Reevaluation of the Risk of Fetal Death and Malformation After Q Fever

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A meta-analysis of 136 Q fever pregnancies, including 4 new cases and 7 population-based serological studies, revealed significant increases in fetal death and malformation after Q fever during pregnancy. This poor obstetric outcome is prevented by antibiotic treatment.

Keywords. Q fever; Coxiella burnetii; pregnancy; fetal death; fetal malformation.

Q fever is a zoonosis caused by the bacterium Coxiella burnetii and is associated with epizootic abortion in ungulates. In humans, the role of Q fever during pregnancy has been recently questioned because of the discrepancy between the high risk of obstetric complications among women infected with Q fever in published case series [1, 2] and the absence of increased risk of adverse pregnancy outcomes in population-based serological studies [3–6]. To elucidate the role of Q fever in fetal death and malformation, we cultured the bacterium from a new malformed aborted fetus. We performed a meta-analysis to study the links between Q fever and fetal death and malformation and analyzed study design bias by comparing clinical case series and population-based serological studies. We also examined research center bias using subgroup analyses differentiating studies from our and other centers.

METHODS

A literature search, unrestricted by date or language, was performed using PubMed, Google, and Google Scholar with the following keywords: human, Coxiella burnetii, Q fever, pregnancy, pregnant, fetal death, abortion, and fetal malformation.

Clinical Case Series of Q Fever During Pregnancy

A clinical case was defined as an infection diagnosed by a medical doctor. Women were considered to be “treated” if they received at least 1 of the following antibiotics: cotrimoxazole, tetracyclines, macrolides, or fluoroquinolones. Fetal death was defined as the sum of spontaneous abortions, stillbirths, intrauterine fetal deaths, and deaths in the hours following delivery. Fetal malformations were defined according to the International Clearinghouse for Birth Defect Surveillance and Research [7]. Fetal death rates were compared with the rate in the general population estimated by the largest existing population-based study [8]. Fetal malformations were compared with 2 French registries [7]. The cumulative incidence ratios were estimated by age-controlled Mantel-Haenszel stratification using Stata statistical software, version 12 (StataCorp, College Station, Texas). The cumulative incidence ratio of fetal malformation was computed without age stratification because of the low number of cases. Meta-analysis was performed with the Mantel-Haenszel method and a random-effects model using Review Manager version 5.2 (Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was assessed using I2 analysis. Publication bias was estimated by funnel plot, Egger regression intercept, and Duval and Tweedie trim and fill analyses.

Population-Based Serological Studies

Population-based serological studies were defined as studies in which an investigator screened sera from pregnant women for C. burnetii–positive serology (using investigator-defined criteria) and evaluated the results for an association with fetal death. A meta-analysis was performed as described above. Study design bias was tested by comparing the summary odds ratios of the association between Q fever and fetal death in both clinical case series and population-based serological studies. The methods are described in further detail in the Supplementary Data.

RESULTS

In April 2012, a 20-year-old woman presented with fever, cough, and flu-like symptoms. A 6-week pregnancy was
Figure 1. Q fever and pregnancy. A, Significantly increased fetal death rate was found in untreated Q fever inside (62%; odds ratio [OR], 12.7; *P* < .00001) or outside (35%; OR, 4.22; *P* = .007) the French national referral center (NRC) for Q fever vs the general population (11%) [8]. The difference was not significant between our center and the other centers (*P* = .16). aData from the largest population-based study published to date have been considered as the reference (104 840 fetal deaths for 914 485 pregnancies [11%]) [8]. bIncluding 1 untreated case from the 2 cases reported by Marrie et al [9]. B, Antibiotic treatment significantly reduces the death rate when administered to pregnant women with Q fever inside (OR, 0.15) or outside (OR, 0.10) the French national referral center for Q fever.
diagnosed serendipitously. Two months later, an anterior wall-closing defect was observed in the fetus, whereas the mother was completely asymptomatic. Amniocentesis identified a normal karyotype. At 18 weeks of pregnancy, serology was positive for Q fever, and cotrimoxazole was prescribed. However, the patient experienced spontaneous abortion just before the initiation of treatment. Analysis of the fetus revealed a large omphalocele containing the liver and small bowel, along with adrenal hypoplasia. Placental examination revealed ischemic lesions with acute intervillitis and microabscesses. The placenta and fetus were positive for *C. burnetii*–specific polymerase chain reaction; the bacterium was isolated from the placenta (minimal inhibitory concentration of 0.25 g/L for doxycycline), and the strain was sequenced (NCBI BioProject: PRJEB4272).

Analysis of all published cases and 4 new cases diagnosed in our center identified 136 relevant cases of pregnant women with Q fever in 10 case series and 13 case reports. Controlling for age, the fetal death rate in the untreated Q fever population was higher than that in the general population (cumulative incidence ratio of 3.9; 95% confidence interval [CI], 3.2–4.8; *P* < .001), but no significant difference was observed between the treated Q fever population and the general population (cumulative incidence ratio = 1.2; 95% CI, .7–2.1; *P* = .48). Among the 136 cases, 7 (5%) malformed fetuses were observed including hypospadias (2 cases, 1 associated with hydrocele), Potter syndrome with bilateral agenesis (1), congenital hydronephrosis (1), syndactyly (1), and the case described in the present study. Nielsen et al observed a severely malformed fetus, but details were not provided. The cumulative incidence ratio of fetal malformations for Q fever patients compared with the general population was estimated as 16.1 (95% CI, 6.1–42.7; *P* = .0001).

Meta-analysis also revealed a significant increase in the fetal death rate in untreated Q fever pregnancies compared with pregnancies in the general population (53% and 11%, respectively; odds ratio [OR], 8.6; 95% CI, 4.2–17.6; *P* < .0001; *I*² = 32%; Figure 1A). After the exclusion of 1 outlier [1], this increase remained significant, and publication bias was unlikely (Egger test, *P* = .35). Based on Duval and Tweedie trim and fill analysis, 1 study was added, resulting in a similar increase in death rate (45%; *P* < .05). This increased fetal death rate was also observed in Q fever pregnancies diagnosed outside of our center compared with the general population (35% and 11%, respectively; OR, 4.2; 95% CI, 1.5–12.0; *P* = .007; *I*² = 0%).

The preventive effects of antibiotics on fetal death in Q fever during pregnancy were consistent in case series published by our center (OR, 0.15; 95% CI, .05–.46; *P* = .001; *I*² = 2%) and by other centers (OR, 0.10; 95% CI, .01–1.05; *P* = .05; *I*² = 0%, Figure 1B). Publication bias was unlikely based on analyses including funnel plot, Egger test (*P* = .66), and Duval and Tweedie trim and fill procedure.

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**C Positive Coxiella burnetii serology and fetal death**

<table>
<thead>
<tr>
<th>Outside the French NRC for Q fever</th>
<th>Positive serology</th>
<th>Negative serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langley (Canada)</td>
<td>4 104</td>
<td>41 4483</td>
</tr>
<tr>
<td>van der Heuk (Netherlands)</td>
<td>0 49</td>
<td>24 1125</td>
</tr>
<tr>
<td>Gujada (Spain)</td>
<td>70 109</td>
<td>203 392</td>
</tr>
<tr>
<td>Niels (Denmark)</td>
<td>2 169</td>
<td>6 6937</td>
</tr>
<tr>
<td>Egy (Turkey)</td>
<td>10 12</td>
<td>26 46</td>
</tr>
<tr>
<td>Munster (Netherlands)</td>
<td>0 183</td>
<td>6 1046</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>625 7779</td>
<td>1.97 [1.22, 3.19]</td>
</tr>
</tbody>
</table>

Total events: 86 306

Heterogeneity: *I*² = 11% (*P* = .36)

Test for overall effect: *Z* = 2.76 (*P* = .006)

<table>
<thead>
<tr>
<th>French NRC for Q fever</th>
<th>Positive serology</th>
<th>Negative serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rey (France)</td>
<td>2 16</td>
<td>736 9493</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>16 9493</td>
<td>1.70 [39, 7.49]</td>
</tr>
</tbody>
</table>

Total events: 2 736

Heterogeneity: Not applicable

Test for overall effect: *Z* = 0.70 (*P* = .48)

<table>
<thead>
<tr>
<th>Total (95% CI)</th>
<th>Positive serology</th>
<th>Negative serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>641 17272</td>
<td>1.89 [1.31, 2.72]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 88 1042

Heterogeneity: *I*² = 0% (*P* = .47)

Test for overall effect: *Z* = 3.42 (*P* = .0006)

Test for subgroup differences: *I*² = 0% (*P* = .85)
The association between *C. burnetii*–positive serology and fetal death was analyzed in 7 population-based serological studies and 17,913 pregnancies after the exclusion of 1 outlier [10] ($I^2$ decreased from 47% to 0%). Significant associations were observed between *C. burnetii*–positive serology and fetal death both with (OR, 1.9; 95% CI, 1.3–2.7; P = .0006) and without the only study from our center (OR, 2.0; 95% CI, 1.2–3.2; P = .006; Figure 1C). Publication bias was unlikely based on Egger test ($P = .9$) and Duval and Tweedie trim and fill procedure. Overall, the risk of fetal death was significantly higher ($P < .05$) in Q fever case series (OR, 8.6; 95% CI, 4.2–17.6) than in seropositive pregnant women screened in population-based studies (OR, 1.9; 95% CI, 1.3–2.7). The results are described in further detail in the Supplementary Data.

**DISCUSSION**

*Coxiella burnetii* infection during pregnancy is a cause of poor obstetric prognosis based on the Bradford Hill criteria, including a 4- and 16-fold increased risk for fetal death and birth defects, respectively, and because fetal death has been observed in at least 7 different countries for >30 years. A temporal effect was observed because the prognosis is worse when the infection occurred in the first trimester, as in our case. The specificity of the disease and the underlying mechanism are supported by the typical placentitis aspects, including chronic intervillositis and microthrombus. Antiphospholipid antibodies, which are a key pathogenic factor in Q fever endocarditis [11] and are associated with early abortion [12], may also play a critical role in first-trimester fetal deaths. As seen in our patient, fetal infection might play a role in malformation and have an effect later in pregnancy. The biological gradient and reversibility of the disease are supported by the effectiveness of antibiotics. The fetal death and malformation data in animals meet the experimental criteria [13]. Finally, the consistency between current epidemiologic results and analysis of the fetus in this study is the strongest argument for a causal link between *C. burnetii* maternal infection and fetal death and malformation.

The absence of evidence of increased risk of abortion among women from the Netherlands [3, 4] or Denmark [5, 6] with *C. burnetii*–positive serology may be due to strain specificity, a bias in reporting or, most likely, study design (as shown in this study). Notably, the same group studying the same population observed no increased risk of adverse pregnancy outcomes in population-based serological studies [5, 6] but observed poor obstetric outcomes in Q fever case series [2, 14]. Although there is a risk of overrepresentation of pregnant women experiencing fetal death or malformations, 70% of the cases are from France, where Q fever screening in pregnant women (irrespective of problems during pregnancy) is more frequently performed on women living in at-risk areas. Therefore, the overrepresentation remains low and is less likely to affect estimates of the association of Q fever and pregnancy outcomes.

Therefore, it might be reasonable to screen all pregnant women who consult a doctor in endemic areas and to treat all pregnant women who have *C. burnetii*–positive serologies indicating either primary infection (immunoglobulin G [IgG] titers ≥200 and immunoglobulin M [IgM] titers ≥50 in phase II) or persistent infection (phase I IgG titers ≥800).

**Supplementary Data**

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**