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INFECTIOUS DISEASE: MINIREVIEW

Ovine Toxoplasmosis: A New Look at its Pathogenesis

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Summary

Conditions causing reproductive failure are a significant concern in the livestock industry, and amongst these, ovine toxoplasmosis is one of the most important. Despite decades of research, there remain gaps in knowledge about this disease, especially regarding the pathogenesis of abortion in sheep. As for other diseases causing ovine abortion, such as chlamydial abortion or border disease, the consequences of infection with *Toxoplasma gondii* depend largely on the stage of gestation, but the mechanisms involved are not well understood. Immunological modulation occurring during gestation has been proposed as the main mechanism accounting for this clinical variation. However, the extent and effect of such modulation has not yet been identified clearly in sheep and the involvement of other unknown factors has been proposed. Recent experimental studies have defined an unacknowledged clinical presentation of ovine toxoplasmosis, where abortions occur during the acute phase of infection, resulting in as high as 100% fetal loss in susceptible sheep. The pathogenesis of this clinical form differs from that of classically described ovine toxoplasmosis, and its pathological features resemble those of the perinatal syndrome known as cerebral palsy in man. A range of variables, including individual susceptibility, isolate virulence and infective dose, have been proposed as key factors in the development of one or the other of these clinical forms and warrants further investigation in this important disease.

Keywords: abortion; pathology; sheep; *Toxoplasma gondii*

Introduction

Toxoplasma gondii is an important zoonosis as well as being one of the major causes of abortion in sheep worldwide. Although the aetiological agent *T. gondii* has been known for more than 100 years, there are still gaps in knowledge of its pathogenesis. In most cases, sheep become infected through the ingestion of *Toxoplasma* spp. oocysts that were shed by cats. For abortion to occur, infection must be initiated in a susceptible sheep during gestation; however, the stage of gestation determines the outcome of the infection. Ingestion of oocysts in early pregnancy poses the greatest danger for the fetus, while infection in late pregnancy favours vertical transmission to the fetus and the delivery of weak or even clinically normal live lambs.

The reason for this variation in the pathogenesis of abortion is unclear, but several hypotheses have been proposed, all of them related to the immune response of the host. Both maternal and fetal immune responses are subject to change during pregnancy, but the precise role of immunity is not known. While fetal immunocompetence evolves throughout gestation, it is not until mid-gestation onwards that more specific immune responses can be elicited. Therefore, from mid-gestation there is more control of parasite replication in fetal tissues and hence greater fetal survival. At the same time

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the maternal immune response also influences the pathogenesis of any infection. As such, it is widely accepted that the placenta is under immunomodulation during pregnancy and that local and peripheral immune responses differ at this time; however, how immunity varies during gestation and the influence of the immune response on the outcome of *T. gondii* infection remain in large part to be elucidated.

Variation in the Lesions of Toxoplasmosis

The histopathological changes in the placenta and fetal viscera instigated after *T. gondii* infection are basically the same, and comprise of non-purulent inflammation and necrosis, regardless of the period of gestation when infection occurred. However, the stage of gestation does influence the severity of these lesions and the time post infection when they appear. In the fetal viscera, infection early in gestation is associated with lesions where necrosis is the main finding, while later in pregnancy, the infiltration of inflammatory cells predominates. The brain is the most frequent location of lesions, which appear as scattered foci of necrosis following infection in early pregnancy, while in infections initiated in older fetuses foci of gliosis with central areas of necrosis and occasional mineralization predominate. Skeletal muscle, heart, lung and liver are the other target locations where lesions may be found. When evaluating lesion severity, those occurring due to infection in mid-gestation are more severe in terms of size and involvement of inflammatory cells. These findings appear to be related directly to the maturation of the fetal immune system, as from mid-gestation the immune system becomes able to respond to the infection and promote a specific inflammatory reaction.

In the placenta, lesions are mainly of necrosis and the number and size of lesions increases as gestation advances. Infection in early gestation causes necrotic lesions affecting the caruncular septa and there is an increase in the number of inflammatory cells, mainly macrophages and lymphocytes, in the fetal villi adjacent to the lesions. Infection later in gestation is associated with greater damage to the placenta, which shows more frequent and more extensive necrotic foci involving both maternal and fetal tissues. There is also a greater inflammatory component, which is mainly mononuclear and more evident in the fetal villi, but also includes scant neutrophils in maternal tissue. These lesions are usually appreciable grossly as multiple white foci in the cotyledons. Inflammation in the maternal compartment of the placenta is largely similar during the different stages of gestation, and is not the main pathological feature. In the fetal part of the placenta, the infiltration of inflammatory cells is greater in late gestation than in mid-gestation and very scant in early pregnancy, as is the case in the fetal viscera.

Pathogenesis of the Lesions of Toxoplasmosis

The precise mechanisms responsible for the lesions in the placenta and fetus are not fully understood. The number of organisms in relation to the extent of the necrotic foci does not appear to be sufficient to be a direct cause of necrosis, especially in early gestation, when the infiltration of inflammatory cells and parasite burden are lowest. On the other hand, in-vitro studies with *T. gondii* show that it induces cellular death in trophoblast cell cultures. Surprisingly, shortly after infection, only the non-parasitized cells of the culture die, as trophoblasts with parasitophorous vacuoles appear to be protected against apoptosis. The precise mechanism of this *T. gondii*-induced paracrine cellular toxicity is not known, but it might contribute to an explanation of the pathogenesis of the necrotic lesions found in the placenta and fetus.

Maternal and fetal immune responses to the infection are the other key players in its outcome, and the influence of stage of gestation is also crucial. The maturation of the fetal immune system from mid-gestation contributes to control of multiplication of the parasite in the fetal viscera and explains the increased number of inflammatory cells as the main component of the lesions at this stage of pregnancy. While this influence on the pathogenesis of toxoplasmosis is generally accepted, the role and modulation of the maternal immune response during gestation is a more controversial issue, not only in toxoplasmosis, but in other infections occurring during pregnancy. The T helper (Th)1/Th2 paradigm of immunoregulation by $CD4^+$ Th lymphocytes, which has been used to explain a shift towards Th2 immunity in the maternal immune response from mid-pregnancy, has been under reappraisal in recent years, as it fails to explain several immunological aspects of gestation, such as the role of innate immunity or the role of Th1-derived cytokines and/or cells in supporting gestation. Previous studies in sheep have shown that there are no clear differences in the peripheral mitogen-driven or antigen-specific cytokine response during gestation. However, it appears clear that for ovine toxoplasmosis at least, there is variation in the maternal response to infection depending on the stage of pregnancy. These differences can be observed at the peripheral level, with levels of interferon (IFN)-γ that are greater in maternal serum after infection in early gestation compared with in mid- or late-gestation, or higher rectal temperatures in sheep infected at mid-