Human Granulocytic Anaplasmosis During Pregnancy: Case Series and Literature Review

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We describe the clinical and laboratory manifestations and pregnancy outcomes of 6 women who received a diagnosis of human granulocytic ehrlichiosis during pregnancy. Human granulocytic ehrlichiosis did not seem to present in a fulminant fashion, and all treated patients had excellent responses to rifampin or doxycycline therapy. Perinatal transmission was documented in 1 neonate, who responded well to treatment. There do not appear to be any long-term adverse sequelae in children born from these pregnancies (mean follow-up duration, 21 months).

Human granulocytic anaplasmosis (HGA; previously known as “human granulocytic ehrlichiosis”) is caused by an obligate intracellular bacterium, *Anaplasma phagocytophilum*, and is transmitted by certain *Ixodes* ticks [1, 2]. HGA was first described in 1994 [3]. Since then, >2000 cases have been described in the United States and western Europe [2, 3]. The disease is underreported, as revealed by seroprevalence studies demonstrating that as much as 15%–36% of the population in some areas of HGA endemicity have been exposed to *A. phagocytophilum* [4, 5]. Transmission of HGA may occur together with transmission of *Borrelia burgdorferi* and *Babesia microti*, because *Ixodes* ticks are also vectors for infection with these bacteria. HGA is an acute febrile illness with nonspecific symptoms. Serious manifestations of HGA, including a fatal outcome in <1% of patients, have been reported in patients with suppressed immune response associated with advanced age, immunosuppressive therapy, chronic inflammatory illness, or underlying malignant disease [6, 7]. HGA has been reported rarely in children and pregnant individuals [8]. Its occurrence in pregnant persons is of particular concern, because of the mild immunosuppression during pregnancy, which increases the potential for more-severe disease; because of the diagnostic and therapeutic dilemmas caused by pregnancy; and because of the risk of perinatal transmission. In this series, we describe women treated at our institutions who received a diagnosis of HGA during or shortly after pregnancy and review other cases of HGA during pregnancy reported in the English-language literature.

**Patients and methods.** During 1997–2006, six women (1 of whom was described elsewhere [9]) who were evaluated at Westchester Medical Center (WMC; Westchester, NY) received a diagnosis of HGA infection during or shortly after pregnancy. Five patients underwent follow-up clinical and laboratory evaluation at 1, 3, 6, and 12 months after diagnosis. One patient was evaluated at the time of infection and 1 month after diagnosis and was subsequently lost to follow-up. For most patients, blood specimens were obtained at the time of diagnosis foruffy coat smear, PCR, and culture for detection of *A. phagocytophilum*. Complete blood cell counts and liver function tests were performed at the time of diagnosis and at the 1-month follow-up visit. Serologic testing for antibodies against *A. phagocytophilum* was performed at all follow-up visits. Patients gave written informed consent, and the institutional review board at New York Medical College (Valhalla, NY) approved the study.

Children were initially evaluated at birth and were later examined at WMC or by telephone contact with their pediatricians. Abnormal findings at birth were recorded. Growth and development were assessed during the 5–60-month follow-up period via telephone interviews with the children’s parents and pediatricians.

Blood collected in EDTA was used for buffy coat smear, PCR, and culture for *A. phagocytophilum*, as described elsewhere [10]. Buffy coat smears were Wright stained, and 1000 granulocytes were examined for intragranulocytic morulae (original magnifications, ×500 and ×1000). PCR was performed on EDTA-treated whole blood by using a nested reaction with primers HS1/HS6 and HS43/HS45 [11]. Antibodies against *A. phagocytophilum* were detected using a local *A. phagocytophilum* isolate with an indirect immunofluorescence assay [5].

**Case series.** Including the 5 cases that are described here for the first time, there are, to our knowledge, 9 documented...
cases of HGA in pregnant women. The demographic characteristics, clinical presentation, laboratory findings, diagnostic test results, treatment, and pregnancy outcomes for the 6 cases from WMC and the 3 cases reported elsewhere in the literature [12, 13] are shown in tables 1, 2, and 3.

The cases were diagnosed at gestational ages of 10–39 weeks. Patients presented with fever (9 [100%] of 9), myalgia and/or arthralgia (7 [100%] of 7 for whom data were available), headache (6 [67%] of 9), mildly elevated transaminase levels (7 [78%] of 9), thrombocytopenia (6 [75%] of 8 for whom data were available), and leukopenia (1 [13%] of 8 for whom data were available). Four patients (44%) recalled having recently received a tick bite. One case was complicated by perinatal transmission. HGA did not seem to present in a fulminant fashion in any of these women. In fact, 1 patient was not treated for HGA and did well. The delay in suspecting, diagnosing, and treating HGA in the women was not associated with any immediate or late adverse pregnancy events, except for persistent fever in 3 women (patients 1, 4, and 9) who were treated with inappropriate antibiotics. For these 3 patients with fever toward the end of term, initial antibiotics used to treat suspected infections were not active against A. phagocytophilum. Nevertheless, the diagnosis of HGA was made in the neonate in only 1 instance (patient 1) and was based on the isolation of A. phagocytophilum in a blood culture [9].

Once the diagnosis was confirmed, all treated patients had excellent responses to antibiotic therapy with either doxycycline or rifampin. The mean duration of follow-up was 21 months at the time of writing, and evaluations conducted either by telephone or at an office visit have revealed that the children’s health and development have been normal.

Discussion. HGA is an increasing public health concern in the United States and Europe. Symptomatic infection occurs in areas where ticks are endemic and varies in severity from mild, self-limited illness to death. In a recent meta-analysis of 10 studies, with a cumulative of up to 685 patients, most of the patients presenting clinically were noted to have fever (92%), malaise (94%), myalgia (77%), and headache (75%).
<table>
<thead>
<tr>
<th>Patient, study</th>
<th>Treatment</th>
<th>Duration of pregnancy</th>
<th>Delivery</th>
<th>Presentation</th>
<th>Test (result)</th>
<th>Perinatal transmission</th>
<th>Treatment</th>
<th>Follow-up duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [9]</td>
<td>Dox, 100 mg twice daily for 5 days&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Full term</td>
<td>Fetal tachycardia, AROM, vaginal</td>
<td>Fever (day 9 after delivery), leukopenia, thrombocytopenia</td>
<td>PCR, buffy coat smear, culture, serologic analysis (all positive)</td>
<td>Yes</td>
<td>Dox, 5 days</td>
<td>5 years</td>
</tr>
<tr>
<td>2, PR</td>
<td>Rif, 300 mg twice daily for 7 days&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Full term</td>
<td>Normal vaginal</td>
<td>Healthy</td>
<td>Not available</td>
<td>No</td>
<td>None</td>
<td>2 years</td>
</tr>
<tr>
<td>3, PR</td>
<td>Rif, 600 mg daily for 7 days</td>
<td>Full term</td>
<td>Not available</td>
<td>Asthma, pneumonia</td>
<td>Blood PCR (negative)</td>
<td>No</td>
<td>None</td>
<td>2 years</td>
</tr>
<tr>
<td>4, PR</td>
<td>Dox, 100 mg twice daily for 10 days</td>
<td>PROM at 34 weeks</td>
<td>Fetal tachycardia, cesarean section</td>
<td>CHD,&lt;sup&gt;c&lt;/sup&gt; otherwise healthy</td>
<td>Blood PCR (negative)</td>
<td>No</td>
<td>None</td>
<td>1 year</td>
</tr>
<tr>
<td>5, PR</td>
<td>Rif, 600 mg daily for 7 days</td>
<td>Full term</td>
<td>Normal vaginal</td>
<td>Healthy</td>
<td>Not available</td>
<td>No</td>
<td>None</td>
<td>Lost to follow-up after 1 month</td>
</tr>
<tr>
<td>6, PR</td>
<td>None&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Full term</td>
<td>Normal vaginal</td>
<td>Healthy</td>
<td>Not available</td>
<td>No</td>
<td>None</td>
<td>5 months</td>
</tr>
<tr>
<td>7 [13]</td>
<td>Rif, 600 mg daily for 7 days&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Full term</td>
<td>Not available</td>
<td>Healthy</td>
<td>Not available</td>
<td>No</td>
<td>None</td>
<td>Not available</td>
</tr>
<tr>
<td>8 [13]</td>
<td>Rif, 600 mg daily for 7 days</td>
<td>Full term</td>
<td>Normal vaginal</td>
<td>Healthy</td>
<td>Blood PCR (negative)</td>
<td>No</td>
<td>None</td>
<td>Not available</td>
</tr>
<tr>
<td>9 [12]</td>
<td>Dox, 2 weeks</td>
<td>Induction of labor at 36 weeks</td>
<td>Normal vaginal</td>
<td>Healthy</td>
<td>Blood PCR (negative)</td>
<td>No</td>
<td>None</td>
<td>Not available</td>
</tr>
</tbody>
</table>

**NOTE.** AROM, artificial rupture of membranes; CHD, congenital heart disease; Dox, doxycycline; PR, present report; PROM, premature rupture of membranes; Rif, rifampin.

<sup>a</sup> Received after delivery.

<sup>b</sup> Treated for suspected Lyme disease with β-lactam agents, which are not known to be effective treatment against HGA.

<sup>c</sup> Diagnosis made prior to presentation.
The most frequent laboratory abnormalities noted were thrombocytopenia (71% of patients), elevated hepatic transaminase levels (71%), leukopenia (49%), and anemia (37%) [14]. In our study, leukopenia appeared somewhat less frequently (in 13% of cases), compared with the rate reported by Dumler et al. [14]. The diagnosis of HGA in pregnant women presenting with acute fever and the laboratory findings presented above might be delayed, because similar findings may also be associated with either physiologic or pathologic processes during pregnancy (table 4) [15, 16].

Evidence from animal studies suggests that maternal infection with some members of the Anaplasmataceae family is associated with adverse outcomes of pregnancy. Phylogenetic studies now recognize the bacteria previously classified as *Ehrlichia phagocytophila*, *Ehrlichia equi*, and the agent of human granulocytic ehrlichiosis as a single species, *A. phagocytophilum* [14]. In sheep and cows, this organism causes stillbirth or abortion [17, 18]. Previous experiments have shown that *E. phagocytophila* can be transmitted across the placenta in cows, leading to clinically apparent disease in newborn calves [19]. In experimentally infected pregnant cows, *E. phagocytophila* was detected in the newborn calves as well as in the leukocytes of milk samples during the acute phase of the disease [20]. There is 1 reported case of human monocytic ehrlichiosis (caused by *Ehrlichia chaffeensis*) diagnosed in a pregnant woman at 13 weeks of gestation who presented with abdominal pain and acute appendicitis. She was treated successfully with doxycycline, with no long-term sequelae reported in her or her infant during a 1-year follow-up period [21].

Human perinatal transmission of HGA has been documented only once. The mother was infected with *A. phagocytophilum* toward the end of the pregnancy [9]. HGA was diagnosed following a normal delivery (gestation period, 39 weeks), and the mother was successfully treated with doxycycline. The newborn presented with acute onset of fever 9 days after birth, a normal WBC count with 12% bands, thrombocytopenia, and normal results of liver function tests. HGA in the neonate was confirmed by documentation of morulae on the buffy coat smear of a peripheral blood specimen, isolation of *A. phagocytophilum* in a blood culture, and positive results of PCR and a serologic test. Although perinatal transmission was highly suspected, it could not be determined whether the transmission occurred in utero, at the time of delivery, or through breast milk. The neonate was treated with doxycycline and had an excellent clinical response.

Our laboratory evaluation for perinatal transmission of HGA was limited, with only 3 newborns (other than the infected newborn) evaluated with PCR. Although the risk of perinatal transmission is unknown, clinical evidence of HGA transmission was absent in the offspring of all 7 pregnant mothers who were treated with either doxycycline or rifampin. In 1 instance (patient 6), the mother was not treated for HGA. She had experienced clinical improvement by the time that results of culture and serologic tests were received and declined treatment.

Consideration should be given to treating symptomatic pregnant women for HGA when they present with a nonspecific viral-type illness during the summer in an area of HGA endemicity [6]. Doxycycline is the first line of therapy and will treat potential coinfection with *B. burgdorferi*. However, doxycycline may affect the musculoskeletal development of the fetus and may cause staining of teeth in young children [22, 23]. Although doxycycline is relatively contraindicated for children aged <10 years, it tends to cause less tooth staining than

### Table 4. Onset times and types of conditions occurring during or soon after pregnancy that may mimic human granulocytic anaplasmosis (HGA).

<table>
<thead>
<tr>
<th>Characteristic or condition</th>
<th>HGA</th>
<th>HME</th>
<th>HELLP syndrome</th>
<th>Acute fatty liver of pregnancy</th>
<th>TTP</th>
<th>HUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset</td>
<td>Any time</td>
<td>Any time</td>
<td>3rd trimester</td>
<td>3rd trimester</td>
<td>2nd trimester, term</td>
<td>After delivery</td>
</tr>
<tr>
<td>Fever</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Variably present</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Absent</td>
<td>Present</td>
<td>Variably present</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Abnormal LFT results</td>
<td>Present</td>
<td>Present</td>
<td>Present (high AST level)</td>
<td>Present (usually indicative of cholestasis)</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Present</td>
<td>Present</td>
<td>Present (&lt;100,000 platelets/µL)</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Hemolyis</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>Variably present</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

NOTE. Data are adapted from Burrows and Kelton [15] and McCrae [16]. AST, aspartate aminotransferase; HELLP, hemolysis elevated liver enzyme low platelet count; HME, human monocytic ehrlichiosis; HUS, hemolytic uremic syndrome; LFT, liver function test; TTP, thrombotic thrombocytopenic purpura.
tetracycline, because it binds less well to calcium [23]. Furthermore, a short course of doxycycline therapy seems to be safe in children and is recommended for treatment of several rickettsial diseases [8, 23–25]. In vitro studies suggest that rifampin is active against *A. phagocytophilum* [26–28]. Although rifampin has been reported to cross the placental barrier and appear in cord blood, its long-term use in pregnant women with tuberculosis has not been associated with any congenital abnormalities [29, 30]. Rifampin was used in 3 of the 5 new cases from WMC that are described in this report and in 2 of the 3 cases reported in the literature. All patients had excellent clinical response. Successful use of rifampin to treat HGA in children has previously been described [31].

On the basis of the limited number of cases reported to date, HGA appears to be a relatively mild disease during pregnancy and is not associated with serious immediate or long-term adverse problems. This diagnosis should be considered in pregnant women who present with acute febrile illness in regions where HGA is endemic, particularly during the late spring and summer months, when nymphal *Ixodes scapularis* ticks are most active. In patients in whom this illness is suspected, attempts should be made to confirm the diagnosis by using a buffy coat smear of blood and performing serologic analysis. PCR and/or blood cultures may also be performed, if possible. In addition, we also suggest evaluating the neonate for HGA. When suspicion is high, empirical treatment with either doxycycline or rifampin is warranted.

**Acknowledgments**

We thank Donna McKenna and Diane Holmgren, for helping with data collection, and Ira Schwartz, for performing PCR analysis.

**Financial support.** New York State Department of Health (grant 47–182 to H.W.H.) and Westchester County Department of Health (grant CMC-2502 to H.W.H. and grants HLT 27017, HLT 27028, and HLT 27019 to M.A.R.)

**Potential conflicts of interest.** All authors: no conflicts.

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