

# Intracellular bacteria and adverse pregnancy outcomes

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## Abstract

This review considers the role of intracellular bacteria in adverse pregnancy outcomes, such as miscarriage, stillbirths, and preterm labour. The cause of miscarriage, stillbirth and preterm labour often remains unexplained. Intracellular bacteria that grow either poorly or not at all on media used routinely to detect human pathogens could be the aetiological agents of these obstetric conditions. For example, *Listeria monocytogenes* and *Coxiella burnetti* are intracellular bacteria that have a predilection for the fetomaternal unit and may induce fatal disease in the mother and/or fetus. Both are important foodborne or zoonotic pathogens in pregnancy. Preventive measures, diagnostic tools and treatment will be reviewed. Moreover, we will also address the importance in adverse pregnancy outcomes of other intracellular bacteria, including *Brucella abortus* and various members of the order *Chlamydiales*. Indeed, there is growing evidence that *Chlamydia trachomatis*, *Chlamydia abortus* and *Chlamydia pneumoniae* infections may also result in adverse pregnancy outcomes in humans and/or animals. Moreover, newly discovered *Chlamydia*-like organisms have recently emerged as new pathogens of both animals and humans. For example, *Waddlia chondrophila*, a *Chlamydia*-related bacterium isolated from aborted bovine fetuses, has also been implicated in human miscarriages. Future research should help us to better understand the pathophysiology of adverse pregnancy outcomes caused by intracellular bacteria and to determine the precise mode of transmission of newly identified bacteria, such as *Waddlia* and *Parachlamydia*. These emerging pathogens may represent the tip of the iceberg of a large number of as yet unknown intracellular pathogenic agents.

**Keywords:** Fetal loss, intracellular bacteria, miscarriage, pregnancy, preterm labour

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## Introduction

There is accumulating epidemiological and experimental evidence that maternal infection is a significant risk factor for adverse pregnancy outcomes. Untreated infection may cause miscarriage, stillbirth and preterm labour by several mechanisms, including direct fetal infection, placental damage, and severe maternal illness. In many instances, however, no pathogens are identified, despite increases in the levels of inflammatory markers in the mother or histological evidence of chorioamnionitis. Intracellular bacteria, which do not grow on media that are used routinely to detect human pathogens from clinical samples, could be the aetiological agents of these obstetric complications.

The effects of several human infections with intracellular bacteria on the outcome of pregnancy have been recognized for many years. Indeed, *Listeria monocytogenes*, *Coxiella burnetti* and *Chlamydia* species are known agents of adverse pregnancy outcomes. However, owing to their fastidious growth requirements, their role probably remains largely underestimated. With the increased availability of modern diagnostics and rigorous screening, a higher proportion of agents may now be detected during pregnancy. Moreover, much of what is known about the pathogenesis of these intracellular microorganisms has emerged within the past few years as a result of improved molecular-based tools being available for their detection.

**TABLE 1. Epidemiology, clinical presentation, diagnosis and treatment of intracellular bacteria that are potentially implicated in miscarriage**

	<i>Listeria monocytogenes</i>	<i>Coxiella burnetii</i>	<i>Chlamydia trachomatis</i>	<i>Chlamydia pneumoniae</i>	<i>Waddlia chondrophila</i>	<i>Parachlamydia acanthamoebae</i>
Zoonotic potential from:	+ Ruminants Foodborne Soil, vegetables, milk	+ Placenta from ruminants (pets) Aerosols Between pregnant women Stillbirth and spontaneous abortion	- Sexually transmitted disease (vertical transmission)	- Aerosols	+ Ruminants? Pets? Aerosols? Water? Food? Uncooked meat? Milk?	(+) Ruminants? Pets?
Main clinical presentation in animals	Non-specific influenza-like symptoms Febrile gastroenteritis, sepsis, meningitis	Non-specific influenza-like symptoms Hepatitis or pneumonia, chronic Q-fever (endocarditis)	Urethritis, cervicitis and PID	Respiratory tract infections	Abortion	Abortion
Main clinical presentation in humans	Miscarriage, stillbirth Premature labour Granulomatosis infantiseptica	Spontaneous abortion, IUGR, stillbirth, premature labour			?	Respiratory tract infections
Clinical presentation during pregnancy			Miscarriage Premature labour	Pre-eclampsia, IUGR, peripartum cardiomyopathy	Miscarriage Premature labour	Miscarriage Premature labour IUGR
Diagnostic tests						
PCR	(+)	+	+	(+)	+	+
Serology			(+)	(+)		
Culture			(+)	(+)	(+)	(+)
Treatment during pregnancy	+ Ampicillin	Co-trimoxazole (azithromycin, erythromycin)	Azithromycin	Azithromycin	Azithromycin	Azithromycin

IUGR, intrauterine growth restriction; PID, pelvic inflammatory disease.  
+ gold standard; (+) possible diagnostic test, but not considered as gold standard.

We will first describe well-known intracellular infections during pregnancy, such as those caused by *L. monocytogenes*, *C. burnetii* and *Chlamydia* species, and then summarize current knowledge on the role of *Chlamydia*-like pathogens during pregnancy. This review will focus on the epidemiology, pathogenesis, zoonotic potential and mode of transmission of all of these intracellular bacteria (Table 1).

## Listeria

*L. monocytogenes* is a small, facultative, intracellular, Gram-positive bacterium. The bacterium is particularly successful in causing foodborne diseases, because it can continue to slowly multiply even in properly refrigerated foods. *Listeria* infects many types of animal, especially ruminants, and is thus an important cause of zoonoses. However, soil, vegetables and milk may also be contaminated. In recent years, an increasing rate of listeriosis has been reported [1,2]. Whereas much has now been learned about outbreaks of listeriosis, sporadic listeriosis still represents the majority of cases.

The rate of infection is highest among neonates, adults >60 years of age, immunocompromised patients and pregnant women. Pregnant women account for 27% of all cases, and 60% of cases occur among 10–40-year-olds. Moreover, pregnant women have a 20-fold increased risk of developing diseases as compared with the general population [3,4], indicating that pregnancy may constitute a risk factor for the acquisition of listeriosis. In contrast to the other groups at risk cited above, pregnant women rarely present with gastroenteritis or meningitis. However, more than 30% of infections during pregnancy result in miscarriage, stillbirth or premature labour [5]. Most maternal infections occur following ingestion of the organism in food during the third trimester of pregnancy, when maternal T-cell immunity is most impaired [4]. Alkalinization of the stomach by antacids or iron supplements [6], which are frequently prescribed during pregnancy, promotes infection. *Listeria* crosses the mucosal barrier of the intestine to disseminate haematogenously to any site, with a unique tendency to infect the fetoplacental unit. Bacteraemia generally manifests clinically as non-specific influenza-like symptoms, and may remain asymptomatic. The fetus may be stillborn or die within hours of a disseminated form of listerial infection known as granulomatosis infantiseptica, which is characterized by the widespread presence of microabscesses and granulomas. The highest concentrations of bacteria are found in the lung and gut, suggesting that infection is acquired *in utero* via inhalation of infected amniotic fluid.

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