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Original Research

Pregnancy outcomes in female multiple sclerosis patients exposed to intramuscular interferon beta-1a or peginterferon beta-1a reported in a German Patient Support Programme – results from the non-interventional post-authorization safety study PRIMA

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Abstract

Background: Based on data from two large cohort studies, a label update became applicable for the class of interferon beta therapies in 9/2019, allowing interferons during pregnancy and breastfeeding.

Objective: To assess pregnancy outcomes of women with multiple sclerosis (MS) exposed to peginterferon beta-1a or intramuscular interferon beta-1a therapy (IFN).

Design: Non-interventional post-authorization safety study.

Methods: PRIMA was conducted from April to October 2021 in Germany. Retrospective pregnancy data were retrieved from adult female patients diagnosed with relapsing-remitting MS or clinically isolated syndrome, exposed to IFN before or during pregnancy and registered in the patient support programme (PSP) of the marketing authorization holder's MS Service Centre. The primary endpoint was the outcome of pregnancy. Prospective postpartum data were collected from mothers reporting live births.

Results: In total, 426 women reporting 542 pregnancies between December 2001 and July 2020 (14 pregnancies after the label update) were enrolled. Among patients with confirmed exposure during pregnancy ($N=362$), 306 pregnancies (84.5%) resulted in live births (77.6% without defects, 1.9% with defects and 4.4% preterm). Spontaneous abortion, elective termination and stillbirth were reported in 10.9%, 2.8% and 0.2% of the cases, respectively. Higher rates of spontaneous abortions were reported in women with continuous IFN use.
A total of 162 women completed the questionnaire for 192 live births within the prospective study part. Mothers restarted IFN therapy or switched to another disease-modifying therapy postpartum in 51.0% and 14.1% of cases, respectively. 158/192 infants (82.3%) were breastfed [34/158 (21.5%)] during IFN therapy. Postpartum relapse activity was low (mothers of 87.3% of breastfed infants remained relapse-free during lactation).

Conclusion: Overall, the prevalence of spontaneous abortions and congenital anomalies of females exposed to IFN exposure before or during pregnancy was within the range reported for the general population. Most mothers paused IFN during pregnancy and breastfeeding. Relapse activity during pregnancy and lactation was observed to be low. These real-world data from a PSP corroborate European and Scandinavian registry data.

Trial registration: NCT04655222, EUPAS38347.

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Introduction

Pregnancy and birth outcomes are major concerns for many women with multiple sclerosis (MS). The advancement of effective disease-modifying therapies (DMTs) in recent decades has enabled disease activity to be well controlled and lifted family planning to the forefront of regularly addressed topics in patient–physician consultations. Many registries have been established worldwide to investigate the impact of DMTs on pregnancy.[1,2] According to recent data from a mildly affected MS population, the return of disease activity in the initial 6-month postpartum period is significantly less pronounced than the previously described 30% from historical populations with more severe disease and may not exceed the pre-pregnancy level.[3] Furthermore, evidence suggests that exclusive breastfeeding prompts a protective effect against postpartum relapses.[4,5]

As clinical trials rarely include pregnant women, there is limited safety information on the use of DMTs in pregnancy. Most DMTs are either contraindicated or their use is limited based on benefit–risk evaluations. Interferon beta therapies are well-established platform DMTs with long-term experience for patients with relapsing MS.[6,7] As of 30 June 2022, over 81,000 patients have been treated with peginterferon beta-1a, and over 627,000 patients have been treated with intramuscular (IM) interferon beta-1a, based on clinical trials and post-marketing settings.[8] Two large prospective cohort studies have provided safety data in women of childbearing age with MS exposed to interferon beta. An analysis of cumulative data from 2447 prospective pregnancies with 948 outcomes reported in the European Interferon Beta Pregnancy Registry showed that the prevalence of spontaneous abortions (10.7%) and live births with congenital anomalies (1.8%) was comparable with the numbers reported in the general population (up to 21% spontaneous abortions, 2.1–4.1% congenital anomalies).[9] A population-based cohort study examining healthcare registry data from two Nordic countries (Finland and Sweden) including 2831 pregnancies found no evidence that interferon beta exposure before conception and/or during pregnancy adversely affected pregnancy or infant outcomes in comparison with women not exposed to DMTs.[10] Assessing the safety of potential breast milk exposure to interferon beta therapy in women from the German Multiple Sclerosis and Pregnancy Registry indicated no increase in the risk of common adverse infant outcomes in the first year of life,[11] supporting results from earlier observations.[12,13]

Based on clinical evidence from the cohort studies, the European Medicines Agency (EMA) approved a label update for the class of interferon beta therapies in September 2019: If clinically needed, the use of interferon beta may be considered during pregnancy. Interferon beta therapies can be used during breastfeeding.[14–18] In 2020, the US Food and Drug Administration (FDA) approved interferon beta therapies for use during breastfeeding.

To complement pregnancy label updates with patient-reported real-world data from a German patient support programme (PSP), this study was conducted to evaluate the impact of exposure to peginterferon beta-1a or IM interferon beta-1a before and during pregnancy on pregnancy outcome, breastfeeding behaviour and child development.

Methods/patients

Study design and patients

The single-centre non-interventional, open-label voluntary post-authorization safety study PRIMA (Pregnancy outcomes in patients exposed to Peginterferon beta-1a and Interferon beta-1a reported in a German patient support programme) was conducted from April to October 2021 in Germany. The study design, consisting of a retrospective and a prospective part, was reviewed and approved by the Ethics Committee of the Ärztekammer Berlin (file no. Eth-19/21)

and is consistent with the ethical standards included in the Declaration of Helsinki of 1964 and its later amendments. The PSP of the marketing authorization holder's German MS Service Centre (MSSC) provided the patient pool for this study. Patients diagnosed with relapsing-remitting multiple sclerosis (RRMS) or clinically isolated syndrome receiving either peginterferon beta-1a therapy (RRMS only) or IM interferon beta-1a therapy were eligible to participate in the PSP if they provided their written informed consent to the privacy policy of the registration form. For patients reporting a pregnancy, a pregnancy form was completed at the MSSC. Pregnant women were considered exposed if they had received at least one dose of interferon beta at any time before conception or during pregnancy. After the expected date of birth, the pregnancy outcome was completed in the pregnancy form (pregnancy outcome report) containing data from births and infants. Adult females with a pregnancy report and a pregnancy outcome report available at the MSSC were eligible for the retrospective study part of this study. The prospective part was restricted to patients whose pregnancy outcome in the retrospectively collected data was a live birth. Participants in the prospective study part were required to understand the purpose of the study and provide a signed and dated study-specific informed consent form. To systematically collect pregnancy outcome data, MS patients reporting 'live birth' outcomes completed a standardized questionnaire *via* telephone interview. The questionnaire was based on the German children's medical check-up booklet. These results have been published separately.[19] The study was registered at clinicaltrials.gov (NCT04655222) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EUPAS38347).

Outcomes

The primary objective was to evaluate the impact of exposure to peginterferon beta-1a or IM interferon beta-1a before and during pregnancy. Accordingly, the primary endpoint was the outcome of pregnancy as reported by the mother in the pregnancy outcome report. Secondary endpoints were: (a) treatment behaviour with peginterferon beta-1a or IM interferon beta-1a therapy during pregnancy; (b) disease-modifying therapy (DMT) after pregnancy; (c) breastfeeding under peginterferon beta-1a or IM interferon beta-1a therapy; (d) MS relapses in women with peginterferon beta-1a or IM interferon beta-1a therapy before, during and after pregnancy; (e) time to first MS relapse after the introduction of the first supplemental feedings in women with peginterferon beta-1a or IM interferon beta-1a therapy during lactation and (f) Expanded Disability Status Scale (EDSS) before, during and after pregnancy.

Statistical analysis

Descriptive statistical analysis of all collected data was performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA). Subgroup analyses included stratification by interferon exposure during pregnancy (stopped during pregnancy and resumed postpartum, stopped during pregnancy and not resumed postpartum, continuous exposure, whereby continuous was defined as having no stop date reported on the pregnancy form) as well as type of interferon (pegylated *versus* non-pegylated). Due to the observational nature of the study, no confirmatory hypothesis testing was performed, and all statistical tests were considered exploratory. Generally, no imputation methods (such as the last observation carried forward) were applied for missing data. The primary endpoint included all patients enrolled. All other secondary endpoints were analysed in the live birth population, which included patients with live birth who had completed the standardized questionnaire. Due to the exploratory nature of the study, which did not include formal hypothesis testing, no formal sample size calculation was conducted. The sample size depended on how many patients were eligible to participate in this observation and agreed to provide data for the questionnaire.

Results

A total of 426 women reporting 542 pregnancies were enrolled in the study (Figure 1). Pregnancies occurring during IM interferon beta-1a therapy were registered from 21 December 2001 onwards and those occurring during peginterferon beta-1a therapy from 25 August 2015 onwards. Only 14 pregnancies (2.6%) were reported after the label update. A total of 466 pregnancies resulted in live births and qualified for the prospective study part. The standardized patient questionnaire was completed for 192 live births from 162 women. In this live birth population, only one pregnancy (0.5%)

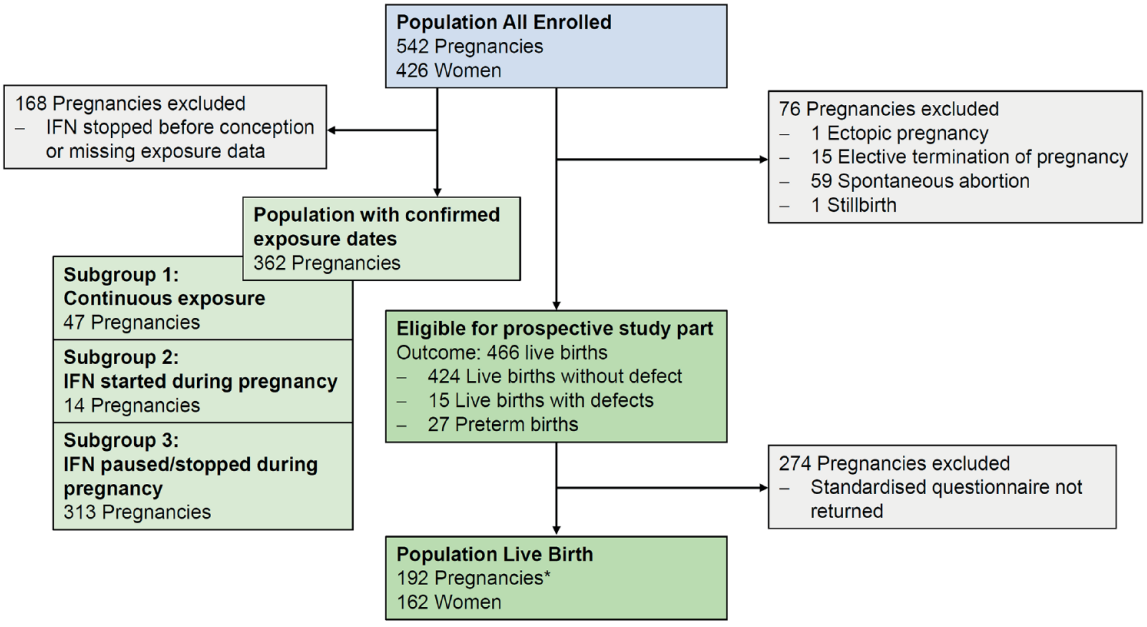

Figure 1. Patient flow. The subgroups of patients starting IFN during pregnancy and those who paused or stopped during pregnancy were not mutually exclusive and overlapped in 12 cases in the population with confirmed exposure dates. *The live birth population consisted of seven pregnancies with continuous exposure, 5 pregnancies, in which IFN was started during pregnancy, 2 pregnancies, in which IFN was paused during pregnancy and restarted within 1 week postpartum, 96 pregnancies, in which IFN was paused during pregnancy and restarted >1 week postpartum, 20 pregnancies, in which IFN was stopped during pregnancy and not restarted postpartum, and 62 pregnancies, in which IFN therapy was either stopped before pregnancy or data was missing.
IFN, IM interferon beta-1a or peginterferon beta-1a; IM, intramuscular.

was reported after the label update. The mean (SD) time between birth and postpartum data collection was 4.7 ± 2.5 years (interquartile range: 3.1–5.3). The mean (±SD) duration of interferon exposure during pregnancy in the live birth population was 7.2 ± 8.8 weeks, based on available data to calculate the extent of exposure (126/192, 65.6%). Treatment was stopped most frequently during the first trimester (n = 117). The mean exposure time for females who paused during pregnancy and restarted more than a week after live birth (n = 96) was 5.2 ± 4.2 weeks and for those who stopped during pregnancy and did not restart after live birth (N = 20) 5.2 ± 3.4 weeks.

Patient demographics are summarized in Table 1. The mean (±SD) age of the women was 32.9 ± 4.7 years and ranged from 19 to 50 years. The number of children per mother ranged from 1 to 4, including 10 pairs of twins and 1 triplet. Most patients had none (42.7%) or one (38.0%) previous pregnancy. The birth occurred spontaneously in about half of the cases (49.4%); the caesarean section was medically indicated in 21.0% and elective in 7.2%. The median duration of pregnancy was 39.5 gestation weeks. A *post hoc* analysis of gestational age stratified by exposure subgroups of the live birth population did not show a difference between continuous exposure (mean 39.6 ± 1.4 weeks, based on n = 7) and those who paused therapy (mean 39.3 ± 2.1 weeks, based on n = 96). It should be borne in mind, however, that data for the calculation of gestational age were available only for seven children in the subgroup with continuous exposure; thus, these data cannot be regarded as representative. The degree of maternal disability (assessed only in the live birth population) was in the lower range [mean (±SD) EDSS before pregnancy 0.3 ± 0.8, range 0–4] and remained unchanged during and after pregnancy. Of note, too few EDSS assessments (N = 14) during pregnancy were reported to allow a statistically valid interpretation.

Table 1. Patient demographics.

Population all enrolled	***N*=426**
Age (years), mean (SD)[a,b]	32.9 ± 4.7
Number of children, *N* (%)	
1	329 (77.2)
2	80 (18.8)
3	14 (3.3)
4	3 (0.7)
Number of previous pregnancies, *N* (%)[b]	
0	182 (42.7)
1	162 (38.0)
2	36 (8.5)
3	12 (2.8)
4	2 (0.5)
Missing	32 (7.5)
Type of birth, *N* (%)[b]	
Spontaneous	268 (49.4)
Induced	44 (8.1)
Instrumentally supported	12 (2.2)
Elective caesarean	39 (7.2)
Medically indicated caesarean	114 (21.0)
Missing	65 (12.0)

[a]Refers to the age documented on the pregnancy report form.
[b]In case of more than one documented pregnancy under treatment, data from the most recent pregnancy report were used.
SD, standard deviation.

Primary outcome

Overall, 78.2% (424/542) of pregnancies resulted in live births without defects, 2.8% (15/542) of babies had defects and 5.0% (27/542) were born prematurely, that is, born before 37 completed weeks of gestation. Spontaneous abortion occurred in 10.9% (59/542), whereas pregnancy was terminated electively in 2.8% (15/542). One baby (0.2%) was stillborn (gene defect) [Figure 2(a)]. The majority of spontaneous abortions occurred at gestation week 10 (22/59). Five premature births occurred in gestation week 27 and the remaining from weeks 29 through 37. Among live births with defects, 3/15 occurred prematurely (weeks 30, 32 and 34) and the remaining 12/15 between weeks 38 and 41. Elective terminations were performed predominantly between weeks 6 and 14, with two terminations in week 20 and one in week 21. Of the 15 reported birth defects, 13 showed no certain pattern and 2 were upon further analysis no birth defects. Data on weight and size were obtained within the prospective study part from 192 infants of the live birth population. The median weight was 3360 g (range 1240–4750) and the median length was 51 cm (range 34–57). Nine infants (4.7%) were small for gestational age.

Excluding patients who stopped interferon before conception or had missing exposure data led to a similar distribution of outcomes: 77.6% (281/362) live births without defects, 1.9% (9/362) live birth with defects, 4.4% (16/362) preterm, 0.3% (1/362) ectopic pregnancies, 3.3% (12/362) elective termination, 12.2% (44/362) spontaneous abortion and 0.3% (1/362) stillborn [Figure 2(b)].

Stratified by product, the distribution of outcomes differed between the groups. In the peginterferon beta-1a group, the rate of spontaneous abortions [15.4% (37/241) *versus* 7.3% (22/301)], preterm births [6.4% (13/241) *versus* 4.7% (14/301)], stillbirths [0% (0/241) *versus* 0.3% (1/301)] and elective terminations [3.3% (8/241) *versus* 2.3% (7/301)] was higher and the rate of live births with defects [1.2% (3/241) *versus* 4.0% (12/301)] was lower than in the IM interferon beta-1a group [Figure 2(c) and (d)]. Overall, the proportion of live births was higher in the IM interferon beta-1a group than in the peginterferon beta-1a group [89.7% (270/301) *versus* 81.3% (196/241)].

The prevalence of spontaneous abortions and elective terminations of pregnancy was particularly high in the subgroup of patients who took peginterferon beta-1a or IM interferon beta-1a continuously before and during pregnancy [36.2% (17/47) and 10.6% (5/47), respectively] [Figure 2(e)]. Birth defects did not occur more frequently in the subgroup of patients with continuous exposure. Only one infant out of 47 was born with defects. Figure 2(f) and (g) shows the outcomes for the subgroups starting IFN during

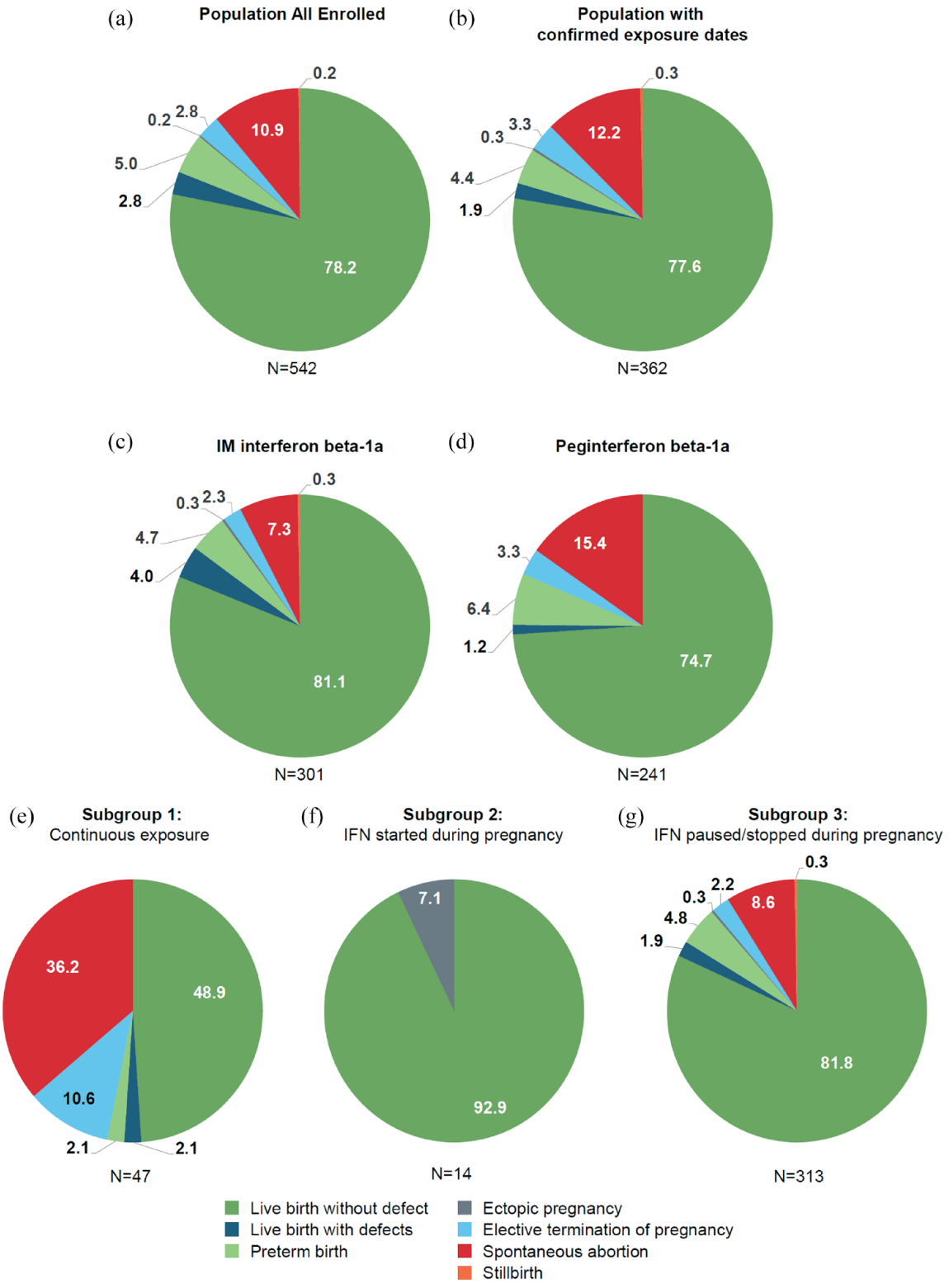

Figure 2. Pregnancy outcome for the total population with exposure to IFN (a), the population with confirmed exposure dates (b), subgroups, stratified by product (c and d) and by time of exposure (e–g). *N* and percentages refer to the number of pregnancies. Patients who stopped IFN before conception or had missing exposure data were excluded from this analysis.
IFN, IM interferon beta-1a or peginterferon beta-1a; IM, intramuscular.

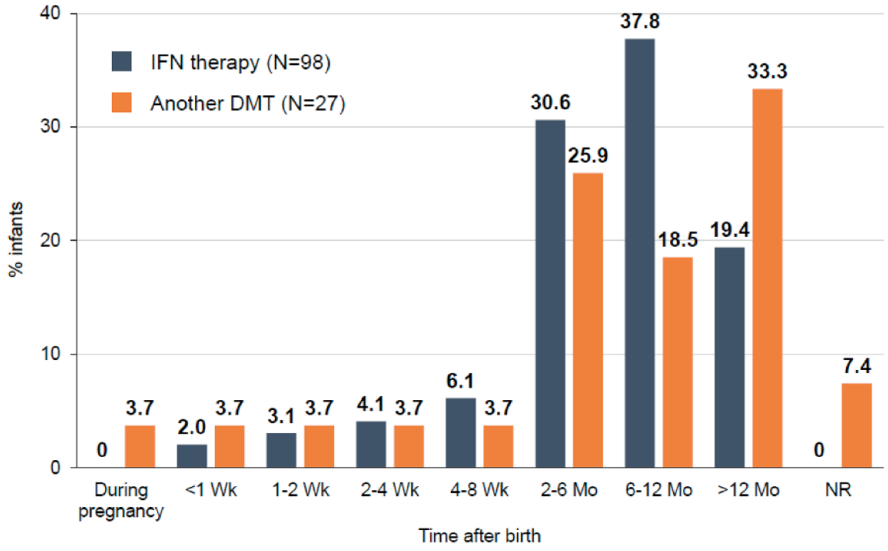

Figure 3. Restart of MS medication postpartum. *N* and percentages refer to the number of infants.
DMT, disease-modifying therapy; IFN, IM interferon beta-1a or peginterferon beta-1a; Mo, months; MS, multiple sclerosis; NR, not reported; Wk, weeks.

pregnancy [Figure 2(f)] and pausing or stopping IFN during pregnancy [Figure 2(g)]. Stratified by product, the rates for spontaneous abortions were 23.8% (5/21) in the continuous IM interferon beta-1a subgroup and 46.2% (12/26) in the continuous peginterferon beta-1a subgroup.

Complications during pregnancy (e.g. bleeding, gestational diabetes, pre-eclampsia, MS relapse, abortion, cervical weakness) occurred in 110 cases (20.3%). The occurrence of complications was similar between the treatment groups (20.6% in the IM interferon beta-1a group *versus* 19.9% in the peginterferon beta-1a group).

To eliminate the influence of sibling data, sensitivity analyses were conducted for the total and live birth populations limited to one pregnancy per woman. Except for the primary endpoint, results did not differ from the analyses including multiple pregnancies per woman. The sensitivity analysis yielded a higher prevalence of live births without defects than the primary analysis (85.0% *versus* 78.2%) and a lower prevalence of spontaneous abortions (6.1% *versus* 10.9%).

Secondary endpoints

All secondary endpoints were analysed in the live birth population ($N=192$).

DMT exposure postpartum

In total, peginterferon beta-1a or IM interferon beta-1a therapy was restarted after 98 live births (51.0%). The time when treatment was restarted postpartum was heterogeneous in the population (Figure 3). Another DMT was started after 27 (14.1%) live births [glatiramer acetate, $n=7$; fingolimod, $n=6$; teriflunomide, $n=6$; ozanimod, $n=2$; SC interferon beta-1a, $n=2$; ocrelizumab, $n=1$; others (rituximab, intravenous immunoglobulin, high-dose vitamin D (Coimbra protocol)), $n=3$], whereby in one-third of cases (33.3%) mothers waited more than 1 year to start another DMT (Figure 3). Concomitant medication was used during 171 pregnancies. The most frequent concomitant medication was folic acid, administered during 155 pregnancies (90.6%), followed by iron supplements ($n=39$), thyroid hormone ($n=35$), vitamins ($n=18$) and magnesium supplements ($n=14$).

Lactation

In total, 158/192 children in the live birth population (82.3%) were breastfed. Of those, only 34/158 (21.5%) were breastfed while the mother was taking interferon (peginterferon beta-1a, $n=16$; IM interferon beta-1a, $n=18$). The duration of breastfeeding was heterogeneous. In the peginterferon beta-1a group, a higher proportion

Table 2. Duration of breastfeeding and occurrence of relapses during lactation.

Parameter	Total	Breastfeeding under exposure		
	n = 158	All IFN *n* = 34	IM IFN *n* = 18	PegIFN *n* = 16
Duration				
⩽1 week	11 (7.0)	7 (20.6)	1 (5.6)	6 (37.5)
>1 week and up to 1 month	13 (8.2)	8 (23.5)	3 (16.7)	5 (31.3)
>1 month and up to 6 months	90 (57.0)	13 (38.2)	9 (50.0)	4 (25.0)
>6 months and up to 12 months	30 (19.0)	5 (14.7)	4 (22.2)	1 (6.3)
>12 months	14 (8.9)	1 (2.9)	1 (5.6)	0
Relapses				
Relapse-free during lactation	138 (87.3)	30 (88.2)	16 (88.9)	14 (87.5)
Relapses during lactation	18 (11.4)	3 (8.8)	2 (11.1)	1 (6.3)
Relapse-free after the introduction of supplementary feeding	102 (64.6)	22 (64.7)	14 (77.8)	8 (50.0)
Relapses during supplementary feeding	45 (28.5)	10 (29.4)	3 (16.7)	7 (43.8)
Relapses prior to first supplemental feeding	8 (5.1)	1 (2.9)	1 (5.6)	0

IFN, intramuscular interferon beta-1a or peginterferon beta-1a; IM IFN, intramuscular interferon beta-1a; PegIFN, peginterferon beta-1a.

stopped breastfeeding within the first month postpartum compared to the IM interferon beta-1a exposed group (Table 2). The majority of infants (121/158; 76.6%) had additional food introduced between the fourth and sixth months of life.

MS relapses before, during and after pregnancy

In 34/192 cases (17.7%) in the live birth population, at least one MS relapse occurred within 12 months before pregnancy, mostly a single relapse (85.3%, data not shown). During pregnancy, relapses occurred in 16 cases (8.3%) but rarely more than one. Postpartum relapses were reported in 63/192 cases (32.8%) at various timepoints (Figure 4). Up to 18 months postpartum, relapse activity remained low, not exceeding one relapse within each 2-month time period (data not shown). The proportion of relapses occurring before, during and after pregnancy was similar between peginterferon and IM interferon beta-1a groups (Figure 4).

Data on the occurrence of relapses during lactation are summarized in Table 2. During lactation, the mothers of 138/158 breastfed infants (87.3%) remained relapse-free, and most of them (mothers of 102/158 infants, 64.6%) remained so after the introduction of supplementary food. Mothers with exposure to peginterferon beta-1a during breastfeeding had more relapses during supplementary feeding than mothers exposed to IM interferon beta-1a; however, patient numbers in these subgroups were too small ($N = 16$ and 18, respectively) to back this observation (Table 2).

Discussion

PRIMA – a post-authorization safety study under real-world conditions, systemically assessed 542 pregnancy outcomes in 426 women with MS receiving interferon therapies before or during pregnancy under real-world conditions. The majority (78.2%, 424/542) resulted in live birth. The prevalence of spontaneous abortions (10.9%, 59/542) was within the lower range reported for

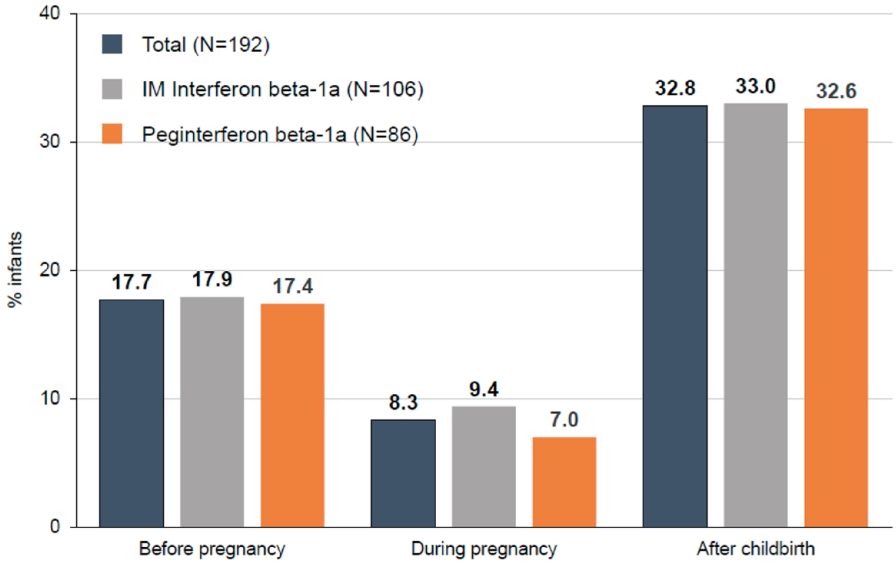

Figure 4. MS relapses within 12 months before, during and after pregnancy. Data are shown for the total live birth population and stratified by product. *N* and percentages refer to the number of infants.
IM, intramuscular; MS, multiple sclerosis.

the general population (10–21%)[20] and similar to that observed in the European Interferon Beta Pregnancy Registry (10.7%)[9] as well as in Finnish and Swedish registries for interferon-exposed women with MS (8.3%) and DMT-unexposed women with MS (12%).[10] The prevalence of congenital anomalies (2.8%, 15/542) was similar to the proportion reported in the European Interferon Beta Pregnancy Registry (1.8%) and within the range reported in the general population (2.1–4.1%).[21,22] Pregnancy was terminated electively in 2.8% (15/542) and 0.2% of pregnancies (1/542) resulted in stillbirth. Swedish and Finnish registries reported a higher prevalence of elective terminations (0.7% due to congenital anomalies and 16.3% due to other reasons) and a similar prevalence for stillbirth (0.3%).[10] Overall, these results confirm previous evidence collected from large cohort studies on the safety of pregnant women and interferon exposure that interferon beta therapies do not increase the risk for spontaneous abortions, preterm birth, or major congenital malformations.[10,23,24] In addition, the inclusion of women who received their last interferon dose prior to conception indicated that late complications from interferon exposure are not expected regardless of timing.

In the small subgroup of patients who took interferons continuously before and during pregnancy (47/542), the prevalence of spontaneous abortion (17/47; 36.2%) exceeded the rate reported for the general population, which raises the question of teratogenic effects. Preclinical studies in animal models (rhesus monkeys) with a comparable form of interferon beta-1a at very high doses (exceeding the dose for use in humans 40-fold) have shown anovulatory and abortive effects.[15] Similar dose-dependent reproductive effects were also observed with other forms of interferon alpha or beta.[25] However, no teratogenic effects or effects on foetal development have been observed with doses used in clinical practice so far.[9,10,26–28] The age of the women in the subgroup was comparable between the outcomes (data not shown). Due to the descriptive nature of the analysis, no additional risk factors were explored that may predispose women to spontaneous abortion, for example, environmental factors. However, a recent population-based cohort study using the Finnish and Swedish registries indicated no impact of maternal and newborn characteristics on the prevalence of serious adverse pregnancy outcomes.[23] Due to the extended injection interval of peginterferon beta-1a (once every 2 weeks), exposure times may be similar in the continuous group and that of women stopping interferon beta-1a after realizing pregnancy, which is normally at about sixth to seventh week. Furthermore, the higher rates may be a result of reporting bias.

Patients experiencing complications during pregnancy might seek counsel with the PSP more often than patients having a subjectively inconspicuous course of pregnancy. In particular, peginterferon beta-1a was new on the market which may prompt a higher rate of vigilance. Nevertheless, the effect of long-term interferon exposure on the rate of spontaneous abortions warrants further investigation. So far, studies have not shown higher rates of spontaneous abortion when exposed to interferon in the first trimester.[9,29,30] As none of the larger registries (European Interferon Beta Pregnancy Registry, the Scandinavian registries) provided data on continuous exposure so far,[9,10] data on longer exposure rates with more detailed information of exposure weeks from the newly initiated Pregnancy Registry within MSBase (implemented 11 May 2020)[31] and the INFORM registry[32] are eagerly anticipated.

The prevalence of elective termination of pregnancy (5/47; 10.6%) was higher in the subgroup who took interferons continuously before and during pregnancy than in women who stopped or paused treatment during pregnancy. However, the sample size of this subgroup was too small to draw statistically robust conclusions. Most pregnancies occurred before the 2019 label update. At this time, interferon therapies were regarded as contraindicated in pregnant women. If women decided to terminate the pregnancy once it became known, the question of whether to stop medication became unnecessary. This may have led to selection bias predisposing women with elective termination to the continuous group.

Stratified by product, the rate of spontaneous abortions was surprisingly higher in the peginterferon than in the IM interferon beta-1a group (15.4% *versus* 7.3%), although still within the range reported for the general population.[20] The age reported on the pregnancy form as well as EDSS before pregnancy was similar between the groups. Although pegylation of the native interferon beta-1a molecule leads to enhanced exposure (half-life: 10 h for interferon beta-1a[15] *versus* 78 h for peginterferon beta-1a[18]) through increased molecular size and thereby reduced the rate of clearance by glomerular filtration, peginterferon beta-1a did not show any accumulation after repeated applications in a phase I study.[33] Therefore, the approval of peginterferon beta-1a with regard to fertility and pregnancy corresponds to that of non-pegylated interferon beta-1a formulations. This could be confirmed in the registry studies.[9,10]

Only 14 pregnancies (2.6%) were reported after the September 2019 label update and before the data cut. As most in the PSP registered pregnancies occurred before the label update, treatment was paused or stopped during the majority of pregnancies (57.7%). Whereas the contraindication prior to the label update may account for the small percentage of exposure during pregnancy (8.7% continuous intake, 2.6% treatment initiation during pregnancy), another reason may be that interferon beta therapies are recommended to treat mild to moderate MS[34] and the protective effect of pregnancy[35] was considered sufficient in pregnant women with MS. Data from the Pregnancy in Multiple Sclerosis (PRIMS) study indicated the protective effect of pregnancy on relapse risk.[1,36] Hence, the common practice for women was to avoid any substance exposure after performing a benefit–risk assessment when pregnancy becomes known and to discontinue the DMT. The mean duration of exposure in the live birth population (7.2 weeks) was longer than the time reported in the European Interferon Beta Pregnancy Registry (4.3 weeks)[9]; however, only 65.6% of the population provided sufficient data to calculate the timeframe. Thus, exposure time should be regarded as an estimate.

Although breastfeeding has been allowed during interferon beta-1a or peginterferon beta-1a therapy since September 2019, only one-fifth of infants were breastfed during their mother's exposure to interferon (21.5%). This proportion is much lower than the 53% (39/74) reported in the German Multiple Sclerosis and Pregnancy Registry, which enrolled a population between 2011 and 2018, thus prior to the label update.[11] Overall, relapse activity remained low up to 18 months postpartum, corroborating results from previous studies including mildly affected populations.[3] Most mothers remained relapse-free during lactation (87.3%). A rise in relapses was observed after the introduction of supplementary feeding, confirming a potential benefit of exclusive breastfeeding on the risk of postpartum relapses that have been reported in a systematic review and meta-analysis.[4] This protective effect abates with the introduction of supplementary feeding.[4,5]

The high rate of folic acid use may indicate a high rate of planned pregnancies as timely commencement of folate-containing pre-natal vitamins, ideally before conception, is generally recommended during pregnancy to avoid neural tube defects in the foetus.[37] However, our data do not provide information on whether folic acid was initiated before conception or when pregnancy became known.

This study is limited by its non-interventional design, reliance on patient questionnaires and the absence of a direct comparator group. The major proportion of pregnancies (97.4%) were registered before the interferon pregnancy and lactation label update in September 2019, which limits conclusions regarding the peginterferon beta-1a or IM interferon beta-1a treatment behaviour for pregnant women or women becoming pregnant in real life since the timepoint of the label update. The main data source for the retrospective data capture was the MSSC database, that is the entered pregnancy report, which was completed as soon as pregnancy became known, and the pregnancy outcome report, which was completed after completion of pregnancy. Data missing on the pregnancy report or the pregnancy outcome report as well as prospective data were collected during a single point of time telephone interview. These data may be prone to patients' recall bias. Since the outcomes were documented as reported by the mothers, the data in the call centre's database may include medical inaccuracies and misconceptions. The entries are not checked for medical plausibility as that is not the purpose of the MSSC database. Among participants in the PSP with live births ($N = 466$), only 162 women with 192 pregnancies (35.4%) agreed to answer the questionnaire of the prospective study part. Due to the time gap between birth and data collection (mean 4.7 years), many patients could not be reached anymore because they moved on or did not feel inclined to participate in a telephone survey. Notwithstanding, the high rate of non-participants limits the reliability of study findings. There may be selection bias towards patients experiencing potential issues being more likely to decline participation in the survey. Data were analysed descriptively, which did not allow any predictive analyses with regards to regression models. Hence, no conclusions can be drawn regarding the cause of spontaneous abortions or congenital anomalies. Another limitation was the incomplete data set, which is a common issue in non-interventional studies. In particular, the small patient numbers in the subgroups who received interferon therapies continuously during pregnancy did not provide statistically robust results. In case of incomplete data regarding MS medication, it was assumed that the treatment was interrupted, which may lead to underreporting of patients continuing therapy during pregnancy. The study design has advantages in terms of patient heterogeneity as it collected data in a real-world setting. The strength of this study is the use of a unified pregnancy report form, which was completed as soon as the pregnancy and its outcome became known. Sensitivity analyses have been performed to rule out bias from sibling data. The higher prevalence of live births without defect (85.0% *versus* 78.2%) and lower prevalence of spontaneous abortions (6.1% *versus* 10.9%) in the population limited to one pregnancy per woman compared to the primary analysis indicated that some of these women required multiple pregnancies to bear a living child.

Despite the nationwide inclusion of MS patients, the patient population registered in the PSP of the MSSC included in this descriptive research can be prone to bias and may not be representative of the entire RRMS population in Germany. PSPs are accompanying treatment support programmes designed to address the needs of the individual patient and support adherence and persistence to DMTs.[38–40] Current PSPs can assist patients in a variety of ways: the components of the PSP of the MSSC include patient coaching, education on side effect management, addressing individual needs, promoting awareness of monitoring and assessing individual patient safety *via* individual phone calls. In addition, digital service offerings are particularly helpful for scheduling and keeping doctor's appointments, for information about the disease, and tips on everyday life and lifestyle. The observed participation in PSPs offered by companies was very low (7.6%), as was patient's awareness in real-world settings.[39]

The updated label indications for pregnancy and breastfeeding include all approved interferon beta products. The present non-interventional study investigated patients receiving peginterferon beta-1a or IM interferon beta-1a registered in a PSP. Whether results can be extrapolated to other interferon beta formulations cannot be derived from these study data, it is however supported by

data from the European Interferon Beta Pregnancy Registry[9] as well as Swedish and Finnish registry data,[10] which led to the label update of all interferon beta products by the EMA and FDA.

In conclusion, these real-world data obtained within the scope of a PSP are in line with German, Scandinavian and European registry data. Overall, the prevalence of spontaneous abortions and congenital anomalies of females exposed to interferon beta before or during pregnancy was within the range reported for the general population. As most registered pregnancies occurred before the label update, the majority of women paused treatment during pregnancy and breastfeeding. The observed low relapse activity corroborates data indicating a reduced relapse risk during pregnancy and lactation. The impact of interferon exposure during the second and third trimesters will be further explored in the new Pregnancy Registry within MSBase (implemented 11 May 2020)[31] and the INFORM registry.[32]

Declarations

Ethics approval and consent to participate

The study design was reviewed and approved by the Ethics Committee of the Ärztekammer Berlin (file no. Eth-19/21). Patients registered in the patient support programme provided their written informed consent to the privacy policy of the registration form. Participants in the prospective study part were required to provide a signed and dated study-specific informed consent form.

Consent for publication

Not applicable.

Author contributions

Juliane Klehmet: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

Yvonne Begus-Nahrmann: Conceptualization; Methodology; Writing – review & editing.

Kirsi Taipale: Conceptualization; Formal analysis; Methodology; Writing – review & editing.

Gabriele Niemczyk: Conceptualization; Methodology; Writing – review & editing.

Karin Rehberg-Weber: Conceptualization; Formal analysis; Methodology; Project administration; Supervision; Writing – review & editing.

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Competing interests

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Availability of data and materials

Data insight can be provided on reasonable request.

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