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Brucella Infection Mechanisms Responsible for Abortion in Pregnant Women

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Abstract

Brucella spp,. is a Gram-negative bacteria responsible for the disease brucellosis. It is currently known that this disease also causes abortion in domestic animals and women. The pathogenesis of the disease in women has not yet been correctly determined; various studies point to trophoblasts as the main cell affected by the bacteria, which triggers an entire process that culminates in the characteristic clinical sign of the disease.

Keywords: Brucella, Brucellosis, Abortion, woman, Pregnancy, Trophoblasts

Abbreviations: TC: Trophoblasts Cytotrophoblast; EVT: Extravillous Cytotrophoblast; ST: Syncytiotrophoblast; CTB: Cytotrophoblasts; SYN: Syncytiotrophoblasts

Introduction

The genus Brucella is responsible for brucellosis, a severe febrile zoonotic disease. Brucellosis is a global problem, causing abortion and infertility in domestic and wild animals [1]. Brucellosis can also be a

cause of abortion in humans, although the incidence of this complication varies widely between studies, ranging between 7% and 40% [2]. Cases of brucellosis in pregnant women have been underestimated since the first cases were reported in the first decade of the 1900s, but recent epidemiological studies describe greater risks of adverse obstetric outcomes such as premature birth, spontaneous abortion, fetal death or undercarriage birth weight [3].

Within the first weeks of pregnancy, the human placenta generates epithelial trophoblast with various biological functions, including attachment of the conceptus to the uterine wall, establishment of early histiotrophic nutrition (nutrition of the fetus by decidual glandular secretions), and adaptation of the maternal uterine vasculature (Figure. 1) [4]. In the human placenta, there are three main subpopulations of trophoblasts: the cytotrophoblast (TC), the extravillous cytotrophoblast (EVT), and the syncytiotrophoblast (ST) [5].

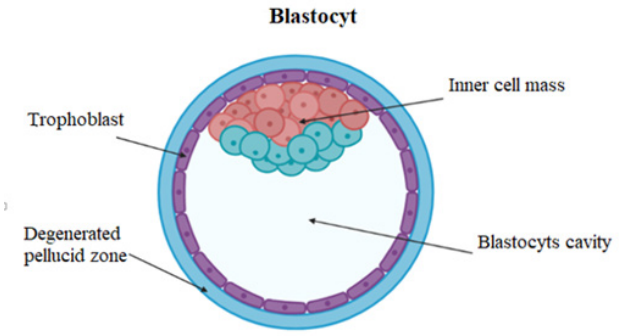

Figure 1: Scheme of a blastocyst. Within the structure is the trophoblast. Illustration created by Biorender. Courtesy by Olaf Rodríguez Pérez and Claudia Mancilla Simbro.

Brucella Pathology in Women

Nowadays, it has not been possible to know in detail the pathophysiology of brucellar abortion, however, studies carried out in animals have found clues to understand the mechanism. A characteristic of the pathogen is its ability to replicate within host cells, specifically within fetally derived trophoblasts [6]. Pioneering studies in ruminants showed that the bacteria first infect specialized placental cells called trophoblasts and then spread to other cells and the fetus. Trophoblasts are cells derived from the fetus that form the outer layer of the blastocyst and play an important role in embryo implantation and interaction with the maternal uterus [3]. Bacterial replication within these cells induces inflammatory cell infiltration, trophoblastic necrosis, vasculitis, and ulceration of the chorioallantoic membrane, ultimately leading to abortion [2]. The Brucella strains of greatest interest in these cases are Brucella abortus, Brucella *melitensis* and Brucella papionis. Experiments carried out at the laboratory level have described the mechanism by which these strains affect the organism through trophoblasts.

Studies Related to The Mechanism of Action of Brucella Spp., In Human Trophoblasts

The first study by García-Méndez et al. (2019) was carried out with the B. *melitensis* and B. *papionis* strains where the latter demonstrated activity on epithelial-type cytotrophoblasts (CTB), multinucleated syncytiotrophoblasts (SYN) or extravillous trophoblasts (EVT). These three structures are related since they have the function of exchanging oxygen and nutrients with maternal blood, and remodeling the tissues of the uterus and the vasculature that is required to anchor the placenta and supply blood to the fetus. These trophoblastic functions are well controlled and a defect in these can result in complications during pregnancy and precisely in these three structures is CD98hc, which is a surface glycoprotein that modulates the transport of amino acids, the regularization of integrin-dependent signaling and cell fusion [7].

The results indicate that B. *papionis* can infect human CTB, EVT, and SYN. However, they actively replicate in CTB and SYN, while their replication is highly restricted within EVT. Infection with B. *papionis* or B. *melitensis* was also observed to affect the levels of the eukaryotic CD98hc protein and some trophoblastic functions: the invasion capacity of EVT, the ability of CTB to form SYN, and the production of several pregnancy-related hormones.

The second study carried out by Fernández et al (2016) used the human trophoblast cell line Swan-71 and the Brucella abortus strain with the justification of the results expressed in other investigations that determined that the exposure of the human trophoblast cell line with different agents etiologies such as E. coli, Staphylococcus aureus or S. agalactiae resulted in increased secretion of tumor necrosis factor α (TNF-α) and IL8. The result showed that Brucella abortus invades and replicates in the human trophoblastic cell line Swan-71 and that the intracellular survival of the bacteria depends on a functional virB operon.

Infection caused significant increases in interleukin 8 (IL8), monocyte chemotactic protein 1 (MCP-1), and IL6 secretion, but the levels of IL1beta and tumor necrosis factor alpha (TNF-alpha) did not change significantly. These results suggest that human trophoblasts may provide a local inflammatory environment during B. abortus infections, either through a direct response to the pathogen or through interactions with monocytes/macrophages or neutrophils, which could contribute to complications of the brucellosis pregnancy.

Discussion and Conclusion

Brucellosis in humans has become a public health problem where the population of pregnant women is also vulnerable to the disease. The results of the studies emphasize the importance of trophoblasts for the survival and replication of the disease, which leads to serious consequences for the woman and the fetus. Although there are preventive vaccines in animals, there is no vaccine or effective treatment for human beings, so the only way to avoid the disease is to establish preventive policies that guarantee good health for animals so that they do not reach infect people.

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