Immunomodulation and postpartum relapses in patients with multiple sclerosis

Kerstin Hellwig, **Christian Beste**, **Sebastian Schimrigk and Andrew Chan**

Abstract: Multiple sclerosis (MS) mainly affects young women during a life period with desire for children. Relapse rate decreases during pregnancy and rises after delivery. Therefore, studies on satisfactory postpartum relapse prevention and its efficacy are essential. Previous smaller and uncontrolled studies suggested that intravenous immunoglobulin (IVIG) administration reduced the relapse rate following delivery. The objective of our observational study was to compare the efficacy of IVIG application, treatment with other immunomodulatory compounds or no treatment at all on the postpartal relapse rate in female MS patients from our pregnancy database. One hundred and twenty four pregnancies were followed in a partly prospective design. Relapse rate was reduced during pregnancy ($p<0.001$) and increased during the initial 3 months after delivery in all MS patients ($p<0.001$). The relapse rate reduction showed only a trend in favour of the IVIG-treated women, probably due to the small number of patients. However, analysing the expected number of relapses, IVIG treated patients had significantly less relapses postpartum than the untreated control group matched for disease activity before and during pregnancy (χ^2, $p=0.013$). The results suggest that IVIG could be an option to prevent postpartum relapse of MS.

Keywords: pregnancy, birth, intravenous immunoglobulin, disease-modifying therapy

Introduction

Multiple sclerosis (MS) is the most common disabling neurological disease in young women of childbearing age with an increasing incidence [Orton *et al.* 2006]. Pregnancy has no negative long-term impact on MS progression in general, but a decreased relapse rate (RR) occurs in the short term. This is followed by an increased RR after delivery [Vukusic *et al.* 2004; Dwosh *et al.* 2003]. Risk factors are relapses in the year before pregnancy and exacerbations during pregnancy [Vukusic *et al.* 2004]. Nearly 30% of all patients suffer from relapses during the initial 3 months after birth, and almost 50% during the first 6 months [Hellwig *et al.* 2008; Vukusic *et al.* 2004]. Little is known about potent postpartal relapse prevention. Prophylactic application of intravenous steroids showed some effect in a small cohort [de Seze *et al.* 2004], but this may interact with wound healing after delivery. A contraindication exists for the current available disease-modifying therapies (DMTs; i.e., interferon (IFN) beta or glatiramer acetate) during pregnancy and breast-feeding [Hoffmann *et al.* 2006; Coyle *et al.* 2004]. Moreover when women do not breastfeed, the efficacy of DMT on postpartal relapse prevention is not proven to date [Vukusic *et al.* 2004]. A retrospective data analysis suggested that administration of polyclonal 7S intravenous immunoglobulin (IVIG) reduces the RR postpartum and during pregnancy and concomitantly allows breastfeeding [Achiron *et al.* 2004]. The GAMPP study investigated two IVIG dosages without placebo control due to ethical concerns. Since the RR did not increase after birth, beneficial effects of IVIG application were assumed [Haas and Hommes, 2007]. The objective of our present study was to evaluate the effects of IVIG or early DMT initiation after birth on postpartum relapses.

Methods

This study was approved by the local ethical committee (314108). Participants gave written or oral witnessed consent. Data from our

Correspondence to:
Kerstin Hellwig, MD
Department of Neurology,
St Josef Hospital, Ruhr
University Bochum,
Bochum, Germany
**k.hellwig@
klinikum-bochum.de**

Christian Beste
Andrew Chan
Department of Neurology,
St Josef Hospital, Ruhr
University Bochum,
Bochum, Germany

Sebastian Schimrigk
Department of Neurology,
Lüdenscheid, Germany

nationwide MS pregnancy database from female relapsing remitting MS (RRMS) and secondary progressive MS (SPMS) patients with a pregnancy or child delivery during the last 10 years were analysed. To date, we have included 180 pregnancies in the database. Patients were recruited by announcements on websites of the national German MS Society (www.dmsg.de) and other MS organisations, advertisements in journals for MS patients and MS organisations, and by our MS outpatient unit. We completed a questionnaire consisting of standardised topics in combination with freely phrased questions by telephone or personal interview (K.H.). Data on the MS course, treatment, obstetrical history and characteristics of the newborns were obtained.

For prospective follow up, patients were contacted shortly after giving birth, after 3 and 6 months. Our own patients were followed by regular visits at our outpatient clinic. Because IVIGs are not approved for MS in Germany, only the minority of women are treated after delivery. As patients were recruited nationwide, three different dose regimens, depending on treating neurologists, were included. To create a control group, we then included postpartum treatment-naïve patients in the database with similar disease activity (annual relapse rate, ARR) in the year before pregnancy and during pregnancy compared with the IVIG-treated patients, as these are the only known risk factors for postpartum relapses [Vukusic *et al.* 2004]. This matching explains the difference between the 180 pregnancies in the database and the 124 pregnancies included in this study. Matching of patients from the database was blinded for disease activity postpartum to exclude any selection bias. In group 3, we included all patients in whom DMT was initiated 2 weeks after birth at the latest, as this is a common practice of treating neurologists for women who do not want to breastfeed, without evidence of efficacy in postpartum relapse prevention. Details of the three groups are given in Table 1. Group 1 consisted of 51 patients who were given IVIG after birth with three different dosage regimens: 10 g IVIG 3 days following delivery, 10 g IVIG every 4 weeks for 6 months after delivery and 20 g IVIG every 4 weeks after birth. Group 2 consisted of patients with no treatment postpartum. Group 3 consisted of 22 patients with conventional DMT initiated 2 weeks after birth at the latest (14 with IFN beta: 5 on Avonex®, 3 on Betaferon®, 6 on Rebif®; 6 on glatimer acetate (Copaxone®), 2 on azathioprine) and continued

this medication regularly as prescribed during the 6 month interval following birth.

Statistics

The ARR for the three trimesters of pregnancy and the first 6 months after birth, subdivided into three monthly intervals, were calculated and then compared with ANOVA. Distribution of relapses across the groups were compared with chi-square (χ^2) test and tested against equal distribution across groups. A value of $p < 0.05$ we considered statistically significant.

Results

We followed 124 pregnancies in total, 42 of them in a prospective fashion. Table 1 shows the characteristics of the three patient groups; 23 patients were treated 3 days after birth with 10 g IVIG, 19 with a short pulse after birth and consecutively 10 g every 4 weeks for 6 months, and 9 with 20 g after delivery and 20 g every 4 weeks for 6 months.

Relapses

Because we matched the IVIG and control group for disease activity, the ARR before and during pregnancy were very similar (see Table 1). The ARR decreased during pregnancy in the whole cohort ($p < 0.001$). After birth, the ARR increased again, as can be seen in the significant difference in the ARR between the third trimester during pregnancy (0.19 ± 0.07) and the first trimester after birth (0.93 ± 0.15) ($p < 0.001$) (Table 2). Similar to the GAMPP study, we did not observe any statistical difference in the postpartal relapse rate between the three different IVIG dose regimens ($p = 0.172$), therefore we combined these patients into a single IVIG group.

In the first trimester postpartum, 7 patients in the IVIG group, 16 of the control group and 4 of the DMT group experienced a MS relapse. Analysing the ARR postpartum, no differences between the postpartal relapse rates appeared ($F = 0.55$; $p = 0.853$). Evaluating the expected number of relapses, significantly more patients without treatment postpartum ($n = 16$ *versus* $n = 7$ of IVIG-treated patients) experienced relapses in the first 3 months after birth ($p = 0.013$) compared to the IVIG-treated patients. In the second trimester postpartum we did not observe any differences between the three groups ($p = 0.119$). Table 1 shows that the control group was statistically significantly without any DMT at all during

Table 1. Characteristics of cohorts.

Cohort	IVIG	Control	DMT
Number of patients	51	51	22
Age (years)	31.4 ($\pm$4.35)	30.3 ($\pm$4.33)	29.9 ($\pm$2.78)
Duration of MS years (SD)	5.7 ($\pm$4.05)	4.6 ($\pm$3.18)	5.4 ($\pm$2.78)
RRMS	48	49	21
SPMS	3	2	1
EDSS > 4	7	4	1
DMT before pregnancy	36	19	22
Pregnancy with DMT	19	6	13
Total time without DMT/years (SD)	1.96 ($\pm$1.50)	3.93 ($\pm$2.96)***	0.8 ($\pm$0.38)
Number of postpartum relapses in the first 3 months n/%	7/13.7	16/31.4	4/18.2
ARR before(SD)	0.91 ($\pm$0.63)	0.97 ($\pm$0.72)	0.79 ($\pm$0.72)
ARR I (SD)	0.55 (1.39)	0.55 ($\pm$1.39)	0.35 ($\pm$1.17)
ARR II (SD)	0.16 ($\pm$0.78)	0.24 ($\pm$0.95)	0
ARR III (SD)	0.24 ($\pm$0.95)	0.16 ($\pm$0.78)	0.18 ($\pm$0.85)
ARR I postpartal(SD)	0.56 ($\pm$1.46)	1.28 ($\pm$1.90)	0.87 ($\pm$1.57)

DMT, disease modifying therapy; IVIG, intravenous immunoglobulin application; MS, multiple sclerosis; RRMS, relapse remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis. Data are given as mean $\pm$ SEM, respectively, of total number. ***, $p<0.001$ of the ANOVA between the three cohorts. Age, duration and total time is given in years.

Table 2. Annual relapse rate (ARR) before and during pregnancy.

ARR before pregnancy (SD)	0.89 $\pm$0.06
ARR I (SD)	0.49 $\pm$0.13*
ARR II (SD)	0.13 $\pm$0.07**
ARR III (SD)	0.19 $\pm$0.08***
ARR I postpartum (SD)	0.93 $\pm$0.15***

I, II, III refer to first, second and third trimester respectively. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$ of the comparison ARR before *versus* ARR I, ARR II, and ARR III, respectively. Data are given as mean $\pm$ SEM.

the course of the disease ($p<0.001$). No impact of relapse rate in the year before pregnancy was observed for the postpartal relapse rate ($p=0.607$).

Neonates

No differences regarding birth weight ($F=0.19$; $p=0.661$), body length of the newborn babies ($F=1.15$; $p=0.284$) and gestational age ($F=0.82$; $p=0.776$) were observed between groups.

Pregnancy, abnormalities and DMT exposure

Out of 124 pregnancies in total, 38 pregnancies had conception under DMT exposure (19 IFN beta (7 on Avonex®, 4 on Betaferon®, 8 on Rebif®); 17 on glatiramer acetate; 2 on azathioprine). Three patients continued the treatment throughout the whole pregnancy (1 on Avonex®, 2 on azathioprine), due to the advice of the external treating neurologist. One patient accidentally injected 22 µg Rebif® until the second trimester. The remaining patients stopped DMT during the first trimester. Abnormalities of babies following drug exposure of the mothers during pregnancy included urinary bladder anomaly in one patient given glatiramer acetate, hip dysplasia in another patient given glatiramer acetate, and a small ventricular septum defect (VSD) in one patient given Avonex®. Abnormalities of babies in the group without DMT were medium-chain acryl CoA dehydrogenase deficiency ($n=1$), enzymatic deficiency of glycogen metabolism ($n=1$), Down's syndrome and VSD ($n=1$), large nevus cell nevi ($n=1$), which was removed by surgery and VSD alone ($n=1$).

Discussion

This observational study is the first study comparing the effect of IVIG on postpartum relapses with a control group matched for disease activity and a third group in which DMT was reinitiated shortly after birth. Our data show a lower postpartum relapse risk for women with MS treated with IVIG compared with nontreated patients. The relapse rate showed only a trend to relapse rate reduction in the first 3 months after birth, which is probably due to the small number of women treated with IVIG and the large variance between the groups. As relapse rates before and during pregnancy were not different between the

IVIG and treatment-naïve patients, this underlines the beneficial effects of IVIG. However, comparing the expected distribution of relapses between the IVIG-treated and the nontreated patients as a surrogate, we saw a statistical significance in favour of IVIG treatment with 7 of 51 relapses in the IVIG patients versus 16 of 51 in the nontreated women (χ^2, $p = 0.013$). In contrast to the GAMPP study [Haas and Hommes, 2007] and the study of [Achiron *et al.* 2004], we compared the IVIG-treated patients with a treatment-naïve control group. Moreover, this was matched for disease activity – described as risk factors for postpartal relapse [Vukusic *et al.* 2004]. In addition, we confirmed the known reduction of RR during pregnancy, which is followed by an increased relapse rate after birth, indicating reliability of the database [Hellwig *et al.* 2008; Vukusic *et al.* 2004; Dwosh *et al.* 2003].

This study is limited by its observational character due to the character of the database itself (recruitment per internet and partially retrospective character), so that paraclinical disease parameters are lacking. Nevertheless, as many as 124 pregnancies could be analysed, 42 of them prospectively. A further limitation is the small number of participants in the DMT group, since most patients preferred to breastfeed their infants. We only observed a tendency towards a lower relapse rate in this group, probably due to the small number of cases. Moreover DMT (INF-β and even more so glatiramer acetate) have a delayed onset of efficacy beyond the peak of the postpartal exacerbations [Comi *et al.* 2001; Li and Patty, 1999]. DMT is not recommended after birth in breastfeeding mothers, since there are no reliable data on its transfer into the milk and its effects on babies [Hoffmann, 2006; Coyle, 2004]. IVIG application is considered an alternative, but not approved for the treatment of MS patients, at least in Germany [Haas and Hommes, 2007; Hoffmann *et al.* 2006].

We did not observe an increased risk for premature birth, birth weight reduction or abnormalities in the neonates. There was no increase of foetal malformation in our study in the small group of drug-exposed pregnancies. Nevertheless, according to current guidelines [Hoffmann *et al.* 2006], we clearly advise that DMT should be stopped during pregnancy. The number of study participants is not high enough to evaluate the risks related to the administration of immunomodulatory drugs and to allow firm conclusions with regard to safety. By contrast, steroids can be used to treat acute relapses during pregnancy [Hoffmann *et al.* 2006].

In conclusion, our results confirm a reduced RR during pregnancy, followed by an increased RR after birth in all groups. Our data indicate that IVIG could have beneficial effects if given after delivery to prevent postpartum relapses in women who want to breastfeed. Our study is limited by its observational character without a proper control group and the partly retrospective design. As our limited data set and the GAMPP study did not show significant differences between the different doses of IVIG, we actually propose 10 g directly after birth followed by 10 g every 4 weeks for 6 months in breastfeeding women for high-risk patients with relapses during pregnancy or higher disease (ARR > 1) activity before pregnancy, as these correlated in the PRIMS study with higher disease activity postpartum. Current practice such as early DMT initiation show a trend to relapse reduction and should be evaluated in larger cohorts.

Conflict of interest statement
None declared.

References
Achiron, A., Kishner, I., Dolev, M., Stern, Y., Dulitzky, M., Schiff, E *et al.* (2004) Effect of intravenous immunoglobulin treatment on pregnancy and postpartum-related relapses in multiple sclerosis, *J Neurol* 251: 1133–1137.

Comi, G., Filippi, M. and Wolinsky, F.S. (2001) European/Canadian multicenter, double-blind, randomized placebo controlled study of the effects of glatiramer acetate on magnetic resonance imaging – measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group, *Ann Neurol* 49: 290–297.

Coyle, P.K., Christie, S., Fodor, P., Fuchs, K., Giesser, B., Gutierrez, A. *et al*. (2004) Multiple sclerosis gender issues: clinical practices of women neurologists, *Mult Scler* 10: 582–588.

de Seze, J., Chapelotte, M., Delalande, S., Ferriby, D., Stojkovic, T. and Vermersch, P. (2004) Intravenous corticosteroids in the postpartum period for reduction of acute exacerbations in multiple sclerosis, *Mult Scler* 10: 596–597.

Dwosh, E., Guimond, C., Duquette, P. and Sadovnick, A.D. (2003) The interaction of MS and pregnancy: a critical review, *Int MS J* 10: 38–42.

Haas, J. and Hommes, O.R. (2007) A dose comparison study of IVIG in postpartum relapsing-remitting multiple sclerosis, *Mult Scler* 13: 900–908.

Hellwig, K., Brune, N., Haghikia, A., Müller, T., Schimrigk, S., Schwödiauer, V. *et al*. (2008) Reproductive counselling, treatment and course of pregnancy in 73 German MS patients, *Acta Neurol Scand* 118: 24–28.

Hoffmann, L.A., Kumpfel, T., Heer, I. and Hohlfeld, R. (2006) Pregnancy and immunomodulatory therapy in multiple sclerosis patients, *Nervenarzt* 77: 663–668, 670.

Li, D.K. and Paty, D.W. (1999) Magnetic resonance imaging results of the PRIMS trial: a randomized, double-blind, placebo controlled study of interferon- beta 1a in relapsing remitting multiple sclerosis. Prevention of Relapses and Disability by Interferon-beta1a Subcutaneously in Multiple Sclerosis, *Ann Neurol* 46: 197–206.

Orton, S.M., Herrera, B.M., Yee, I.M., Valdar, W., Ramagopalan, S.V. and Sadovnick, A.D. (2006) Sex ratio of multiple sclerosis in Canada: a longitudinal study, *Lancet Neurol* 5: 932–936.

Vukusic, S., Hutchinson, M., Hours, M., Moreau, T., Cortinovis-Tourniaire, P., Adeleine, P. *et al*. (2004) Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse, *Brain* 127: 1353–1360.