Chlamydia And Incidental Carcinoid Tumor In Spontaneous Abortion

John V. Jurica, M.D., and Dennis J. Baumgardner, M.D.

Abstract: Maternal ***Chlamydia trachomatis*** infections have been associated with premature rupture of the membranes, preterm labor, premature birth, and fetal wastage. Women with acute infection may be at particular risk. We report the case of an unexplained second trimester spontaneous abortion with serologic evidence of recent infection with *C. trachomatis*. Serum IgG antibody titer ultimately exceeded 1:10,240. This patient also had an incidental finding of appendiceal carcinoid tumor. While treatment of asymptomatic chlamydial infections in early pregnancy is controversial, we suggest that delaying treatment may result in fetal loss. (J Am Bd Fam Pract 1989; 2:126-9.)

Chlamydia trachomatis, the most prevalent sexually transmitted organism in the United States, infects about 5 percent of pregnant women.[1] Vertical transmission results in neonatal conjunctivitis and respiratory tract disease.[1,2] The ability of *Chlamydia* to affect pregnancy outcome adversely is controversial. Recent studies have associated *C. trachomatis* with preterm premature rupture of the membranes, preterm labor, low-birth-weight infants, spontaneous abortion, and neonatal death.[3-5] Others have suggested that this is restricted to women with recent or invasive infection.[6-8] At least one group has concluded that delaying identification and treatment of *C. trachomatis* until the third trimester is not associated with adverse pregnancy outcome.[9]

We describe a case of second trimester spontaneous abortion with serologic evidence of recent, invasive chlamydial infection. This case may represent a subset of pregnant women for whom delayed treatment of *Chlamydia* may result in prematurity or fetal loss.

An incidental finding of carcinoid tumor is discussed in light of this case.

Case Report

A 24-year-old gravida 4, para 2, single black woman was admitted at 21 weeks' gestation with an 18-hour history of fever, abdominal pain, and uterine contractions. The pain was initially crampy in quality, then became constant and moved from the lower midabdomen to the right lower abdomen. She was most comfortable when lying in a fetal position on her left side. Motion aggravated the pain. She denied nausea, vomiting, diarrhea, dysuria, vaginal bleeding, and prior abdominal surgery.

Her prenatal care had begun at 13 weeks' gestation. Her examination at that time was normal and all prenatal laboratory studies, including cervical culture for *Neisseria gonorrheae*, were unremarkable. Her first and third pregnancies had resulted in the spontaneous vaginal deliveries of full-term male infants weighing 3304 g and 3276 g, respectively. Her second pregnancy ended in elected abortion. Her prenatal course before admission was remarkable only for a dental abscess at 13 weeks' gestation, which was treated with a tooth extraction and antibiotics. She had been seen at 2-week intervals before hospitalization.

The patient at the time of admission was alert, but uncomfortable. Her temperature was 99.8°F (37.6°C); heart rate, 110 beats per minute; blood pressure, 110/70 mmHg; and respiratory rate, 18 per minute. Positive physical findings were limited to the abdomen. Fundal height was 22 cm, with cephalic presentation by Leopold maneuvers. The fetal heart rate was 140 beats per minute. The patient had diffuse abdominal tenderness, most severe in the right lower quadrant, where rebound tenderness was elicited. Digital vaginal examination showed a closed and uneffaced cervix. Cervical cultures for *N. gonorrheae*, *C. trachomatis*, and aerobic and anaerobic bacteria were obtained.

From a private practice, Kankakee, IL, and the Department of Family Medicine, St. Luke's Family Practice Center, Medical College of Wisconsin, Milwaukee. Address reprint requests to Dennis J. Baumgardner, M.D., Department of Family Medicine, St. Luke's Family Practice Center, Medical College of Wisconsin, 1110 South 24th Street, Milwaukee, WI 53204.

Electronic fetal monitoring showed a normal fetal heart rate and contractions every 3 to 4 minutes. From the urinalysis, we recorded 20 to 50 white cells per high power field. A urine culture was obtained. The patient's white-cell count was 19,500/μL with 73 segmented neutrophils, 21 band forms, and 5 lymphocytes. Our clinical impression was that of acute appendicitis versus intrauterine infection.

A perinatologist was consulted who performed amniocentesis in an effort to rule out chorioamnionitis. The fluid did not appear grossly infected; however, 184 white cells/μL were present. There were no organisms seen on gram stain. Cultures for bacteria, including *Chlamydia*, were obtained.

The patient was then seen by a general surgeon who thought that the patient had acute appendicitis. She was given terbutaline to suppress labor while arrangements were made for urgent appendectomy. However, she was precipitously delivered of a 315 g stillbirth before the operation. The infant was born with intact membranes and had no gross anomalies. Amniotic fluid was not foul smelling or frankly purulent. No autopsy was performed. Placental pathology showed no diagnostic changes. Because of persistent abdominal pain and tenderness, the patient underwent laparotomy. At the time of surgery, the appendix appeared normal and was removed. The uterus, adnexae, and gallbladder were also normal, and there was no evidence of intraabdominal infection.

Cervical cultures ultimately grew normal urogenital flora and heavy amounts of *Gardnerella vaginalis*. No *Chlamydia* or pathogenic streptococci were isolated. Amniotic fluid cultures were sterile as was the urine culture. Histologic examination of the appendix showed that the distal 2.0 cm of the organ were replaced by carcinoid tumor. Near its tip, the tumor had extended to the muscle side of the serosa.

Chlamydia immunofluorescent IgG antibody titer was elevated at 1:2560. Three weeks later, the IgG chlamydia titer was greater than 1:10,240.

Discussion

Prospective prenatal studies have inconsistently associated genital colonization by *C. trachomatis* with prematurity and fetal wastage. Martin, et al.[3] reported an increased risk of prematurity, stillbirth, and perinatal death when maternal *C. trachomatis* cervical infections were identified before 19 weeks' gestation. This study, however, failed to investigate coexisting infections with other known or postulated pathogens. Pathological studies and cultures of fetal casualties were not performed in this investigation of 18 culture-positive patients.

In a prospective study of genital pathogens in 534 gravid women, Gravett, et al.[4] found an independent association of *C. trachomatis* with preterm labor, preterm premature rupture of the membranes, and low birth weight.

Bacterial vaginosis was independently associated with preterm premature rupture of the membranes, preterm labor, and amniotic fluid infection but not significantly associated with low birth weight. This study did not seek for *Mycoplasma hominis*, *Ureaplasma urealyticum*, or group B streptococci, though the former two organisms are known to be more prevalent among women with bacterial vaginosis.[4]

Harrison and associates[6] investigated the presence of *C. trachomatis*, *M. hominis* and *U. urealyticum* in their pregnant population. No increased risk of spontaneous abortion, stillbirth, or prematurity was shown for cervical infection by any of these organisms except for a subset of women who were seropositive for antichlamydial IgM. This group of women had a greater risk of low-birth-weight infants and premature rupture of the membranes than the groups with presumed chronic infection or negative cultures. Similarly, Navajo women with positive antichlamydia IgM titers or IgG seroconversion had a greater risk of low-birth-weight infants than women with chronic infections.[7] An earlier case-controlled study of 270 women with endocervical *C. trachomatis* infection also showed worse pregnancy outcomes in those patients with elevated IgM titers.[8]

Quinn, et al.[5] have recently reported a higher number of *C. trachomatis* antibodies in women with repeated abortion compared with normal pregnant women and nonpregnant infertile women. None of the women in any group was *Chlamydia* culture-positive. IgM antibody titers were not performed, and the occurrence of other pathogenic organisms was not reported. In addition, the nonpregnant controls were from an earlier infertility study.

In a retrospective study of infertile couples who had suffered one or more spontaneous abortions, Toth, et al.[10] found a significantly lower subsequent spontaneous abortion rate in a subset of 100 antibiotic-treated couples. *C. trachomatis*,

alone, or in combination with other potential pathogens, was isolated from 38 of the 100 couples. Antibiotic regimens for treated couples included a minimum of 2 weeks of doxycycline or tetracycline. Subsequent premature rupture of the membranes was also significantly less in the treated couples.

In contrast to the above findings, FitzSimmons, et al.[9] noted no difference in pregnancy outcomes between 33 *Chlamydia*-positive patients and 188 controls. Antibodies to *Chlamydia* were not measured. This study may have suffered from a lack of statistical power, however, because of the relatively small number of culture-positive subjects.

Our patient suffered a spontaneous abortion at 21 weeks' gestation after presenting with evidence of an acute surgical abdomen. Amniocentesis was performed in an attempt to rule out chorioamnionitis[11]; however, the white-cell count in the amniotic fluid was 184/μL. Counts of this magnitude (greater than 100/μL) have been associated with chorioamnionitis and failure of tocolysis in patients with preterm labor.[12] Because our initial fluid results did not exclude an adjacent extra-uterine inflammatory process in the face of clinical signs of appendicitis, laparotomy was performed, but this failed to reveal appendicitis, periappendicitis,[13] or any other abdominal cause for her signs and symptoms. Although amniotic fluid cultures were sterile, this would not rule out *Chlamydia*, *M. hominis*, or *U. urealyticum*. Special cultures for the latter two organisms, unfortunately, were not available.

Although IgM antibody studies were not done on this patient, the fourfold rise in IgG antibody titer indicates recent *C. trachomatis* infection. The extremely high IgG antibody titers (greater than 1:10,240) is consistent with invasive infection. Titers of this magnitude have been associated with perihepatitis and other forms of dissemination.[14] Because *Chlamydia* is an intracellular microorganism, amniotic fluid, like peritoneal fluid,[15] may be poor substrate for chlamydia culture due to the paucity of cells. Chlamydial cervical culture was also negative in this patient, but this does not exclude upper-tract infection.[16,17] Whether this phenomenon is due to inactivity of the previous lower-tract infection or to immunologic attenuation is unclear.

Cervical culture did reveal growth of *G. vaginalis*. This is often indicative of bacterial vaginosis and the presence of potentially more virulent anaerobes. This condition has also been associated with amniotic fluid infection and preterm labor; however, *C. trachomatis* and bacterial vaginosis together do not seem to act synergistically in producing adverse pregnancy outcomes.[4]

Our patient also had an appendiceal carcinoid tumor, without symptoms of the carcinoid syndrome. While appendiceal carcinoids may occasionally spread locally, especially if greater than 1 cm by 2 cm, distant metastasis and the carcinoid syndrome are extremely rare.[18] Previously reported cases of carcinoid tumor in pregnancy have not clearly associated this tumor with adverse pregnancy outcome. Durkin reviewed nine previously reported cases of appendiceal carcinoid in pregnancy.[19] One patient had an appendectomy at 6 weeks' gestation, which revealed a carcinoid tumor, and she aborted at 15 weeks' gestation. The other 8 patients apparently had uncomplicated pregnancies. Sommer and Marzotko[18] reported two additional cases of appendiceal carcinoid diagnosed in the second trimester of pregnancy, and neither had evidence of the carcinoid syndrome. The first patient underwent an appendectomy at 26 weeks' gestation, and a carcinoid tumor confined to the appendix was found. Subsequently, she was delivered of a 34-week preterm male infant. The second case involved spread of the tumor to the mesentery, and complete resection could not be achieved during laparotomy at 24 weeks' gestation. In spite of this, the patient later was delivered of a healthy full-term male infant by Cesarean section.

Summary

We have reported a young woman who suffered a spontaneous abortion at 21 weeks' gestation with serologic evidence of acute infection with *C. trachomatis* and the finding of appendiceal carcinoid. In the absence of carcinoid syndrome or other evidence of tumor activity, we believe that the tumor was an incidental finding. The chlamydial infection, however, appeared to represent an active chorioamnionitis based on findings of fever, tenderness, amniotic fluid analysis, negative laparotomy, and serial antibody titers. Studies dealing with the risk of chlamydial infection during pregnancy are conflicting and difficult to compare. This case report, however, illustrates what these studies have predominantly shown statistically, that a subset of *Chlamydia*-infected women are at risk for prematurity and fetal loss. Large, well-designed studies are needed to define the risk

and to determine whether this subset of women are efficiently and reliably diagnosed by serologic testing.

Until research clarifies the wisdom of delaying treatment of *Chlamydia* until the third trimester, as has been suggested,[9] family physicians will be increasingly faced with the dilemma of chlamydial infection in early pregnancy. Proponents of delayed treatment may argue that early detection and treatment will only increase the number of acute infections (and risk) when possible reinfection occurs later in pregnancy. Katz, et al.,[20] however, have reported that reinfection rates are lower if previous chlamydial infection and treatment have occurred within the past 6 months. Perhaps, a reasonable alternative would be to treat pregnant patients at the time the infection is diagnosed, endeavor to have the partner(s) treated, and to reculture the patient near term. While the efficacy and cost-effectiveness of such a strategy remains to be shown, in individual cases such as ours, this may prevent fetal loss.

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References

1. Schachter J, Grossman M, Sweet RL, Holt J, Jordan C, Bishop E. Prospective study of perinatal transmission of *Chlamydia trachomatis*. JAMA 1986; 255:3374-7.
2. Harrison RH, English MG, Lee CK, Alexander RE. *Chlamydia trachomatis* infant pneumonitis: comparison with matched controls and other infant pneumonitis. N Engl J Med 1978; 298:702-8.
3. Martin DH, Koutsky L, Eschenbach DA, et al. Prematurity and perinatal mortality in pregnancies complicated by maternal *Chlamydia trachomatis* infections. JAMA 1982; 247:1585-8.
4. Gravett MG, Nelson NP, DeRouen T, Critchlow C, Eschenbach DA, Holmes KK. Independent associations of bacterial vaginosis and *Chlamydia trachomatis* infection with adverse pregnancy outcome. JAMA 1986; 256:1899-1903.
5. Quinn PA, Petric M, Barkin M, et al. Prevalence of antibody to *Chlamydia trachomatis* in spontaneous abortion and infertility. Am J Obstet Gynecol 1987; 156:291-6.
6. Harrison HR, Alexander ER, Weinstein L, Lewis M, Nash M, Sim DA. Cervical *Chlamydia trachomatis* and mycoplasmal infections in pregnancy. Epidemiology and outcomes. JAMA 1983; 250: 1721-7.
7. Berman SM, Harrison HR, Boyce WT, Haffner WJ, Lewis M, Arthur JB. Low birth weight, prematurity, and postpartum endometritis. Association with prenatal cervical *Mycoplasma hominis* and *Chlamydia trachomatis* infections. JAMA 1987; 257:1189-94.
8. Sweet RL, Landers DV, Walter C, Schachter J. *Chlamydia trachomatis* infection and pregnancy outcome. Am J Obstet Gynecol 1987; 156:824-33.
9. FitzSimmons J, Callahan C, Shanahan B, Jungkind D. Chlamydial infections in pregnancy. J Reprod Med 1986; 31:19-22.
10. Toth A, Lesser ML, Brooks-Toth CW, Feiner C. Outcome of subsequent pregnancies following antibiotic therapy after primary or multiple spontaneous abortions. Surg Gynecol Obstet 1986; 163:243-50.
11. Bobitt JR, Hayslip CC, Damato JD. Amniotic fluid infection as determined by transabdominal amniocentesis in patients with intact membranes in premature labor. Am J Obstet Gynecol 1981; 140:947-52.
12. Hameed C, Tejani N, Verma UL, Archbald F. Silent chorioamnionitis as a cause of preterm labor refractory to tocolytic therapy. Am J Obstet Gynecol 1984; 149:726-30.
13. Mardh PA, Wolner-Hanssen P. Periappendicitis and chlamydial salpingitis. Surg Gynecol Obstet 1985; 160:304-6.
14. Baumgardner DJ, McCanse DE. Peritonitis and small bowel obstruction. IMJ 1987; 171:75-8.
15. Mardh PA, Westrom L, Colleen S, Wolner-Hanssen P. Sampling, specimen handling, and isolation techniques in the diagnosis of chlamydial and other genital infections. Sex Transm Dis 1981; 8:280-5.
16. Moller BR, Kaspersen P, Kristiansen FV, Mardh PA. *Chlamydia trachomatis* in the upper female genital tract with negative cervical culture. Lancet 1986; 2:390.
17. Jones RB, Mammel JB, Shepard MK, Fisher RR. Recovery of *Chlamydia trachomatis* from the endometrium of women at risk for chlamydia infection. Am J Obstet Gynecol 1986; 155:35-9.
18. Sommer VJ, Marzotko F. Appendix- und dunndarmkarzinoide als seltene nebenbefunde bei gynakologischen operationen innerhalb und ausserhalb der gravidat. Zentralbl Gynakol 1984; 106:314-24.
19. Durkin JW Jr. Carcinoid tumor and pregnancy. Am J Obstet Gynecol 1983; 145:757-61.
20. Katz BP, Batteiger BE, Jones RB. Effect of prior sexually transmitted disease on the isolation of *Chlamydia trachomatis*. Sex Transm Dis 1987; 14:160-4.