Acute Q fever in third trimester pregnancy

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SUMMARY

A 29-year-old gravida 2 para 1 woman presented at 29 weeks gestation with fevers, back pain, thrombocytopenia and hepatitis. PCR testing of blood samples detected *Coxiella burnetii* and paired serology later confirmed the diagnosis of acute Q fever in pregnancy. The patient was treated empirically with oral clarithromycin and experienced a symptomatic and biochemical improvement. Therapy was changed to oral trimethoprim/sulphamethoxazole but was complicated by a delayed cutaneous reaction, prompting recommencement of clarithromycin. Therapy continued until delivery of a healthy girl at 39 weeks and 3 days. Q fever in pregnancy is likely under-reported and is associated with the development of chronic infection and obstetric complications. Treatment with clarithromycin is an alternative to trimethoprim/sulphamethoxazole in the setting of drug intolerance.

BACKGROUND

Q fever is a zoonotic infection caused by the bacterium *Coxiella burnetii*.[1] The illness was first described among meatworkers in 1935 by Derrick in Queensland, Australia, and was named 'Query fever'. The most common source of Q fever worldwide is farm animals, with infections also reported from pets and wild mammals. The disease spectrum of Q fever is broad in severity and manifestations. Most commonly, acute infection manifests as a 'flu-like' illness characterised by fevers, fatigue and myalgia.[2] Hepatitis, pneumonia and acute endocarditis are also described. Deranged liver transaminases and thrombocytopenia are commonly reported. A chronic form of infection is also described, associated with persistently elevated antiphase I antigen Igs and intravascular or osteoarticular involvement.

Q fever in pregnancy presents multiple challenges for the mother, fetus and clinicians. First, Q fever is associated with complications of pregnancy including spontaneous abortion, intrauterine foetal death and premature delivery.[3 4] Second, Q fever in pregnancy is often associated with the rapid appearance of antiphase I IgG, which can be followed by the development of chronic Q fever. Third, the use of tetracyclines is contraindicated in pregnancy, owing to the risk of foetal bone and teeth malformation, mandating the use of second-line treatment options, namely trimethoprim/sulphamethoxazole. These adverse pregnancy outcomes have been described by varying methodology in both endemic and epidemic settings.[3 5–7]

While there is some evidence to support prolonged courses of trimethoprim/sulphamethoxazole to prevent complications of Q fever in pregnancy, guidance on alternative agents in the setting of drug intolerance is limited.[8]

We report the case of a 29-year-old woman diagnosed with acute Q fever at 29 weeks gestation, with pregnancy continuing until induced delivery of a healthy girl at 39 weeks and 3 days gestation.

CASE PRESENTATION

A 29-year-old gravida 2 para 1 woman, at 29 weeks gestation, presented to a rural North Queensland hospital with a 5-day history of fevers, back pain and headache. Until that point the pregnancy had progressed without complication and the patient had no significant prior medical history. Her obstetric history included one uncomplicated pregnancy with vaginal delivery 2 years prior and she took no regular medications.

On admission a fever was recorded and other vital signs were normal. A clinical examination was unremarkable and cardiotocography was normal. An exposure history revealed that the patient lived opposite to a property with grazing animals and in an area of scrub typhus endemicity, raising the possibility of a zoonotic or rickettsial infection.

INVESTIGATIONS

Blood collected on the day of presentation revealed mild elevation of hepatic enzymes and thrombocytopenia which improved on subsequent testing (table 1). An ultrasound scan of the liver and gallbladder was reported as normal.

A PCR test for Q fever detected *C. burnetii* DNA on blood collected from the day of presentation. The diagnosis of acute Q fever was subsequently confirmed with paired Q fever serological testing (table 2). A transthoracic echocardiogram revealed no valvular abnormality.

The patient was referred to a tertiary centre for specialist obstetric review and an ultrasound scan revealed no foetal or placental abnormality.

TREATMENT

At the time of presentation, the patient was commenced on oral clarithromycin 500 mg two times per day to empirically treat both Q fever and rickettsia pending further investigations. The patient's symptoms and laboratory markers improved on clarithromycin and she was discharged after 2 days. After 3 days of treatment, a positive Q fever PCR was returned and the patient was changed therapy to oral trimethoprim/sulphamethoxazole 160/800mg two times per day, on the advice of the infectious diseases unit. This was coadministered with oral folic acid, 5mg daily.

On day 13 of treatment with trimethoprim/sulphamethoxazole, the patient developed pruritus on the legs which progressed to painful nodules by day

Table 1 Laboratory findings at presentation

Laboratory marker	Day 5 of illness	Day 6 of illness	Day 7 of illness
Platelet count (×10^9/L)	134	116	167
ALT (U/L)	464	362	356
AST (U/L)	323	312	172
CRP (mg/L)	112	–	71

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, c-reactive protein.

15, at which time she was instructed to cease therapy. The rash resolved with cessation.

A consensus was reached to treat until delivery with oral clarithromycin given the patient tolerated this agent well and had apparent clinical and biochemical improvement with initial treatment. A further course of oral clarithromycin 500 mg two times per day was completed until medical induction of labour at 39 weeks and 3 days gestation.

OUTCOME AND FOLLOW-UP

The patient vaginally delivered at a tertiary centre following a planned medical induction of labour, at 39 weeks and 3 days gestation. Airborne and contact precautions were observed by the birthing staff. The patient gave birth to a girl child without complications. Samples of amniotic fluid, foetal blood and placental tissue were tested with PCR and *C. burnetii* DNA was not detected. PCR testing of breastmilk was unsuccessful secondary to the fatty nature of the sample; however, breastfeeding was deemed safe given the duration of treatment and negative PCR testing of all non-milk specimens. A regimen of serial serological testing of the newborn was proposed after consultation with paediatric infectious diseases.

The patient was followed up 1 month post delivery with repeat Q fever serology (table 2) demonstrating an expected rise in anti-phase I IgG at 4 months post infection. Both patient and infant were asymptomatic at follow-up. Plans were made for yearly Q fever serology as surveillance for chronic Q fever.

DISCUSSION

Q fever is a common illness in endemic areas and yet the diagnosis, treatment and follow-up are subject to some controversy, not least of all in pregnant patients. *C. burnetii* resides and occasionally causes disease in livestock which are the main source for human infection via bacteria shed in urine, faeces, milk and placenta. Placental tissue of infected mammals is known to be particularly infectious containing 10^9 organisms/g of tissue.[1] Despite this known link, among 1366 cases in the USA from 2000 to 2012, approxmately 61% of patients recalled no direct exposure to livestock, in keeping with other studies showing proximity to forests and drinking unpasteurised milk as other risk factors.[9] Of note, in that same series there were no cases of Q fever in pregnancy, which may be the result of undetected cases as symptomatology is typically less severe in pregnant women.

Table 2 Q fever diagnostic tests

Q fever serology/PCR	At presentation	+1 month	+4 months
Q fever Ph2 IgG (EIA)	Reactive	Reactive	Reactive
Q fever Ph2 IgM (EIA)	Equivocal	Reactive	Reactive
Q fever Ph1 IgG (IF)	<10	80	160
Q fever Ph2 IgG (IF)	160	≥1280	640
Q fever Ph2 IgM (IF)	40	640	80
Q fever PCR (blood)	Detected	Not Detected	–

EIA, enzyme immunoassay; IF, immunofluorescence; Ph1, Phase 1; Ph2, Phase 2.

C. burnetii infects host cells and resides in acidic vacuoles.[1] This presents challenges with antimicrobial therapy and mandates the use of agents targeted against intracellular pathogens. The bacteria undergo an antigenic phase variation and an antibody response against phase I antigens is related to chronic infection. *C. burnetii* has been shown to infect human gestational trophoblasts and therein induce a transcription programme associated with an inflammatory response.[10] This is a postulated as the mechanism for increased obstetric complications associated with Q fever and is consistent with findings that correlate placental infection with complications of pregnancy.[8]

This case presented with an acute, symptomatic illness in the final trimester. This is in contrast to a majority of pregnant patients who present without symptoms of a typical Q fever syndrome, as described in a French centre's experience of 30 patients where 97% were asymptomatic.[3] Our patient's symptoms, with clinical and epidemiological suspicion, allowed for initiation of empiric therapy from the day of presentation and diagnosis confirmed by the PCR 3 days after presentation. In contrast, studies show a large number of cases may go undiagnosed at time of infection, with one Spanish serological study suggesting 12% of spontaneous abortions were attributable to Q fever.[5]

Treatment of Q fever in pregnancy is recommended.[4] While the effects of timely treatment are not well described, prolonged treatment with greater than 5 weeks of trimethoprim/sulphamethoxazole has been demonstrated to protect against maternal chronic Q fever, obstetric complications and placental infection when compared with therapy of a shorter duration.[8] Of note, the same study showed obstetric complications occurred significantly more frequently in women who were infected in the first trimester of pregnancy. In keeping with these findings, the Australian therapeutic guidelines suggest treatment with trimethoprim/sulphamethoxazole until 32 weeks gestation and other sources recommend treatment for the duration of pregnancy. Even though obstetric complications are less frequent in late pregnancy, placental infection confirmed by PCR is described even in the presence of appropriate antibiotics, therefore ongoing treatment and infection control measures are still required for this reason.[11]

C. burnetii has specific tropism for placental tissue with associated risk of chronic Q fever.[8 10] It is therefore instructive to examine the placenta histologically for granuloma and with PCR for *C. burnetii* DNA. In this case, these examinations were negative but a positive finding would prompt continuation of postpartum treatment, as is the recommendation for those with a chronic Q fever serological profile.[12] PCR of the viscera of aborted fetuses has demonstrated transplacental transmission.[7] Given this possibility and the availability of PCR, testing of neonatal and cord blood is also prudent. Despite the plausibility of vertical transmission, neonatal Q fever is not reported in the literature and robust evidence-based guidelines for paediatric disease are lacking.[13] Accordingly, positive cord or neonatal PCR samples should prompt discussion with paediatric infectious disease specialists.

The mainstay of treatment for acute Q fever is doxycycline which is relatively contraindicated in pregnancy because of irreversible teeth staining and reversible bone growth inhibition.[4] Trimethoprim/sulphamethoxazole is shown to be bacteriostatic against *C. burnetii* and is the guideline recommended therapy for pregnant patients, despite a theoretical risk of hyperbilirubinaemia in neonates.[14] The continued use is supported by reviews of case series, involving pregnant patients with HIV using trimethoprim/sulphamethoxazole prophylaxis, demonstrating safe use in late pregnancy. In this case, the patient developed a delayed cutaneous reaction to trimethoprim/sulphamethoxazole at 2-week therapy, contraindicating further use. By this point, the patient was at 32

weeks gestation and had received therapy in keeping with Australian guidelines, however a multidisciplinary consensus, among infectious diseases, obstetric medicine and maternal-foetal medicine was made to continue treatment until delivery. The goal of ongoing therapy was to prevent chronic Q fever and placental shedding at the time of delivery. It was deemed unsafe to rechallenge trimethoprim/sulphamethoxazole and other agents such as doxycycline and ciprofloxacin were relatively contraindicated by pregnancy. The patient therefore continued clarithromycin, the use of which was supported by her initial therapeutic response to this agent with resolution of laboratory abnormalities and easing of symptoms.

Further, studies of the concentration of oral clarithromycin achieved in respiratory epithelial cells suggest the agent can target the intracellular phagosome in which *C. burnetii* resides in human infection.[15] Additionally, in vitro bacteriostatic susceptibility to clarithromycin has been demonstrated, compared with resistance against erythromycin.[16] The favourable outcome of this case, namely an uncomplicated pregnancy with *C. burnetii* PCR negative placenta, amniotic fluid, foetal and maternal blood, further supports the use of clarithromycin as an alternative agent in the management of Q fever in pregnancy.

Patient's perspective

I was so unwell. I felt awful with the fevers and headaches. I just could not shake them. I felt scared for my baby that he/she would be affected or die. I was not confident because of lack of information and studies around Q fever in pregnancy. I was scared to take the treatment too, worried it would hurt my baby.

There was so much relief for my husband and I to know that my results were negative at the end.

Learning points

- Q fever has a wide range of presentations in pregnancy and should be considered as a differential in complicated pregnancy in endemic regions.
- Adverse sequalae including spontaneous abortion, placental infection, intrauterine foetal death, intrauterine growth restriction and progression to chronic Q fever are common in pregnant patients.
- Clarithromycin is an alternative agent to trimethoprim/sulphamethoxazole in the treatment of Q fever in pregnancy.

This case demonstrates the use of clarithromycin to initiate therapy for acute Q fever in pregnancy and then continue as a safe and likely effective alternative in the setting of trimethoprim/sulphamethoxazole intolerance. The case further highlights vigilance to presentations of Q fever in pregnant women in areas of endemicity even without direct livestock exposure. Finally, Q fever should be considered as a differential diagnosis in pregnant women with haematological and liver enzyme abnormalities, especially in the setting of supportive infective symptoms or epidemiology.

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