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Review article

Vertical transmission and fetal damage in animal models of congenital toxoplasmosis: A systematic review

José Antonio Vargas-Villavicencio, Alejandro Besné-Mérida, Dolores Correa*

Lab. de Inmunología Experimental, Instituto Nacional de Pediatría, SSa. Torre de Investigación, Av. Insurgentes Sur 3700-C, Col. Insurgentes Cuicuilco, Ciudad de México 04530, Mexico

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ABSTRACT

In humans, the probability of congenital infection and fetal damage due to *Toxoplasma gondii* is dependent on the gestation period at which primary infection occurs. Many animal models have been used for vaccine, drug testing, or studies on host or parasite factors that affect transmission or fetal pathology, but few works have directly tested fetal infection and damage rates along gestation. So, the purpose of this work was to perform a systematic review of the literature to determine if there is a model which reflects these changes as they occur in humans. We looked for papers appearing between 1970 and 2014 in major databases like Medline and Scopus, as well as gray literature. From almost 11,000 citations obtained, only 49 papers fulfilled the criteria of having data of all independent variables and at least one dependent datum for control (untreated) groups. Some interesting findings could be extracted. For example, pigs seem resistant and sheep susceptible to congenital infection. Also, oocysts cause more congenitally infected offspring than tissue cysts, bradyzoites or tachyzoites. In spite of these interesting findings, very few results on vertical transmission or fetal damage rates were similar to those described for humans and only for one of the gestation thirds, not all. Moreover, in most designs tissue cysts – with unknown number of bradyzoites – were used, so actual dose could not be established. The meta-analysis could not be performed, mainly because of great heterogeneity in experimental conditions. Nevertheless, results gathered suggest that a model could be designed to represent the increase in vertical transmission and decrease in fetal damage found in humans under natural conditions.

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1. Introduction

Congenital toxoplasmosis is an infection caused by the parasite *Toxoplasma gondii* in diverse warm-blooded animals (Ambroise-Thomas and Petersen, 2000). A key factor influencing the probability of embryo/fetus infection and clinical outcome in humans is the gestation period at which maternal challenge occurs (Dunn et al., 1999). At the beginning of pregnancy, the risk of infection is low but if it occurs, the effect on the embryo is severe, frequently causing miscarriage. Conversely, if the infection occurs during the final third of gestation, the rate of vertical transmission reaches around 72%, but the probability of fetal harm is low. Thus, most cases born with symptoms are infected during the second trimester. In Europe, where this phenomenon was observed, the predominant *T. gondii* variants are of low virulence (or "type II"). Type I or atypical strains have also been isolated from congenital toxoplasmosis cases, but they fre-

* Corresponding author.
E-mail address: mariadol@yahoo.com (D. Correa).

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quently cause severe clinical symptoms regardless of gestation period at infection (Dardé 2004; Dardé 2008; Rico-Torres et al., 2012). Thus, both parasite and host aspects are of relevance to determine outcome in terms of fetal infection and damage. To study them and their causes, it would be important to have a model that resembles the human infection as closely as possible.

Many years ago animal models of congenital toxoplasmosis were attempted and are still used for several purposes, like vaccine or drug testing. Some of them have directly assessed host factors and parasite stage, dose and type upon pathology or transmission, but very few have performed observations at different thirds of gestation.

We non-objectively observed that there were many articles using animal models of congenital toxoplasmosis including control (untreated) groups in which transmission and pathology were determined. So, we decided to perform a systematic review of the literature in order to identify the animal model that best simulates the gestation-time dependent values of vertical transmission and fetal damage observed in humans.

2. Material and methods

2.1. Data sources

Scientific publications related to animal models of congenital infection by *T. gondii*, which appeared between 1940 and 2014 were searched in indexed journals and grey literature. The consulted databases were ARTEMISA, COCHRANE, EBSCO, HERMES, ISI WEB, LILACS, OVID, PUBMED, SCIELO, SCIENCE DIRECT, SCOPUS, GOOGLE SCHOLAR, as well as digital libraries of the Universidad Nacional Autónoma de México and Instituto Politécnico Nacional, which contain the best suited books and newspaper libraries, and include pre and postgraduate theses. MeSH terms were ["*T. gondii* or toxoplasmosis or congenital toxoplasmosis"] and ["vertical transmission or fetal infection or placental infection or trophoblast infection"] and ["animal model or mouse or rat or hamster or guinea pig"]. Language was restricted to English, Spanish, French and Portuguese. A database was built-up with all references and repeated articles were eliminated. All reviewers read the titles and independently selected those that potentially were related to animal models of congenital toxoplasmosis. The summaries of those selected by at least one reviewer were analyzed by two of the readers, in order to select those that deserved full text reading; so, each reviewer read at least two thirds of summaries.

2.2. Selection criteria

Full papers were analyzed by at least two reviewers and only those which full-filled the following criteria were included in the database: each paper must have all independent variables, i.e. host species, parasite genotype (strain types I, II, and III) and stage, dose, period during gestation at which the mother was infected and infection route. Values of at least one dependent variable had to be present in a form that it could be directly taken from the article or calculated from the text, figures or tables. The variables were: number of offspring per litter, proportion of infected progeny and proportion of fetuses/newborns damaged from total infected descendants.

The fertility rate was calculated as the proportion of offspring per mother found in the document, divided by the value reported for the corresponding species, data gathered from different sources (Reinhardt, 2013; Foxcroft et al., 2006; Sanchez and Silva, 2002; Milligan et al., 2001; Harlan laboratories; University of Michigan Museum of Zoology; Taconic Biosciences; National Laboratory Animal Center, Mahidol University; Dog Breed Info Center; International Union for Conservation of Nature and Natural Resources).

In order to compare infected and damaged offspring proportions per period of pregnancy among hosts, the gestation-time of different host species was converted to thirds with the formula: day at which the mother was infected/total days of the gestation length of the specific species. The gestation length of each species was gathered from the references cited above.

3. Results

In the first search 10785 documents were gathered. After repeated papers were eliminated, 2029 items were selected, from which 293 summaries were chosen for further analysis. We chose 164 full documents, read by at least two reviewers. Only 49 papers contained all independent and at least one dependent variable to include in the final database. The meta-analysis could not be performed, basically because each model was unique in terms of design, methods of infection, diagnosis of congenital infection and damage evaluation; therefore, only descriptive findings are shown (Tables 1–4).

The results of experiments in which the mother was infected before pregnancy, are shown in Table 1. As can be seen, there is a great variability, even within works, like that published by Van der Waaij (1960), who tested several periods using the same conditions. In this table it can be seen that *Mus musculus* and *Apodemus sylvaticus* presented high transmission rates.

Results published on challenges of the first third of pregnancy are shown in Table 2. The lowest fertility values were seen in ovines, without significant alteration of this parameter in other species, regardless of parasite strain, stage or dose. In guinea pigs, the RH strain apparently infected less offspring than three type II strains: PRU, 76K and Beverly.

Table 3 shows the results on vertical transmission, fertility and fetal damage of infections of the second gestation third. As it can be seen, pigs are resistant and guinea pigs susceptible to congenital infection during this period of pregnancy in comparison to other species. Likewise, PRU but not ME49 parasites affect fertility in BALB/c and Swiss-Webster mice. On the other hand, Fischer rats infected with the PRU strain delivered a larger proportion of infected offspring than those infected with 76k parasites (64% vs 32%). The parasite stage is important in this period of gestation, since infection with oocysts induces 75–91% vertical transmission in rats, whereas cysts does it from 27 and 58%, using the type I strain CT-1.

Table 4 summarizes the results of animal models of the last third of gestation. It can be observed that the researchers focusing in this period used a great variety of designs in terms of host, parasite and dose/route.

Some articles compared more than one period of pregnancy under the same conditions: Flori et al., (2002, 2003) found larger vertical transmission rate in the second third (around 100%) as compared to the first (77%) or before pregnancy (27%) in a model of guinea pigs inoculated with cysts of the PRU (type II) strain. Likewise, Dubey et al., (1997) found a larger proportion of congenitally infected fetuses during the second third (around 60%) as compared to the first one (30%) in a model of rats inoculated with oocysts of the VEG (type III) strain. Also, Zenner et al. (1993, 1999) found great differences between pre-gestational infections and those of the second period in rats, with both with type I (RH) and type II (PRU) strains; interestingly, they found that another type II strain (76K) produced less infected offspring than the PRU (see Tables 1 and 3). Even within the second gestation period