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Pregnancy and Infant Outcomes with Interferon Beta: Data from the European Interferon Beta Pregnancy Registry and Population Based Registers in Finland and Sweden

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INTRODUCTION

- Women with multiple sclerosis (MS) are often diagnosed and treated at child bearing age.[1] Therefore, family planning is frequently an important consideration for female patients undergoing treatment.
- There is no consensus in the literature regarding MS treatment up to and during pregnancy.
- Systematic reviews and registry studies suggest that MS and interferon-beta (IFNβ) exposure do not adversely affect pregnancy outcomes;[2,3] however, data on the risks of IFNβ during pregnancy were limited at the time of launch.
- To address this lack of evidence, a European IFNβ Pregnancy Registry was established and a population-based cohort study was conducted leveraging healthcare register data from two Nordic countries (Finland and Sweden).

OBJECTIVE

- To assess the prevalence of pregnancy and infant outcomes in IFNβ exposed pregnant women with MS from the pharmacovigilance databases of Bayer, Biogen, Merck and Novartis as well as the Nordic healthcare registers of Finland and Sweden.

METHODS

Study design and participants

- In the European IFNβ Pregnancy Registry, information on women identifying themselves to the Marketing Authorization Holders (Bayer, Biogen, Merck, Novartis) or healthcare professionals (HCP) as pregnant and exposed to IFNβ during pregnancy or within one month before conception between 2009 and 2017 were analysed.
  - Women were included for prospective follow-up if they met the following criteria:
    - Diagnosed with MS
    - Treated with one of the five approved IFNβ therapies
    - Pregnant with unknown outcome
  - Since 2015, women without a confirmed MS diagnosis, pregnancies not confirmed by a HCP and solicited reports from prospectively identified appropriate Patient Support Programmes (PSPs) were included in the European IFNβ Pregnancy Registry.
- In Finland and Sweden, linked data from several national health registers covering the study period 1996–2014 were analysed (EPID study, EUPAS13054, NCT02749396).
  - Women were included if they met the following criteria:
    - Diagnosed with MS
    - Pregnancy with a recorded outcome during the study period
  - Women with MS treated with IFNβ regardless of treatment with other disease modifying drugs (DMDs) during pregnancy or within three months (six months for mitoxantrone and cladribine) prior to last menstrual period were considered as exposed. Women with MS unexposed to any MS DMD were considered non-exposed.

Study Size

- In the European IFNβ Pregnancy Registry, ≥827 women exposed to IFNβ with known pregnancy outcomes were required to detect a doubling in prevalence of congenital anomalies compared with the general population (prevalence: 3/100), with 80% power and a 5% level of significance.
- In the Nordic registers, the minimum detectable effect size between patients exposed to MS treatments and those non-exposed was approximately 1.72 (IFNβ only) and 1.66 (IFNβ ± other DMDs) in terms of relative risk using 80% power and a 5% two-sided significance level.
  - These calculations were based on estimated sample sizes of 294 (IFNβ only), 368 (IFNβ ± other DMDs) and 1270 (non-exposed).

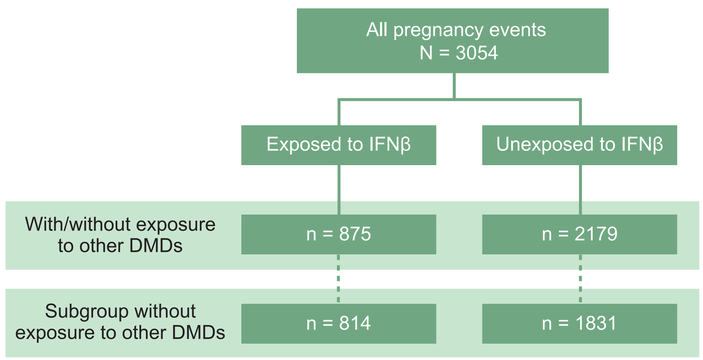
Study Analysis

- Pregnancy outcomes collected and analysed in the European IFNβ Pregnancy Registry and Nordic registers included live births, congenital anomalies, ectopic pregnancy, spontaneous abortions, elective pregnancy terminations and still births.
  - The European IFNβ Pregnancy Registry calculated prevalence rates for each pregnancy outcome using the cumulative number of reported pregnancy outcomes as the denominator.
  - The Nordic registers calculated prevalence rates based on the number of cases in which that outcome would be possible, therefore the denominator was subject to change.
    - All pregnancy events were used as the denominator for the ectopic pregnancies and spontaneous abortions.
    - Elective terminations, stillbirths and live births were used as the denominator for serious adverse pregnancy outcomes.
- Sensitivity analyses were conducted to evaluate selection biases resulting from the inclusion of cases without a confirmed MS diagnosis, pregnancies not confirmed by a HCP and solicited reports from appropriate PSPs in the European IFNβ Pregnancy Registry.

RESULTS

- The European IFNβ Pregnancy Registry collected 2447 pregnancy reports, of which 948 (38.7%) had reported pregnancy outcomes.
- There were 3054 pregnancy events with known pregnancy outcomes from the Nordic registers. The disposition of pregnancies from the Nordic registers are shown in **Figure 1**.

Figure 1. Disposition of pregnancies from the Nordic registers



Pregnancy outcomes

Table 1. Cumulative number of pregnancy individual case safety reports by pregnancy outcome from the European IFNβ Pregnancy Registry

	Total (N = 948)	Exact 95% CI
Outcome of pregnancy, n (%)		
Ectopic pregnancy	4 (0.4)	0.12–1.08
Spontaneous abortion	101 (10.7)	8.76–12.79
Elective termination (fetal defects)	6 (0.6)	0.23–1.37
Elective termination (no fetal defects/unknown)	40 (4.2)	3.03–5.70
Stillbirth with fetal defects	1 (0.1)	0.00–0.59
Stillbirth without fetal defects	2 (0.2)	0.03–0.76
Live birth with congenital anomaly	17 (1.8)	1.05–2.86
Live birth without congenital anomaly	777 (82.0)	79.36–84.36

CI, confidence interval; **IFNß**, interferon beta; **n**, number of pregnancy events.

- Overall, 82% (777/948) of pregnancies with known outcomes from the European IFNβ Pregnancy Registry had an outcome of live birth without congenital anomalies. Ectopic pregnancies, spontaneous abortions, elective terminations, stillbirths and live births with congenital anomalies comprised the other 18% of pregnancies with known outcomes (**Table 1**).
- The prevalence of spontaneous abortions and live births with congenital anomalies was consistent with those reported in the general population (10.7% vs. up to 21%[4] and 1.8% vs. 2.1–4.1%,[5,6] respectively).
  - The prevalence of malformations in live births was 2.1% (17/794).
- Data from the Nordic registers showed that up to 98.2% (728/741) of pregnancies in the exposed cohort had an outcome of live birth without congenital anomalies. This is similar to the 96.7% (1457/1506) of pregnancies in the non-exposed cohort that also had an outcome of live birth without congenital anomalies (**Table 2**).

Table 2. Cumulative number of pregnancy individual case safety reports by pregnancy outcome from the Nordic registers

	Exposed Cohorts				Non-exposed Cohort	
	IFNβ only		IFNβ ± Other DMDs			
	Total	Exact 95% CI	Total	Exact 95% CI	Total	Exact 95% CI
Outcome of pregnancy, n/N* (%)						
Ectopic pregnancy	13/814 (1.6)	0.85−2.72	13/875 (1.5)	0.79–2.53	54/1831 (2.9)	2.22–3.83
Spontaneous abortion	66/814 (8.1)	6.33−10.20	69/875 (7.9)	6.19–9.87	204/1831 (11.1)	9.74–12.67
Elective termination (fetal defects)†	2/295 (0.7)	0.08−2.43	2/307 (0.7)	0.08–2.33	4/474 (0.8)	0.23–2.15
Elective termination (no fetal defects/ unknown)†	48/295 (16.3)	12.25−20.99	48/307 (15.6)	11.76–20.19	55/474 (11.6)	8.86–14.83
Stillbirth (unknown)	2/735 (0.3)	0.03−0.98	2/793 (0.3)	0.03–0.91	8/1573 (0.5)	0.22–1.00
Live birth with congenital anomaly	12/683 (1.8)	0.91−3.05	13/741 (1.8)	0.94–2.98	49/1506 (3.3)	2.42–4.28
Live birth without congenital anomaly	671/683 (98.2)	97.0–99.1	728/741 (98.2)	97.0–99.1	1457/1506 (96.7)	95.7–97.6

*Denominators may vary according to the possibility of an outcome as calculated by Nordic healthcare registers;
†Swedish data not included.
CI, confidence interval; **IFNβ**, interferon beta; **n**, number of pregnancy events; **N**, denominator for the specific analysis.

- Analyses showed a comparable prevalence of spontaneous abortions versus the non-exposed cohort; 8.1% (IFNβ only), 7.9% (IFNβ ± DMDs) vs. 11.1%.
- A comparable prevalence of congenital anomalies in live births was observed versus the non-exposed population (1.8% in both exposed cohorts) vs. 3.3%.
- The prevalence of ectopic pregnancies versus the non-exposed population (1.6% IFNβ only, 1.5% IFNβ ± DMDs vs. 2.9%) were found to be numerically lower in women treated with IFNβ.

Birth weights

- A systematic literature review has shown that IFNβ may be associated with a lower mean birth weight but not a low birth weight (<2,500 g).[7]
- A study of 251 IFNβ-exposed pregnancies from a prospective German pregnancy registry found no difference in birth weight between newborns with or without IFNβ exposure.[2]
- The birth weights of newborns in pregnancies with live births without congenital anomaly collected in the Nordic registers are presented in **Table 3**.
- In the Nordic registers, birth weights ranged from 580.0 g to 5160.0 g, with 5.0%, 4.7% and 5.8% of newborns recorded as having a low or very low birth weight in the IFNβ and IFNβ ± DMD exposed and non-exposed cohorts, respectively (**Table 3**).
- Overall, the mean birth weights in the exposed (3421.2 g, IFNβ, and 3434.3 g, IFNβ ± DMD) and non-exposed cohorts (3389.3 g) are similar and consistent with results from the prospective German pregnancy registry.[2]
- Due to the characteristics of the European IFNβ Pregnancy Registry, birth weights were not collected systematically.

Table 3. Birth weight in pregnancies with live birth without congenital anomaly from the Nordic registers

	Exposed Cohorts		Non-exposed Cohort (N = 1506)
	IFNβ only (N = 683)	IFNβ ± Other DMDs (N = 741)	
Birth Weight, n (%)			
Very low, <1500 g	8 (1.2)	8 (1.1)	16 (1.1)
Low, 1500–2499 g	26 (3.8)	27 (3.6)	71 (4.7)
Normal, 2500–3999 g	551 (80.7)	597 (80.6)	1224 (81.3)
High, 4000–4500 g	83 (12.2)	92 (12.4)	166 (11.0)
Very high, >4500 g	14 (2.0)	16 (2.2)	26 (1.7)
Missing	1 (0.1)	1 (0.1)	3 (0.2)
Range, g (min – max)	(580.0–5160.0)	(580.0–5160.0)	(685.0–5100.0)
Mean, g (+/-SD)	3421.2 (602.0)	3434.3 (598.6)	3389.3 (584.1)

SD, standard deviation; **n**, number of low birth rates reported; **N**, number of pregnancy events.

CONCLUSIONS

- **The European IFNβ Pregnancy Registry showed no evidence that IFNβ exposure before conception and/or during pregnancy, adversely affected pregnancy or infant outcomes; this is consistent with data collected from the Nordic registers.**

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DISCLOSURES

KH has received honoraria and research support from Bayer, Biogen, Teva, Novartis, Sanofi Genzyme and Merck. **YG** is an employee of Novartis Pharma AG. **MS** is an employee of Merck KGaA, Darmstadt, Germany. **CP** is an employee and stockholder of Biogen. **AA** is an employee of Bayer AG. **JK** is an employee of Synteract GmbH. **PH** is a member of the European Interferon Beta Pregnancy Study Group. **AO** has nothing to disclosure. **PK** is an employee of StatFinn and EPID Research which performs commissioned pharmacoepidemiological studies for several pharmaceutical companies.

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