Q Fever During Pregnancy

Diagnosis, Treatment, and Follow-up

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Background: Q fever, caused by *Coxiella burnetii*, may result in abortions, premature deliveries, and stillbirths in infected pregnant women.

Objective: To evaluate the best treatment strategy for Q fever during pregnancy.

Methods: We evaluated the prognosis of 17 pregnant women who developed Q fever with and without co-trimoxazole (trimethoprim-sulfamethoxazole) treatment.

Results: The outcome of the pregnancy was found to depend on the trimester. Abortions occurred in 7 of 7 insufficiently treated patients infected during the first trimester vs 1 of 5 patients infected later. Co-trimoxazole given until delivery protected against abortion (0/4) but not against the development of chronic infections, and it did not significantly reduce the colonization of the placenta (2/4 vs 4/4).

Conclusions: Our results show that *C burnetii* infections cause abortion and that women who develop Q fever while pregnant should be treated with co-trimoxazole for the duration of pregnancy, specifically when infected during the first trimester.

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Q FEVER IS A zoonosis caused by *Coxiella burnetii* and occurs worldwide. Although the organism may infect mammals, birds, and arthropods, domestic animals and pets are the most frequent sources of human infections. Q fever is usually acquired by inhalation of aerosols from parturient fluids or the placenta of infected animals. In female animals, *C burnetii* infections are often chronic and have been associated with abortions in sheep, goats, and mice, and low birth weight and infertility in cattle and mice. Acute infections result in granuloma formation in infected viscera, and IgM and IgG antibodies develop mainly against the laboratory-derived avirulent form of *C burnetii* (phase II). In some people, the infection is not controlled by the immune response or by granuloma formation, and very high antibody levels of IgG and IgA types develop, which are directed against both the virulent (phase I) and the avirulent forms (phase II) of *C burnetii*.

Previously there were few data on Q fever in pregnant women. Five new cases have recently been reported and 21 others reviewed from the literature, subsequently other cases have been described. This work has shown that Q fever, when contracted during pregnancy, can result in abortions or neonatal deaths (9 cases, 38%), premature births, low birth weight (8 cases, 33%), or no abnormalities (7 cases, 29%). In some cases, pregnancy was found to be associated with the development of chronic infections and relapses.

We have now collected additional data on 17 patients who contracted Q fever while pregnant and who were treated and followed up as we have proposed. We herein report our findings.

RESULTS

We were involved in the diagnosis and follow-up of 17 pregnant women who developed Q fever (Table), with 15 of the women having been examined and followed up by one of us (D.R. or A.S.). From 1 to 4 cases were diagnosed each year of the study, with 13 patients coming from Marseille or the vicinity, 2 from other locations in France, 1 from Africa, and 1 from Iceland. Eleven patients developed Q fever during the first trimester of their pregnancy, 3 during the second, and 3 during the third trimester. Two patients had a heart murmur. In 1 patient the murmur...
PATIENTS AND METHODS

PATIENT CHARACTERISTICS

As a reference center for the diagnosis and study of rickettsial diseases, our laboratory regularly receives specimens from France and internationally for the diagnosis of Q fever. This enabled us to identify pregnant women who presented with unexplained fever and/or abortion and were tested for Q fever. The physician in charge of each patient completed a questionnaire to provide data on epidemiologic and clinical features. Age, permanent address, and occupation were recorded, and the presence of valvular disease was noted. Other infectious diseases were excluded on the basis of negative blood cultures and lack of serologic evidence of evolutive infection with *Toxoplasma gondii*, rubella virus, cytomegalovirus, human immunodeficiency virus, hepatitis B, influenza viruses, parvovirus B19, adeno virus, *Chlamydia* species, and *Mycoplasma pneumoniae*. The administration of antibiotics and the length of treatment were also recorded. Finally, the outcome of the pregnancy was categorized as abortion, premature delivery (<36 weeks), low birth weight (<3 kg), or normal outcome.

SEROLOGIC PROCEDURES

Indirect immunofluorescent antibody tests were carried out as described previously. As cutoff values, titers of 200 or higher anti–phase II IgG and 50 or higher anti–phase II IgM were required for the diagnosis of acute Q fever, and titers of 1600 or higher anti–phase I IgG for the diagnosis of chronic Q fever. On collection, placental tissue samples were frozen and stored at −80°C until tested for the presence of *C. burnetii* by polymerase chain reaction and culture as previously reported.

TREATMENT AND FOLLOW-UP

Beginning in 1996, women developing Q fever while pregnant were treated with co-trimoxazole (320 mg of trimethoprim in combination with 1600 mg of sulfamethoxazole) until term. Serologic testing was performed each month during the pregnancy, and after delivery patients with serologic evidence of chronic disease were treated with a combination of doxycycline (200 mg/d) and hydroxychloroquine (600 mg/d) for 1 year. The hydroxychloroquine dose was adapted to obtain a drug plasma level of 1±0.20 µg/mL. Every 6 months, a specific ophthalmologic examination was performed to detect intraretinal accumulation of hydroxychloroquine. A clinical follow-up was performed each month to observe compliance, tolerance, and efficiency of the treatment. Data were analyzed using the Fisher exact test; *P*<0.05 was considered significant.

had been detected before the pregnancy and followed rheumatic fever. The second patient had mitral insufficiency, which was first identified in our study but was not investigated further.

None of the pregnancies were normal. In 8 cases the fetus died, and in 9 cases delivery was premature or there was a low birth weight. Co-trimoxazole was administered throughout pregnancy to 4 patients, for 6 months to 1 patient, and for 3 weeks to another. The drug was not administered to the remaining 11 patients. In the untreated patients who became infected in the first trimester, 6 of the 6 aborted compared with 1 of 5 who became infected during the second or the third trimester (*P*=.01). One patient treated from the 8th to the 21st week aborted during the 24th week. *Coxiella burnetii* was found in both placenta and fetus.

Seven of the patients seroconverted during the study, and 12 had serologic profiles consistent with chronic infections; 12 of the 14 women who had Q fever in the 2 first trimesters developed chronic infections. Of the 2 patients infected in the first trimester who did not develop chronic infections, one aborted soon after the diagnosis was made (patient 7, Table) and the other was treated with co-trimoxazole for the remaining 6 months of her pregnancy (patient 17). Her placenta was found to be negative for *C. burnetii* by culture and polymerase chain reaction.

Nine patients with chronic infections were given doxycycline and hydroxychloroquine for 18 months. Subsequent pregnancies occurred in 7 patients and were normal. One patient completed only 3 months of treatment and had a normal pregnancy 1 year later. A patient who did not receive this treatment was given co-trimoxazole for the duration of a subsequent normal pregnancy.

There were no abortions in 4 women treated with long-term co-trimoxazole, but abortions occurred in 8 of 11 untreated women and in 1 treated for only 3 weeks (*P*=.01). During the first trimester, all untreated women aborted (7/7) compared with none of the 4 who were treated (*P*<0.01). During the second and third trimesters, no differences were observed, and only 1 woman infected during the second trimester experienced a fetal death.

*Coxiella burnetii* was detected by culture and/or polymerase chain reaction in the placentas of all 4 women who were not treated and in 2 of 4 of those treated with co-trimoxazole. Long-term treatment started during the first trimester did not prevent the development of chronic infections: 4 of the 5 treated patients and 8 of the 9 untreated patients developed high anti–phase I titers.

Q fever is a therapeutic challenge because *C. burnetii* is an intracellular bacterium that lives in an acidic vacuole, which may protect it from the bacteriocidal effect of antibiotics. Several antibiotics, however, have bacteriostatic effects on the organism, including tetracyclines, rifampin, co-trimoxazole, and fluoroquinolones. The only effective bacterioidal regimen in vitro is the concurrent use of doxycycline and chloroquine. Chloroquine affects intracellular pH, and when it is present at a concentration of 1 µg/mL the pH of the phagolysosome increases from 4.8 to 5.7, which restores the bacteriocidal effect of doxycycline.

COMMENT

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Chronic infections with Coxiella burnetii develop only in some individuals whose immune system is unable to control the organism. A good indicator of such chronic infections is a high level of antibodies to the phase I stage of Coxiella burnetii. Patients with existing valvular or vascular diseases are at particular risk of developing chronic infections, as are immunocompromised patients and pregnant women.

As in other mammals that become infected with Coxiella burnetii, in pregnant women the bacteria colonize and multiply in the uterus, mammary glands, and placenta. Chronic infections develop if the woman is pregnant at the time of the primary infection, and this could be related to lack of an appropriate immune control. Apparently, women who have acute Q fever before they become pregnant do not have increased risks of abortion or premature delivery. There are few data, however, on the effects of Q fever contracted during pregnancy.

In our study we found abnormalities in all the pregnancies associated with acute Q fever. Fetal death occurred in two thirds of the untreated patients we studied, and one third gave birth prematurely. Our finding of abortions occurring in all untreated or incompletely treated pregnant women shows for the first time that a primary infection with Coxiella burnetii during the first trimester of pregnancy is a specific risk for abortion. We have previously isolated organisms directly from fetal tissues to show that fetal death is caused by infection. Teratogenicity has not been associated with Coxiella burnetii infections, and our findings show that specific therapy is indicated to attempt to save the fetus in pregnant women who develop Q fever during the first trimester.

Doxycycline and quinolones are contraindicated during pregnancy. Co-trimoxazole and rifampin may be used with caution, but they are not bacteriocidal. Case 2 showed us that short-term treatment was unable to prevent abortion, so we tested long-term therapy. We have used co-trimoxazole to treat pregnant women with acute Q fever since 1996, and this prevented fetal death in 5 of the women and prevented infection of the placenta in 2 of 4 women. Although all 5 treated women gave birth early, and all of their babies had low birth weights, we believe that treatment with co-trimoxazole should be recommended routinely.

In our study, most patients infected with Coxiella burnetii during the first 6 months of pregnancy developed chronic Q fever, regardless of treatment (Figure). The major factor influencing the development of chronic Q fever seemed to be the duration of the infection during pregnancy. Of the 5 patients who did not develop chronic infections, 1 had an early abortion, 1 received long-term treatment (patient 17), and 3 were infected only late in their pregnancies.

We used the treatment recommended for Q fever endocarditis on our chronically infected patients to prevent the possible development of endocarditis, as may occur in mice, and to prevent recurrent abortions. After this treatment, all pregnancies were normal. Coxiella burnetii has been isolated from the milk of women in several studies, and we believe that breastfeeding should not be recommended for women who have had Q fever during their pregnancy. The presence of Coxiella burnetii has been reported in the placenta of asymptomatic women, but the significance of this has yet to be determined.

In conclusion, our study has confirmed that Q fever endocarditis on our chronically infected patients to prevent the possible development of endocarditis, as may occur in mice, and to prevent recurrent abortions. After this treatment, all pregnancies were normal. Coxiella burnetii has been isolated from the milk of women in several studies, and we believe that breastfeeding should not be recommended for women who have had Q fever during their pregnancy. The presence of Coxiella burnetii has been reported in the placenta of asymptomatic women, but the significance of this has yet to be determined.

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ccline and hydroxychloroquine for a year after their pregnancy resulted in the elimination of C burnetii, and subsequent pregnancies were normal.

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REFERENCES


Anti–Coxiella burnetii IgG phase I serologic evolution for 13 patients during pregnancy. Numbers in parentheses indicate patient number (see Table). The shaded area indicates the titer range for chronic Q fever.