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# Immunopathogenesis of Toxoplasmosis in Pregnancy

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ABSTRACT

**The immunopathogenesis of toxoplasmosis during pregnancy is not completely understood. This paper will try to discuss the most frequently asked questions about the immunopathogeny of congenital toxoplasmosis: differential virulence of *Toxoplasma* isolates, genetic susceptibility to infection, facilitation of placental transfer, models of congenital toxoplasmosis, and transmission in seropositive hosts. Most published data suggest a role of the genetic background of the host and of the parasite. Models of congenital toxoplasmosis have been evaluated, but it appears that the conclusion drawn would be barely appropriate to understand the pathogenesis in pregnant women. Infect. Dis. Obstet. Gynecol. 5:121–127, 1997.** © 1997 Wiley-Liss, Inc.

KEY WORDS
*Toxoplasma gondii*, immune response, pregnancy, strains, congenital

Toxoplasmosis is a parasitic infection caused by the protozoan *Toxoplasma gondii* that, when contracted by a pregnant woman, can pose a serious risk to her unborn baby. Fortunately, a pregnant woman can follow some simple precautions that can reduce her risk of infection. A pregnant woman who contracts toxoplasmosis for the first time during pregnancy has about a 30 percent chance of passing the infection on to her fetus.[1] However, the risk and severity of the baby's infection depend partly on the timing of the mother's infection. Studies suggest that, when mothers are infected in the first trimester, 14 percent of fetuses become infected, as compared to 29 percent in the second trimester and 59 percent in the third.[2] Babies whose mothers had toxoplasmosis in the first trimester usually have the most severe infections. If no screening program is carried out, most infected babies appear normal at birth. However, most of them will develop sight-threatening eye infections months to years after birth. Some also will develop hydrocephalus, mental retardation, learning disabilities or seizures. Toxoplasmosis during pregnancy also can result in miscarriage or stillbirth. Other infected babies have a severe *Toxoplasma* infection that is evident at birth with severe eye infections, hepatosplenomegaly, icterus and hydrocephalus.[3]

The parasite is most often picked up through exposure to cat feces or by eating raw or undercooked meat that is contaminated with the parasite. Cats often become infected when they eat an infected rodent or bird. The parasite reproduces in the cat's intestine, and a form of the parasite (oocysts) ends up in the cat's litter box, sand or soil. This form of the parasite becomes infectious within days and is resistant to most disinfectants. Under the right temperature and humidity conditions, the parasite may live in soil for more than a year. Infected cats usually appear healthy.

Toxoplasmosis is one of the most common infections in the world as proven by the high prevalence of antibodies in the adult population, although there are important geographic discrepancies.[1] Most cases of toxoplasmosis are undiagnosed. Symptoms, if any, tend to resemble flu. Active infection normally occurs only once in a lifetime. Although the parasite remains in the body indefinitely, it is generally harmless and inactive unless the immune system is not functioning properly. If

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a woman develops immunity to the infection before pregnancy, there is rarely any danger of passing it on to her baby (see general information at http://babynet.ddwi.com/tlc/pregnancy/toxoplas.html).

If basic knowledge concerning the biology of this parasite or the immune response in experimental animals is important, the knowledge on the pathogenesis of congenital toxoplasmosis is relatively scarce. This paper will try to discuss the most frequently asked questions about the immunopathogeny of toxoplasmosis in pregnancy.

## ARE SOME ISOLATES OF *TOXOPLASMA GONDII* MORE VIRULENT?

*Toxoplasma gondii* was discovered at the beginning of the century in North Africa and is considered as the only representative of the genus *Toxoplasma.*

### Parasitic Stages

Three stages of the parasite can be found in infected mammals: the sporozoite, the tachyzoite and the bradyzoite. Sporozoites are liberated by the digestion of infective oocysts (result of the sexual multiplication of the parasite in the cat intestine) and will penetrate through the intestinal epithelium to infect host cells. The tachyzoite is a rapidly intracellular dividing form responsible for the acute phase of the disease and able to penetrate in practically all types of cells. The host immune response will lead to the transformation of the tachyzoites in bradyzoites. This conversion could depend on environmental triggers such as pH, temperature via induction of heat-shock proteins, anti-mitochondrial drugs, nitric oxide and TNF-alpha.[4] The bradyzoite is a slowly dividing form giving cerebral or muscular cysts and responsible for a life-long immune stimulation of the infected host. Hosts can be infected by these three parasitic stages: oocysts by contact with contaminated cat feces, tachyzoites by transplacental contamination, bradyzoites by ingestion of raw meat-containing cysts. The virulence of these stages should be similar but antigenic differences have been described.[5,6]

### Parasitic Strains

One of the characteristics of many *Toxoplasma* strains is their variation in virulence. For example the highly virulent RH strains will kill experimentally infected mice in less than a week, whereas most strains isolated from congenital cases of toxoplasmosis or animals will give a chronic disease in mice characterised by the presence of cysts in the brain. There is no correspondence between virulence in humans and virulence in mice. Analysis of different strains by isoenzymes allowed the description of at least five zymodemes.[7] Isolates highly pathogenic for mice (e.g., RH strain) belong to zymodeme 1 or 5. Isolates giving a chronic infection in mice belong to zymodeme 2 (e.g., Prugnaud, 76K, Me49, Beverley), zymodeme 3 (e.g., C56) or zymodeme 4. Isolates from human congenital toxoplasmosis belonged to the five groups.[7,8] More recent data with restriction fragment length polymorphism indicate that *Toxoplasma gondii* consists of three clonal lineages, designated I, II and III. Group I corresponds to zymodeme 1, group II to zymodemes 2 and 4, group III to zymodeme 3. More than 70% of human disease cases are associated with type II strains.[9] The type II strain would also be the most prevalent in food animals such as pigs and sheep. Acute virulence in mice is strictly observed in type I strains, indicating that a genetic determinant(s) unique to this lineage controls acute pathogenesis.[10,11]

### Strains and Congenital Infections

No link is proven between a particular type of strain and transplacental passage. However, in an experimental model in Fisher rats, Zenner et al.[12] using three different strains (RH, 76K & Prugniaud) obtained significant differences of congenital toxoplasmosis between the two strains RH and Prugniaud and strain 76K. The rates of infected fetuses were 58.2% for RH, 62.8% for Prugniaud and 35.2% for 76k, respectively. However, though having apparently different rates of placental transmission, strains 76K and Prugniaud belong to the same zymodeme. These different types of virulence could be linked to different surface receptors or antigens whose role in pathogenesis is not fully elucidated.

## ARE SOME INDIVIDUALS MORE SENSITIVE TO INFECTION?

It is well proven that different mouse strains exhibit different levels of resistance to *Toxoplasma gondii.*

### Genetic Control

Genetics of survival after oral *Toxoplasma gondii* infection were studied by using recombinant inbred strains of mice derived from resistant A/J (A) and susceptible C57BL/6J (B) progenitors, F1 progeny of crosses between A/J and C57BL/6J mice, and congenic mice (B10 background). Analysis of the pattern of survival indicated that survival was regulated by a minimum of five genes. One of these genes appears to be linked to the H-2 complex.[13,14] BALB/c mice infected intraperitoneally will have fewer brain cysts than C57/BL mice (15); B10 mice (H-2b) are cyst susceptible and B10.A mice (H-2a) are cyst resistant,[16] confirming that susceptibility to *Toxoplasma gondii* and the number of brain cysts in mice are affected by genes linked to the H-2 locus. In a study by Deckert-Schluter et al.,[17] the influence of genetic factors in congenic B10 and BALB mice of H-2q, H-2k, and H-2b haplotypes was examined following oral infection with a low-virulence strain. Whereas B10 mice were highly susceptible, BALB mice had a less severe and more protracted disease. Within the two congenic groups, the major histocompatibility complex haplotype had a strong impact on the disease. The H-2k haplotype was associated with early death in B10 mice but with a favourable outcome in BALB mice, whereas the reverse was observed for the H-2q haplotype. These findings indicate that genetically determined factors are critically involved in determining the intracerebral immune response and the course of murine toxoplasmosis, but significant differences between B10 and BALB mice point to a modulating role of additional genetic loci. Moreover, this genetic control of resistance against acute infection depends on the strain of *Toxoplasma gondii*.[18] The use of transgenic mouse models has shown that human MHC genes had a role on the number of brain cysts. Introduction of HLA-B27 into B10 mice made them more susceptible to cyst formation.[14] Interestingly, recent preliminary results have shown that in infants with severe congenital toxoplasmosis the frequency of HLA class II allele DQ3 was increased though the frequency of this allele in the mother did not differ from that in the normal population.[4] In addition, marked differences in infection patterns have been observed between dizygotic twins compared to the similar patterns between monozygotic twins.[14]

### Sex Susceptibility

Female mice were found to be more susceptible to acute infection, as determined by higher mortality levels, than male mice. Female mice surviving chronic infections harboured more cysts in their brains than did surviving males. Spleen cells from male mice produced higher levels of interferon (INF)-gamma in the early stages of infection than those from female mice.[19] Male severe combined immunodeficiency (SCID) mice were also more resistant than female mice to infection with *Toxoplasma gondii* producing interleukin (IL)-12 more rapidly and exhibiting higher levels of INF-gamma.[20] There is no data concerning differential susceptibilities to toxoplasmic infections between human males and females.

## ARE THERE FACTORS FACILITATING TRANSPLACENTAL TRANSMISSION OF *TOXOPLASMA*?

A primary infection with *Toxoplasma gondii* will induce in the infected host a humoral and cellular immune response.

### Factors Involved in the Immune Response

The acute phase of the disease is characterised in humans and mammals by a significant increase of specific IgA and IgM antibodies directed against the main major antigenic component P30 or SAG1.[21] This SAG1 has an important role in the invasion of host cells: monoclonal antibodies directed against SAG1 will block invasion,[22] the chronic stage being characterised by the presence of specific IgG. However, these circulating antibodies, witnesses of the infection, are useless to control the disease. As with most intracellular parasites, this role should be set down to cellular immunity and particularly to T cells. INF-gamma has a crucial role against this infection: mice treated by anti-INF-gamma or deficient for INF-gamma gene will die of toxoplasmosis.[23,24] The first cells to be activated are natural killer (NK) and monocytic cells which will produce INF-gamma and IL-12. IL-12 induces the lymphocyte population (CD4+ and CD8+) to a Th1 phenotype inhibiting *Toxoplasma* growth. The Th2 derived cytokines will have a counter-regulatory effect.[25]

### Influence of Pregnancy on the Immune Response

Some authors have recently shown that human placenta was escaping the maternal immune system by releasing immunosuppressive cytokines such as IL-4, IL-6 and IL-10.[26] This pattern of cytokine secretion, characteristic of a relative increase in Th2-associated immunity and decreased Th1 immunity, could facilitate the survival and/or the passage of the parasite through the placenta, but this point remains unproven for *Toxoplasma.* Candolfi et al. orally infected BALB/c mice and showed that pregnant mice had a larger lung parasite load 7 days post infection and a significantly higher number of brain cysts 30 days post infection.[27] The different patterns of cytokines described failed to explain this increase susceptibility, though high titers of the immunosuppressive IL-10 were observed. Hohlfeld et al. reported in 1990[28] the different subsets of T cells observed in infected pregnant women and their fetuses. Women infected by *Toxoplasma* during their pregnancy showed an increase of CD8 suppressor T cells and a decrease of CD4 helper T cells. These alterations were more important when the fetus was infected, suggesting that transmission could be enhanced by an impaired T cell immunity secondary to pregnancy. Interestingly, children with congenital toxoplasmosis have a specific immunological tolerance for *Toxoplasma gondii* with a selective reduction of INF-gamma production.[25]

## ARE ANIMAL MODELS USEFUL TO UNDERSTAND PATHOGENESIS OF HUMAN TOXOPLASMOSIS DURING PREGNANCY?

The human placenta structure (hemochorial) is similar to the placental structure of mice, rats, rabbits and monkeys (but different from the placental structure of dogs, cats, sheep, and pigs). Therefore, a lot of information could have been obtained from easy to handle experimental animals, but, curiously, the number of papers describing models of congenital toxoplasmosis are relatively few.

### Rodent Models

Older studies with outbred mice showed that transmission was possible through successive generations. However, studies conducted by Roberts et al.[15] with BALC/c mice demonstrated that transmission occurred only in mice infected for the first time during pregnancy. In an experimental model using orally infected Fisher rats, transmission to fetuses was only possible in rats infected for the first time.[12] These results were obtained with two different strains of *Toxoplasma* and with different modes of infection (orally and intraperitoneally).

### Primate Model

Schoondermark-Van de Ven described a very interesting rhesus monkey model of *Toxoplasma* congenital infection. Transmission to the fetus was investigated after maternal infection at day 90 or day 130 of pregnancy. A parasitemia was induced and lasted for about 10 days as proven by mouse inoculation and nested polymerase chain reaction (PCR) on blood samples. An overall transmission rate of 61% was found; this rate is similar to that found in humans.[29] A lot of interesting results were obtained on the efficacy of treatments usually prescribed in humans. Spiramycin accumulated in the soft tissues, especially in the liver and spleen, of both the mother and the fetus and was concentrated in placental tissue and in amniotic fluid.[30] In four monkeys that received treatment for about 7 weeks, the parasite was not present at birth in the placenta nor in amniotic fluid or neonatal organs.[31] Pyrimethamine and sulfadiazine was administered to six monkeys, in whose fetuses infection was diagnosed antenatally. The parasite was no longer detectable in the next consecutive amniotic fluid sample, taken 10 to 13 days after treatment was started. Furthermore, *Toxoplasma gondii* was not found in the neonate at birth. The parasite was still present at birth in three of four untreated fetuses that served as controls.[32] Immune responses (beside circulating antibodies) were not studied in these experiments.

### Absence of In Vitro Models

Important data could be obtained from in vitro models similar to what was described for malaria.[33] Cultivation of human synctiotrophoblast with *Toxoplasma* would permit the study of molecules mediating attachment and their expression in presence of different cytokines and hormones. An up-regulation of adhesion molecules has been described in the pathogenesis of murine toxoplasmic encephalitis.[34]

## CAN A SEROPOSITIVE HOST TRANSMIT *TOXOPLASMA* TO THE FETUS?

This important point has been already discussed previously in rodents where older data reported that vertical transmission through successive generations was the normal situation in outbred mice.[15] The dogma for humans (and ovids) is that only infection for the first time during pregnancy results in congenital infections. But this dogma could be run down by recent observations. Desmonts et al.[35] reported five cases of congenital toxoplasmosis consecutive to a maternal *Toxoplasma* infection that had preceded pregnancy. One woman with a normal immune system had developed a well-documented lymph node toxoplasmosis 2 months before conceiving. Four women had chronic toxoplasmosis diagnosed in the course of an immunosuppressive disease: Hodgkin's disease in one case, systemic lupus erythematosus in two cases and pancytopenia in one case. Toxoplasmosis had been recognised 3, 5 and 10 years respectively before conception in three women, and at an uncertain date in one woman. Three women had received corticosteroids during pregnancy, and two had undergone splenectomy. Among the six children (two were twins), one presented with severe fetal disease at birth, one developed lethal systemic toxoplasmosis after birth, one showed hydrocephalus with therapeutically well-controlled chorioretinitis, one had an isolated eye lesion and two had asymptomatic infection. The parasite seems to have been transmitted after the 20th week of pregnancy in all cases. Pons et al.[36] and Vogel et al.[37] reported a few years later two additional woman with normal immune systems who developed toxoplasmosis 2 months before conceiving and who transmitted the disease to their fetuses. Though Marty et al.[38] reported a case of severe fetal toxoplasmosis resulting of toxoplasmic reactivation in an human immunodeficiency virus (HIV)-1 seropositive woman, this phenomenon appears very uncommon as proven by subsequent studies in cohorts of HIV-positive pregnant women.[39,40]

### Reinfection During Pregnancy

More disturbing is the case we have recently reported.[41] This case of congenital transmission was revealed by macular chorioretinitis in a nine-month-old child and confirmed by a retrospective serological analysis of the mother's sera. This woman tested positive for anti-*Toxoplasma* antibodies at 11 weeks of amenorrhoea (moderate titers of IgG antibodies without IgM, thus reflecting an old infection). No further toxoplasmic surveillance was therefore carried out during pregnancy. At delivery, clinical examination of the newborn was normal. However, 9 months later, the child developed divergent strabismus. Ophthalmologic examination revealed a macular chorioretinitis scar, with loss of right-sided vision. Congenital toxoplasmosis was confirmed by the detection of IgM antibodies in the child's serum. As the mother took part in a hematological survey during pregnancy, stored sera were available for analysis. Reinfection during the pregnancy was strongly suggested by the emergence of IgM and IgA antibodies and a rise in IgG titers between 11 and 28 W.A. The maternal reinfection was probably linked to oocysts, as her personal diary referred to contacts with kittens on week 18 of amenorrhoea, and to a flu-like illness a week later. There were no iatrogenic or apparent pathological factors of immunodeficiency, or abnormalities in lymphocyte subsets. To our knowledge, two other similar case have been reported.[42,43] Reinfection of apparently immunocompetent women during pregnancy is fortunately uncommon, but raises the possibility that ingestion of *Toxoplasma* cysts contained in meat does not protect against reinfection by oocysts. This could be explained by the antigenic differences between sporozoites and tachyzoites described by Kasper and Ware[5] but also by strain differences. Recently Araujo et al. published evidences that chronic infection in SW mice with the ME49 *Toxoplasma gondii* strain did not prevent acute disease or colonisation of the brain after reinfection with cysts of a variant of the C56 strain resistant to atovaquone.[44]

## CONCLUSION

The immunopathogenesis of toxoplasmosis during pregnancy is not completely understood. However, most published data suggest a role of the genetic background of the host and of the parasite. Models of congenital toxoplasmosis have been evaluated, but it appears that the conclusion drawn would be barely appropriate to understand the pathogenesis in pregnant women. A lot of trials (not reviewed here) have been performed to evaluate *Toxoplasma* proteins which could be used as vaccines. Most

trials were performed with the P30 protein (SAG1) but had limited efficiency. In France, a national survey has recently shown a 54.3% prevalence of *Toxoplasma* antibodies in pregnant women, and the incidence of seroconversion in nonimmune women at the beginning of pregnancy was of 1.5%.[45] In France, a national prevention program was set up in the late seventies requiring compulsory serology before wedding and during the first trimester of pregnancy. If the serology is negative at the beginning of pregnancy, hygienic recommendations will be prescribed and the woman's serum should be checked every 3–4 weeks in order to detect a toxoplasmic infection very early. In case of a seroconversion, the fetus will be assessed regularly by echography and a prenatal diagnosis will be performed at 20–22 weeks of pregnancy. This French national prevention program could prevent 700 to 2650 cases per year of congenital toxoplasmosis with an annual cost of $30 to 60 million.

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