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# Disease activity and neonatal outcomes after exposure to natalizumab throughout pregnancy

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## ABSTRACT

**Background** After natalizumab discontinuation severe relapses can occur despite pregnancy, but third trimester exposure is associated with neonatal haematological abnormalities (HA). The best time point for stopping natalizumab during pregnancy is unclear.

**Methods** Prospective, observational cohort with 350 natalizumab exposed pregnancies from the German Multiple Sclerosis and Pregnancy Registry. Clinical disease activity and neonatal outcomes are compared between women with natalizumab discontinuation during (1st Trim-group) versus after the first trimester (maintaining-group) and for subgroup analysis before (<30-subgroup) or after (≥30-subgroup) the 30th gestational week (gw).

**Results** Baseline characteristics did not significantly differ between the 1st Trim-group (n=179; median exposure duration: 2.60 gw, IQR 1.30–3.60) and the maintaining-group (n=171; median exposure duration: 30.9 gw, IQR 26.9–33.3). Fewer relapses occurred during pregnancy and the postpartum year in the maintaining-group (25.7%) compared with the 1st Trim-group (62.6%; p<0.001). Women in ≥30-subgroup had a significantly lower relapse risk in the first 6 months postpartum (relapse rate ratio: 0.36, 95% CI: 0.15 to 0.84). In total, 7.5% retained meaningful disability 12 months postpartum. No significant effect on neonatal outcomes were observed, but anaemia (OR: 2.62, 95% CI: 1.12 to 6.52) and thrombocytopaenia (OR: 2.64, 95% CI: 1.15 to 6.46) were significantly more common in the ≥30-subgroup. 21.8% of all neonates were born small for gestational age, independent of the timing of natalizumab discontinuation.

**Conclusion** Continuing natalizumab during pregnancy after gw 30 decreases the relapse risk postpartum going along with a higher risk for HA in the newborns. These results add relevant knowledge as a basis for informed risk–benefit discussion.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The discontinuation of natalizumab due to family planning can lead to severe relapses and permanent disability accrual, but as monoclonal antibodies are actively transferred over the placenta during pregnancy, the continuation might affect newborns with haematological abnormalities (HA) as anaemia or thrombocytopaenia. To what extent natalizumab exposure throughout pregnancy impacts clinical disease activity and disability during pregnancy and postpartum as well as neonatal outcomes including HA and the best time point to stop natalizumab during pregnancy, with the lowest possible risk for mother and child is unknown.

## WHAT THIS STUDY ADDS

⇒ In this prospective cohort study including 350 pregnancies, the maintenance of natalizumab during pregnancy beyond the 30th gestational week (gw) reduced the relapse and disability risk during pregnancy and postpartum, especially when coupled with early (28 days) treatment restart postpartum, but was also associated with a higher number of newborns with HA.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results should lead to a distinct risk–benefit-discussion between neurologist and natalizumab treated women who are considering maintaining natalizumab beyond gw 30 and restart in the first 4 weeks after delivery to reduce relapse activity and disability accumulation just prior to or after birth.

## INTRODUCTION

Natalizumab (NTZ) is an effective disease modifying therapy (DMT) for relapsing remitting multiple sclerosis (RRMS) but the discontinuation has been associated with severe rebound.<sup>1 2</sup> Planning a pregnancy is a common reason to discontinue NTZ. In contrast to DMT untreated women,<sup>3</sup> women with high disease activity do not necessarily experience a decrease in relapse rate during pregnancy, and studies observed an increased relapse and disability risk after NTZ discontinuation.<sup>4–8</sup> This reinforces the importance of an effective and

safe treatment during pregnancy in patients with highly-active RRMS.

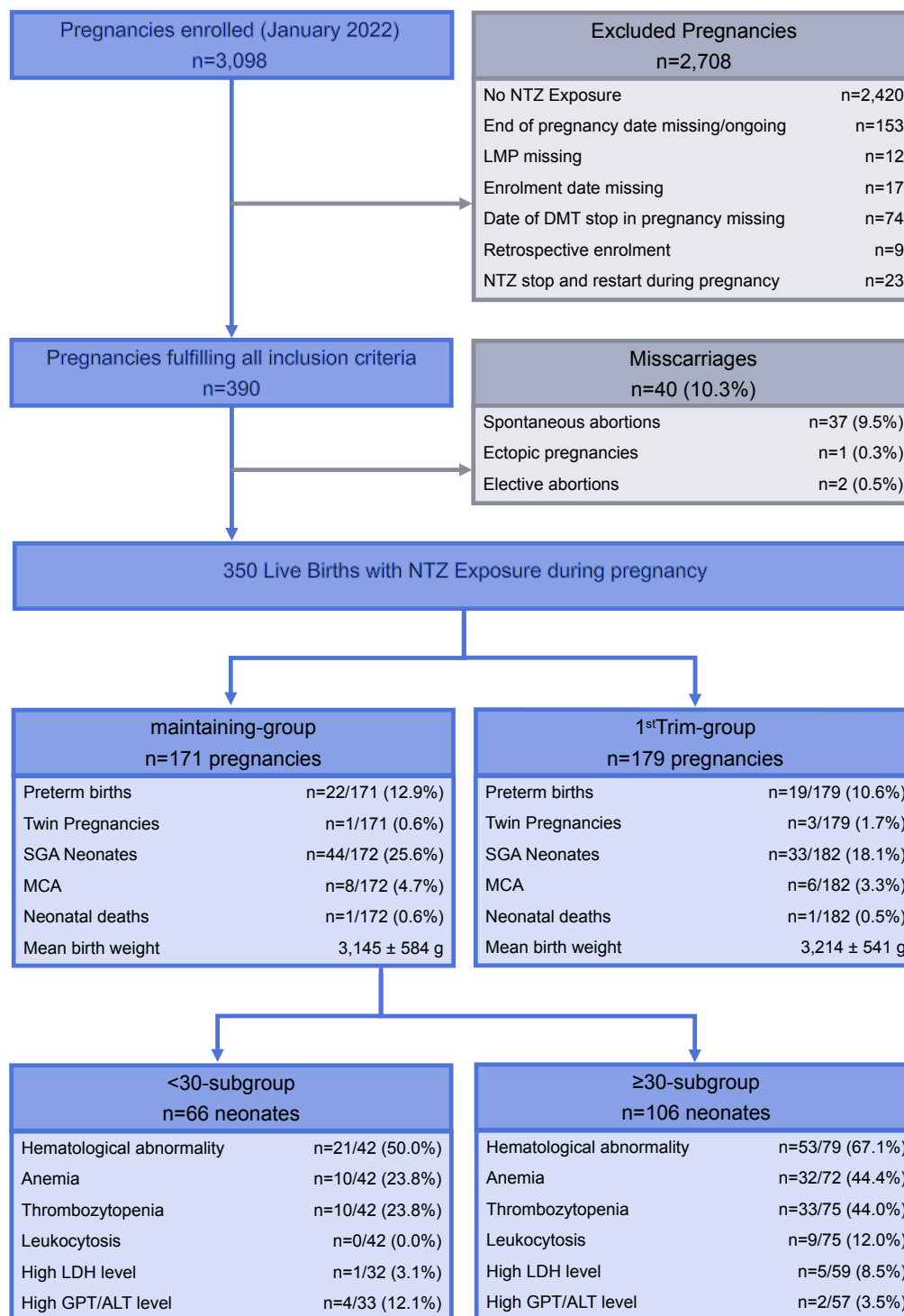
The European Medicines Agency did not rate a higher malformation risk after NTZ first trimester exposure,<sup>9</sup> but the active transfer of the monoclonal antibody after treatment throughout pregnancy was measured in newborns cord blood and yielded haematological abnormalities (HA), usually as thrombocytopaenia or anaemia.<sup>10</sup> First observations described abnormalities that were mostly mild and reversible,<sup>10 11</sup> but the cohorts were very small.

Treating pregnant women with RRMS requires careful risk–benefit-consideration taking maternal and fetal health into account. Therefore, the aim for this study was twofold, to analyse: (1) clinical



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**Figure 1** Inclusion criteria, pregnancy and neonatal outcomes. Depicted are pregnancies fulfilling the inclusion criteria as well as neonatal outcomes. Proportions of preterm births and twin pregnancies are calculated with the total number of live births as denominator; small for gestational age, congenital abnormalities and neonatal deaths with the total number of neonates (maintaining-group: n=172; first Trim-group: n=182) as denominator. Proportions of other neonatal outcomes are calculated with the total number of pregnancies and haematological abnormalities with the number of available blood counts for every specific variable as denominator. 1st Trim-group stopped natalizumab during the first trimester (completed gestational week 12) of pregnancy, maintaining-group maintained natalizumab after the first trimester of pregnancy. The maintaining-group was further stratified by latest natalizumab exposure prior to completed gestational week 30 (<30-subgroup) or after/at completed gestational week 30 (≥30-subgroup). Natalizumab stop and restart during pregnancy was defined as a therapy break of at least 12 weeks during pregnancy. Haematological abnormality: Any kind of haematological abnormality in the infant's blood count immediately after birth. Anaemia: Haemoglobin under the days-of-life specific standard value lower range.<sup>15</sup> Thrombocytopaenia: Platelets under the days-of-life specific standard value lower range.<sup>15</sup> Leukocytosis: over the days-of-life specific standard value upper range.<sup>15</sup> High LDH level: LDH over the days-of-life specific standard value upper range.<sup>16</sup> High GPT/ALT level: GPT/ALT over the days-of-life specific standard value upper range.<sup>16</sup> ALT, alanine aminotransferase; DMT, disease modifying therapy; GPT, glutamic pyruvic transaminase; LDH, lactate dehydrogenase; LMP, last menstrual period; MCA, major congenital abnormality; n, number of cases; NTZ, natalizumab; SGA, small for gestational age.

**Table 1** Characteristics of the study sample

	First Trim-group N=179	Maintaining-group N=171	P value
<b>Demographic characteristics</b>			
Age at LMP (years), mean (SD)	31.3 (4.1)	31.9 (4.6)	0.22
BMI, kg/m <sup>2</sup> , mean (SD)	23.9 (5.0)	23.8 (5.0)	0.84
Smoking during pregnancy, n (%)	8 (6.4)	5 (3.2)	0.32
Alcohol during pregnancy, n (%)	1 (0.8)	3 (1.9)	0.64
Gw at enrolment, median (IQR)	11.3 (7.2–19.4)	8.4 (6.3–13.5)	<b>0.001</b>
NTZ pregnancy exposure duration (weeks), median (IQR)*	2.6 (1.3–3.6)	30.9 (26.9–33.3)	NA
<b>Clinical disease activity and disability at baseline</b>			
Disease duration (years), median (IQR)	6.1 (3.8–10.1)	8.0 (3.9–11.2)	0.13
NTZ treatment duration prior to pregnancy (years), median (IQR)	1.7 (0.8–2.9)	2.2 (0.7–4.9)	0.03
At least one relapse during the prepregnancy year, n (%)	57 (31.8)	50 (29.2)	0.68
At least one relapse under NTZ during the prepregnancy year, n (%)	22 (12.3)	14 (8.2)	0.28
Available EDSS, n (%)†	160 (89.4)	162 (94.7)	0.11
No disability (EDSS 0–2.0), n (%)	95/160 (59.4)	94/162 (58.0)	0.89
Some disability, (EDSS 2.5–3.5), n (%)	48/160 (30.0)	54/162 (33.3)	0.60
Some ambulatory impairment (EDSS 4.0–5.5), n (%)	16/160 (10.0)	7/162 (4.3)	0.08
Cane required (EDSS 6.0–6.5), n (%)	1/160 (0.6)	6/162 (3.7)	0.12
Wheelchair required (EDSS ≥7.0), n (%)	0 (0.0)	1/162 (0.6)	1.00
<b>Postpartum behaviour</b>			
NTZ treatment post partum, n (%)‡	110/170 (64.7)	145/162 (89.5)	<b>&lt;0.001</b>
Duration of NTZ therapy break (days), median (IQR)	289 (264–354)	69.5 (49.0–100)	<b>&lt;0.001</b>
Early NTZ treatment post partum, n (%)§	47/110 (42.7)	109/144 (75.7)	<b>&lt;0.001</b>
Breast feeding, n (%)¶	114/178 (64.0)	80/166 (48.2)	<b>0.004</b>
Exclusive breast feeding, n (%)**	50/107 (46.7)	36/73 (49.3)	0.22

1st Trim-group stopped natalizumab during the first trimester (completed gestational week 12) of pregnancy, maintaining-group maintained natalizumab after the first trimester of pregnancy. A two-sided p < 0.05 is considered as statistically significant (bold)

\*No p value available, as group affiliation is based on natalizumab pregnancy exposure duration.

†EDSS values were reported in 322 (92.0%) pregnancies.

‡18 pregnancies are lost to follow-up before natalizumab restart postpartum. Denominator is the number of pregnancies with available data on natalizumab restart postpartum per group.

§Early natalizumab treatment is defined as natalizumab treatment during the first 28 days postpartum. For one pregnancy the date of natalizumab restart postpartum is missing. Denominator is the number of pregnancies with available data on early natalizumab restart postpartum per group.

¶Breast feeding data available for n=344 (98.3%) pregnancies. The denominator is the number of pregnancies with available breastfeeding data per group.

\*\*Exclusive breast feeding is defined as breast feeding without supplemental feedings for at least 2 months. In 14 pregnancies data on exclusive breast feeding was not available. The denominator is the number of pregnancies breast feeding and with available data on exclusive breast feeding per group.

BMI, body mass index; EDSS, Expanded Disability Status Scale; gw, gestational week; LMP, last menstrual period; n, number of women; NA, not applicable; NTZ, natalizumab.

disease activity during pregnancy and up to 1-year postpartum; and (2) neonatal outcomes including HA in newborns of mothers with NTZ exposure throughout pregnancy.

## METHODS

### Study design, setting and participants

We included women voluntarily enrolled during pregnancy between November 2006 and January 2022 in the German Multiple Sclerosis and Pregnancy Registry (DMSKW), with the following inclusion criteria: available minimal data set (last menstrual period (LMP), end of pregnancy date, enrolment date, DMT stop date during pregnancy) and NTZ treatment between LMP and end of pregnancy. As this analysis focuses on clinical disease activity and neonatal outcomes, pregnancies with a duration less than 22 weeks or with NTZ stop and restart during pregnancy were excluded (figure 1).

Data were collected via standardised, telephone-administered questionnaires at each remaining trimester after enrolment and up to 12 months postpartum.<sup>12</sup> Self-reported relapses were confirmed and Expanded Disability Status Scale (EDSS) obtained from the treating neurologist by phone during the postpartum follow-up period. Infant's blood cell counts immediately after

birth were collected from delivery hospitals, if available. 193 pregnancies included in this analysis have been previously analysed with regard to various objectives.<sup>8 10 13 14</sup>

### Outcomes

Clinical MS disease activity outcomes: relapses, glucocorticosteroid-treatments and EDSS values were collected between 1 year prepregnancy and up to 1-year postpartum. To assess disability, we used the established definition for disability progression (defined as a worsening of at least 1.5 EDSS points if baseline EDSS=0, at least 1 point for baseline EDSS 1–5.5 and 0.5 point for baseline EDSS ≥6.0)<sup>4</sup> and the Severe Relapse Disability Composite Score (SRDCS, defined as any relapse during pregnancy or post partum leading to either (1) an increase of 2 EDSS points, (2) new ambulatory impairment in those without significant prepregnancy ambulatory impairment (EDSS increase from ≤3.5 to ≥4.0 points) or (3) significant worsening in women with at least some pre-existing ambulatory impairment (EDSS increase from ≤5.5 to ≥6.0 points (cane or worse); 6.0 to ≥6.5 points (walker or worse); 6.5 to ≥7.0 points (wheelchair or worse); and 7.0 to ≥8.0 points (bedbound with some arm function or worse))).<sup>8</sup> We defined neonatal outcomes preterm births (before

**Table 2** Clinical disease activity and disability during pregnancy and the postpartum year

	First Trim-group N=179	Maintaining-group N=171	P value	<30-subgroup N=66	≥30-subgroup N=105	P value
Clinical disease activity and disability during pregnancy**						
At least one relapse during pregnancy, n (%)	58 (32.4)	10 (5.9)	<0.001	5 (7.6)	5 (4.8)	0.51
More than one relapse during pregnancy, n (%)†	19 (10.6)	0 (0.0)	<0.001	0 (0.0)	0 (0.0)	NA
At least one relapse during first trimester, n (%)	5 (2.8)	4 (2.3)	>0.99	1 (1.5)	3 (2.9)	>0.99
At least one relapse during second trimester, n (%)	38 (21.2)	4 (2.3)	<0.001	2 (3.0)	2 (1.9)	0.64
At least one relapse during third trimester, n (%)	32 (18.0)	2 (1.2)	<0.001	2 (3.0)	0 (0.0)	0.15
At least one steroid treatment during pregnancy, n (%)	41 (22.9)	3 (1.8)	<0.001	1 (1.5)	2 (1.9)	>0.99
At least one steroid treatment during first trimester, n (%)	1 (0.6)	2 (1.2)	0.62	1 (1.5)	1 (1.0)	>0.99
At least one steroid treatment during second trimester, n (%)	21 (11.7)	0 (0.0)	<0.001	0 (0.0)	0 (0.0)	>0.99
At least one steroid treatment during third trimester, n (%)	29 (16.2)	1 (0.6)	<0.001	0 (0.0)	1 (1.0)	>0.99
Disability progression during pregnancy, n (%)‡	23/160 (14.4)	5/162 (3.1)	0.001	1/63 (1.6)	4/99 (4.0)	0.65
SRDCS in pregnancy, n (%)§	16/160 (10.0)	0 (0.0)	<0.001	0 (0.0)	0 (0.0)	NA
Clinical disease activity and disability post partum¶¶						
At least one relapse during the postpartum year, n (%)	89 (49.7)	39 (22.8)	<0.001	25 (37.9)	14 (13.3)	<0.001
At least one relapse during the first postpartum trimester, n (%)	57/175 (32.6)	24/152 (15.8)	0.001	16/59 (27.1)	8/93 (8.6)	0.005
At least one relapse during the second postpartum trimester, n (%)	35/174 (20.1)	11/145 (7.6)	0.003	8/59 (13.6)	3/86 (3.5)	0.05
At least one relapse during the third postpartum trimester, n (%)	18/171 (10.5)	8/128 (6.3)	0.28	4/52 (7.7)	4/76 (5.3)	0.71
At least one relapse during the fourth postpartum trimester, n (%)	7/168 (4.2)	4/127 (3.2)	0.76	3/52 (5.7)	1/75 (1.3)	0.30
At least one postpartum relapse before NTZ restart, n (%)	48 (26.8)	24 (14.0)	0.005	16 (24.2)	8 (7.6)	0.005
At least one postpartum relapse under NTZ treatment, n (%)**	12 (6.7)	9 (5.3)	0.70	4 (6.1)	5 (4.8)	0.74
Disability progression post partum, n (%)‡	24/160 (15.0)	16/162 (9.9)	0.22	6/63 (9.5)	10/99 (10.1)	1.00
SRDCS post partum, n (%)§	16/160 (10.0)	8/162 (4.9)	0.13	5/63 (7.9)	3/99 (3.0)	0.26

1st Trim-group stopped natalizumab during the first trimester (completed gestational week 12) of pregnancy, maintaining-group maintained natalizumab after the first trimester of pregnancy. The maintaining-group was further stratified by latest natalizumab exposure prior to completed gestational week 30 (<30-subgroup) or after/at completed gestational week 30 (≥30-subgroup). A two-sided p < 0.05 is considered as statistically significant (bold)

\*EDSS values were reported in 322 (92.0%) pregnancies for three periods (at baseline 3 months before last menstrual period, third trimester of pregnancy and postpartum 12 months±6 weeks, all at least 30 days after a relapse).

†14 women experienced two relapses and 5 women experienced three relapses during pregnancy.

‡Disability progression defined as a worsening of at least 1.5 EDSS points if baseline EDSS=0 points, at least 1 point for baseline EDSS of 1–5.5 points and 0.5 point for baseline EDSS≥6.0 points. Denominator is the number of pregnancies with reported EDSS values per group.

§SRDCS defined as any relapse during pregnancy or postpartum leading to either (1) a change of 2 EDSS points, (2) new ambulatory impairment in those without significant prepregnancy ambulatory impairment (EDSS increase from ≤3.5 to ≥4.0 points) or (3) significant worsening ambulatory impairment in women with at least some pre-existing ambulatory impairment (EDSS increase from ≤5.5 to ≥6.0 points (cane or worse); 6.0 to ≥6.5 points (walker or worse); 6.5 to ≥7.0 points (wheelchair or worse); and 7.0 to ≥8.0 points (bedbound with some arm function or worse)). Denominator is the number of pregnancies with reported EDSS values per group.

¶55 pregnancies have no complete 1-year postpartum follow-up. Denominator is the number of pregnancies with completed follow-up per postpartum trimester

\*\*at least 12 weeks after natalizumab restart

EDSS, Expanded Disability Status Scale; n, number of women; NA, not applicable; NTZ, natalizumab; SRDCS, Severe Relapse Disability Composite Score.

completed gestational week (gw) 37), small for gestational age (SGA, birth weight under the 10 national age-specific and sex-specific percentile), major congenital abnormalities (according to the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT)-guidelines), neonatal death (during the first 28 completed days of life) and birth weight as previously described.<sup>12</sup> HA were defined as follows: haemoglobin,<sup>15</sup> platelets,<sup>15</sup> haptoglobin<sup>16</sup> under the days-of-life specific standard value lower range; or leucocytes,<sup>15</sup> lactate dehydrogenase (LDH),<sup>16</sup> aspartate aminotransferase (AST),<sup>16</sup> alanine aminotransferase (ALT),<sup>16</sup> bilirubin total<sup>16</sup> over the days-of-life specific standard value upper range.

## Statistical analyses

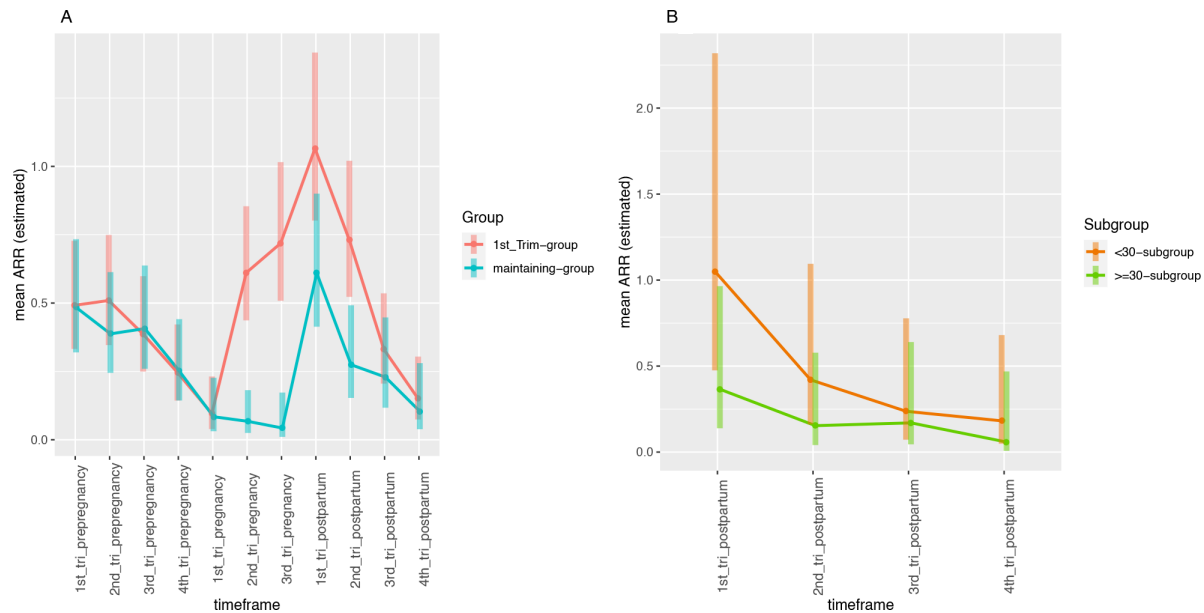
For the analysis of clinical disease activity during pregnancy and neonatal outcomes, we compared NTZ discontinuation during (1st Trim-group) or after the first trimester (maintaining-group). For the analysis of HA and postpartum clinical disease activity, the maintaining-group was stratified by latest NTZ exposure before (<30-subgroup) or after 30th gw (≥30-subgroup).

Descriptive statistics include Kruskal-Wallis test, Fisher/ $\chi^2$  test and t-test.<sup>12</sup>

Annualised relapse rates (ARR) per trimester between the prepregnancy year (baseline) and 1-year postpartum were calculated using a multivariable mixed-effects Poisson-regression model; groups and subgroups were compared with relapse rate ratios (RRR with 95% CIs).

We used multivariable logistic/linear regression to estimate ORs (OR)/ $\beta$ -coefficients with 95% CIs to compare for clinical disease activity during pregnancy and postpartum and neonatal outcomes with the covariables 'gw of last NTZ during pregnancy' (linear), 'extended dosing interval' (yes/no), 'number of NTZ infusions during pregnancy' (linear), 'NTZ exposure after 1<sup>st</sup> trimester' (yes/no) and 'NTZ exposure after 30<sup>th</sup> gw' (yes/no).

We considered the following adjustments in the regression models, depending on outcomes (see online supplemental tables and figure legends): maternal age, body mass index (BMI) and disease duration at conception; gw at enrolment and birth; relapse and EDSS prior to pregnancy; relapses, high-dose glucocorticosteroids, EDSS, antibiotics, gynaecological complications



**Figure 2** Course of annualised relapse rates during pregnancy and postpartum. Depicted are mean annualised relapse rates as estimated by Poisson regression stratified by timing of natalizumab cessation (A) during (1st Trim-group) or after (maintaining-group) the first trimester or (B) before (<30-subgroup) or after (≥30-subgroup) gestational week 30. Error bars represent 95% CIs. Adjustment for (A) maternal age at conception, disease duration and gestational week at entry into the cohort and (B) maternal age at conception, disease duration, gestational week at entry into the cohort, relapse during pregnancy, exclusive breast feeding and early natalizumab restart in the first 28 days post partum. ARR, annualised relapse rate; tri, trimester.

or tobacco/alcohol during pregnancy; newborns gender; DMT restart, early NTZ restart in the first 28 days and exclusive breastfeeding postpartum. Covariates were checked for possible correlation with the correlation coefficient of Pearson or with Cramer's V.

All analyses were performed at a two-sided significance level of  $\alpha=0.05$  and conducted with R V.4.1.2 (R Core Team 2021).

## RESULTS

### Study population

We identified 390 pregnancies with NTZ treatment in the first trimester or beyond (figure 1). Spontaneous abortions ( $n=37$ , 9.5%), ectopic pregnancies ( $n=1$ , 0.3%), elective abortions ( $n=2$ , 0.5%; 1 in gw 26 due to trisomy 13 and 1 in gw 13 due to trisomy 21) were excluded for this analysis.

As no stillbirths were observed, baseline characteristics of 350 pregnancies with live births in 320 women are shown in table 1, stratified by NTZ cessation during ( $n=179$ ; 1st Trim-group) or after ( $n=171$ ; maintaining-group) the first trimester. Most enrolled during the first trimester (median gw 9.9, IQR 6.7–15.5), with women in the maintaining-group enrolling statistically significantly earlier (table 1).

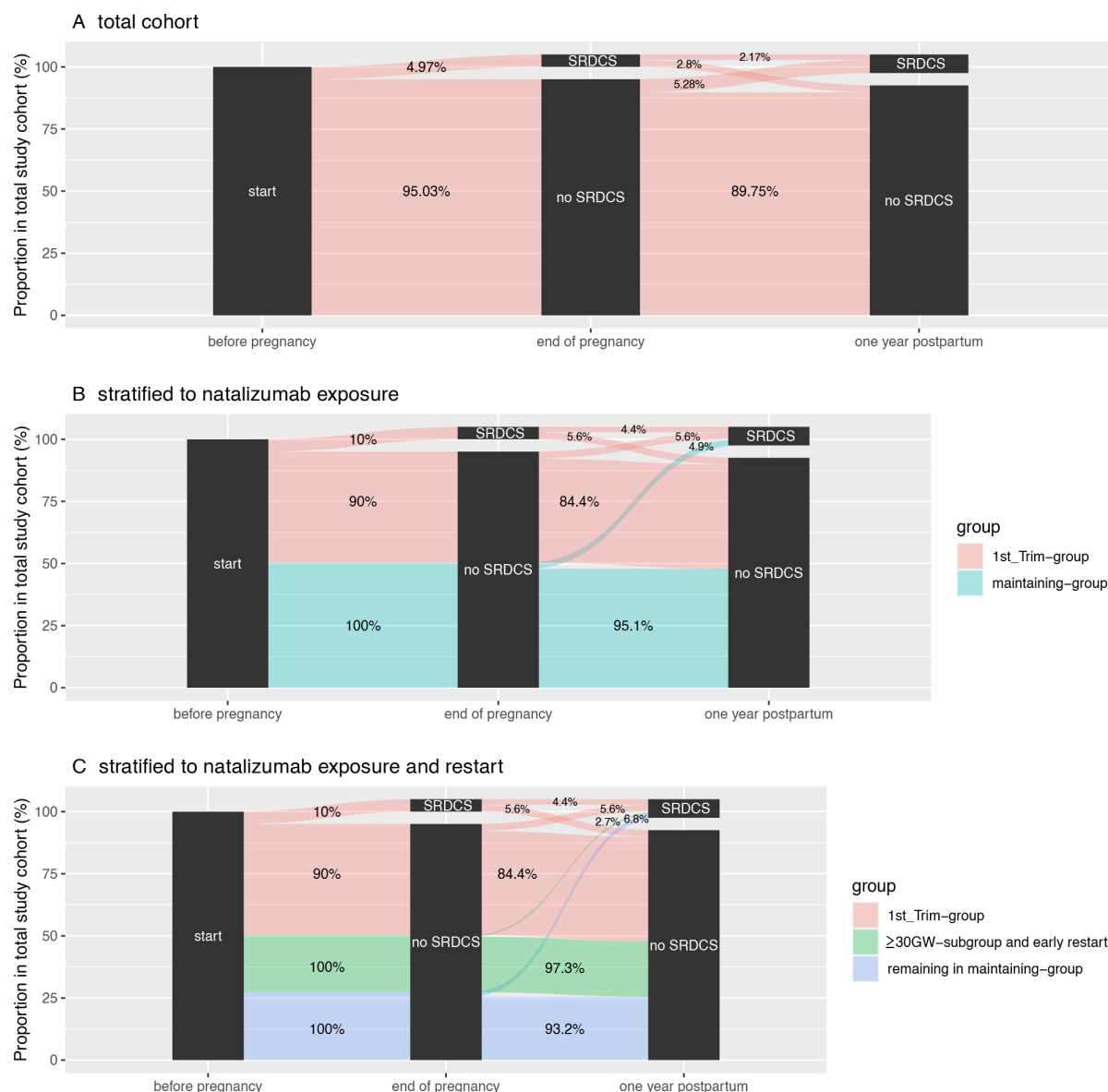
The maintaining-group was treated until median gw 30.9 (IQR 26.9–33.3). The majority of women for whom the dosing frequency was available (137/159; 86.2%) were on extended dosing intervals ranging from 6 to 8 weeks, and receiving a median number of 5 (IQR 5–6) NTZ infusions during pregnancy. Women in the maintaining-group, who reintroduced NTZ post partum, had a median therapy break of 69.5 days (IQR 49.0–100.0). Most (75.7%) restarted NTZ during the first 4 weeks, with 18 breast feeding under NTZ. Women in the 1st Trim-group decided more often to breast feed (64.0%), four under NTZ treatment, and fewer (42.7%) started NTZ early postpartum (table 1).

### Clinical disease activity during pregnancy and postpartum

Statistically significant fewer relapses occurred during pregnancy and postpartum in the maintaining-group (44/171, 25.7%) compared to the 1st Trim-group (112/179, 62.6%;  $p<0.001$ ). Out of 10/171 (5.9%) women in the maintaining-group suffering from a pregnancy relapse, only 3 were treated with high dose corticosteroid treatments during pregnancy. Of note, we still observed 22.8% postpartum relapses in the maintaining-group, but statistically significantly fewer in the ≥30-subgroup (13.3%), especially during the first postpartum trimester (8.6%, table 2). Only 8/79 (10.1%) in the ≥30-subgroup who restarted during the first 28 days postpartum had a postpartum relapse.

Figure 2 demonstrates statistically significant lower ARR in the maintaining-group during pregnancy and postpartum (RRR: 0.35, 95% CI: 0.23 to 0.53) than in the first Trim-group. Highest relapse rates were observed during the first trimester post partum in both groups, but statistically significantly lower in the maintaining-group (RRR: 0.57, 95% CI: 0.36 to 0.92). Subgroup analysis demonstrated statistically significant lower ARRs in the ≥30-subgroup during the first 6 months postpartum (RRR: 0.36, 95% CI: 0.15 to 0.84) than in the <30-subgroup. Online supplemental table 1 gives a summary of all ARRs per time frame.

16 (10%) relapses reached the SRDCS at the end of pregnancy, all in the 1st Trim-group (table 2). In total, 24 fulfilled the SRDCS criteria up to 1-year postpartum (figure 3), but only 2 (2.70%) in the ≥30-subgroup who restarted during the first 28 days postpartum. Online supplemental table 2 gives an overview of the 12 most severe relapses, with an EDSS increase  $\geq 3$  during pregnancy or postpartum, only 1 in the ≥30-subgroup with NTZ restarted during the first 28 days post partum (stop in gw 30, restart 8 days postpartum). Pregnancy relapses were treated with high-dose and one with intrathecal corticosteroids or an additional apheresis treatment, respectively. Only two women recovered to the baseline EDSS at 12 months post partum.



**Figure 3** Disability development during pregnancy and the postpartum year using the SRDCS in 320 pregnancies with available EDSS (A) in the total cohort, (B) stratified by natalizumab exposure during (1st Trim-group) or after (maintaining-group) the first trimester of pregnancy and (C) with stratification of the maintaining-group by natalizumab maintenance  $\geq 30$ th gestational week and early restart during the first 28 days postpartum. EDSS, Expanded Disability Status Scale; GW, gestational week; SRDCS, Severe Relapse Disability Composite Score.

In the adjusted logistic regression model, having a later timing of the last NTZ infusion during pregnancy (covariable: GW of last NTZ during pregnancy) was statistically significant associated with fewer pregnancy (OR: 0.93, 95% CI: 0.90 to 0.96) and postpartum relapses (OR: 0.97, 95% CI: 0.95 to 0.99) as well as fewer disability progression (OR: 0.94, 95% CI: 0.90 to 0.97) and reaching the SRDCS during pregnancy (OR: 0.85, 95% CI: 0.71 to 0.93; table 3), while having an extended dosing interval did not (online supplemental table 3).

Regarding postpartum relapses, an early NTZ restart during the first 28 days postpartum was associated with a reduced risk (OR: 0.26, 95% CI: 0.13 to 0.50), whereas exclusive breast feeding was not (OR: 1.24, 95% CI: 0.62 to 2.44). In addition, pregnancy relapses were associated with reaching the SRDCS postpartum (OR: 4.05, 95% CI: 1.34 to 12.3).

### Neonatal outcomes

Neonatal outcomes were similar between groups (figure 1). In total, 11.7% preterm births (median 35.3 gw; IQR 34.1–36.3) were observed. In 354 neonates (4 twin pregnancies) we observed 4.0% congenital abnormalities, without a specific pattern (online supplemental table 4). Two extremely preterm newborns (gw 24+3 and 26+1, respectively) died within the first week after delivery. 21.8% neonates were born SGA in the total cohort (figure 1), but mean birth weights did not differ between groups. 2/77 (2.6%) SGA neonates were twins and 8 were also born preterm.

In the adjusted regression models, neither NTZ exposure after the first trimester (tables 3,4), nor the dosing scheme (online supplemental tables 3 and 5) had a statistically significant effect on any neonatal outcome. Next to the known predictors for negative pregnancy outcomes (maternal BMI, tobacco and alcohol consumption), high-dose glucocorticosteroid treatment

**Table 3** Adjusted logistic regression of clinical disease activity and neonatal outcomes

Outcome	Covariable	OR	95% CI	OR	95% CI
		Crude		Adjusted	
Clinical disease activity outcomes					
Pregnancy relapse*	GW of last NTZ during pregnancy	0.93	0.90 to 0.95	0.93	0.90 to 0.96
	NTZ exposure after first trimester	0.14	0.07 to 0.27	0.11	0.04 to 0.24
Disability progression in pregnancy*	GW of last NTZ during pregnancy	0.95	0.91 to 0.98	0.94	0.90 to 0.97
	NTZ exposure after first trimester	0.19	0.06 to 0.48	0.15	0.05 to 0.38
SRDCS in pregnancy*	GW of last NTZ during pregnancy	0.86	0.73 to 0.94	0.85	0.71 to 0.93
	NTZ exposure after first trimester†	NA	NA	NA	NA
Postpartum relapse‡	GW of last NTZ during pregnancy	0.95	0.93 to 0.97	0.97	0.95 to 0.99
	NTZ exposure after 30th gw	0.25	0.11 to 0.52	0.27	0.11 to 0.64
Disability progression post partum‡	GW of last NTZ during pregnancy	0.99	0.96 to 1.01	1.01	0.97 to 1.04
	NTZ exposure after 30th gw	1.08	0.35 to 3.70	1.53	0.45 to 5.83
SRDCS post partum‡	GW of last NTZ during pregnancy	0.97	0.94 to 1.00	1.00	0.96 to 1.04
	NTZ exposure after 30th gw	0.43	0.08 to 2.02	0.58	0.10 to 3.00
Neonatal outcomes					
Preterm birth§	GW of last NTZ during pregnancy	1.01	0.98 to 1.03	1.02	0.98 to 1.05
	NTZ exposure after first trimester	1.24	0.65 to 2.41	1.66	0.65 to 4.58
SGA§	GW of last NTZ during pregnancy	1.02	1.00 to 1.04	1.02	1.00 to 1.04
	NTZ exposure after first trimester	1.53	0.92 to 2.57	1.43	0.79 to 2.62
Congenital abnormality¶	GW of last NTZ during pregnancy	1.01	0.97 to 1.05	1.01	0.97 to 1.06
	NTZ exposure after first trimester	1.43	0.49 to 4.43	1.54	0.43 to 6.16
Haematological abnormalities					
Anaemia**	GW of last NTZ during pregnancy	1.16	1.06 to 1.30	1.17	1.06 to 1.32
	NTZ exposure after 30th gw	2.56	1.12 to 6.20	2.62	1.12 to 6.52
Thrombocytopaenia**	GW of last NTZ during pregnancy	1.10	1.02 to 1.20	1.10	1.03 to 1.21
	NTZ exposure after 30th gw	2.51	1.11 to 6.07	2.64	1.15 to 6.46
Leucocytosis††	GW of last NTZ during pregnancy	1.38	1.11 to 1.81	1.39	1.11 to 1.83
	NTZ exposure after 30th gw‡‡	NA	NA	NA	NA
High LDH level††	GW of last NTZ during pregnancy	1.11	0.95 to 1.44	1.11	0.94 to 1.44
	NTZ exposure after 30th gw	2.87	0.44 to 56.30	2.81	0.42 to 55.70
High GPT/ALT level§§	GW of last NTZ during pregnancy	0.98	0.89 to 1.13	0.98	0.86 to 1.15
	NTZ exposure after 30th gw	0.26	0.04 to 1.43	0.23	0.03 to 1.52

Summary of the results of the multivariable logistic regression models to estimate adjusted OR with 95% CIs. For CIs highlighted in bold the effect is considered as statistically significant.

\*Models for the outcomes pregnancy relapse, disability progression in pregnancy, SRDCS in pregnancy adjusted for: maternal age, maternal BMI, disease duration, relapse in the year prior to pregnancy and EDSS prior to pregnancy.

†No event in the maintaining-group.

‡Models for the outcomes postpartum relapse, disability progression postpartum, SRDCS postpartum adjusted for: maternal age, maternal BMI, disease duration, DMT restart first year postpartum, early natalizumab restart in the first 28 days postpartum, relapse during pregnancy, EDSS score during pregnancy.

§Models for the outcomes preterm birth, SGA adjusted for: maternal age, maternal BMI, alcohol/tobacco pregnancy exposure, high dose glucocorticosteroid pregnancy exposure, antibiotic treatment during pregnancy, gynaecological complications during pregnancy.

¶Models for the outcome congenital abnormality adjusted for: maternal age, maternal BMI, high dose glucocorticosteroid pregnancy exposure, antibiotic pregnancy exposure, gynaecological complications during pregnancy.

\*\*Models for the outcomes anaemia, thrombocytopaenia adjusted for: maternal age, maternal BMI, alcohol/tobacco pregnancy exposure, high dose glucocorticosteroid pregnancy exposure.

††Models for the outcomes leucocytosis, high LDH level adjusted for: maternal age, maternal BMI.

‡‡No event in <30-subgroup.

§§Models for the outcome high GPT/ALT level adjusted for: maternal age, maternal BMI, alcohol/tobacco pregnancy exposure.

ALT, alanine aminotransferase; BMI, body mass index; DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale; GPT, glutamic pyruvic transaminase; GW, gestational week; LDH, lactate dehydrogenase; NA, not applicable; NTZ, natalizumab; SGA, small for gestational age; SRDCS, Severe Relapse Disability Composite Score.

during pregnancy was statistically significantly associated with preterm birth (OR 9.43, 95% CI: 3.07 to 30.8), but not with lower mean births weight ( $\beta$  -23, 95% CI: -181-136) or SGA (OR: 0.59, 95% CI: 0.19 to 1.55).

### Haematological abnormalities

We received blood cell counts immediately after birth from 121/172 (70.3%) neonates in the maintaining-group of which 74/121 (61.2%) were born with HA, mainly with anaemia

(42/114, 36.8%) or thrombocytopaenia (43/117, 36.8%; figure 1). Anaemia, thrombocytopaenia and leucocytosis were statistically significantly more common in the  $\geq 30$ -subgroup (table 3). High LDH and ALT were rare; high total bilirubin, AST and low haptoglobin were not observed.

At least one follow-up blood count was available in 30/74 (40.5%) neonates with HA. After a median of 2 days (IQR 1-4), 7/30 (23.3%) were reversible. Only 2/42 (4.8%) neonates with anaemia received a specific treatment and substituted iron orally.

Table 4 Adjusted linear regression of neonatal outcomes

Outcome	Covariable	$\beta$	95% CI	$\beta$	95% CI
		Crude		Adjusted	
Births weight*	GW of last NTZ during pregnancy	-2.2	-5.7 to 1.2	-3.2	-6.6 to 0.30
	NTZ exposure after first trimester	-42	-138 to 55	-61	-160 to 37
Births length*	GW of last NTZ during pregnancy	-0.01	-0.03 to 0.00	-0.02	-0.04 to 0.00
	NTZ exposure after first trimester	-0.39	-0.94 to 0.16	-0.42	-1.0 to 0.17
Head circumference at birth*	GW of last NTZ during pregnancy	-0.01	-0.02 to 0.00	-0.01	-0.02 to 0.00
	NTZ exposure after first trimester	-0.41	<b>-0.77 to 0.05</b>	-0.36	-0.73 to 0.02
GW at birth excluding preterm birth†	GW of last NTZ during pregnancy	0.00	-0.01 to 0.01	0.01	-0.01 to 0.02
	NTZ exposure after first trimester	0.01	-0.28 to 0.31	0.13	-0.19 to 0.46

Summary of the results of multivariable linear regression models to estimate adjusted  $\beta$ -coefficient with 95% CIs. For CIs highlighted in bold the effect is considered as statistically significant.

\*Models for the outcomes births weight, birth length, head circumference at birth adjusted for: maternal age, maternal BMI, alcohol/tobacco pregnancy exposure, gender of the newborn, GW at entry into the cohort, high dose glucocorticosteroid pregnancy exposure, antibiotic pregnancy exposure, gynaecological complications during pregnancy.

†Models for the outcome GW at birth excluding preterm birth adjusted for: maternal age, maternal BMI, alcohol/tobacco pregnancy exposure, high dose glucocorticosteroid pregnancy exposure, antibiotic treatment during pregnancy, gynaecological complications during pregnancy.

$\beta$ ,  $\beta$ -coefficient; BMI, body mass index; GW, gestational week; NTZ, natalizumab.

Five neonates with first trimester exposure and available blood cell count showed no HA.

The earliest gw of last NTZ infusion we observed an HA (thrombocytopenia) was in gw 13.

## DISCUSSION

In our pregnancy cohort study, pregnancy and postpartum relapses were much rarer in women maintaining NTZ (25.7%), compared with those who stopped in the first trimester (62.6%). The early 3 months postpartum relapse risk was lower (8.6%), when NTZ was last administered after gw 30, and lowest in the combination with an early restart of NTZ postpartum (6.3%). In total, 7.5% reached the SRDCS 12 months postpartum, but only 2.7% in the  $\geq 30$ -subgroup with NTZ restart during the first 28 days post partum. Our results indicate that relapses after NTZ discontinuation can be mostly prevented by maintaining treatment during pregnancy and starting shortly after delivery. Adverse neonatal outcomes were not more common with the continuation of NTZ, except for HA occurring in 61.2% of all newborns. Another important finding of our study is that independent of NTZ discontinuation the number of newborns with SGA is nearly doubled compared with German newborns. The results of our study add relevant knowledge of fetal and maternal risks after NTZ long-term pregnancy exposure, as a basis for informed risk-benefit discussion between neurologists and patients with MS, who plan a pregnancy.

Our results on low pregnancy relapse risk (5.9%) are in line with previous studies on pregnancies maintaining NTZ during the first trimester (4%)<sup>17</sup> or even throughout pregnancy (2%),<sup>11</sup> and confirm an increased relapse risk in pregnancies stopping NTZ during the first trimester (32% vs 20–39%).<sup>4 8 17</sup> In accordance with other cohorts,<sup>4 6 8</sup> we observed highest ARR in the first 3 months postpartum, and a similar ARR during the postpartum year in maintaining-group (ARR: 0.25, 95% CI: 0.17 to 0.36) compared with the postpartum ARR (ARR: 0.12, 95% CI: 0.05 to 0.22) previously published by Landi *et al.*<sup>11</sup> Smaller studies have reported a higher disability risk after NTZ discontinuation in the setting of pregnancy using various definitions (16.2–19%)<sup>4 18</sup> compared with that observed in our larger cohort (7.5% reaching the SRDCS 12 months post partum). We recently reported 12.8% reaching the SRDCS 1-year postpartum in pregnancies stopping NTZ during the prepregnancy year or the first trimester and 1.1% catastrophic relapses.<sup>8</sup> In

contrast, we did not observe catastrophic relapses in women who continued NTZ during pregnancy. Therefore, our results indicate that maintaining NTZ beyond the first trimester may protect against disability worsening including severe relapses.

We found the early NTZ restart to be protective against postpartum relapses, as reported previously,<sup>4 6 19</sup> and pregnancy relapses associated with an increased postpartum relapse risk,<sup>4 6 7</sup> especially for severe relapses. In contrast, two other large studies could not confirm a beneficial effect of early NTZ treatment<sup>8</sup> or NTZ treatment during the postpartum year,<sup>11</sup> which might be explained by the short NTZ therapy break in our cohort of a median of 70 days in the maintaining-group versus approximately 100 days reported by Landi *et al.*<sup>11</sup> Consistent with this, the randomized 24-week Natalizumab treatment interruption study (RESTORE) reported most relapses 112 days after NTZ discontinuation.<sup>20</sup>

In our observation, extending NTZ dosing intervals to 6–8 weeks was not associated with pregnancy or postpartum relapses, in line with the comparison of switching to 6-week dosing of natalizumab versus continuing with 4-week dosing in patients with relapsing-remitting multiple sclerosis (NOVA) trial, which demonstrated similar disease control,<sup>21</sup> but extending dosing intervals to 12 weeks was associated with increased clinical and MRI disease activity in other studies.<sup>22 23</sup> A recent analysis also describes a decrease in NTZ efficacy with increasing dosing intervals, but every-6-week dosing was likely to maintain the efficacy of NTZ, particularly at body weights <80 kg,<sup>24</sup> which applies to our study population.

The theoretical advantage of extending dosing intervals is the reduction of fetal NTZ exposure. In our cohort we did not discover essential differences between neonatal outcomes; both preterm births and congenital abnormalities were in line with the general population.<sup>23–25</sup> Of importance more infants were smaller than expected, with 20% being SGA. The SGA rate in European countries is specified with 10%, using national reference percentiles to avoid misclassification.<sup>25</sup> Reassuringly, we observed no significant difference for SGA between exposure groups. Significantly lower birth weights compared with healthy<sup>14</sup> or unexposed control groups<sup>26</sup> and a significant birth weight reduction of 169 g<sup>27</sup> for NTZ first trimester exposure has been previously described. However, the mean birth weight of term born neonates in our cohort (3296 g  $\pm$  433) was within the expected range in the German population (3362 g  $\pm$  557).<sup>28</sup>

Two small case series of pregnancies with third trimester NTZ exposure reported birth weights under the expected range, with mean birth weight  $2723 \pm 416$  g and median birth weight 2778 g (range 2100–3790), respectively,<sup>10 29</sup> which is substantially lower than recently reported (median birth weight male: 3168 g; female: 3315 g)<sup>13</sup> and in our study population. This birth weight reduction might be explained by the high number of relapses and glucocorticosteroid treatments during pregnancy, although high-dose glucocorticosteroid exposure was not associated with a lower mean birth weight or SGA newborns in this cohort, but has been described in the literature.<sup>30</sup> Also, there has been a long lasting discussion on the effect of the MS disease itself on birth weight reduction in further observations.<sup>31</sup> A recent systematic review indicates an increased risk for SGA among women with MS<sup>32</sup> depending on three cohort studies,<sup>33–35</sup> but the association between high disease activity and reduced birth weight has not been adequately studied so far. Thus, this finding needs further investigation, to rule out an increased risk of intrauterine growth restriction after NTZ pregnancy exposure or active MS itself, as low birth weight is a risk factor for several diseases in adult life.<sup>36</sup>

HA, as described in cynomolgus monkeys<sup>37</sup> and humans,<sup>10</sup> were common in neonates exposed to NTZ after 30th gw (67% with all kinds of HA) and can be explained by the pharmacokinetic and pharmacodynamic characteristics of the substance. NTZ, as a monoclonal IgG4 antibody acting as an  $\alpha 4$ -integrin inhibitor, is actively transported over the blood–placenta barrier by the fetal Fc-receptor, which is increasingly expressed from the 22nd gw.<sup>38</sup> Studies indicate that  $\alpha 4$ -integrins are important for the migration of erythroid progenitors and pre-B-cells beneath the stroma.<sup>39</sup> Therefore, it is possible that NTZ interferes with fetal hematopoiesis through  $\alpha 4$ -integrin inhibition. The frequency of HA occurrence has been inconsistently described so far, from 10/13 (77%) in a small case series<sup>10</sup> to 4/69 (6%) in a smaller cohort study.<sup>11</sup> The difference to our finding of 36.8% of newborns with anaemia or thrombocytopaenia can most likely be explained by the median gw of last NTZ exposure in gw 34 (range 32–36)<sup>10</sup> compared with 30.9 (IQR 26.9–33.3) in our cohort. Landi *et al* stated, that only a minority of their cohort was exposed to NTZ after the 30th gw.<sup>11</sup> Different definitions for HA might also lead to an underestimation, therefore we decided to define abnormalities with days-of-life specific standard value, as especially the normal circulating concentrations of haemoglobin, platelets, leucocytes and bilirubin are known to be influenced by neonatal age.<sup>16</sup>

### Strengths and limitations

Strengths of this study include a high enrolment rate during the first trimester of pregnancy, resulting in reliable, robust and prospective long-term data of high-quality, along with a large sample size and including a control group. By measuring the fetal HA risk in the majority of our cohort on the one hand and the maternal disability risk on the other hand, this study provides important information and supports decision-making for women with highly-active MS and their treating clinicians in the field of pregnancy planning.

Our study also has several limitations. It is not population based and we cannot rule out that more severely affected women contact our registry.<sup>12</sup> The lack of MRI data limits the conclusion on disease activity, especially in the postpartum period. Therefore, this data is in high demand. Also, the lack of blood counts in the 1st Trim-group as well as the relatively low rate of follow-up blood counts is a major limiting factor. Although a blood count monitoring is recommended for all neonates exposed to NTZ

during pregnancy, only 70.3% received a blood count, of which only 40.5% had a follow-up blood count available. Given the follow-up blood count was a median of 2 days later, we cannot provide sufficient information on the duration until HAs are reversible. The reversibility has been described before,<sup>37</sup> and is also biologically plausible as the  $\alpha 4$ -integrin inhibition is reversible as well.<sup>40</sup> The duration should be investigated in further studies.

### CONCLUSION

Overall the chance of women achieving stable MS status despite high disease activity before pregnancy has been greatly improved by continuing NTZ. We found that maintaining NTZ beyond the 30th gw week reduces the maternal relapse and disability risk. In combination with an early postpartum restart, the lowest risk was observed. Neonatal outcomes seem not to be affected by NTZ exposure throughout pregnancy, with the exception of a higher fetal risk for HA, mostly without specific treatment required. Despite the knowledge of the HA risk, only a small proportion of neonates had follow-up blood counts available, which underscores the need for improving the interaction among the members of the multidisciplinary team.

Our finding should lead to a distinct risk–benefit-discussion between neurologist and women and highlights the importance of evaluating cohorts breastfeeding under monoclonal antibodies and examining child development in the future.<sup>13</sup>

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