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Clinical Commentary

Delivery of healthy babies after natalizumab use for multiple sclerosis: a report of two cases

Hoevenaren IA, de Vries LC, Rijnders RJP, Lotgering FK. Delivery of healthy babies after natalizumab use for multiple sclerosis: a report of two cases.
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Background – In current literature, no data on safety in pregnancy for new drugs in the treatment of multiple sclerosis (MS) like natalizumab (Tysabri®), a humanized monoclonal antibody against α4 integrins, are yet available. In the management of MS, natalizumab is the first monoclonal antibody approved to the market. *Methods* – We describe the pregnancy and outcome in two women with MS using natalizumab. The first patient used it in the periconceptional period, and the second patient used it in both the periconceptional period and throughout gestation. *Results* – The antenatal course of the first patient was complicated by an exacerbation of MS. The second patient did not experience MS relapses during pregnancy, while still using natalizumab. The newborns did not show any abnormalities postnatal and at 6 weeks' follow-up. *Conclusions* – This is the first detailed report on pregnancy and delivery of two babies after maternal treatment of MS with natalizumab. From the small number of cases on the usage of natalizumab during pregnancy in literature, we cannot conclude whether the use of natalizumab is safe, and long-term effects are not known. Further research is needed to establish the exact effects on pregnancy and intrauterine development as well as the long-term effects. Prenatal counseling with thorough explanation of the risks and careful decision making is advisable.

I. A. Hoevenaren[1]*, L. C. de Vries[2], R. J. P. Rijnders[1], F. K. Lotgering[3]

[1]Department of Obstetrics and Gynaecology, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands; [2]Teratology Information Service, RIVM/National Institute for Public Health and the Environment, Bilthoven, the Netherlands; [3]Department of Obstetrics and Gynaecology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

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L. C. de Vries, RIVM/National Institute for Public Health and the Environment, Teratology Information Service, PO Box 1, 3720 BA Bilthoven, the Netherlands
Tel.: +31302748628
Fax: +31302744460
e-mail: loes.de.vries@rivm.nl

*Present address: Department of Anatomy and Embryology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

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Introduction

Multiple sclerosis (MS) is a neurological disorder with focal lymphocytic infiltration in the central nervous system leading to a complex process of demyelinization and axon degeneration (1). A considerable number of women in their childbearing age need treatment for MS. In the treatment of MS, some drugs are considered safe, whereas others are either teratogenic or otherwise harmful. For most modern drugs insufficient data are available to establish a safety level (2).

We report the pregnancy and delivery of two babies after both mothers have been treated during the periconceptional period with natalizumab (Tysabri®; Biogen Idec B.V., Hoofddorp, the Netherlands), a humanized monoclonal antibody against α4 integrins.

Case reports

Case 1 concerns a 28-year-old nulliparous woman with relapsing–remitting MS since 9 years, clinically not responding to interferon-β-1a (Avonex®). Treatment with intravenous administration of natalizumab at a dose of 300 mg every 4 weeks was started. Despite the risks and unknown effects of natalizumab on pregnancy that were explained repeatedly to the patient, she intentionally became pregnant. She received her last dose of natalizumab

on day 9 of the menstrual cycle in which she became pregnant on the 14th day. Without the usage of any medication, the pregnancy developed normally with biometry following normal growth curves and with normal fetal movements. The antenatal course was complicated by an episode of hyperemesis gravidarum at 22 weeks' gestation, treated by intravenous fluid therapy and tube feeding for 11 days, after which she recovered completely. At 36 weeks' gestation, the patient experienced an exacerbation of MS, mainly resulting in visual disturbances (expanded disability status scale not formally assessed). For that reason, labor was induced with prostaglandins. At 37 weeks and 3 days' gestation, a healthy girl was born by vacuum extraction because of obstructed labor, birth weight 3160 g (80th percentile), Apgar scores 10 and 10 at 1 and 5 min, the umbilical artery pH was 7.19, BE −6.6 mM. Clinical examination by the pediatrician revealed no abnormalities, and white blood cell count was not performed. The patient has restarted treatment with natalizumab from 10 days post-partum onward.

Case 2 concerns a 34-year-old nulliparous woman with relapsing–remitting MS since 8 years, who became pregnant while on treatment with natalizumab intravenously, 300 mg every 4 weeks, while fully aware of the unknown risks of the drug on the fetus. She felt that she needed the drug to remain free of relapsing MS and intentionally did not inform her neurologist until she was 20 weeks pregnant. She continued to use natalizumab throughout gestation. The patient did not experience manifest MS relapses during pregnancy; expanded disability status scale was not formally assessed. Her general history revealed allergy for latex, penicillin, azitromycin, and various metals, and borderline lupus erythematodes with positive antinuclear antibodies but all specific tests negative. On advanced ultrasound examination at 20 and 22 weeks, the head circumference was on the fifth percentile, while the other biometric data and Doppler flow in the umbilical artery were normal. Amniocentesis was performed, quantitative PCR and karyotyping were normal, 46 XX, tests for TORCHES, and parvovirus B19 were negative. The pregnancy developed normally with normal fetal movements, absence of oligohydramnios and biometry following normal growth curves. At 39 weeks' gestation, she was started on methyldopa for pregnancy-induced hypertension (maximum 140/100 mmHg, no proteinuria). At 41 weeks, induction of labor with prostaglandins resulted in cesarean section because of suspected fetal distress. A girl was born, with birth weight 2940 g (10th percentile), Apgar scores 5 and 8 at 1 and 5 min, the umbilical artery pH was 7.20, BE −6.6 mM. The placenta was 385 g (10th percentile) and showed no infarcts or other signs of placental insufficiency. Clinical examination by the pediatrician revealed no abnormalities, and white blood cell count was not performed. Mother and infant on formula feeding did well at 6 weeks' follow-up. The patient reported mild MS complaints (burning feeling in the legs, sensibility changes in arms, and face) that started 10 days after delivery and resolved at 21 days postpartum after using additional methylprednisolon for 4 days. She considers another pregnancy on continued use of natalizumab.

Discussion

We describe two successful pregnancies in women with MS while using natalizumab in the periconceptional period and one even throughout pregnancy. In the first case, the last infusion was 5 days before the estimated conception. Most likely, exposure to natalizumab persisted during early pregnancy as the reported half-life is 16 days (3). In the second case, the patient intentionally continued the use of natalizumab during gestation. Monoclonal antibodies (mAbs) are a broad group of new therapeutics. Natalizumab is a recombinant humanized monoclonal IgG4-antibody against the α-unit of integrins (α4β1 and α4β7). These integrins are expressed on leukocytes, except for neutrophils. It blocks the adhesion and subsequent migration of the leukocytes into the target tissue by binding to α4-integrin (4).

The effect of exposure to an α4-integrin inhibitor in human pregnancy is not clear. α4-Integrins are not only expressed by leukocytes but also by human uterine glandular epithelium and embryonic tissues. Therefore, it may play a role in uterine receptivity and in embryogenesis (5). Consequently, natalizumab might interfere with normal implantation and/or embryonic development.

Little is known about the effect of natalizumab during pregnancy. The company reports in an abstract on 143 pregnancies with natalizumab exposure. These include 6 retrospective cases, 32 ongoing cases, 4 cases with unknown outcome (including one retrospective case), and 102 prospectively followed cases with known outcomes. In 102 prospectively followed pregnancies, there were 103 known outcomes (one twin) consisting of 55 (53.4%) live birth, 27 (26.2%) elective terminations, 21 (20.4%) spontaneous abortions, and no stillbirths. No congenital malformations were reported (6).

In our second case, the fetal growth and birth weight were on the 10th percentile. This was not caused by placental insufficiency or infection.

Although one may speculate that use of natalizumab during pregnancy might negatively affect fetal growth, in this case we have no reason to assume another explanation than the known genetic variation in birth weight. Villard-Mackintosh first suggested a trend toward an increased incidence of small for gestational age (SGA) infants in women who later developed MS (7). Dahl et al. reported that mothers with MS have a higher risk of delivering an SGA infant (8) and that the risk of SGA is more obvious in women with manifest MS than in women who later develop MS (9). The increased risk of an SGA infant was independently confirmed by two other studies. Chen et al. (10) reported a 1.9-fold risk of SGA in MS women compared to controls in an east Asian nationwide population-based data set. Hellwig et al. (11) reported lesser birth weight of infants of MS patients compared with infants of age-matched controls in a retrospective study. Furthermore, they discussed the possible role of neuronal-mediated dysfunction of blood circulation in the pelvic organs and the use of interferon treatment. However, as in our second case, the exact reasons remain unclear.

Exposure of the embryo to immunoglobulins in early human gestation is limited (12). Fetal levels approach 5–10% of maternal levels in week 17–22 of gestation. As pregnancy progresses, a gradual rise in transport of immunoglobulins across the placenta is seen, resulting at term in higher levels of IgG4 in the fetus compared to the mother. IgGs are most efficiently transported in the rank order IgG1, IgG4, IgG3, and IgG2 (13). Maternal immunoglobulins provide passive immunity to the newborn, whereas the exogenously administered immunoglobulins are likely to cause pharmacological effects. So, after organogenesis, as transfer of immunoglobulins increases, pharmacological effects cannot be excluded. In case of natalizumab use during pregnancy, one might expect an effect on fetal white blood cell counts (14). From our cases, we cannot confirm this, because unfortunately no intra-uterine or postnatal blood tests were done.

A reversible effect partly consistent with the pharmacological effect of natalizumab was seen in animal reproductive studies. There was no abortifacient or teratogenic effect, but in prenatal exposed cynomolgus monkeys increased lymphocyte and nucleated red blood cell counts, consistent with the pharmacological effect of natalizumab, and reductions in platelet counts were observed (15). Clinical relevance for humans is not known.

In summary, we describe the pregnancy and delivery of two healthy babies after maternal treatment of MS with the monoclonal antibody natalizumab. Currently, our two cases and cases reported by the company are the only known cases in literature of natalizumab use during conception or pregnancy. From this small number, we cannot conclude whether the use of natalizumab during pregnancy is safe. Given the lack of data and the pharmacological characteristics of natalizumab, it seems prudent to advise women not to get pregnant within 3 months after the last administration of natalizumab. Discontinuation of treatment seems advisable whenever a pregnancy occurs during treatment. However, there is deficient evidence of harm to advice termination of pregnancy in every case of unexpected pregnancy. Further research as well as post-marketing surveillance is needed to establish the effects of natalizumab on pregnancy and intrauterine development as well as on long-term outcomes. In expectation of future research, thorough explanation of the risks and careful decision making are advisable.

References

1. Compston A, Coles A. Multiple sclerosis. Lancet 2008;**372**:1502–17.
2. Ferrero S, Pretta S, Ragni N. Multiple sclerosis: management issues during pregnancy. Eur J Obstet Gynecol Reprod Biol 2004;**115**:3–9.
3. European Medicines Agency. Summary of product characteristics Tysabri. In: Human Medicines, EPARs for authorized medicinal products for human use [online]. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/tysabri/emea-combined-h603en.pdf.
4. Davenport RJ, Munday JR. Alpha4-integrin antagonism – an effective approach for the treatment of inflammatory diseases? Drug Discov Today 2007;**12**:569–76.
5. Bowen JA, Hunt JS. The role of integrins in reproduction. Proc Soc Exp Biol Med 2000;**223**:331–43.
6. Mahadevan U, Nazareth M, Cristiano L, Kooijmans M, Hogge G. Natalizumab use during pregnancy. Am J Gastroenterol 2008;**103**(s449):1150.
7. Villard-Mackintosh L, Vessey MP. Oral contraceptives and reproductive factors in multiple sclerosis incidence. Contraception 1993;**47**:161–8.
8. Dahl J, Myhr KM, Daltveit AK, Hoff JM, Gilhus NE. Pregnancy, delivery, and birth outcome in women with multiple sclerosis. Neurology 2005;**65**:1961–3.
9. Dahl J, Myhr KM, Daltveit AK, Gilhus NE. Pregnancy, delivery and birth outcome in different stages of maternal multiple sclerosis. J Neurol 2008;**255**:623–7.
10. Chen YH, Lin HL, Lin HC. Does multiple sclerosis increase risk of adverse pregnancy outcomes? A population-based study. Mult Scler 2009;**15**:606–12.
11. Hellwig K, Brune N, Haghikia A et al. Reproductive counseling, treatment and course of pregnancy in 73 German MS patients. Acta Neurol Scand 2008;**118**:24–8.
12. Jauniaux E, Jurkovic D, Gulbis B, Liesnard C, Lees C, Campbell S. Materno-fetal immunoglobulin transfer and passive immunity during the first trimester of human pregnancy. Hum Reprod 1995;**10**:3297–300.
13. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins

during human pregnancy. Am J Reprod Immunol 1996;**36**:248–55.

14. Polman CH, O'Connor PW, Havrdova E et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006;**354**:899–910.
15. Wehner NG, Shopp G, Osterburg I, Fuchs A, Buse E, Clarke J. Postnatal development in cynomolgus monkeys following prenatal exposure to natalizumab, an α4 integrin inhibitor. Birth Defects Res B Dev Reprod Toxicol 2009;**86**:144–56.