Introduction
Multiple sclerosis (MS) is common in young women1 and due to the early start of disease-modifying therapies (DMTs),2 it is important to evaluate the risk of drug exposure during pregnancy. Although interferon-beta (IFN-beta) was the first class of approved immunmodulatory drugs in MS, available data on the safety of IFN-beta exposure during pregnancy are still conflicting.3–19 The risk for spontaneous abortions was seen in animal studies under high doses of IFN-beta,20 but this was not confirmed in most of the human studies.3,4,10,12,13,15,18

The most concerning risk observed in humans is a possible reduction in the mean birth weight,4,12,15,19 length,4,12 and preterm birth.12 These risks are potentially troublesome, because preterm birth and lower birth weight are associated with an increased risk of adverse health outcomes well into adulthood.21–23 However, limitations of the previous studies were a small sample size,4,7,12,13,15,17–19 a retrospective study design,4,7,9,14,16,17 the lack of confounder analysis,4,7,10,18 or the absence of a control group.3,10,13 This is of special importance, as MS itself might be associated with a
reduction in birth weight. Therefore, the objective of our study was to compare pregnancy outcomes of women with MS exposed to IFN-beta after the last menstrual period with pregnancy outcomes of women not exposed to DMTs during pregnancy.

Methods

Participants

We collected information on pregnancy outcomes of 445 women with relapsing-remitting MS who voluntarily enrolled in the nationwide German Multiple Sclerosis and Pregnancy Registry (Deutsches Multiple Sklerose und Kinderwunsch Register; DMSKW) between January 2008 and December 2013. Only pregnant women were included in this study. The majority of women responded to advertisements or were actively recruited after referral by their treating clinicians or MS nurses. We published the details of the registry established in 2006 elsewhere and the outcomes of 95 pregnancies of the unexposed group were already analyzed and published. The registry is supported by industry funding, but the sponsors have no role in the registry design, data collection, analyses, or dissemination of results. The registry is approved by the local institutional review board of the Ruhr University Bochum and all women gave their written informed consent.

Data collection

Women were asked to complete a structured, interviewer-administered questionnaire primarily by phone or in-person during visits to our outpatient clinic after study entry, in each remaining trimester of pregnancy and months 1, 3, 6, and 12 postpartum. Briefly, during pregnancy a detailed history of MS (diagnosis, disease activity, treatments) and reproductive history are obtained along with exposure to other medications and potential confounders (including alcohol, smoking, and drug abuse). Follow-up interviews obtained other information on the state of pregnancy/delivery, any alteration in pregnancy status, type of delivery, outcome of pregnancy, medication, and well-being of the child. For any adverse outcome in the newborns, the treating pediatrician was contacted to verify the medical problem.

Definition of exposures

IFN-beta-exposed pregnancies were defined as last injection administered after the last menstrual period (LMP). A pregnancy was considered unexposed to DMTs if (1) the last injection of IFN-beta or glatiramer acetate was administered any time before the LMP, (2) the last infusion of natalizumab was given more than 3 months before the LMP, (3) the last dosage of fingolimod was given more than 2 months before the LMP, (4) the last infusion of rituximab was given more than 4 months before the LMP, (5) the last dosage of azathioprine was given any time before the LMP, (6) the last infusion of mitoxantrone was given more than 6 months before the LMP, or (7) the woman was never been treated with DMTs. All definitions of exposure are based on five half-life times or the genotoxic effect (for mitoxantrone) of the molecule.

Maternal smoking status was defined as smoking (in any trimester yes/no). The body mass index (BMI) from the expectant mothers’ record of prenatal and natal care at the beginning of pregnancy was defined as the weight in kilograms divided by the square of the height in meters (kg/m²). Steroid exposure during first trimester (yes/no) and any steroid use during any trimester of pregnancy (yes/no) were obtained.

Definition of outcomes

Our primary outcomes of interest were the mean birth weight and mean birth length of newborns born at term and the number of newborns born preterm. We also looked for babies small for gestational age (SGA) defined as live birth greater than 37 completed gestational weeks (gws) and fetal weight <2500 g. Preterm delivery was defined as live birth less than 37 completed gw. Other outcomes were defined as follows—spontaneous abortion: fetal loss before 22 completed gw; fetal death: fetal loss 22 gw or fetal weight >500 g; early neonatal death: death of the newborn occurring during the first 7 days of life (0–6 days); live birth with one or more congenital anomaly (CA). CA was specified as a defect in organogenesis, major CA as structural defects of the body and/or organs that impair viability and/or require intervention. Minor CA was defined as small structural developmental disturbances that do not impair viability and do not need to be treated. CAs were rated and classified in accordance with the guidelines of European Surveillance of Congenital Anomalies (EUROCAT) by a teratologist (A.Q.-W.). Birth weight and birth length of the newborns were analyzed as reported in the expectant mothers record of prenatal and natal care. Elective abortion and ectopic pregnancies were also documented.

Statistical analysis

The means and standard deviation for the descriptive statistics were compared using the two-sided t-test if

http://msj.sagepub.com
the continuous variables were normally distributed. In case of non-normality distributed continuous variables, the Wilcoxon rank sum test was used and chi-square/Fisher test to assess differences between categorical variables.

We used multivariate logistic regression to estimate the crude odds ratio (OR) with 95% confidence intervals (CIs) to compare IFN-beta-exposed pregnancies to non-DMT-exposed pregnancies and 79 of the unexposed pregnancies who were treated with IFN-beta before pregnancy, but had stopped IFN-beta before pregnancy for binary outcomes and linear regression to compare birth weights and length of full-term newborns among the groups. We considered the following potential confounders in the linear regression model: age at conception, BMI at the beginning of pregnancy, smoking during pregnancy (yes/no), steroid use during any trimester of pregnancy due to MS relapses (yes/no), and gender of the newborn.

We also assessed propensity score (PS)-adjusted logistic regression, as a method of observational studies to account for bias in a choice of treatment or behavior (in our case being exposed to IFN-beta) in a nonrandomized setting. We controlled for sufficient overlap in the PSs between IFN-beta-exposed and -unexposed women. PS quintiles were then used in the logistic regression model. We considered the following potential confounders in the PS model for all outcomes: age at conception, BMI, smoking during pregnancy (yes/no), disease duration, steroid use during any trimester of pregnancy due to MS relapses (yes/no), and gender of the newborn.

Results

Study sample
In all, 445 pregnancies of women with MS exposed to IFN-beta (n = 251; 174 exposed to IFN-beta 1a; 77 exposed to IFN-beta 1b) or without DMT exposure during pregnancy (n = 194) were analyzed. All pregnancies were included into the registry during pregnancy and no woman was lost to the follow-up. Most women were enrolled at the beginning of the second trimester. The vast majority (n = 246; 98.01%) of IFN-beta-exposed patients stopped treatment during the first trimester of pregnancy, mostly (n = 179; 71%) with the detection of pregnancy before gw 6. Only three women stopped their IFN-beta medication during the second trimester and two women during the third trimester. The median duration of exposure was 32 days (range 0–252 days).

We included 194 non-DMT-exposed pregnancies as a control group without any significant differences in basic demographics between the two groups (Table 1). A total of 137 (70.62%) women in the control group were treated with a DMT at some point prior to pregnancy, but had stopped treatment prior to pregnancy. Most (n = 79; 40.72%) were treated with IFN-beta, 33 (17.01%) with glatiramer acetate, 18 (9.28%) with natalizumab, 3 (1.55%) with fingolimod, 2 (1.03%) with rituximab, and 1 (0.52%) with mitoxantrone prior to pregnancy.

In all, 89 women experienced one or more relapses during pregnancy; 16 women experienced two relapses and 3 had three relapses. Women unexposed to DMTs at the onset of pregnancy had significantly more relapses during the entire pregnancy and during the first trimesters and received more corticosteroid treatments during pregnancy than women with early pregnancy exposure to IFN-beta (Table 1).

Pregnancy outcomes
We documented 405 live births, 226 exposed to IFN-beta and 179 in the non-DMT-exposed group. The details of the pregnancy and delivery outcomes are presented in Figure 1.

The mean gw at birth was nearly identical between both groups. We only observed a mean difference of 5 g between the birth weight of the exposed newborns, compared to the unexposed. The mean birth length also was very similar between the exposed and unexposed newborns (Table 2). Excluding preterm births only maternal BMI (p = 0.004) and the sex of the newborn (p = 0.007) were associated with a significant influence of the birth weight in the adjusted linear regression model.

Corticosteroid use during any trimester of pregnancy (β = −108,02; p = 0.145) and smoking (β = −180,05; p = 0.199) were associated with lower birth weight, although not statistically significant.

The number of live births was similar in both groups (Table 2). Early pregnancy exposure to IFN-beta was not associated with an increased risk of spontaneous abortion, malformations, preterm birth, or SGA (Table 2).

In all, 37 of 40 pregnancies not resulting in live births were spontaneous abortions in the first trimester.
We observed a fetal death and an early neonatal death in the only twin pregnancy in our cohort (Table 3). The female twin (NB8) was born dead at the 23rd gw with a birth weight of 475 g. She was reanimated and died a few hours later. The male twin (NB9) was born alive with a birth weight of 550 g and survived for 2 days.

The mother received IFN-beta for 4 years, stopped treatment in the 8 gw, and was not exposed to other substances during pregnancy. Another fetal death (NB20) occurred in the control group at 22nd gw. The mother received IFN-beta for 1 year, stopped treatment 1 month prior to pregnancy, and was not exposed to other substances during pregnancy. Most women delivered naturally in both groups. In 21

---

**Table 1. Characteristics of the study sample.**

<table>
<thead>
<tr>
<th></th>
<th>Exposed to IFN-beta* (# 251)</th>
<th>Non-exposed to DMTs (# 194)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at conception, mean (SD), years</td>
<td>31.54 (4.09)</td>
<td>32.20 (4.28)</td>
<td>0.101</td>
</tr>
<tr>
<td>Disease duration, mean (SD), years</td>
<td>5.23 (3.96)</td>
<td>5.78 (4.66)</td>
<td>0.711</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>24.05 (4.86)</td>
<td>24.21 (4.44)</td>
<td>0.737</td>
</tr>
<tr>
<td>Smoking during pregnancy (#, %)</td>
<td>7 (2.79)</td>
<td>8 (4.12)</td>
<td>0.439</td>
</tr>
<tr>
<td>Gestational week of entry into the cohort, median (range), gw</td>
<td>13 (1–39)</td>
<td>15 (1–39)</td>
<td>0.178</td>
</tr>
<tr>
<td><strong>Relapses and steroid treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapses during pregnancy (#, %)*</td>
<td>36 (14.34)</td>
<td>53 (27.32)</td>
<td>0.001</td>
</tr>
<tr>
<td>Relapses during first trimester (#, %)</td>
<td>16 (6.37)</td>
<td>31 (15.98)</td>
<td>0.001</td>
</tr>
<tr>
<td>Relapses during second trimester (#, %)*</td>
<td>17 (7.49)</td>
<td>17 (9.50)</td>
<td>0.433</td>
</tr>
<tr>
<td>Relapses during third trimester (#, %)</td>
<td>14 (6.19)</td>
<td>14 (7.82)</td>
<td>0.480</td>
</tr>
<tr>
<td>Steroids during pregnancy (#, %)</td>
<td>24 (9.56)</td>
<td>28 (14.43)</td>
<td>0.113</td>
</tr>
<tr>
<td>Steroids during first trimester (#, %)</td>
<td>12 (4.78)</td>
<td>14 (7.22)</td>
<td>0.277</td>
</tr>
<tr>
<td>Steroids during second trimester (#, %)*</td>
<td>8 (3.52)</td>
<td>10 (5.60)</td>
<td>0.296</td>
</tr>
<tr>
<td>Steroids during third trimester (#, %)</td>
<td>9 (3.98)</td>
<td>10 (5.59)</td>
<td>0.417</td>
</tr>
</tbody>
</table>

# : number of pregnancies; IFN: interferon; DMT: disease-modifying therapy; SD: standard deviation; BMI: body mass index; gw: gestational week.

a Median duration of exposure: 32.0 days, range 0–252 days.

b Sixteen women experienced two relapses and three women three relapses during pregnancy.

c Based on the number of women at risk in the respective trimester; exposed group: first trimester n = 251, second trimester n = 227, third trimester n = 226; unexposed group: first trimester n = 194, second trimester n = 180, third trimester n = 179.

---

**Figure 1.** Outcomes of IFN-beta-exposed and non-DMT-exposed pregnancies. Flowchart of the IFN-beta-exposed and -unexposed pregnancies enrolled in the study. Presented are the details of the pregnancy and delivery outcomes. IFN-beta: interferon-beta; CA: congenital anomaly; CS: cesarean section. CA-, CS-, and preterm birth-rates are based on the number of live births, elective abortions, early neonatal, and fetal death; exposed n = 227; unexposed n = 181.

*One twin pregnancy ended in a fetal death and an early neonatal death.
cases, the use of vacuum extractors (exposed: 5.29%; unexposed: 5.03%; \( p = 0.907 \)) and in four cases the use of forceps (exposed: 0.88%; unexposed: 1.12%; \( p = 0.811 \)) was needed. Delivery via cesarean section (c-section) was similar between IFN-beta-exposed women compared with controls (Table 2), but women with IFN-beta exposure were more likely to deliver with emergency c-section (\( p = 0.010 \)).

We also compared the exposed group with the 79 women who were treated with IFN-beta and stopped this therapy before pregnancy. We could not observe any significant differences regarding mean birth weight (85.78 g higher in IFN-beta exposed newborns, \( p = 0.196 \)), mean birth length (0.44 cm longer in IFN-beta-exposed newborns, \( p = 0.356 \)), or the number of live births (OR = 1.02; 95% CI 0.44–2.36; \( p = 0.966 \)), spontaneous abortions (OR = 1.29; 95% CI 0.51–3.27; \( p = 0.597 \)), CAs (OR = 0.54; 95% CI 0.15–1.89; \( p = 0.333 \)), c-sections (OR = 1.15; 95% CI 0.66–1.99; \( p = 0.619 \)), or SGA (OR = 1.11; 95% CI 0.23–5.43; \( p = 0.903 \)). Only the risk for a preterm birth was higher in the 79 women who stopped IFN-beta before pregnancy (OR = 0.40; 95% CI 0.17–0.90; \( p = 0.026 \)).

### Fetal abnormalities

A total of 16 (3.94%) major malformations of non-genetic origin and one Wolf–Hirschhorn syndrome (aberration of chromosome 4) occurred in our cohort (Table 3). More newborns of women with corticosteroid exposure during first trimester (4/26; 15.38%; \( p = 0.013 \)) were born with malformations.

### Discussion

In this large prospective cohort with 251 IFN-beta-exposed pregnancies, we did not observe any negative impact of early pregnancy exposure on pregnancy outcomes compared to unexposed pregnancies born to women with MS.

In our cohort, the birth weight and length of IFN-beta-exposed babies were nearly identical between exposed and unexposed newborns. Newborns with IFN-beta exposure during early pregnancy were not at higher risk of preterm birth or being SGA. These findings are important, as both birth weight and preterm birth are associated with future health outcomes. Infants with lower birth weight have an increased risk for learning difficulties and behavioral problems, and lower birth weight has been associated with several cardiovascular risk factors. Preterm birth also is linked to lower birth weight and to many other complications impacting health well into adulthood. Except one, all previous studies have not shown an increased risk for preterm birth after IFN-beta exposure during early pregnancy, so these findings are inconsistent. Prior studies in exposed to IFN-beta during early pregnancy had shown a birth weight reduction in IFN-beta-exposed pregnancies around 100 g. But these studies were much smaller (\( n = 17, 488, 12, 69, 15, 2319 \)) and a higher percentage of women smoked during pregnancy (13% and 11%) compared to our cohort (3%).

Besides smoking, the most common confounder of an association between drug exposure and pregnancy outcomes in MS pregnancy registries is corticosteroid use. Corticosteroid use during pregnancy

---

**Table 2.** Crude odds ratios and propensity scores of pregnancy outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Crude odds ratio</th>
<th>Propensity score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>p-Value</td>
</tr>
<tr>
<td>Live birth</td>
<td>0.76 (0.39–1.48)</td>
<td>0.416</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>1.47 (0.73–2.97)</td>
<td>0.281</td>
</tr>
<tr>
<td>Major CA</td>
<td>0.53 (0.20–1.41)</td>
<td>0.204</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>0.60 (0.29–1.22)</td>
<td>0.156</td>
</tr>
<tr>
<td>c-Section</td>
<td>1.12 (0.75–1.68)</td>
<td>0.572</td>
</tr>
<tr>
<td>SGA</td>
<td>0.77 (0.26–2.22)</td>
<td>0.624</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjusted</th>
<th>OR 95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>3272.28 (563.61)</td>
<td>3267.46 (609.81)</td>
</tr>
<tr>
<td>Birth length, mean (SD), cm</td>
<td>50.73 (3.30)</td>
<td>50.88 (3.45)</td>
</tr>
<tr>
<td>gw, mean (SD)</td>
<td>38.91 (2.25)</td>
<td>38.78 (2.36)</td>
</tr>
</tbody>
</table>

OR: odds ratio; PS: propensity score; CI: confidence interval; CA: congenital anomaly; c-section: cesarean section; SGA: small for gestational age; SD: standard deviation; gw: gestational week.
is considered a weak teratogen, with an increased risk for cleft lip or palate if given between gws 8 and 11\(^\text{28}\) and associated with a lower birth weight.\(^\text{29}\) High-dose corticosteroid treatment for relapses reduced birth weight by 108 g on average in our cohort. Interestingly, women without IFN-beta exposure during early pregnancy experienced significantly more relapses during the first trimester of pregnancy and for this reason also received more corticosteroids. This was also observed by the Italian group\(^\text{30}\) and is a noteworthy finding. Although we observed more malformations in corticosteroid-exposed pregnancies, the specific pattern of cleft lip or palate\(^\text{28}\) was not detected. This finding requires further investigation.

Our results, that early pregnancy exposure to IFN-beta, a large molecule with a short half-life time, does not affect the birth weight, is pharmacological plausible as the human fetus gains most of its weight at the end of pregnancy.

We did not observe a higher risk for other important adverse pregnancy outcomes in our study including second trimester miscarriages, or congenital anomalies. The incidence of congenital anomalies was similar in the IFN-beta-exposed and the non-DMT-exposed group, reflecting the background risk (6.7%) of all congenital malformations (minor and major) in the general unexposed population in Germany.\(^\text{26}\)

This study was not designed to assess the risk of spontaneous abortions, the majority of which occur by 13 weeks of gestation. Although we did not detect a difference between groups, less than 50% of women joined our study prior to 13 weeks. Interpreted in the
context of other similar studies,3,4,10,12,13,15,18 it does not appear that exposure to IFN-beta causes a large increase in risk of spontaneous abortions. However, future studies that enroll women prior to pregnancy are needed to adequately address this question.

The assumption that IFN-beta exposure does not affect adverse pregnancy outcomes can be explained by pharmacokinetic characteristics of the substance. The placental barrier is only permeable for lipophilic and small substances with a molecular weight between 600 and 800 Da. It is not permeable for polypeptides and protein-bound substances. IFN-beta is a polypeptide consisting of 166 (IFN-beta 1a) or 165 (IFN-beta 1b) amino acids and in case of IFN-beta 1a it is glycosylated by oligosaccharides. The molecular weight is 22.5 kDa for IFN-beta 1a and 18.5 kDa for IFN-beta 1b.31 Therefore, our results of a lacking adverse effect of IFN-beta during early pregnancy exposure are biological plausible as it is very unlikely that IFN-beta passes the placental barrier.

The limitations of our study are common to most pregnancy registries of drug safety in rare diseases. Since the vast majority of the women included in our study had stopped treatment during the first trimester, we cannot draw any conclusions about the safety of IFN-beta exposure later in pregnancy. Through the structure of our registry, we cannot exclude a certain selection bias as many women contact us by themselves. Another limitation is the variability in the first week of contact to the registry. Later then, first trimester inclusion into the registry can lead to an underestimation of early events, particularly spontaneous abortions. None of our patients started IFN-beta accidentally while already being pregnant, therefore immortal time bias, a common problem in pregnancy registries, is not relevant.32 Finally, although we have the largest cohort of IFN-beta-exposed pregnancies beside the manufacturers’ databases, with our current sample size we are only able to show a statistical significant three-fold increase in malformations (3% underlying general risk compared to 9%; power 80%, two-sided $p=0.05$).

The German Multiple Sclerosis and Pregnancy Registry overcomes many of the challenges of studying the effects of DMT exposure on pregnancy outcomes. The large number of pregnancies collected over a short period of time with a high proportion of women continuing DMTs into early pregnancy allows for meaningful comparisons of exposed with unexposed but diseased controls from the same source population to exclude any potential impact of the disease itself. The prospectively collected data make overreporting and recall bias, problems with retrospective reporting, unlikely.33 Finally, this study controlled for possible confounders for adverse pregnancy outcomes by collecting information on BMI, smoking, relapses, and corticosteroid use during pregnancy.

The findings from this study are consistent with the pharmacologically plausible safety of IFN-beta exposure in early pregnancy. Taken together with the existing literature, our study provides further reassurance that IFN-beta treatment can be safely continued up until the time women with MS become pregnant.

Acknowledgements
We thank all patients for their voluntary participation and the German MS society (DMSG) as well all referring neurologists and MS nurses for their support.

Conflict of interest
S.T. reports no disclosures. A.L.-G. is the site principal investigator for two industry-sponsored randomized clinical trials (Biogen Idec and Roche). M.R. reports no disclosures. A.H. is supported by the German Research Council (Deutsche Forschungsgemeinschaft—DFG). A.Q.-W. reports no disclosures. R.G. has received payments for consultancy from Biogen and Teva; speaker honoraria and research grants from Biogen Idec Germany, Teva, Sanofi-Aventis, Novartis, Bayer Healthcare, and Merck Serono. K.H. is supported by the German Research Council (Deutsche Forschungsgemeinschaft—DFG) and has received speaker honoraria from Biogen Idec, Teva Sanofi-Aventis, Novartis, Bayer Healthcare, and Merck Serono.

Funding
The German Multiple Sclerosis and Pregnancy Registry was partly supported by Bayer Healthcare, Biogen Idec Germany, Merck Serono, Novartis Pharma, Teva Pharma, and Sanofi-Aventis Genzyme Pharmaceuticals.

References


