INTRODUCTION

- Women with multiple sclerosis (MS) are often diagnosed and treated at childbearing age. Therefore, family planning is 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 study registries suggest that MS and interferon-beta (IFN) exposure do not adversely affect pregnancy outcomes. However, data on the risks of IFN during pregnancy were limited at the time of launch.
- To address this lack of evidence, a European IFN Pregnancy Registry was established and a population-based cohort study was conducted leveraging healthcare registry data from two Nordic countries (Finland and Sweden).

OBJECTIVE

- To assess the prevalence of pregnancy and infant outcomes in IFN-exposed pregnant women with MS from the pharmaceutical databases of Bayer, Biogen, Merck and Novartis as well as the national healthcare registries of Finland and Sweden.

METHODS

Study design and participants

- In the European IFN Pregnancy Registry, information on women identified through the Marketing Authorization Holders (Bayer, Biogen, Merck, Novartis) or healthcare professionals (HCPs) as pregnant with a recorded outcome during the study period 1996–2014 were included.
- In Finland and Sweden, linked data from several national health registers covering the study period 1996–2014 were used.
- Women were included if they met the following criteria:
  - Diagnosed with MS
  - Treated with one of the five approved IFN therapies
  - Pregnant with a recorded 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 IFN Pregnancy Registry.
- In Finland and Sweden, linked data from several national health registers covering the study period 1996–2014 were used.
- 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 (DMTs) 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 IFN Pregnancy Registry, ≥27 women exposed to IFNβ without confirmed outcome during pregnancy 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% two-sided significance level.
- 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 1.68 (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 IFN Pregnancy Registry and Nordic registries included live births, congenital anomalies, ectopic pregnancy, spontaneous abortions, elective terminations, stillbirths and neonatal deaths.
- The European IFN 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 estimations of adverse pregnancy outcomes and stillbirths.
- 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 not confirmed by a HCP and solicited reports from appropriate PSPs in the European IFN Pregnancy Registry.

RESULTS

- The European IFN Pregnancy Registry collected 2447 pregnancy reports, of which 948 (38.7%) had reported pregnancy outcomes. There were 3554 pregnancy events with known pregnancy outcomes from the Nordic registers. The disposition of pregnancies from the Nordic registers are shown in Figure 1.

- Overall, 82% (777/948) of pregnancies with known outcomes from the European IFN 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 were consistent with those reported in the general population (10.7% vs. up to 21% and 1.8% vs. 2.1–4.1%, respectively).
- The prevalence of malformations in live births was 2.1% (1779/948).

- Data from the Nordic registers showed that up to 9.8% (738/741) of pregnancies in the exposed cohort had an outcome of live birth without congenital anomaly. This is similar to the 96.7% (4517/4699) of pregnancies in the non-exposed cohort and this is consistent with data on the outcome of live birth without congenital anomaly (Table 2).

- The prevalence of ectopic pregnancies versus the non-exposed population (1.6% IFNβ only) was similar to 1.5% (IFNβ + DMDs vs. 2.9%) to be found numerically lower in women treated with IFNβ.

- 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).
- 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.
- 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 589.0 g to 5160.9 g with 5.0%, 7.7% 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.

- Due to the characteristics of the European IFN Pregnancy Registry, birth weights were not collected systematically.

CONCLUSIONS

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

REFERENCES

7. PK HealthCare, Chester, UK, and funded by Bayer AG, Biogen, Merck KGaA, and Novartis Pharma AG.
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DISCLOSURES

K.H. has received research and travel support from Bayer, Biogen, Teva Neuroscience, and Merck Serono, and is a member of the European Interferon Beta Pregnancy Study Group. K.H. is on the speaker's and advisory boards of Merck Serono and Biogen. E.K. is a consultant and speaker for Bayer, Biogen, Novartis, and Merck Serono. E.K. is an employee of Merck KGaA, Darmstadt, Germany, and has received unrestricted grants and/or speaker honoraria and/or scientific advisory board honoraria PK HealthCare, Chester, UK, and funded by Bayer AG, Biogen, Merck KGaA, and Novartis Pharma AG.

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