Natalizumab is very effective at reducing relapses in patients with multiple sclerosis (MS). However, once natalizumab treatment is withdrawn—as recommended during pregnancy—severe rebound disease activity can occur. Although pregnancy can fail to protect against natalizumab-withdrawal relapses, sometimes restarting natalizumab treatment may be the best option for the mother; however, the consequences for the infant are unclear. Teratogenic effects with late-pregnancy exposure to natalizumab would not be expected because organogenesis is completed. However, animal studies have shown hematological abnormalities in the offspring with exposure throughout pregnancy. A similar effect in humans is plausible because natalizumab is a monoclonal antibody and maternal antibodies are actively transported to the fetus at increasing rates during pregnancy starting in the second trimester. However, it is unknown to what extent natalizumab is transported to the human fetus—particularly during late pregnancy. Previous single case reports of late third-trimester exposure did not thoroughly assess hematological abnormalities or measure natalizumab levels in the offspring.

Here we describe the hematological and birth outcomes of 13 infants born to 12 mothers exposed to natalizumab during the third trimester of pregnancy. The natalizumab levels in 5 of the mother-infant pairs are also presented.

**Report of Cases**

Women were recruited through our nationwide MS pregnancy registry as previously described. The registry was approved by the institutional review board of Ruhr University Bochum. Written informed consent was obtained from all patients. We included 11 unique mother-infant pairs with third-trimester exposure to natalizumab and additional details on 2 previously described similarly exposed mother-infant pairs. Information was obtained directly from the treating physicians of the mothers and infants.

Serum natalizumab concentrations were determined using a validated sandwich enzyme-linked immunosorbent assay method (0.25-μg/mL lower detection level; Biogen Idec). Laboratory findings reported in the tables were obtained via routine blood analyses in certified diagnostic laboratories.

Demographic details of the mothers with MS and their clinical course are described in Table 1. Of the 12 women treated...
### Table 1. Clinical Characteristics of the Mothers

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Disease Duration, y</th>
<th>Natalizumab Infusions, No.</th>
<th>Natalizumab Infusion at Conception</th>
<th>Relapses, Trimester (No.)</th>
<th>Relapse Treatment (Excluding Natalizumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>32</td>
<td>4.6</td>
<td>24</td>
<td>Yes, stopped 1st trimester</td>
<td>1st (1)</td>
<td>Steroids, 5 g</td>
</tr>
<tr>
<td>M2</td>
<td>37</td>
<td>3.9</td>
<td>27</td>
<td>No, stopped prior to pregnancy</td>
<td>1st and 2nd (2)</td>
<td>Steroids, 13 g; intrathecal TCA (2 d); PLEX (5 d); immunoadsorption (4 d)</td>
</tr>
<tr>
<td>M3</td>
<td>29</td>
<td>5.2</td>
<td>33</td>
<td>Yes, stopped 1st trimester</td>
<td>2nd (1)</td>
<td>Steroids, 5 g</td>
</tr>
<tr>
<td>M4</td>
<td>37</td>
<td>5.1</td>
<td>29</td>
<td>Yes, continuously during pregnancy</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>M5</td>
<td>27</td>
<td>6.1</td>
<td>31</td>
<td>No, stopped prior to pregnancy</td>
<td>1st (2)</td>
<td>Steroids, 8 g; IVIG, 30 g</td>
</tr>
<tr>
<td>M6</td>
<td>34</td>
<td>10.1</td>
<td>38</td>
<td>Yes, stopped 1st trimester</td>
<td>2nd and 3rd (3)</td>
<td>Steroids, 9 g</td>
</tr>
<tr>
<td>M7</td>
<td>31</td>
<td>12.5</td>
<td>25</td>
<td>Yes, stopped 1st trimester</td>
<td>2nd (1)</td>
<td>Steroids, 10 g</td>
</tr>
<tr>
<td>M8</td>
<td>38</td>
<td>18.0</td>
<td>44</td>
<td>Yes, stopped 1st trimester</td>
<td>2nd (1)</td>
<td>Steroids, 5 g</td>
</tr>
<tr>
<td>M9</td>
<td>26</td>
<td>8.8</td>
<td>24</td>
<td>No, stopped prior to pregnancy</td>
<td>1st (1)</td>
<td>Steroids, 5 g</td>
</tr>
<tr>
<td>M10</td>
<td>27</td>
<td>2.6</td>
<td>16</td>
<td>Yes, continuously during pregnancy</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>M11</td>
<td>27</td>
<td>10.2</td>
<td>49</td>
<td>Yes, continuously during pregnancy</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>M12</td>
<td>25</td>
<td>1.8</td>
<td>16</td>
<td>Yes, continuously during pregnancy</td>
<td>NA</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: IVIG, intravenous immunoglobulin; M, mother; NA, not applicable; PLEX, plasma exchange; TCA, triamcinolone acetate.

### Table 2. Clinical Characteristics of the Infants

<table>
<thead>
<tr>
<th>Patient</th>
<th>Natalizumab Infusions During Pregnancy</th>
<th>Hematological Abnormalities at Birtha</th>
<th>Birth Outcomes</th>
<th>Length, cm</th>
<th>Weight, g</th>
<th>Mode of Delivery</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NB1</td>
<td>2</td>
<td>RBC count: 3.91 ×10⁶/μL (4.8-8.2); WBC count: 27 670/μL (8800-18 000); LDH: 660 U/L (&lt;451)</td>
<td>NA 38 52 2855</td>
<td>Natural</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB2</td>
<td>5</td>
<td>RBC count: 3.57 ×10⁶/μL (3.97-5.01); WBC count: 15 500/μL (&lt;13 200); platelet count: 77 000/μL (&lt;247 000); bilirubin: 14.8 mg/dL (&lt;8.7); LDH: 1736 U/L (&lt;225); IgG: 190 mg/dL (&lt;300)</td>
<td>14 39 45 1830</td>
<td>Cesarean</td>
<td>Bradycardia; icterus; hypoxia; small for gestational age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB3</td>
<td>3</td>
<td>WBC count: 22 180/μL (&lt;15 400)</td>
<td>NA 38 48 2755</td>
<td>Cesarean</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB4</td>
<td>9</td>
<td>No abnormalities</td>
<td>41 50 3290</td>
<td>Cesarean</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB5</td>
<td>4</td>
<td>RBC count: 2.8 ×10⁹/μL (&gt;3.45); hb: 11.1 g/dL (15.1); platelet count: 171 000/μL (&lt;247 000); bilirubin: 4.7 mg/dL (&lt;6.7); LDH: 678 U/L (&lt;600)</td>
<td>16 38 52 2730</td>
<td>Cesarean</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB6</td>
<td>6</td>
<td>No abnormalities</td>
<td>38 52 3270</td>
<td>Natural</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB7</td>
<td>2</td>
<td>RBC count: 4.1 ×10⁹/μL (&gt;4.7)</td>
<td>1 37 51 2550</td>
<td>Vacuum</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB8</td>
<td>4</td>
<td>hb: 10.5 g/dL (&lt;12.7); platelet count:149 000/μL.</td>
<td>&gt;12 6 38 49 2640</td>
<td>Natural</td>
<td>Subclinical ICHa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB9</td>
<td>1</td>
<td>No abnormalities</td>
<td>38 50 3100</td>
<td>Natural</td>
<td>Pylorusstenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB10</td>
<td>1</td>
<td>RBC count: 3 ×10⁶/μL (&gt;4.2); hb: 11 g/dL (&lt;12)</td>
<td>NA 38 52 3040</td>
<td>Cesarean</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB11</td>
<td>6</td>
<td>RBC count: 25.2/μL (&lt;24.3); y-glutamyltransferase: 297 U/L (&lt;203)</td>
<td>37 47 2120</td>
<td>Cesarean</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB12</td>
<td>9</td>
<td>RBC count: 3.15 ×10¹²/L (&gt;4.3); hb: 12.8 g/dL (&lt;15); WBC count: 39.4 ×10⁹/μL (&lt;38); platelet count: 71 ×10⁹/μL (&lt;150)</td>
<td>16 39 48 2575</td>
<td>Natural</td>
<td>ASD I and II; coloboma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB13</td>
<td>9</td>
<td>RBC count: 2.9 ×10⁶/μL (&gt;4.5); hb: 11.5 g/dL (&lt;14); WBC count: 21 000/μL (&lt;10 000); platelet count:92 000/μL (&lt;140 000)</td>
<td>4 40 48 2620</td>
<td>Natural</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ASD, atrial septal defect; hb, hemoglobin; ICH, intracranial hemorrhage; LDH, lactate dehydrogenase; NA, not applicable; NB, newborn; RBC, red blood cell; WBC, white blood cell.

* SI conversion factors: To convert bilirubin to micromoles per liter, multiply by 17.104; y-glutamyltransferase to microkatal per liter, multiply by 0.01667; hb to grams per liter, multiply by 10.0; IgG to grams per liter, multiply by 0.01; LDH to microkatal per liter, multiply by 0.0167; RBC count to ×10⁶ per liter, multiply by 1.0; WBC count to ×10⁹ per liter, multiply by 0.001.

* Abbreviations in RBC, WBC, and platelet counts with normal ranges in parentheses; if not indicated, these laboratory values were within normal limits.

* Initial screening cerebral ultrasonography after showed a small cystic formation in the caudalthalamic region that was no longer detected on follow-up ultrasonography at 12 weeks, compatible with a minor ICH.

* Gestational weeks at time of natalizumab infusions; for those with more than 3 infusions, it was typically administered every 4 to 6 weeks.

a Abnormalities in RBC, WBC, and platelet counts with normal ranges in parentheses; if not indicated, these laboratory values were within normal limits.
Natalizumab Use in Third Trimester of Pregnancy

Case Report/Case Series  Research

Discussion

In this case series, we observed that exposure to natalizumab during the third trimester of pregnancy in women with aggressive MS led to hematological abnormalities in 10 of the 13 newborns. These hematological abnormalities included thrombocytopenia, anemia, and leukocytosis. In most of the infants, the hematological abnormalities resolved during the 4 months after birth and none of the infants needed any specific treatment, although 1 subclinical bleeding complication was reported.

That natalizumab can interfere with fetal hematopoiesis has been shown in vitro and in cynomolgus monkey studies. The newborns of monkeys treated with natalizumab throughout pregnancy (at dosages higher than administered in patients with MS) were generally healthy with the exception of hematological abnormalities including thrombocytopenia, significantly reduced lymphocytes despite the anticipated leukocytosis, and mild anemia. We found detectable cord blood levels of natalizumab in all 5 infants tested. In general, the concentrations were higher in those exposed closer to the time of delivery and with more frequent late-pregnancy exposures. This is consistent with normal placental immunoglobulin transport mechanisms. Active transport of maternal immunoglobulins across the placenta increases throughout pregnancy starting during the second trimester, with only minimal transport of antibodies earlier in pregnancy. These findings are also similar to case reports of placental transfer of other therapeutic monoclonal antibodies. In women treated with tumor necrosis factor antagonists during pregnancy, later exposure and more frequent infusions led to higher cord blood concentrations often exceeding that of the mother. In addition, these monoclonal antibodies were still detectable in some infants up to 6 months of age, consistent with infants’ delayed antibody clearance mechanisms.

All of the mothers treated with natalizumab during late pregnancy had experienced serious natalizumab-withdrawal relapses either prior to or during pregnancy.
Many treatment strategies to prevent natalizumab-withdrawal relapses have been reported in nonpregnant patients (some of which were tried in these mothers); however, so far, only resuming natalizumab treatment appears effective. These unsuccessful strategies include prophylactic pulse steroids with or without glatiramer acetate or beta-interferons. In addition, in utero exposure to some of these agents has been associated with other fetal risks including low birth weight and potential teratogenicity.

Our observation was limited by the sample size and was not designed to identify risk factors for rebound or severe relapses after natalizumab withdrawal. Also, we were not able to analyze the infants’ natalizumab levels longitudinally nor do we have long-term developmental outcomes in most of the children. However, in view of the various limitations and inherent difficulties of investigating the safety of drugs with potential fetotoxic adverse effects, our results are useful for therapeutic decisions in women with similarly severe disease activity as those described here.

Conclusions
Given the high frequency of hematological abnormalities observed, we recommend that late-pregnancy natalizumab treatment be a last resort, be administered by experienced MS centers, and that the pregnancy be considered high risk. These women should deliver in a hospital with an affiliated pediatric department, a pediatrician should be available at the time of delivery to evaluate the infant for potential complications of anemia and thrombocytopenia, and all newborns should undergo careful hematological evaluation. We propose a standardized blood draw with a full blood cell count, bilirubin lactate dehydrogenase, transaminases, and haptoglobin.

Additional Contributions: We thank all the patients contributing data to the registry and all referring physicians and multiple sclerosis nurses. We also thank the German National Multiple Sclerosis Society (DMSS) for supporting the advertisement of the registry. The society did not receive compensation from any funder for its contribution.

REFERENCES


