental Table 2(c)].
[f]Duration of MS treatment at LMP refers to refers to any MS treatment the patient may have ever received.
IFNB, interferon beta; LMP, last menstrual period; MS, multiple sclerosis; MSDMD, multiple sclerosis disease-modifying drug; *n*, number of pregnancy events; Q, quartile; SD, standard deviation.

MCA

The prevalence of MCA in live births was 1.8% (95% CI 0.9–3.1%) for the only IFNB-exposed pregnancies and 3.3% (95% CI 2.4–4.4%) for the MSDMDs-unexposed pregnancies (Table 4). In live births, stillbirths or elective terminations, the prevalence of MCA was 1.9% (95% CI 1.1–3.2%) and 3.5% (95% CI 2.6–4.6%) in the respective cohorts. In the *adjusted base model*, a lower prevalence of MCA was observed for the

only IFNB-exposed compared with the MSDMD-unexposed pregnancies: in live births RR was 0.52 (95% CI 0.27–0.99); and in live births, stillbirths or elective terminations RR was 0.57 (95% CI 0.31–1.03) (Table 4; Supplemental Table 5a). The corresponding results remained similar in the *further adjusted models*: RR 0.52 (95% CI 0.28–0.98) and RR 0.55 (95% CI 0.31–1.00) (Table 4; Supplemental Table 5b).

Spontaneous abortion

The prevalence of spontaneous abortions was 8.3% (95% CI 6.5–10.4%) for the only IFNB-exposed and 12.0% (95% CI 10.4–13.6%) for the MSDMD-unexposed pregnancies (Table 4). No statistically significant differences were observed when comparing the cohorts: *adjusted base model* RR 0.78 (95% CI 0.60–1.02) and *further adjusted model* RR 1.14 (95% CI 0.94–1.38) (Table 4; Supplemental Table 5a–b).

Ectopic pregnancy

The prevalence of ectopic pregnancies was 1.6% (95% CI 0.9–2.8%) for the only IFNB-exposed and 3.2% (95% CI 2.4–4.2%) for the MSDMD-unexposed pregnancies (Table 4). In the *adjusted base model*, the RR for ectopic pregnancies among the only IFNB-exposed pregnancies was 0.53 (95% CI 0.29–0.98), compared with the MSDMD-unexposed pregnancies (Table 4; Supplemental Table 5a). In the *further adjusted model*, the RR was 0.91 (95% CI 0.52–1.61) [Table 4; Supplemental Table 5(b)].

Elective termination

The prevalence of elective TOPFA was 0.7% (95% CI 0.1–2.4%) for the only IFNB-exposed and 0.8% (95% CI 0.2–2.1%) for the MSDMD-unexposed pregnancies, with no difference in the prevalence between the cohorts in the *adjusted base model* nor in the *further adjusted model* [Table 4; Supplemental Table 5(a, b)]. The prevalence of elective termination for other reasons than foetal anomaly was 16.3% (95% CI 12.2–21.0) for the only IFNB-exposed and 11.6% (95% CI 8.9–14.8%) for the MSDMD-unexposed pregnancies. After confounder adjustment, the prevalence of terminations for other reasons than foetal anomaly remained increased in the only IFNB-exposed, compared with the MSDMD-unexposed pregnancies: *adjusted base model* OR 1.71 (95% CI 1.06–2.78; *further adjusted model* OR 1.65 (95% CI 1.02–2.67) [Table 4; Supplemental Table 5(a, b)].

Stillbirth and non-live birth

The prevalence of stillbirth was 0.3% (95% CI 0.0–1.0%) for the only IFNB-exposed and 0.6% (95% CI 0.2–1.1%) for the MSDMD-unexposed pregnancies (Table 4). The corresponding prevalence for non-live births was 7.2% (95% CI 5.5–9.4%) and 4.8% (95% CI 3.7–6.1%). The prevalence of stillbirth or non-live birth did not differ between the cohorts, in the *adjusted base model* (stillbirth RR 0.41, 95% CI 0.09–1.93; non-live birth OR 1.47, 95% CI 0.95–2.28) nor in the *further adjusted model* (stillbirth RR 0.49, 95% CI 0.10–2.28; non-live birth OR 0.47, 95% CI 0.10–2.22) [Table 4; Supplemental Table 5(a, b)].

Complementary and sensitivity analyses

Comparing adverse pregnancy outcomes for the only IFNB-exposed pregnancies with the IFNB-unexposed pregnancies regardless of exposure to other MSDMDs (Supplemental Table 4), the results for all outcomes were consistent with the main analyses. The results on MCA corresponded to the main analyses when the exposure definition was restricted to the pre-pregnancy period or the first trimester (Supplemental Table 7).

Discussion

The prevalence of the composite outcome of serious adverse pregnancy outcome was not increased after exposure to only IFNB before or during pregnancy, compared with pregnancies unexposed to MSDMDs. Furthermore, the prevalence was not increased among the IFNB-exposed for individual adverse pregnancy outcomes, including MCA, spontaneous abortion, ectopic pregnancy, stillbirth, and non-live birth. The results remained, after altering confounder adjustment and exposure definition. An indication of higher prevalence of elective terminations for reasons other than foetal anomaly was detected among the only IFNB-exposed, compared with the unexposed pregnancies.

Serious adverse pregnancy outcome

We observed no increase in the prevalence of the composite outcome *serious adverse pregnancy outcome* for pregnancy events exposed to only IFNB,

Table 4. Prevalence of adverse pregnancy outcomes in pregnancy events of women with MS exposed to only IFNB compared with those unexposed to any MSDMDs ($n = 2831$ pregnancy events).

Adverse pregnancy outcome	Descriptive prevalence				Prevalence comparison	
	Only IFNB-exposed		MSDMD-unexposed		RR or OR[a] (95% CI)	
	n/N	% (95% CI)	*n/N*	% (95% CI)	Adjusted base model[b]	Further adjusted model[c]
Composite outcome: serious adverse pregnancy outcome[d,e] (consisting of elective TOPFA[d] MCA in live birth[e], and stillbirth)	16/718	2.2 (1.3–3.5)	56/1397	4.0 (3.0–5.2)	0.55 (0.31–0.96)	0.55 (0.31–0.95)
Major congenital anomaly (MCA)						
MCA in live births[e]	12/666	1.8 (0.9–3.1)	44/1330	3.3 (2.4–4.4)	0.52 (0.27–0.99)	0.52 (0.28–0.98)
MCA in live births, stillbirths and elective terminations	14/718	1.9 (1.1–3.2)	49/1397	3.5 (2.6–4.6)	0.57 (0.31–1.03)	0.55 (0.31–1.00)
Spontaneous abortion	66/797	8.3 (6.5–10.4)	197/1647	12.0 (10.4–13.6)	0.78 (0.60–1.02)	1.14 (0.94–1.38)
Ectopic pregnancy	13/797	1.6 (0.9–2.8)	53/1647	3.2 (2.4–4.2)	0.53 (0.29–0.98)	0.91 (0.52–1.61)
Elective termination[d]						
Elective TOPFA	2/295	0.7 (0.1–2.4)	4/474	0.8 (0.2–2.1)	1.94 (0.35–10.85)	0.80 (0.15–4.36)[f]
Elective termination for other reasons	48/295	16.3 (12.2–21.0)	55/474	11.6 (8.9–14.8)	1.71 (1.06–2.78)[a]	1.65 (1.02–2.67)[a]
Stillbirth and non-live birth						
Stillbirth	2/718	0.3 (0.0–1.0)	8/1397	0.6 (0.2–1.1)	0.41 (0.09–1.93)	0.49 (0.10–2.28)
Non-live birth[g]	52/718	7.2 (5.5–9.4)	67/1397	4.8 (0.7–6.1)	1.47 (0.95–2.28)[a]	0.47 (0.10–2.22)[a,f]

[a]For outcomes elective termination for other reasons and live birth, it was not possible to fit the log-binomial model and to produce RRs. Therefore, ORs produced by the logistic model are presented for these two outcomes.
[b]Adjusted for the following other covariates: country, year of pregnancy outcome, maternal age at LMP, number of previous pregnancies, any chronic diseases, and exposure to any teratogenic medications including steroids. The adjusted base model uses a predefined set of adjusting variables.
[c]Further adjusted for additional variables selected through variable selection, from the following candidate variables: time since MS diagnosis, duration of MS treatment, university hospital district, pre-pregnancy weight, pre-pregnancy BMI, number of previous abortions, smoking status during pregnancy, and number of foetuses in pregnancy (single *versus* multiple), as available in the data sources. The further adjusted model includes a step by step adjusting method based on a larger set of variables and their correlation with each outcome (Supplement 3). However, few adjusting variables were selected to the further adjusted models [Supplemental Table 5(b)].
[d]Elective terminations not available in the Swedish data, and thus includes exclusively Finnish data.
[e]MCA not available for year 2014 in the Finnish data.
[f]No adjusting variables were selected to the further adjusted models for the outcomes elective TOPFA and non-live birth (Supplemental Table 5b), according to the pre-defined selection criteria (Supplement 3).
[g]Non-live birth, defined as either an elective termination or a stillbirth, was used as an outcome, because the rare disease assumption did not hold for live births, which was defined in the full study protocol.[22]
BMI, body mass index; CI, confidence interval; IFNB, interferon beta; LMP, last menstrual period; MCA, major congenital anomaly; MS, multiple sclerosis; OR, odds ratio; RR, relative risk; TOPFA, termination of pregnancy due to foetal anomaly.

compared with those unexposed to MSDMDs. In fact, we detected decreased prevalence for the composite outcome among the IFNB-exposed, which could, however, result from residual confounding, as discussed in the methodological considerations in the following. The composite outcome has not been reported in the literature, hindering direct comparisons to previous studies.

Nevertheless, previous observational studies have reported no increased risk of MCA[11] or birth defects[17] among IFNB-exposed. Considering that the composite outcome in this study consisted of mainly MCA in live births, our result (from the Nordic settings) is deemed consistent with prior research in that exposure to IFNB does not increase the risk of serious adverse pregnancy outcomes in real-world settings.

MCA

Our results indicated that prevalence of MCA was not elevated among pregnancy events exposed to only IFNB compared with those unexposed to MSDMDs which is consistent with findings from clinical trials[36] and previous observational studies.[11–17] Previous, smaller cohort studies also found no increased risk of MCA among women with MS exposed to IFNB compared to those unexposed to MSDMDs,[11] and no increased risk of birth defects among women with MS exposed to IFNB compared with non-MS controls.[17] In addition, numerous authors have concluded that the observed prevalence of MCA or birth defects among IFNB-exposed pregnant MS patients did not differ from the corresponding prevalence in the general population[12–15] or have detected no MCA among IFNB-exposed.[16] Our and others'[11–17] results are also consistent with pre-clinical studies not finding IFNB teratogenic.[37] Further, the absence of an increased risk of MCA is biologically plausible, because the large IFNB molecule does not cross the placental barrier and therefore is unlikely to cause an independent embryotoxic effect.[37] Thus, this study strengthens the evidence that exposure to IFNB does not appear to increase the risk of MCA.

Spontaneous abortion

Our finding of comparable prevalence of spontaneous abortions among pregnancies exposed to only IFNB and those unexposed to MSDMDs is similar to the results reported in most previous observational studies.[11,14–17] Previous studies have also reported no increase in the prevalence of spontaneous abortions when IFNB-exposed have been compared with non-exposed MS patients,[11,16,18] healthy controls[17] or data on the general population.[13–16] In our study, the observed prevalence of spontaneous abortions among the only IFNB-exposed and MSDMD-unexposed pregnancies was also similar to the prevalence in the general population in Finland (8.6%) and Sweden (12.8%) during the study period (aggregate data obtained from the national authorities). One small prior study including 46 women[38] has reported a 6.9-fold increase in the risk of non-live births (90% spontaneous abortions) when comparing IFNB-exposed pregnancies with healthy women, enrolled in gestational weeks 4.2 and 9.3, respectively. The deviating result of an increased risk[38] may have been caused by overlooking early events in the healthy control group and the high proportion of smoking and alcohol use during pregnancy, and the higher maternal age among the IFNB-exposed. Considering these methodological limitations, our study, together with emerging evidence from other studies[11,14–17] suggests that IFNB exposure does not increase the risk of spontaneous abortions. Although pre-clinical studies report a dose-dependent abortive effect in very large doses of IFNB,[2–5] our results indicate that the effect is not present in humans in real-world settings, with likely dosing within the therapeutic ranges. However, our results represent exclusively spontaneous abortions recorded in hospitals, as discussed under methodological considerations.

Ectopic pregnancy

To our knowledge, our study is the first to compare the prevalence of ectopic pregnancies in women with MS exposed to IFNB, with any comparator group. The few, small, prior studies have detected zero to few ectopic pregnancies among women with MS exposed to IFNB,[11,14–16] hindering comparisons. Our finding of no increased risk was expected, considering that the causes for ectopic pregnancies[39] are unrelated to IFNB. The detected small decrease in the prevalence among the exposed was probably related to residual confounding (see methodological considerations). Nonetheless, our study provides valuable evidence suggesting that exposure to IFNB does not increase the risk of ectopic pregnancies in a large cohort representing real-world settings.

Elective termination

Previous research on elective terminations in IFNB-exposed women with MS, with or without foetal anomaly, is hampered by small study populations, few reported cases and typically, lack of a comparator group.[11,14–16,18] Thus, our study provides novel findings that in real-world settings the

prevalence of elective TOPFA is not increased among only IFNB-exposed, compared with MSDMD-unexposed pregnancies. However, the results suggested that in real-world settings, pregnant women with MS exposed to IFNB may be more likely to terminate their pregnancy for other reasons than foetal anomaly, compared with pregnant MS patients unexposed to MSDMDs. This could be explained by the only IFNB-exposed pregnancies being more commonly unplanned, by higher disease activity and by the women's fear of adverse pregnancy outcomes in the absence of information on the use of IFNB in pregnancy at the time. The result should be interpreted with caution, as residual confounding probably remained despite the confounder adjustment, the result being based on exclusively Finnish data, and the reasons for elective terminations being unknown.

Stillbirth and non-live birth

Previous studies on stillbirths, non-live births, or live births are small, have typically included only pregnant women with MS exposed to IFNB[14,15] or lack formal comparison by exposure status.[16] In the only study with a formal comparison,[11] live births were equally common among women with MS exposed and unexposed to IFNB. In another observational study, the prevalence of live births among women with MS exposed to IFNB was consistent with the general population.[15] Our result was consistent with the previous research,[11,15] suggesting that IFNB exposure among women with MS does not increase the risk of stillbirth or non-live birth. However, the use of non-live birth as the outcome in our study, instead of live births, hinders direct comparison with the prior studies.

Methodological considerations

This is the first large cohort study investigating adverse pregnancy outcomes among women with MS exposed to IFNB before or during pregnancy, with formal comparison by exposure status, adjusting for potential confounding factors. Our results are strengthened by the national coverage of the Finnish and Swedish registers, providing nationally generalisable results.

However, our results were limited by the underrepresentation of several outcomes in the used registries, leading to underestimating prevalence: spontaneous abortions were available exclusively from hospital data (Finland and Sweden); in Sweden, MCA information was extracted exclusively from the Medical Birth Register, and elective terminations were available for research exclusively, in Finland. The underestimation was, however, likely comparable between the cohorts, and thereby unlikely influenced the RR estimates.

Using outpatient pharmacy dispensing data hindered establishing whether the dispensed drugs were actually used; and detecting drugs administered in hospitals (e.g. natalizumab), which may have diluted the possible differences in the prevalence between the cohorts. In addition, exposure time could not be considered using the dispensing data. Further, the composite outcome required defining the drug exposure identically for its individual components, although the timing of exposure affects the individual outcomes differently: exposure before and in early pregnancy affects early pregnancy outcomes and MCA, while exposures during pregnancy affect outcomes at birth. However, our sensitivity analysis on MCA, limited to early exposures, confirmed the result of the main analyses. Yet, a limitation of this study was that exposures could not be investigated exclusively during pregnancy or by trimester, due to inadequate study power.

Our finding of no increased risk was strengthened by the consistency of the results in the analysis with the alternative comparator, in which outcomes were compared between the only IFNB-exposed pregnancies and the IFNB-unexposed pregnancies (regardless of exposure to other MSDMDs). The consistency of the results was expected, considering the low number of additional pregnancies in the alternative comparison group (328 pregnancies unexposed to IFNB and exposed to other MSDMDs). The low number of pregnancies exposed to other MSDMDs did not allow for analyses with adequate study power to directly compare the only IFNB-exposed pregnancies and the pregnancies exposed to MSDMDs other than IFNB.

Despite adjusting for several important potential confounding factors, residual confounding probably remained, possibly explaining the detected inverse associations. We were unable to adjust the analyses for socioeconomic position, some comorbidity, maternal alcohol and substance use,

paternal age, family history of pregnancies, and MS disease status and severity. Moreover, our adjustment for teratogenic drug use and variation in healthcare delivery, practice and behaviour may have been inadequate. Finally, few confounders were selected to the further adjusted models, according to the pre-defined selection criteria.

Lastly, this study was powered to detect an increase in the risk of the composite outcome serious adverse pregnancy outcome, limiting drawing definite conclusions on the less frequent outcomes. Furthermore, this manuscript exclusively reports the pre-defined primary and secondary outcomes of the registered PASS study, while the exploratory outcomes included in the study are reported elsewhere.

Clinical significance

The results of this large cohort study with a formal comparison group strengthen the evidence from prior literature reviews[19–21] and observational studies[11–18] that IFNB use among women with MS may be continued until pregnancy is confirmed, or beyond, if the risk of relapse and disability accumulation during pregnancy is to be reduced. Consequently, this study led to a change in the labels of the IFNB products in September 2019 in the European Union, and IFNB use may today be considered during pregnancy, if clinically needed.[2–6]

Conclusion

This largest cohort study to date on MS treatment in pregnancy found no evidence of an increased prevalence of the composite outcome *serious adverse pregnancy outcome*, MCA, spontaneous abortions, ectopic pregnancy, TOPFA, stillbirth or non-live birth after exposure to only IFNB before or during pregnancy, compared with women with MS who were unexposed to any MSDMDs. These results strengthen the previous evidence that exposure to IFNB does not increase the risk of these adverse pregnancy outcomes. Thus, IFNB use among women with MS may be continued until pregnancy is confirmed, or potentially beyond. Consequently, this study together with other evidence led to a change in the labels of IFNB products in September 2019 in the European Union, and IFNB use may today be considered during pregnancy, if clinically needed.

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The Nordic MS Pregnancy and Interferon Beta Study Group: Riho Klement (StatFinn & EPID Research), Minna Vehkala (StatFinn & EPID Research), Pia Vattulainen (StatFinn & EPID Research), Marta Korjagina (StatFinn & EPID Research), Hanna Gyllensten (StatFinn & EPID Research).

Conflict of interest statement

Katja Hakkarainen is an employee of StatFinn & EPID Research which performs commissioned pharmacoepidemiological studies for several pharmaceutical companies.

Rosa Juuti was at the time of conducting the study an employee of StatFinn & EPID Research which performs commissioned pharmacoepidemiological studies for several pharmaceutical companies.

Sarah Burkill was at the time of conducting the study an employee at the Centre for Pharmacoepidemiology, which receive grants from several entities including pharmaceutical companies.

Yvonne Geissbühler is an employee of Novartis Pharma AG.

Meritxell Sabidó is an employee of Merck KGaA, Darmstadt, Germany.

Catrinel Popescu is an employee and stockholder of Biogen.

Kiliana Suzart-Woischnik is an employee of Bayer AG.

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Juha Mehtälä was at the time of conducting the study an employee of StatFinn & EPID Research which performs commissioned pharmacoepidemiological studies for several pharmaceutical companies.

Shahram Bahmanyar is an employee at the Centre for Pharmacoepidemiology, which receives grants from several entities including pharmaceutical companies.

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ORCID iD

Katja M Hakkarainen https://orcid.org/0000-0002-7313-8532

Supplemental material

Supplemental material for this article is available online.

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