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**WADDLIA CHONDROPHILA: FROM BOVINE ABORTION TO HUMAN
MISCARRIAGE**

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RUNNING TITLE

Bovine *Waddlia* and human miscarriage

CORRESPONDANCE

TO THE EDITOR - Miscarriage is the most common complication of pregnancy affecting every fourth woman during her life [1]. Despite thorough investigations, an etiology is only elucidated in 50% of cases. A recent serological study has suggested a role of *Waddlia chondrophila*, a strict intracellular bacteria belonging to the *Chlamydiales* order, in human miscarriage [2]. Thus, 96 out of 438 women exhibited an anti-*Waddlia* IgG titer $\geq 1/64$. This seroprevalence was significantly higher in patients with miscarriage (32%) as compared to control women with an uneventful pregnancy (7%, $p < 0.001$). Anti-*Waddlia* antibodies were specific as they did not cross-react with antibodies directed against other *Chlamydiaceae* (i.e. *Chlamydia trachomatis*, *C. pneumoniae* and *C. psittaci*) or other intracellular bacteria such as *Rickettsia*, *Coxiella*, *Wolbachia*, and *Anaplasma* [2–4]. Moreover, the strong statistical association between miscarriage and IgG reactivity against *Waddlia* remained when adjusted for possible confounding factors in various multivariate logistic regression models [2]. However, direct demonstration of *Waddlia* in human placenta has not yet been reported. We thus investigated the role of *Waddlia* in human miscarriage prospectively as part of an ongoing study. This study has been approved by the local ethical committee (No. ref. 138/06). We herein document the first case of *Waddlia*-associated miscarriage by demonstrating the direct presence of *Waddlia* in the cervico-vaginal secretion and in the placenta by PCR and immunohistochemistry.

After a normal pregnancy and a first early miscarriage, a 34-years old woman presented with a second miscarriage at week 10 of gestation. The caucasian patient did not report any prior medical or surgical history. She did not have pets, nor contact with animals and did not live in a rural area. The patient underwent a dilatation and curettage, during which retained products of conception, serum and cervico-vaginal swab were collected. Post-operative follow-up was uneventful.

Immunofluorescence was performed as previously described [2] and showed a positive anti-*Waddlia* antibody serology (titer 1/64). In addition, DNA of *Waddlia* was amplified from the cervico-vaginal swab using a *Waddlia* specific real-time PCR [5]. The patient had neither *Chlamydia trachomatis* positive serology nor DNA in cervico-vaginal swab. Placental histology showed the presence of numerous polymorphonuclear cells in the fibrin of the decidua compatible with an early infection (Figure 1A). Moreover, *Waddlia*-immunohistochemistry showed the presence of *Waddlia* infected cells localised in the glandular epithelium (Figure 1B, C and D).

We thus show here strong evidence of human infection with *Waddlia chondrophila*. Indeed, *Waddlia* infection was documented by serology, by PCR and by immunohistochemistry. The latter test confirmed the presence of *Waddlia* in the placenta in area exhibiting signs of recent infection.

Animals are an important infection source and reservoir of emerging human pathogens. *Waddlia* was first identified in bovine abortion [1,3,4]. Other zoonotic pathogens, such as *Toxoplasma gondii*, *Chlamydophila abortus*, *Coxiella burnetti*, are well-known agents of adverse human pregnancy outcomes. Whether human infection with *Waddlia* occurs through contact to animal is still questionable. In the present case, the patient did not have any contact to animals. But transmission might also occur through ingestion of contaminated milk or meat. Since *Waddlia* has also been recovered in the vaginal and respiratory tract area of humans [5], human-to-human transmission is also possible. The high *Waddlia* seroprevalence in women suffering from miscarriage [2] makes further investigations urgently necessary to explore the role of *Waddlia* in this setting. This first report of *Waddlia* in miscarriage might give new insight in the prevention and investigation of miscarriage, the most frequent complication of human pregnancy.

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CONFLICT OF INTERESTS

There are no conflicts of interest.

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FIGURE

(A) Haematoxylin and eosin stained histological sections of the placenta (Magnification 200x). (B, C and D) Immunohistochemistry (Magnification 200x for B, 400x for C and D) using a specific rabbit polyclonal antibody (dilution of 1:12,000) to investigate for the presence of *Waddlia* in the placenta. Detection was performed with the detection Kit (Dako ChemMate, Dako, Glostrup, Denmark) according to the manufacturer's instructions. Histological picture (A) shows infiltration of the placenta with numerous polymorphonuclear cells compatible with early infection. Immunohistochemistry (B, C and D) demonstrated the presence of *Waddlia* in epithelial cells of the endometrial glands.

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Figure

