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Research Paper

Pregnancy and fetal outcomes following natalizumab exposure in pregnancy. A prospective, controlled observational study

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Abstract

Background: Safety data on first-trimester natalizumab exposure are scarce, as natalizumab is usually withdrawn three months before pregnancy.

Objective: The objective of this paper is to investigate the fetal safety of exposure to natalizumab (Tysabri®) during the first trimester of pregnancy using disease-matched (DM) and healthy control (HC) comparison groups.

Methods: A total of 101 German women with RRMS exposed to natalizumab during the first trimester of pregnancy were identified. Birth outcomes in the exposed group were compared to a DM group ($N = 78$) with or without exposure to other disease-modifying drugs, and an HC group ($N = 97$).

Results: A total of 77, 69 and 92 live births occurred in the Exposed, DM and HC groups, respectively. The rates of major malformations ($p = 0.67$), low birth weight (<2500 grams) ($p = 1.0$) and premature birth ($p = 0.37$) did not differ among groups. Higher miscarriage rates ($p = 0.002$) and lower birth weights ($p = 0.001$) occurred among the Exposed and DM groups, as compared to the HC; however, there was no significant difference between the Exposed and DM groups.

Conclusion: Exposure to natalizumab in early pregnancy does not appear to increase the risk of adverse pregnancy outcomes in comparison to a DM group not exposed to natalizumab.

Keywords: Multiple sclerosis, pregnancy exposure, natalizumab, fetal safety

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Introduction

Natalizumab (Tysabri® by Biogen Idec) is a humanized monoclonal antibody indicated for the treatment of active relapsing–remitting multiple sclerosis (RRMS), and Crohn's disease. It acts as an immunomodulator by antagonizing the α4 subunits of the α4β1 and α4β7 integrin molecules in the immune system, and blocking the α4-mediated adhesion of proinflammatory cells to vascular endothelium and their subsequent crossing of the blood-brain barriers.[1,2]

α4-integrins play an active role in the fertilization, implantation, placental and cardiac development, and when antagonized with a synthetic compound in pregnant animals, severe defects have been reported.[3] Hence it is reasonable to assume risks associated with natalizumab exposures during pregnancy and a potential adverse effect on the developing fetus. In several studies in pregnant guinea pigs and cynomolgus monkeys, natalizumab exposure failed to show teratogenic effects and yielded mixed results for increased risk in abortion rates.[3–5]

The registry launched by Biogen Inc, *Tysabri Pregnancy Exposure Registry (TPER)*, with 364 exposed pregnancies, revealed a birth defect rate of 9.5% with no particular clustering in the pattern of defects.[6] One small study with 35 accidental exposures was previously reported by Hellwig et al., with no increase in the baseline risk for defects in comparison to a group of women on other disease-modifying drugs (DMDs).[7]

As many RRMS patients gain excellent control of their highly active disease with natalizumab, and studies have shown a return to baseline disease activity upon interruption of natalizumab, some as early as four weeks,[8] the risk of natalizumab exposure in pregnancy must be weighed against the risk of having relapses requiring steroid treatment during pregnancy following discontinuation.

The objective of the present study was to compare pregnancy outcomes in women with RRMS exposed to natalizumab in early pregnancy, to disease-matched (DM) and healthy control (HC) groups of women.

Methods

In 2006 a nationwide independent pregnancy registry for MS was established in Bochum, Germany. Pregnant women registered to this database are followed prospectively either through telephone interviews every three months, or by visits to the university-based outpatient clinic in Bochum. All self-reported data are collected through standardized questionnaires as previously described.[7]

For this study women accidentally exposed to natalizumab during pregnancy were recruited. Exposure was defined as treatment with natalizumab from eight weeks prior to the start of the last menstrual period (LMP) and onward. Women were followed till six months postpartum. All had confirmed diagnosis of RRMS, and were recruited between 2006 and 2013.

Thirty-five outcomes in this group were previously reported and included in this study to increase power, and because new information was available in some of those outcomes.

The Motherisk program at The Hospital for Sick Children in Toronto, Canada, is a clinical, teaching and research program. It has been providing evidence-based information on drug safety in pregnancy and lactation. Two prospective Motherisk cohorts were used to serve as comparison groups for this study.

The first comparison group is a DM group of pregnant women with confirmed RRMS who were recruited prospectively between 1997 and 2013, and were not treated with natalizumab. Information on maternal characteristics, gestational age at recruitment, maternal age at conception, pre-pregnancy maternal body mass index (BMI), smoking and drinking status, obstetrics history, concomitant medications taken in pregnancy, and educational status was collected.

The second comparison group was the HC group of women with no teratogenic exposures. They contacted the Motherisk general or nausea and vomiting of pregnancy (NVP) lines between 1997 and 2012 to inquire about safety of non-teratogenic drugs, or ways to manage their NVP. These women were matched to the Exposed group by maternal age at conception (±2 years), BMI, and gestational age at recruitment (±1 week).

All Motherisk women were followed-up prospectively at least twice, with many followed up several times during pregnancy and in the postpartum period. The pregnancy outcomes collected included congenital malformations, spontaneous abortions (SA), therapeutic abortions (TA), gestational age (GA) at pregnancy loss, GA at birth, birth weight, head circumference, birth length, gender, and mode of delivery. Details of neonatal health and birth defects were confirmed with the child's physician by letter communication.

Statistical analysis

One-way analysis of variance (ANOVA) was used to compare the means of normally distributed continuous data among the three groups. In cases where significant difference was found, post hoc analysis using Tukey's test was conducted. For non-parametric continuous data, Kruskal Wallis test was used to compare medians. Categorical data were compared among groups in 2 × 3 tables using Chi square or Fisher's exact test for parametric and nonparametric data, respectively. In comparisons where a significant difference was detected ($p < 0.05$) Bonferroni's correction was applied with alpha 0.05 and the groups were compared two at a time with the corrected p value.

Results

We included 276 women in total: 101 natalizumab exposed (Exposed), 78 DM, and 97 HCs. The DM group members were significantly older compared to HC and Exposed ($p < 0.001$) individuals. The rate of alcohol exposure was significantly higher in the HC group compared both to the DM and Exposed groups ($p = 0.003$). No statistically significant difference among the groups on GA at recruitment, pre-pregnancy BMI, smoking status, or obstetric history was detected. Baseline characteristics of the three groups are presented in Table 1.

The Exposed group included 101 women with RRMS reporting on 102 pregnancy outcomes. One hundred reported on singleton pregnancies and one woman a

Table 1. Maternal characteristics in each of the study groups.

Maternal characteristics	Natalizumab exposed	Disease matched	Healthy controls	*p* values
Maternal age (years) Mean±SD (Median)	30.5±5.3[d] (30.2)	33.9±4.7[c,d] (33.3)	30.6 ± 4.9[c] (30.5)	**<0.0001**
Pre-pregnancy BMI Mean±SD (Median)	*N* = 61 24.4±5.3 (23.8)	*N* = 56 24.9±4.6 (24.2)	*N* = 69 23.8±4.5 (23.3)	0.47
Gestational age at call (Weeks) Mean±SD (Median)	*N* = 97 12.5±9.5 (8.7)	*N* = 79 9.4±9·5 (6.0)	*N* = 97 12.2±9.1 (8.9)	0.07
Gravidity	1.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–3.0)	1.0[a]
Parity	0.0 (0.0–1.0)	0.0 (0.0–1.0)	1.0 (0.0–1.0)	
Spontaneous abortions	0.0 (0.0–0.0)	0.0 (0·0–1.0)	0.0 (0.0–0.0)	
Terminations	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	
Alcohol exposure	1/90 (1.1%)[e]	4/94 (4.3%)	11/86 (12.8%)[e]	**0.003**[b]
Smoking exposure	8/86 (9.3%)	8/94(8.5%)	10/85 (11.8%)	0.75

[a]Kruskal Wallis Test; [b]Fisher Exact; [c,d]Matching pairs differ significantly as identified by Tukey's test; [e]matching pairs differ sig. as identified by Bonferonni's test.

Table 2. Disease details of patients with multiple sclerosis in the exposed and disease matched groups.

Disease characteristics	Natalizumab exposed	Disease matched
Subjects (N_{total})	101	78
Total outcomes	102	95
Prospective outcomes	98/102 (95%)	84/95 (88%)
Disease duration (Median years)	5.8	5.6
Age at MS diagnosis (Mean±SD years)	23.7±5.3	N/A
Exposed to disease-modifying drugs (DMD) in pregnancy *N* (%)	101 (100%)	25 (32%)
Type of DMD exposure (*N*)	Natalizumab (101)	Glatiramer acetate (2) INFB-1a (17) INFB-1 (6)

INFB: interferon beta-1a/1b.

twin pregnancy. The median duration of therapy with natalizumab before pregnancy was 18.9 months. Length of exposure during pregnancy can be divided into four periods: eight weeks prior to LMP ($n = 20$), zero to nine weeks of gestation ($n = 76$), 10–13 weeks of gestation ($n = 4$). Only one woman was exposed till the 31st week of pregnancy and her results have been previously reported.[9] Twenty-one women experienced a relapse during pregnancy that required at least one course of steroid treatment.

The DM group included 78 women with RRMS reporting on 95 pregnancy outcomes. Eleven women reported on two pregnancies, two women reported on three pregnancies and one twin pregnancy. Disease duration was reported for 68 pregnancies and the median was 5.6 years at time of pregnancy. Sixty-eight women were on DMDs prior to pregnancy: 53 (56.4%) were on interferon beta-1a/1b (INFB), 11 (11.7%) on glatiramer acetate (GLAT), three (3.2%) on natalizumab, and one on fingolimod. Twenty-two women were untreated. Twenty-five women had exposure to DMDs during the first trimester and seven throughout pregnancy. The most common comorbidity in this group was depression and anxiety. No relapses requiring steroids were reported. Table 2 summarizes the differences between the DM and Exposed groups.

The HC group included 97 women. Most women had called about mild to severe NVP management and had no significant medical history. The most common medical condition reported in this group were mood

Table 3. Pregnancy outcomes in each group.

Outcomes	Exposed	Disease matched	Healthy controls	*p* values
Live births	77/98 (78.6%)∞	69/95 (72.6%)‡	92/98 (93.9%)∞‡	**0.0004**
Terminations	4/98 (4.1%)	6/95 (6.3%)	2/98 (2.0%)	**0.33**
Spontaneous abortions	17/98 (17.3%)∞	20/95(21.1%)‡	4/98 (4.1%)∞‡	**0.002**
Gender	M: 38/76 (50%) F: 38/76 (50%)	M: 17/49 (32%) F: 32/49 (65.3%)	M: 18/36 (50%) F: 18/36 (50%)	0.20
Gestational age at birth (weeks)	38·8±1·6 (38.9)	38·5±2·0 (38.6)	39±1·7 (39.8)	0.17
Birth weight (grams)	3159±478.9[c] Median (3225)	3198.3±515.3[d] Median (3247.5)	3436.7±549.5[c,d] Median (3444.5)	**0.001**
	3247·6± 396.4 Median: (3255)	3198.3±515.3[d] Median (3247.5)	3436.7±549.5[d] Median: (3444.5)	**0.01[a]**
% Birth weight Median (25%–75%)	44.8 (25.1–70.2)	43.6 (23–66·5)	59.2 (22.9–90.0)	0.13[b]
Head circumference Mean±SD (cm)	35.1± 2.2	34.2±1.9	34.1±2.2	0.30
Birth length Mean±SD (cm)	50.3±2.5[c]	50.6±3.4[d]	53.5±2.1[c,d]	**0.003**

M: male; F: female. [a]Excluding birth weights of babies exposed to steroids ($N = 21$) during relapse treatment(s) in natalizumab exposed pregnancies. [b]Kruskal Wallis Test. ∞‡Values that match with one of these symbols identify the pairs that differ significantly as per Bonferonni's test. [c,d]Matching pairs differ significantly as identified by Tukey's test.

disorders ($n = 21$), thyroid-related conditions ($n = 8$), migraines ($n = 7$) and inflammatory bowel disease ($n = 4$). The most commonly used therapy in this group was dimenhydrinate, ginger, vitamin B6, and Diclectin® (pyridoxine and doxylamine succinate) for the management of NVP.

Pregnancy outcomes

The rate of live births was significantly higher in the HC than in both the Exposed and DM groups *($p = 0.0004$).* This corresponded to significantly higher rates of miscarriage in both the Exposed 17.3% and DM 21.1% groups in comparison to HC 4.1% *($p = 0.002$)* (Table 3). Nine of 20 of the miscarriages among the DM occurred in women older than 35years; three of these women had two miscarriages each. Since miscarriage rates increase after age 35,[10] and women with one miscarriage are at a higher risk for subsequent miscarriages, a recalculation of spontaneous abortion rates in both groups after excluding women over the age of 35 changed the miscarriage rates to 11.5% and 12% in the DM and Exposed groups, respectively.

The mean *birth weights* were significantly lower both in the Exposed (3159 ±478.9 grams) and DM (3198.3±515.3 grams) in comparison to the HC (3436.7±549.5 grams) ($p = 0.001$). When excluding women receiving high-dose steroids for relapse treatment in the Exposed group ($n = 21$), the difference in birth weights was significant only between the DM and HC groups—the number of women, if any, requiring steroids to treat relapses in the DM group was not reported. There was a trend toward higher percentile birth weights in the HC babies: 59.2% versus 44.8% and 43.6% in Exposed and DM, respectively, but this difference did not reach statistical significance (Table 3).

Data on *birth length* were available in only 10 of the patients in the HC group, and while a significant difference was detected ($p = 0.003$) the paucity of data in this group precludes definite interpretation (Table 3).

There was no significant difference in the number of TA, GA at birth, gender, head circumference, premature births (<37 weeks), low birth weights (<2500 grams) and birth defects among the three groups (Tables 3 and 4).

Delivery outcomes

The rate of vaginal delivery was significantly higher in the HC compared to the Exposed group ($p = 0.006$) but did not differ from the DM group. The rate of scheduled cesarean sections (SCS) was significantly higher in the Exposed (23/73; 31.5%) compared to both DM (4/66; 6.1%) and HC groups (five of 62; 8.1%) ($p < 0.0001$). The rate of emergency cesarean sections (ECS) were significantly higher in DM in comparison to the Exposed ($p = 0.02$) but did not

Table 4. Adverse neonatal outcomes and mode of delivery.

Outcomes	Natalizumab exposed	Disease matched	Healthy controls	*p* values
All anomalies	4/77 (5·2%)	3/69 (4.3%)	5/92 (5·4%)	1.0[a]
Major birth defects	3/77 (3.9%)	1/69 (1·4%)	2/92 (2·2%)	0.67[a]
Premature (37 weeks)	6/76 (7·9%)	10/67 (14·9%)	9/92 (9·8%)	0.37
Low birth weight (<2500 g)	6/77 (7·8%)	5/68 (7·4%)	7·0/92 (7·6%)	1.0
Delivery method	36/73 (49·3%)‡	43/66 (65·2%)	47/62 (75·8%)‡	**0.0006**
Vaginal	23/73 (31·5%)∞‡	4/66 (6·1%)‡	5/62 (8·1%)∞	**<0.0001**
C/S, planned C/S, emergency/ repeat	8/73 (11·0%)∞	19/66 (28·7%)∞	10/62 (16·1%)	**0.02**

C/S: cesarean section. [a]Fisher's exact test 2 × 3. ∞‡pairs that match on the same symbol in the same row a differ significantly as per Bonferonni's test.

differ from the HC group. Table 4 summarizes the delivery outcomes for the three groups.

Birth defects

Birth defects were detected in (three of 77; 3.9%), (one of 69; 1.4%), and (two of 92; 2.2%) of the live births in the Exposed, DM and HC groups, respectively, with no significant difference among the groups ($p = 0.67$) (Table 4).

In the *Exposed Group*, there was an atrial septal defect (ASD) in a full-term female baby, hernia in a premature male, and hexadactyly in one term male baby. All three mothers had discontinued natalizumab in the first week of conception. In addition, one full-term male baby was diagnosed with neuroblastoma, hepatomegaly, renal and hepatic insufficiency, sepsis and developmental retardation shortly after birth.

Among the *non-live births* three fetuses with genetic anomalies were reported—one case of Trisomy 16, one case of Heterotaxy syndrome with complete atrioventricular septal defect (AVSD) and defected azygos, and one case of Turner Syndrome Mosaicism. All three women had discontinued natalizumab within the first few weeks of pregnancy.

In the *DM group*, there was one case of clubfoot in a premature female baby requiring three surgeries. The mother had reported a positive family history for clubfoot. She had used GLAT all through her pregnancy. One case of cryptorchidism, one case of double hernia, and one hypospadias were also reported. These three cases were not included in the count of major birth defects as they were medically unconfirmed.

In the *HC group*, there was one case of ureter pelvic junction (UPJ) obstruction in a premature baby, and one case of ventricular septal defect (VSD) in a premature male.

Retrospectively exposed cases

Four women in the Exposed group were recruited retrospectively, after pregnancy outcomes were confirmed. The mean disease duration was 7.4 years and one of the four women smoked during pregnancy (10 cigarettes/day). All four women gave birth to full-term babies: three vaginally and one by ECS. There were three males and one female. The mean birth weight was 3251±376 grams, and no birth defects or adverse outcomes were reported in this group.

Discussion

This study demonstrated no apparent increase in the rate of defects of live births in the Exposed group compared both to DM and HC groups. However, to detect a twofold increase in malformation rates with a power of 80% and alpha of 5%, 400 Exposed and 400 DM controls would be needed. Other adverse neonatal outcomes such as low birth weight (< 2500 grams) prematurity and reduced head circumference weren't increased in the Exposed as compared to the DM and HC group babies.

The observed birth weights and birth lengths, while similar between the Exposed and DM groups, were significantly lower than the HC group. Similarly, while the percentile birth weights did not differ significantly, they were lower in the two MS groups. Lower birth weight and birth length among babies

born to mothers with MS have been previously reported.[11,12] A neurologically based defect in pelvic circulation may be potentially contributing to this observation.[11]

The rates of SA, while higher in the Exposed and DM groups, were significantly different only from the HC group. Several selection biases could have affected this result. First, the majority of HC women had sought counseling on ways to manage their NVP, and severity of NVP is associated with a decreased risk for SA.[13] Thus the observed miscarriage rates in the HC group may be lower than the general population rate, leading to a larger difference between HC rates and the rates in the two MS groups.

Secondly, women in the DM group were recruited 2.7 weeks earlier, had higher maternal age at pregnancy, and some had exposure to DMDs in pregnancy. While the difference in GA at recruitment was not statistically significant, and almost identical miscarriage rates were seen in DM and Exposed groups after adjusting for maternal age, and despite a 2012 review claiming there is no strong evidence for increased risk in SA with DMD exposures,[14] we cannot dismiss a possible increased risk. Further investigation using a DM group closely matched on criteria such as disease severity, Expanded Disability Status Score, steroid use during pregnancy, DMD usage and obstetric history would isolate the effect of natalizumab on SA rates more precisely.

The vaginal delivery rate was lowest in the Exposed group, which was significant in comparison to the HC group only. Correspondingly, we observed a much higher rate of SCS in the Exposed compared to both comparison groups. The difference in mode of deliveries might be due to differences between the two countries. In Germany the nationwide cesarean section rate is about 30% and therefore comparable to the natalizumab-exposed pregnancies.

The severity of the disease itself may also pose as an impediment to normal vaginal deliveries in women on natalizumab who are likely to have more active disease; however, we are not able to confirm this as EDSS scores were not available.

The comparison of women from different countries may have affected the results and is addressed. The Canadian comparison groups were selected because of the availability of data both on the healthy and DM groups with the opportunity to closely match for relevant variables known to affect pregnancy outcomes. Canada and the United States have one of the highest immigrant populations and the ethnic diversity can introduce bias. However, an analysis of the ethnic makeup in our Canadian Motherisk groups revealed a significant number of European-Caucasians both in the HC (96%) and DM (93%) groups.

A comparison of national birth weight by gender in Canada and Germany revealed exceptionally similar results with a median 3631 grams, 3613 grams for German and Canadian males, and 3479 grams, 3470 grams for German and Canadian females, respectively, at 40 weeks of gestation.[15,16] Thus the observed birth weights are likely to reflect the influence of the disease only.

Addressing differences in obstetric outcomes between the two countries is a complex issue as nearly 45% of pregnancies are unplanned[17] and early losses are often not recognized. A 2010 study estimated a 5% and 7% miscarriage rate for Western Europe and North America, respectively.[17] While a 20% reduction in accidental pregnancies was observed worldwide with Western and Southern Europe having one of the lowest unintended pregnancy rates, North America has shown no decline in the rates of unplanned pregnancies.[17] Furthermore, North American women are much less likely to undergo induced abortions for unintended pregnancies.[17] Hence, while the proportions of unintended pregnancies leading to live births may differ between Western Europe and North America, the spontaneous miscarriage rates are not expected to vary substantially.

Finally, the higher alcohol exposure among the Canadian HC women reflects a few drinks that were consumed prior to mothers realizing their pregnancies and does not indicate regular consumption throughout pregnancy. Typically, women with chronic medical conditions such as MS are likely to avoid unhealthy habits, and it is not surprising that MS patients abstained from alcohol.

Despite the matching of women on criteria of age, GA at call and BMI, and women in the Canadian groups having European-Caucasian roots, and the shared similarities in obstetric outcomes and health care systems between Germany and Canada, minor differences between Germany and Canada cannot be excluded.

This is the largest controlled study reporting on fetal outcomes following natalizumab exposure during the first trimester. A major strength is the use of two comparison groups with HC women closely matched to the Exposed women on maternal age at conception, BMI

and GA at recruitment, all of which are well-known confounders of pregnancy outcomes. Critically, having a DM group to account for the effects of MS itself on pregnancy outcomes allows identification of any potential impact that natalizumab may have exerted.

Since the majority of the women in the Exposed group (75%) discontinued natalizumab prior to 10 weeks, our findings and interpretations are limited to early exposure in pregnancy only. As maternal antibodies transfer minimally in the first trimester and only 5%–10% between 17 and 22 weeks of gestation,[18] one can surmise the same for natalizumab transfer, which may theoretically have an impact on neonatal immunity. Recent work from the German registry demonstrated hematological abnormalities such as anemia and thrombocytopenia in babies exposed to natalizumab in late pregnancy (This paper was not published at the time this was written. It only came out in July and the this is the reference: JAMA Neurol. 2014 Jul 1;71(7):891–5. doi: 10.1001/jamaneurol.2014.209.).

Conclusion

Natalizumab does not appear to increase the baseline risk for malformations, preterm births and low birth weight babies when compared to DM controls. However, this study's sample size had a limited power to discern small differences in malformation rates.

The risk for miscarriage, however, while very similar to the DM group, may still be of concern and requires further investigation. While these results are reassuring, further studies are needed to ascertain these observations.

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Acronyms

MS: multiple sclerosis
RRMS: relapsing–remitting multiple sclerosis
EDSS: Expanded Disability Status Scale
DMD: disease-modifying drugs
NVP: nausea and vomiting of pregnancy
SA: spontaneous abortion/miscarriage
TA: therapeutic abortion
GA: gestational age
LMP: last menstrual period
BMI: body mass index
ASD: atrial septal defect
VSD: ventricular septal defect
UPJ: ureter pelvic junction
SCS: scheduled cesarean section
ECS: emergency cesarean section
GLAT: glatiramer acetate (Copaxone®)
INFB-1a: interferon beta 1a (Avonex, Rebif®)
INFB-1b: interferon beta 1b (Beta(s/f)eron®)

Conflicts of interest

KH is supported by the German Research Council (Deutsche Forschungsgemeinschaft – DFG He 6841/1-1) and has received speaker honoraria from Biogen Idec, Teva, Sanofi Aventis, Novartis, Bayer Healthcare and Merck Serono. RG has received payments for consultancy from Biogen and Teva, and speaker honoraria and research grants from Biogen Idec Germany, Teva, Sanofi Aventis, Novartis, Bayer Healthcare and Merck Serono. LA has served as a consultant for Biogen, Acorda, Novartis, Genzyme and Questcor. GK serves as a consultant for Novartis. NE and SH have nothing to declare.

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Terminology and definitions

Healthy controls (HC): A comparison group of women with no MS and no exposure to any teratogens.
Disease-matched (DM): A diseased-match comparison group of women with RRMS with or without exposure to DMDs.
Exposed: The study group of women with RRMS with accidental exposure to natalizumab in early pregnancy.

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