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Review Article

Natalizumab exposure during pregnancy in multiple sclerosis: a systematic review

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1. Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system typically affecting young adults. The median onset age of MS is around 30 years which is the childbearing years for many women. Thus, pregnancy is a significant concern for many of them. Although studies suggested that pregnancy played a protective role for MS since disease activity was generally reduced during pregnancy [1]. For those with high disease activity, pregnancy is still a big challenge.

Natalizumab is an effective medicine approved for the highly active relapsing remitting MS. It is a humanized monoclonal antibody which binds to the a4 integrin on the surface of lymphocytes and inhibits peripheral blood lymphocyte migrating to the central nervous system, thus, reducing inflammation in the central nervous system [2,3]. Its efficacy has been demonstrated by meta-analyses and randomized controlled trials [4]. However, since animal studies found that natalizumab produced fetal immunologic and hematologic effects, and no adequate data in pregnant humans are available [1,5], women treated with natalizumab are generally advised to discontinue its use before pregnancy. Unfortunately, there are not too many alternatives for women with highly active MS and the risk for relapses or disability after natalizumab cessation is unknown more or less so far. Besides, many pregnancies are unplanned and natalizumab exposure is a large concern for them. Therefore, the pregnancy outcome after natalizumab exposure is a topic receiving increasing attention. But the data on natalizumab exposure during pregnancy is very limited up to now. The aim of our work was to review the literature systematically and provide some evidence for clinical practice.

2. Methods

2.1. Literature-search strategy

We performed a systematic search for all studies investigating the outcome of natalizumab exposure during pregnancy or within 3 months before conception. The cut-off day was June 12, 2018. Medline, Embase, and Web of Science were searched using a combination of the following keywords: “natalizumab”, “Tysabri”, “multiple sclerosis”, “pregnancy”, and “conception”. References from the relevant studies were also searched for additional studies.

2.2. Inclusion and exclusion criteria

Studies with human subjects written in English were considered. Studies were included if they described the outcome of pregnant women who were exposed to natalizumab 3 months before conception or during pregnancy. To gather the most comprehensive data, all studies, including case reports, were included. Studies were excluded if they were reviews or investigated postpartum treatment rather than the outcome of the pregnancy after natalizumab exposure.

2.3. Data analysis

Two authors (Peng and Qiu) independently searched and reviewed the studies. The following information was extracted from the included studies, using a standardized form: first author, publication year, country, pregnancies enrolled, and completed follow-up; criteria of malformations, evaluator (directly obtained from the pediatrician or mother's self-report and verified by pediatrician), maternal age, and

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duration of natalizumab exposure (before pregnancy, first trimester, second trimester, third trimester, or throughout pregnancy); pregnancies with relapse and pregnancy outcome (healthy live birth, major birth defects, elective termination, and spontaneous abortion); weights and complications of newborns as well as follow-up periods. If any disagreement developed, it was resolved by discussion among all authors. Because of significant heterogeneity among the included studies, we did not apply meta-analysis in this review.

3. Results

3.1. Study identification and selection

The electronic database search yielded 518 records. After reviewing the titles and abstracts, 494 records were moved. The final 24 studies were given full-text reviews, and 9 studies were abandoned for the following reasons: 6 were reviews, and 3 investigated treatment after delivery. Although the subjects in the Haghikia et al. and Hellwig et al. studies were partially covered by Ebrahimi et al., Hellwig et al. specifically described relapses after natalizumab discontinuation, and the patients in Haghikia et al. were specifically exposed to natalizumab during the third trimester. Their results were also described. An additional 2 studies were identified through citation searching. Finally, 17 studies were included [6–22]. Mean gestational ages at the time of enrollment were 12.5 weeks in Ebrahimi et al. and 11.8 weeks in Friend et al.; mean gestational age was not clear in Portaccio et al. Other characteristics of the included studies are summarized in Table 1.

With regard to the spontaneous abortion rate, we only considered the studies of Friend et al., Ebrahimi et al., and Portaccio et al., because the Haghikia et al. recruits of women with MS had known pregnancy outcomes, and the subjects in Hellwig et al. were partially covered in Ebrahimi et al. Spontaneous abortion was defined as fetal loss before 22 gestational weeks in the study of Friend et al., but it was not clear in Ebrahimi et al. or in Portaccio 2018 et al. The spontaneous abortion rate by women with MS who were exposed to natalizumab was 9.4% (32/339) in Friend et al. [11], 17.3% (17/98) in Ebrahimi et al. [9], and 17.4% (12/69) in Portaccio et al. [18]. One spontaneous abortion was found in the additional 15 patients identified from case reports [16]. The spontaneous abortion rate was similar to that of the general population, which varied from 15% to 22% published by previous studies [23] [5].

Friend et al. coded the birth defects according to the Metropolitan Atlanta Congenital Defects Program (MACDP) classification, and Portaccio et al. defined them according to the European Surveillance of Congenital Anomalies (EUROCAT); however, it was unclear in the study by Ebrahimi et al. The major birth defect rates varied from 2.9% to 5.1% in the natalizumab exposure group [9,11,18], which seemed slightly higher than that of the general population registered by the Atlanta Congenital Defects Program (2.67%) [11]. None of these studies found any defects that could be specifically attributed to natalizumab exposure during pregnancy. All 10 infants who were exposed to natalizumab throughout pregnancy were born without major birth defect.

Haghikia et al. found that 10 out of 13 newborns who were exposed to natalizumab in the third trimester had mild to moderate hematologic alterations, including thrombocytopenia, anemia, and leukocytosis. All hematologic alterations were normalized spontaneously 4 months later without special intervention [13]. Hematologic abnormality was also reported in other studies [7,12]. Specifically, during median follow-up periods of 2.2 year, Portaccio et al. observed that one child developed autistic spectrum disorder and another had a mild speech disorder in the natalizumab exposure group.

Mean birth weight of infants exposed to natalizumab during gestation ranged from 2916 g to 3162 g, which was slightly lower than that of the healthy controls but was similar to that of the disease-matched group [9,11,18]. When infants were exposed to natalizumab during the third trimester of gestation, the mean birth weight appeared to be even lower (2723 g) [13].

The relapse rate in the mothers after natalizumab discontinuation during pregnancy varied from 21.4% to 36.5% [9,14,19]. Specifically, patients who experienced 2 to 4 relapses the year before natalizumab was used experienced a higher likelihood of recurrence after natalizumab was suspended during pregnancy [8,13,22].

4. Discussion

The results indicated that the spontaneous abortion rate of MS women who take natalizumab during pregnancy was similar to that of the general population. It was higher in the studies by Ebrahimi et al. and Portaccio et al. than in Friend et al. This difference might result from several factors. Different inclusion criteria, treatment methods after natalizumab cessation and ethnicity all potentially contribute to the different rate of spontaneous abortion among them. What is more, mean gestational ages at the time of enrollment were around 12 weeks in these studies. Thus, they were unable to address the question of early spontaneous abortions. In fact, Friend et al. found that for patients with spontaneous abortion, the mean gestational age was 5.5 weeks [11], so we can speculate that the spontaneous abortion rate should be higher than that reported here.

The birth defect rates seemed slightly higher than that in the general population and disease-matched group. Although neither animal studies using cynomolgus monkeys [2,3] and guinea pigs [2,3], nor clinical studies found any fetal malformation that could be specifically attributed to natalizumab [11]. However, since previous studies showed that a4 integrin play a big role in the epicardium formation [24]. Natalizumab, as a humanized a4 integrin antibody, could generate potential effect on the development of epicardium and coronary vessels and should be paid attention to. On the other hand, we should also notice that the mean maternal ages for included studies were all over 30 years [9,11,18,19] and it is known that the birth defect rate rises with women age. What is more, other drugs like steroids which is used as alternative after natalizumab cessation might also associated with potential teratogenicity [25]. We should take these factors into consideration when considering the spontaneous abortion rate and birth defect rate. In addition, 10 newborns were exposed to natalizumab throughout, and all of them were born without defects.

Hematologic alterations seem common in infants who were exposed to natalizumab, especially in the third trimester [13,26]. Hematopoiesis influenced by natalizumab also approved in animal studies with monkeys [2,3]. Specifically, one infant reported by Haghikia et al. had minor subclinical intracerebral hemorrhage, which was picked up on ultrasonography and spontaneously resolved later. Given the high rate of thrombocytopenia seen with late pregnancy exposure [13,26], this complication should be paid attention to, although all the hematologic abnormalities were spontaneously resolved. Considering the observation from Haghikia et al. that the concentration of natalizumab was higher in patients with the most recent infusions before delivery [13] and the results from Proschmann et al. indicating that natalizumab could be detected in infants if the last infusion was given < 75 days before delivery [27], avoiding natalizumab during the last few weeks may reduce its concentration in infants.

Infants exposed to natalizumab, especially during the third trimester, are often born with relatively lower birth weights. However, besides the effect of natalizumab, other factors should also be taken into consideration. For example, patients who needed to restart natalizumab treatment all experienced relapses during pregnancy which could also influence the birth weight. Some newborns were even prematurely delivered because of catastrophic relapses [8,13]. Besides, Steroids and beta-interferons which are often used as alternatives for the patients after natalizumab discontinuation might also associated with potential risk of lower birth weight [28,29]. As we all know, fetuses gain most of their weight during the third trimester, so avoiding natalizumab use in the last few weeks may reduce the influence of natalizumab on the birth weight of infants.

Table 1
The characteristic of studies included.

Study ID	Country	Pregnancies (enrolled/ completed.)	Malformation criteria	Evaluator	Maternal age,(mean ± SD)	Natalizumab exposure (trimester,%) a	Relapse rate during pregnancy (%)
Ebrahimi 2015	Germany	102/98	NA	Self-reported	30.5 ± 5.3	Before (19.8); First (79.2); Throughout (1)	21.4
Friend 2016	US and ROW	376/363	MACDP	Pediatrician	30.4 ± 5.2	Before (18.9); First (77.1); First and second (2.7); Throughout (0.3)	NA
Haghikia 2014	Germany	13/13	NA	Pediatrician	30.6 ± 4.4	First and third(7.7); Second and third(23.1); Third(30.8) Throughout (38.5)	NA
Hellwig 2011	Germany	35/35	NA	Self-reported	30.6 ± 5.6	Before (17.1) First (82.9)	22.8
Portaccio 2018a and Portaccio 2018b	Italy	69/69	EUROCAT	NA	30.9 (5.1)	First (100)	36.5
De Giglio 2015	Italy	4/4	NA	Pediatrician	36.5 ± 2.6	Before (100)	NA
Hoevenaren 2011	Netherlands	2/2	NA	Pediatrician	31 ± 3	Before (50) Throughout (50)	NA
Bayas 2011	Germany	1/1	NA	Pediatrician	16	Third	NA
Ciron 2016	France	1/1	NA	Pediatrician	25	Throughout	NA
Fagius 2014	Sweden	1/1	NA	Pediatrician	29	Throughout	NA
Guilloton 2017	France	1/1	NA	Pediatrician	24	Throughout	NA
Papeix 2011	France	1/1	NA	Pediatrician	–	Before	NA
Pitarokoili 2017	Germany	1/1	NA	Pediatrician	30	Throughout	NA
Theaudin 2015	France	1/1	NA	Pediatrician	30	Throughout	NA
Van Obberghen 2017	France	1/1	NA	Pediatrician	29	Before	NA
Verhaeghe 2014	Belgium	1/1	NA	Pediatrician	22	Before	NA

Study ID	Pregnant outcome				Birth weight,g (mean ± SD)	Fetal complications (n.)	Follow-up periods (m)
	Healthy live infants (%)b	Major defects (%)	Elective termination (%)	Spontaneous abortion(%)			
Ebrahimi 2015	74.7	3.9	4.1	17.3	3159 ± 479	NA	6
Friend 2016	79.1	5.1	3.9	9.4 d	3162 ± 566	NA	1–3
Haghikia 2014	92.3	7.6	0	0	2723 ± 403	hematological abnormalities (10) c, subclinical ICH (1)	4
Hellwig 2011	80	2.8	2.8	14.3	3159 ± 403	NA	6
Portaccio 2018a and Portaccio 2018b	75.4	2.9	4.3	17.4	2916 ± 547	autistic spectrum disorder (1), mild speech disorder (1)	≥12
De Giglio 2015	100	–	–	–	NA	NA	1
Hoevenaren 2011	100	–	–	–	3050 ± 110	fetal distress (1)	1
Bayas 2011	100	–	–	–	2830	no complication	10
Ciron 2016	100	–	–	–	NA	Thrombocytopenia (1)	1
Fagius 2014	100	–	–	–	NA	no complication	8
Guilloton 2017	100	–	–	–	3140	Pancytopenia (1)	3
Papeix 2011	–	–	–	100	–	–	–
Pitarokoili 2017	100	–	–	–	3200	NA	0.5
Theaudin 2015	100	–	–	–	NA	no complication	0.25
Van Obberghen 2017	NA	–	–	–	NA	NA	6
Verhaeghe 2014	100	–	–	–	NA	NA	1

EUROCAT: European Surveillance of Congenital Anomalies; ICH: intracranial hemorrhage; MACDP: Metropolitan Atlanta Congenital Defects Program classification of birth defects; NA: not available; ROW: rest of the world; SD: standard deviation; US: the United States.

a: Duration of natalizumab exposure was categorized as before pregnancy, first trimester, second trimester, third trimester, or throughout pregnancy.

b: Healthy live birth included those without any congenital anomaly or with minor congenital anomaly.

c: Hematological abnormalities: 8 infants with anemia, 6 infants with elevated white blood cell count, and 6 infants with thrombocytopenia.

d: A total of 339 pregnancies were enrolled before 22 weeks, and the rate of spontaneous abortion was 9.4% among them.

Long-term outcome of the children whose mothers took natalizumab during pregnancy is still unclear. Portaccio et al. observed that 2 out of 54 children in the natalizumab exposure group had developmental abnormalities during a median follow-up period of 2.2 years [18,19]. Although 2 children also developed mild speech disorders in the non-natalizumab exposure group (341 children), whether natalizumab exposure is associated with developmental abnormalities needs further research.

Although pregnancy is generally considered a protective factor against relapse in patients with MS, the relapse rate in women with MS who discontinued natalizumab was still very high [9,14,19]. In those with active MS, the recurrent rate could be higher [30]. The balance between relapses and potential teratogenicity should be evaluated carefully.

There are some limitations in our review. First of all, the studies included in our review were all observational studies with relatively small sample sizes. Thus, the result is not compelling. Besides, because the majority of patients included in the studies discontinued natalizumab prior to gestation or during the first trimester, we are not clear about the safety of natalizumab exposure during later pregnancy. Furthermore, the follow-up periods of the included studies were all short. Thus, the long-term effects of natalizumab exposure on the offspring need further exploration. However, establishing the safety of MS medications during pregnancy is challenging because it is unethical to conduct randomized controlled trials to investigate the safety and adverse effects of the treatments on pregnant women, and prospective cohort studies with large sample sizes and long follow-up periods are difficult to conduct. This review could provide some evidence for therapeutic decisions by women with MS who wish to have a child.

5. Conclusion

Natalizumab exposure during pregnancy does not seem to increase the spontaneous abortion rate but may slightly increase the birth defect rates in women with MS. Hematologic alterations and low birth weight were common in infants who were exposed to natalizumab during late pregnancy. The long-term effects of natalizumab exposure during pregnancy deserve further research.

Disclosures

Authors declare that they have no disclosures to report.

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Conflicts of interest

None.

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