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Narrative review

Q fever during pregnancy: a narrative review

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ABSTRACT

Background: *Coxiella burnetii*, the causative agent of Q fever, causes abortions in animals. Its effects on pregnancy in humans and the management of Q fever in pregnancy are uncertain.
Objectives: To summarize data on the effects of Q fever on pregnancy in women, the effects of pregnancy on Q fever complications and the optimal screening and management of Q fever during pregnancy.
Sources: We searched for studies reporting on Q fever during pregnancy in women. We included randomized and observational studies, seroprevalence studies, case series and case reports, including clinical and histopathological studies.
Content: The accumulating data seems convincing that Q fever increases the risk of abortions in early pregnancy and prematurity or intrauterine fetal demise in late pregnancy. Data are based on sero-epidemiological associations of Q fever and adverse pregnancy outcomes and case reports showing the presence and effects of *C. burnetii* on the placenta and the fetus. Based on observational studies, acquisition of Q fever during pregnancy also increases the risk for maternal chronic Q fever. Treatment of recently infected women seems to improve these outcomes, based on case series only, but the optimal duration of treatment has not been studied. The efficacy of active surveillance during pregnancy, timing and frequency have not been determined in high-endemicity settings. Obstetricians should be aware of the risk for transmission of the disease during delivery. Currently available data are based mostly on case series and case reports, with some discrepancy between the French experience in chronic endemicity settings and Dutch experience in outbreak settings.
Implications: Since infection with Q fever is largely asymptomatic, we believe that the accumulating information linking Q fever to adverse pregnancy outcomes justifies screening in the high-endemicity setting and treatment of infected women. High-quality research addressing the questions raised by this review is needed to determine the optimal public health policy. **N. Ghanem-Zoubi, Clin Microbiol Infect 2020;26:864**

Introduction

Q fever is a zoonotic disease caused by *Coxiella burnetii,* an intracellular Gram-negative bacterium. The main sources of human infections are farm animals, including goats, sheep and cattle. However, infection is typically acquired in endemic settings through inhalation of aerosolized dust from farms, without direct exposure to animals. Infected animals are asymptomatic in most cases, but the bacterium has special tropism for the placenta, multiplying extensively within it [1]. We reviewed the effects of Q fever during pregnancy in humans.

Acute Q fever during pregnancy is asymptomatic in >90% of cases [2]. Pregnancy complications can therefore be detected only when searched for actively. We aimed to assess whether studies show an increased risk of pregnancy complications following Q fever infection, whether *C. burnetii* acquisition during pregnancy is a risk factor for chronic Q fever, whether treatment in pregnancy reduces complications, and to assess the risk of *C. burnetii* transmission to obstetricians during delivery. Finally, we aimed to summarize the public health implications and areas of uncertainty that should be the focus of future research.

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Table 1
Seroprevalence studies assessing the association between Q fever and adverse pregnancy outcomes

Reference	Study design	Country/years	No. of participants/serology test	Results	Presence of significant association
Rey 2000 [4]	Seroprevalence survey in pregnant women and retrospective data collection of pregnancy outcome	France, 1996	12 000/IFA	- Seroprevalence 0.15% - Non-significant higher rates among abnormal pregnancies	Non-significant association
Langley 2003 [5]	Seroprevalence in cord blood and placental PCR	France, 1997–1998	7658 Positive: phase I or phase II $\geq$ 1:8	- Seroprevalence 3.8% - In MV analysis, women with phase I had increased association with previous or current fetal death (OR 3.2, 95% CI 1.09–9.3, p 0.03)	✓
McCaughey 2008 [11]	Seroprevalence in randomly selected samples and association with pregnancy outcome	Northern Ireland, 1986–1987	2394 Phase II ab by ELISA	- Seroprevalence 12.8%. - More seropositive than seronegative women had a history of a miscarriage or still birth (19.5% versus 9.8%, p < 0.001)	✓
Vaidya 2008 [12]	Seroprevalence and molecular testing for QF in spontaneous abortions	India	368 samples from 74 women/IFA PCR, blood, urine, stool, placenta	Positive for QF by IFA 25.6% Positive by PCR 21.6%	✓
van der Hoek 2011 [16]	QF serology testing on week 12 of pregnancy and pregnancy outcome IFA	Netherlands, 2007–2008	1174 women in the prenatal registry programme Group I IgG I and IgG II $\geq$1:64 (past/chronic QF) Group II IgM II and IgG II $\geq$ 1:64 or IgM II $\geq$ 1:64 (recent/acute QF)	- Seroprevalence 3.4% - Any adverse pregnancy outcome was recorded in 271 (24.1%) in seronegative compared with 4 (33.3%) in past QF and 5 (13.5%) in recent QF, p 0.358	Non-significant association
Nielsen 2012 [17]	Seroprevalence in abnormal versus normal pregnancies (case–control)	Denmark, 1996–2002	218 pregnancies with miscarriage versus 482 other pregnancies ELISA confirmed by IFA IgG for phase I $\geq$ 1:512 phase II $\geq$ 1:102 IgM phase I $\geq$ 1:128 or IgM phase II $\geq$ 1:256	- Among abnormal pregnancies, 11 (5%) were *Coxiella burnetii* positive compared with 29 (6%) in the random sample	×
Quijada 2012 [13]	Case–control population-based study	Spain, 2009–2010	500 pregnant women were tested, of whom 273 had a spontaneous abortion and 227 gave birth IFA phase I IgG $\geq$1:16 or phase II IgG $\geq$1:80	- Positive serology was detected in 88/273 (32.2%) pregnancies with abortions and 53/227 (23.3%) with normal birth; p < 0.01, OR 1.5, 95% CI 1.0–2.3	✓
Boden 2012 [6]	Screening of pregnant women	Germany, 2003, 2005	93 IFA	- Acute QF was diagnosed in 11 (11.8%) Three cases had adverse pregnancy outcome	Non-significant association
Nielsen 2013 [7]	The Danish National Birth Cohort collected blood samples and interview data (from 100 418 pregnant women)	Denmark, 1996–2002	397 pregnant women with occupational or domestic exposure to cattle or sheep and 459 women with no animal exposure (random sample) ELISA confirmed by IFA IFA cut-off $\geq$1:128	Among the 856 women, 169 (19.7%) women were IFA positive; 147 (87%) of these had occupational or domestic contact with livestock No significant difference regarding abortion, preterm birth and birthweight	×
Eyigör 2013 [8]	Serology for pregnant women with miscarriage and their spouses compared with women with normal delivery	Turkey	89 Women who had abortion ($n = 36$) along with their husbands ($n = 31$), and 22 women who had normal pregnancy Serology by ELISA and IFA PCR on blood and placentas	- Positive phase II IgG rates in women who had miscarriages, their spouses and in women with normal delivery were found as 27.8% (10/36), 38.7% (12/31) and 4.5% (1/22), respectively	Non-significant association
Munster 2013 [9]	A cluster RCT during an outbreak 55 midwife centres were randomized to recruit pregnant women for an intervention or control strategy	Netherlands, 2010	$n = 536$ intervention group, testing on real time $n = 693$ control group IFA Titres $\geq$1:32	Seroprevalence 15% Overall complications in seropositive was 12% (22/183) versus 13% (133/1046) in seronegative pregnancies, p 0.79	×

(*continued on next page*)

Table 1 (*continued*)

Reference	Study design	Country/years	No. of participants/serology test	Results	Presence of significant association
Nielsen 2014 [14]	Retrospective identification of QF in pregnant women from a national data registry	Denmark, 2007–2011	IFA IgM for phase I or phase II > 64 or IgG for any of the phases >128	- Identified 12 women with equivocal and positive antibody titres for C. burnetii infection who underwent 19 pregnancies during the 5-year study period Obstetric complications were recorded in 9 (47%) of the 19 pregnancies (6 were treated during pregnancy)	✓
de Lange 2015 [10]	Nationwide registry-based ecological analysis of Q fever incidence and pregnancy outcome during an outbreak in the Netherlands	Netherlands 2008–2010	Index group (n = 58 737): pregnant women in 307 areas with more than two Q fever notifications. Reference group (*n* = 310 635): pregnant women in 921 areas without Q fever notifications	- Small-for-gestational-age (adjusted OR 1.06, 95% CI 1.01–1.12) - Preterm delivery (adjusted OR 1.01, 95% CI 0.94–1.08) - Perinatal mortality (adjusted OR 0.87, 95% CI 0.72–1.05)	✓ for small-for-gestational-age × for preterm and perinatal mortality
Khayyat 2016 [15]	Seroprevalence in randomly selected samples from pregnant women	Iran, 2014	400 An indirect ELISA kit for phase II IgG	Overall prevalence 29.3% - Total prevalence of *C. burnetii* infection in serum was significantly higher in women with abnormal pregnancy history (39.8%) compared with normal pregnancies (23.8%)	✓

Abbreviations: ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; MV, multivariate; QF, Q fever; RCT, randomized controlled trial.

Sources

We searched PubMed and Google Scholar for studies reporting on Q fever during pregnancy in humans. We included randomized and observational studies, seroprevalence studies, as well as case series and case reports, including clinical and histopathological studies. We reviewed full-text studies in English and English abstracts of studies published in other languages.

Seroprevalence association of Q fever with adverse pregnancy outcome

One of the earliest studies reporting a potential association between antibodies to *C. burnetii* and prematurity was conducted in the late 1990s in a small town in southern France. The authors identified five cases of Q fever infection during pregnancy resulting in abortion or premature delivery during a 3-year period [3]. This study was followed by a survey conducted during a single season of Q fever in 1996 in obstetric departments in southern France, finding 0.15% seroprevalence of Q fever out of almost 12 000 tested pregnant women. Despite the low rate of seroprevalence, women with recent or chronic serological evidence of infection had two- to three-fold higher rates of abnormal pregnancies compared with seronegative women [4]. Another seroprevalence survey from the same region, testing for *C. burnetii* antibodies from cord blood of 7658 women, found a seroprevalence of 3.8% and showed a significant adjusted association between *C. urnetii* phase I antibodies and fetal death (OR 3.2, 95% CI 1.09–9.3) [5].

Studies from southern France were followed by studies from other countries with varying results. Studies differed widely in their design, the serology test used, the antibody titre defining positive serology, the time during pregnancy when the survey was performed, and the outcomes that were assessed. Most studies found a significant or non-significant association between a recent or past infection with *C. burnetii* and abortions, preterm birth or low birthweight (Table 1) [4–17]. In general, most studies reporting higher baseline seroprevalence rates (e.g. Northern Ireland, India, Spain and Iran) found an association between *C. burnetii* seropositivity and pregnancy complications [11–13,15]. Most studies were retrospective and did not differentiate between acute or recent infection and past infection. Regardless of the results of these studies, a causative association cannot be concluded from epidemiological studies. For example, a positive serology for Q fever may represent simply exposure to farm animals in low socio-economic status populations, the such status being known to affect pregnancy outcomes in itself.

Pregnancy complications among pregnant women with Q fever and treatment effects

Up to the early 1990s there were only a few case reports of Q fever during pregnancy, reported in languages other than English, describing Q fever-associated abortions, intrauterine fetal demise, prematurity and low birthweight. The first well-documented case report in English was reported from southern France [18]; an intensive care unit nurse who was diagnosed with confirmed acute Q fever pneumonia at 8 weeks of gestation. She was treated for 3 weeks with antibiotics and re-hospitalized at 24 weeks of gestation with intrauterine fetal demise. The placenta showed foci of necrosis and was positive for *C. burnetii*. Infection of the fetus was demonstrated with isolation of the bacterium from fetal spleen and kidneys [18]. Following this case, additional case reports of Q fever infection during pregnancy and related complications were reported [3,19–22]. Congenital malformations have been described very rarely, including hypospadias [23], Potter syndrome with

Table 2
Pregnancy complications among pregnant women with Q fever reported in case series, with and without treatment directed against Q fever

Reference	Raoult 2002 [26]	Raoult 2000 [31]	Carcopino 2007 [23]	Angelakis 2013 [24]	Nielsen 2014 [14]	Munster 2013 [9]	Boden 2012 [6]	Million 2014 [25]
Country	France	France	France	France	Denmark	Netherlands	Germany	*[a]
Number of pregnancies with Q fever	17	15	53	30	19	183	11	136
Complication (*n*)								
Fetal death	8	10	16	16	3	0	1	46
Prematurity	8		13	4	1	13	1	
Low birthweight	1	3		1		9		
Intrauterine growth restriction			14	1	2			
Congenital malformation				1			1	7
With treatment	0/4	6/6[b]	7/16	6/14	1/7	12/82	2/3	10/64
Without treatment	8/11	9/9[b]	30/37	16/16	8/12	10/101	1/8	36/67

[a] A meta-analysis of case reports and case series reported from different countries.
[b] A great difference was observed in fetal mortality in favour of treatment.

bilateral renal agenesis [23], congenital hydronephrosis [24], syndactyly [6] and omphalocele with adrenal hypoplasia [25], but only the last with microbiologically proven infection of the fetus. A meta-analysis of 136 case reports claimed an OR for fetal death of 8.62 (95% CI 4.21–17.63) for untreated Q fever during pregnancy [25].

Cases reports were followed by case series, first from France and later from other countries, reporting varying rates of pregnancy complications including fetal death, prematurity, low birthweight and intrauterine growth restriction. In general, the risk of complications was higher if diagnosis of Q fever was made during the first trimester of pregnancy and lower when pregnant women were treated with antimicrobials (Table 2) [23–26]. High rates of pregnancy complications reported from southern France and Denmark, not in an outbreak setting, did not match the results from case series reported from outbreak investigations from the Netherlands and from Germany [6,9]. During the large Q fever outbreak in the Netherlands, the rate of fetal complications observed in pregnant women diagnosed with Q fever during the third trimester was extremely low regardless of treatment (1.4%–2.2%) [9]. This study might have missed cases of complications in early pregnancy resulting in abortion because of the late screening. However, comparing the rate of complications in the French series in the parallel period of pregnancy, the difference is still significant as the latter study had reported a complication rate of 47.2% in women who were diagnosed during the second and third trimesters [23]. Antimicrobial treatment directed against *C. burnetii* was associated with a lower rate of pregnancy complications in most locations (with the exception of the Netherlands looking at late complications).

These reports strongly suggest adverse effects of Q fever infection on pregnancy mainly with abortions, fetal death and prematurity and its consequences. Yet, it is difficult to determine from such studies the real contribution of the infection to the specific adverse pregnancy outcomes. By definition, case reports start from the disease and neglect the population with infection that did not have complications. A benefit of treatment in the prevention of pregnancy complications has been suggested in high endemicity settings in southern France. However, these are unadjusted comparisons of very small numbers and in some studies are biased in favour of treatment effects, as untreated women were diagnosed when presenting with complications.

Pathogenesis

In an *ex vivo* model, *C. burnetii* was able to infect human trophoblasts and replicate within the phagolysosomes inducing inflammatory modulation pathways. The replication within trophoblasts seems to serve as a protective niche for the bacterium within the human placenta [27]. In animals it has been shown that *C. burnetii* induces an inflammatory reaction causing placentitis, necrosis and vasculitis, leading in some cases to abortions [28,29]. In women with Q-fever-related pregnancy complications, placentitis, necrosis of the placenta and placental abruption have been described [20].

The pathogen has been isolated both from the placenta and from fetal tissues. Studies reported varying rates of *C. burnetii* in the placenta, based on nucleic acid amplification tests, ranging from zero [5,8] to 70% [3,23] and up to 84.2% when extending the search to other maternal samples, like vaginal swabs [12]. This broad range of results may be attributed at least partially to the high variability in the seropositive thresholds defining infection in the mother, as well as the sensitivities of different nucleic acid amplification tests used. Case reports reported evidence of pathogen isolation from fetal organs, including spleen and kidneys [18]. Live-born babies with congenital *Coxiella* infection have not been described in the literature, to our knowledge.

Suggested explanations of the pathogenesis of Q fever pregnancy complications include direct damage to the placenta from the pathogen itself, secondary damage due to placental insufficiency caused by modulation of inflammatory response [27] or direct disease of the fetus [18]. One study showed necrosis in symptomatic mothers [18,19] and more chronic and fibrotic changes among asymptomatic treated mothers with Q fever in the Netherlands [30]. These findings suggest that the pathogenesis of pregnancy complications in treated women is mediated by interruption of fetal blood flow or destruction of capillaries due to villitis.

Pregnancy as a risk factor for maternal chronic Q fever

In a retrospective study reporting clinical and epidemiological features of Q fever in France, 20 of 313 patients with chronic Q fever were pregnant women, a percentage much higher than that expected in the general population [31]. Conversely, in a case series of 53 women with Q fever complications during pregnancy in France, 52.8% had a serological profile of chronic Q fever, out of whom three had endocarditis [23]. Treatment was associated with lower risk of progression to chronic disease.

Looking for risk factors for progression from acute to chronic infection in the Dutch cohort, three pregnant women were identified among 105 patients with chronic Q fever, compared with none in the 201 cases of acute Q fever who did not progress to chronic infection, p 0.04 [32]. Hence, the French and Dutch

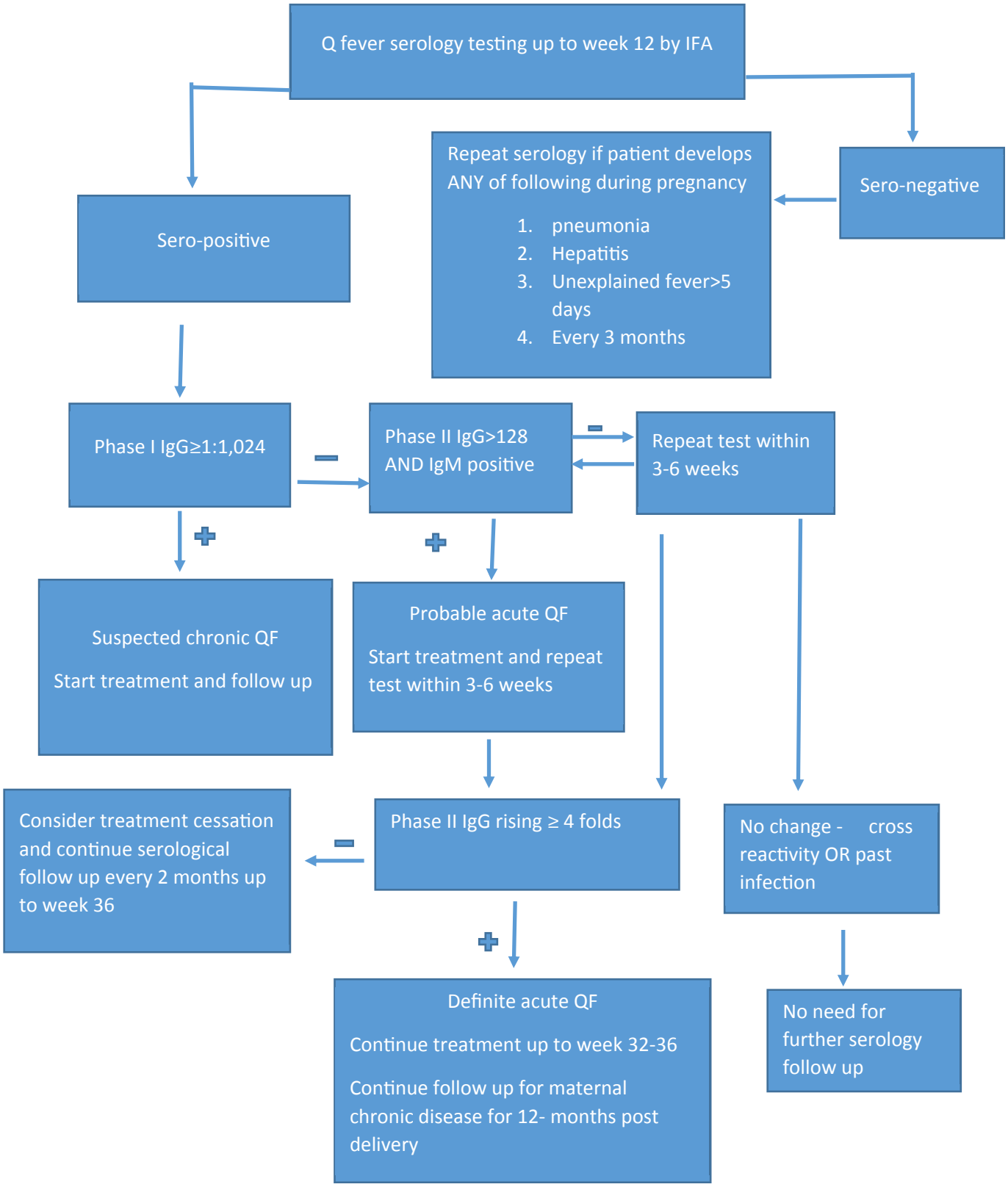

Fig. 1. Diagnostic algorithm for Q fever (QF) serology testing and follow up during pregnancy. Serology thresholds based on commonly published immunofluorescence assay values in the literature. Thresholds might differ between different immunofluorescence assay test kits.

experiences agree on a higher risk of progression of Q fever to chronic Q fever during pregnancy. The mechanism could possibly be due to some degree of immune suppression in pregnancy, as other forms of immune suppression have been associated with chronic Q fever [32,33].

Screening for Q fever in pregnant women

Seroprevalence rates among pregnant women screened for Q fever ranged from 2%–3% in the Netherlands to >25% in Iran and Spain (Table 2). Accepting that Q fever seropositivity is linked to pregnancy complications, then screening seems worthwhile in high-endemicity settings. Its cost-effectiveness would depend on the effects of monitoring for complications and treatment of Q fever. Doxycycline is contraindicated during pregnancy and the recommended treatment is trimethoprim-sulfamethoxazole, whose efficacy is probably inferior to doxycycline.

A strategy of screen-and-treat for Q fever in pregnant women was investigated in a cluster randomized controlled trial in the Netherlands [9]. The trial included 55 midwife centres that were randomized to an intervention group of 536 pregnant women screened and treated if found to have acute or chronic Q fever and a control group of 693 pregnant women who were only screened. The screening was performed using immunofluorescence assay between 20 and 32 weeks of gestation. In both groups 15% were seropositive, none with chronic Q fever. In the intervention group 2.2% of the seropositive women had an obstetric complication, compared with 1.4% in seropositive women in the control group (OR 1.54, 95% CI 0.60–3.96). The very low incidence of Q fever in the study population does not allow extension of this conclusion to other settings, and the study did not target the question of screening in the first trimester, when the risk of pregnancy complications, with miscarriage, might be highest [23].

Risk for transmission of Q fever during delivery

As *C. burnetii* may cause disease from a very small infectious inoculum, it is classified as a category B bioterrorism agent. The risk of transmission from human to human is rare and thought to exist in specific circumstances such as aerosol formation from secretions of infected women during pregnancy or delivery. This was suggested by a study from north Bulgaria that found a high seroprevalence of Q fever in medical workers on obstetric departments [34]. In the previously described case of a nurse with Q fever-related intrauterine fetal demise, a confirmed Q fever pneumonia was diagnosed in the obstetrician who delivered her Q fever stillbirth [18]. Transmission has also been documented in a woman developing Q fever pneumonia 1 week postpartum when sharing a room and toilet with a woman diagnosed with Q fever and chronic placental abruption [35].

Currently, the CDC recommends standard precautions during delivery of known women with Q fever, including the use of a face mask and eye protection or a face shield to protect from splashing of infected material. Conversely, airborne precautions are recommended in procedures that might generate aerosols from infected materials without specific reference to a delivery of infected women [36]. When Q fever is detected only after delivery, post-exposure prophylaxis with doxycycline has been shown to be beneficial in a risk–benefit analysis [37].

Public health and research implications

We believe that in high-endemicity settings and among women at risk for occupational exposure, screening for Q fever using immunofluorescence assays for IgG phase I and II is warranted, with treatment of recently infected women or those with chronic Q fever to prevent pregnancy-related complications. We suggest a diagnostic algorithm for the diagnosis of Q fever during pregnancy following screening during the first trimester of pregnancy (Fig. 1).We base the algorithm on the experience presented, without evidence to back treatment decisions and durations of treatment. Screening should preferably be performed in the first trimester and repeated for seronegative women periodically during pregnancy, although the necessary frequency of repeated testing is not established and should take into consideration cost-effectiveness aspects related to the local epidemiology. The precise definitions for acute Q fever are currently debatable and defining it based on a single test is impossible. A promising avidity test was developed recently and may further help in distinguishing between recent and past infection in pregnant women [38]. The population incidence of Q fever in regions describing significant associations between Q fever seropositivity and adverse pregnancy outcomes ranges between 13% and 30%. This population incidence can serve as a threshold to decide on the cost–benefit of Q screening.

Physicians should be attentive to the diagnosis of Q fever among pregnant women with an undiagnosed febrile disease, in endemic regions. Women diagnosed with symptomatic acute Q fever during pregnancy should be treated and followed up serologically for phase I seroconversion. Doxycycline, the drug of choice for cases of non-pregnant Q fever, is considered a class D in pregnancy due to possible fetal tooth discoloration and dental enamel hypoplasia. The alternative drug for pregnant women is a sulphonamide that should be given with high dose folic acid. Sulphonamides should be avoided near term due to potential fetal kernicterus. There are limited data on macrolides as an alternative drug choice [39]. The appropriate duration of treatment for acute Q fever in pregnancy has not been studied. The CDC guidelines recommend continuation of treatment for the duration of the pregnancy [36], based on the French series in which the treatment was defined as being given for at least 5 weeks but usually for the duration of pregnancy [23].

Table 3
Suggestions for future studies needed regarding Q fever in pregnancy

Objective	Considerations	Study design
To quantify the risk of adverse serious pregnancy outcome when acquiring the infection during pregnancy	Rare disease Largely asymptomatic presentation	Case–case–control design. Q fever serology taken from women with pregnancy complications associated with Q fever and from controls drawn from the same population at risk for Q fever. Cases can be split to those treated for Q fever during pregnancy and those not treated.
To assess the effects of therapy against Q fever on pregnancy complications	Probably not ethical to withhold treatment from pregnant women when diagnosed	
To assess the optimal duration of Q fever treatment for symptomatic and asymptomatic pregnant women detected on screening		
To determine the cost–benefit of screening of Q fever during pregnancy	Should be dependent on the local incidence of Q fever in the population or setting	Cluster-randomized controlled trial similar to the Dutch study, but screening should start in the first trimester of pregnancy and treatment should be longer
To assess the optimal screening schedule		

Raoult recommends treatment until the eighth month of pregnancy [40]. Delivery in a woman with known Q fever should be performed under airborne precautions.

In summary

Q fever during pregnancy carries risks for both the fetus and the mother. Risks for the fetus include developmental delay *in utero* including intrauterine growth restriction, low birthweight, early delivery and, the most concerning, fetal death. For the mother it seems to increase the risk for progression to chronic disease. The damage to the fetus seems to occur by direct inflammatory damage to the placenta and direct infection of fetal organs.

Given the global distribution of Q fever and ongoing high endemicity in many countries, the paucity of studies and robust data on Q fever in pregnancy is surprising. We propose several topics for future research in Table 3.

Transparency declaration

The authors have stated that there are no conflicts of interest.

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