Maternal Fetal Paper: Toxoplasmosis

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NNP 1

GNRS 5631

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March 26, 2014

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**Introduction**

Congenital toxoplasmosis is a rare, acquired disease that may negatively impact the growth and development of the fetus. March of Dimes (2014) estimates between 400 to 4000 newborns in the United States are affected by the sequaele of congenital toxoplasmosis each year. Although infection is relatively uncommon, the implications of the disease may create life-long deficits in the neonate, particularly from a neurological stand point. This paper discusses the epidemiology, pathophysiology, and therapeutic management, social and economic impact of acquired congenital toxoplasmosis on the maturing fetus.

**Maternal Fetal Pathophysiology**

Toxoplasmosis is an intracellular parasite with a complex reproductive life that may invade multiple hosts. Sexual and asexual reproductive life cycles allow the protozoan parasite to rapidly replicate and cause infection. The various life cycles of T. gondii may be prevalent in felines, birds, rodents and humans. The protozoan parasite is described in three different stages: the oocysts, tachyzoites and bradyzoites. As the parasite matures, replication from sexual to asexual reproduction occurs as the organism modifies and becomes established. Once acquired, infection is imminent and poses a life-long threat to its host.

The first method of transmission of T. gondii to the mother involves handling contaminated cat feces. Outdoor cats who hunt are largely responsible for transmission of the disease. Infection of outdoor cats begins with preying and ingesting contaminated animal flesh, mostly from mice and birds. T. gondii encysted tissue ingested by the cat invades the intestinal walls and begins sexual reproduction of the parasite to form millions of oocysts. Upon elimination, the asymptomatic infected cat will begin to shed up to one million unsporolated oocytes in their feces, approximately one to two weeks after initial exposure. Oocysts become infectious within days to weeks and can evade drastic temperature changes for up to 18 months. An ideal climate to foster the oocyst consists of a warm, humid environment, including litter boxes, gardens and sandboxes. Poor hand hygiene from the mother may inadvertently cause ingestion of oocysts after contact with these high risk areas. Ingestion by a secondary host causes the disruption of the oocyst structure, thus dissolving the outer cell layer and releasing sporozoites to the body. Asexual reproduction effectively changes the oocyst into tachyzoites. Tachyzoites invade, replicate and destroy healthy host cells. After cell destruction, migration and wide spread distribution of tachyzoites can be identified throughout the host. Within three to ten days, tachyzoites replicate into the final stage of the disease, bradyzoites. The conversion occurs as the immune system attacks the parasite, thus causing the formation of cysts. Cysts are then deposited into the surrounding tissues. Bradyzoites are slow multiplying organisms that are deposited into brain, muscle and skeletal tissue. Their development occurs over months to years. Infection in humans is believed to remain life-long (Paquet & Yudin, 2013).

The second method of transmission of T. gondii to the pregnant mother is through consumption of undercooked meat. Because oocysts are able to withstand extreme temperatures, tissues cysts may prevail in undercooked meat products. Additionally, consuming unwashed raw vegetables or fruits from contaminated soil pose a substantial threat. Ingestion of infested meat and/or produce then allows asexual reproduction of the parasite. As asexual reproduction occurs, deposits of cysts will soon be evident in distant tissues. Pregnant mothers should be educated to consume meat and vegetable products that are well washed and cooked in order to avoid the risk of ingesting oocysts.

Cultural considerations are important factors that influence maternal lifestyle and dietary intake. In the United States, primary source of infection is related to ingestion of undercooked pork and lamb (Montoya & Remington, 2008). Statistically, infection rates from this route currently remain extremely low. Raw or undercook meats are rarely consumed in the United States as compared to European countries, mainly France and Austria. Currently, France obtains the highest infection rate of toxoplasmosis in pregnant mothers at 54 percent. Other remaining European countries have lower reported rates of infection (46 percent of pregnant women). A large portion of these rates can be attributed to cultural and dietary preference of undercooked meat (Serranti, Buonsenso & Valentini, 2011). Third world countries pose the highest risk of infection, although lack of adequate prenatal care may inadvertently skew the statistical analysis.

Transmission of toxoplasmosis gondii from mother to fetus is dependent on the timing of initial infection. The risk of mother to child transmission is only possible if the mother has acquired the infection during her current pregnancy. Infection of the fetus may occur transplacentally or during vaginal delivery. Mothers who have acquired toxoplasmosis during pregnancy may still provide expressed breast milk for their infants. Currently, no studies have confirmed a link of transmission of toxoplasmosis infection to breastfeeding (Serranti et al, 2011).

Congenital toxoplasmosis is identified once the fetus is infected with bradyzoites. Since transmission of congenital toxoplasmosis occurs only during a current pregnancy, it is rare to have a second child diagnosed with congenital toxoplasmosis. Mothers who are previously infected, prior to pregnancy are not at risk for transmission to the fetus; however, it is recommended that conception occur at least 6 months after initial infection. Rarely, cases of second congenital infection of siblings have been reported in mothers who reach immunocompromised states, i.e. acquired immune deficiency syndrome (AIDS) or who have had long term treatment with corticosteroids. Since permanent immunity is acquired after initial infection, women who later become immunocompromised may have a resurgence of active disease. Reactivation of active toxoplasmosis infection may result in a second congenital infection, mostly in individuals who are immunocompromised and pregnant (Montoya & Remington, 2008).

**Impact of the maternal condition on fetus**

Toxoplasmosis infection during pregnancy has varying effects on the growing fetus. Presentation of congenital infection may be mild or have severe impairment. A variety of clinical manifestations involve prematurity to perinatal death. The characteristic triad of congenital toxoplasmosis; chorioetinitis, hydrocephalus and cerebral calcifications, most commonly identifies the presence of active congenital disease.

The most detrimental fetal implications of congenital toxoplasmosis occur early in pregnancy, generally in the first trimester. Early gestational age transmission correlates with an increase in worsening fetal condition and subsequent prognosis. Grave implications of first trimester transmission of toxoplasmosis include miscarriage, stillbirth and/or severe neurological sequelae in the newborn. The likelihood of transmission is significantly low in the first trimester; however as gestation progresses, maternal sero-conversion and subsequent congenital infection are greatly increased. In a study conducted by Rabilloud, Wallon, & Peyron (2010), maternal infection most frequently occurred during the first trimester, then equally among the second and third trimesters. Of the children infected with congenital toxoplasmosis, seroconversion and transmission to the fetus occurred in over half of the cases during the third trimester, followed by less than a fourth in the second trimester and less than 3.5% in the first. Regardless of maternal infection acquisition, sero-conversion of the organism must occur in order for the fetus to be effected.

The triad of chorioretinitis, hydrocephalus and cerebral calcifications are characteristic features of congenital toxoplasmosis. It is estimated that one in six infected infants present with at least two of the above classic clinical manifestations, mostly involving chorioretinitis and cerebral calcifications (Cortina-Borja, Tan, Wallon, Paul, Prusa, Buffolano & Gilbert, 2010). Retinal disease may not manifest until after the first couple of months of life, but it is progressive and can persist into adulthood. The risk of chorioretinitis increases from 10 percent in infancy to approximately one third by age 12 (Mirza, 2013). Progression from a single to multiple retinochoroidal lesions in the affected eyes is expected. Periods of remission and exacerbation with retinal disease are common. Impairment of vision is permanent due to bilateral inflammation of the retina, the iris and choroid, although more than 90% of children have normal vision in their best eye. If untreated, total or partial vision loss in affected eyes is possible.

Neurological implications are extensive due to hydrocephalus and intracerebral calcifications. Intracerebral calcification should be monitored by magnetic resonance imaging (MRI) and close developmental follow up is indicated. Complications of hydrocephalus may cause early delivery and/or surgical intervention. Seizure disorders, focal neurological deficits, delayed developmental milestones and associations with severe psychiatric disorders have also been linked to congenital toxoplasmosis (Brook, 2013). Severe neurological impairments have been identified in infants whose mothers did not receive any prenatal screening or treatment. Without treatment, seroconversion from mother to child occurs at an earlier gestational age, thus worsening the prognosis by increasing the chances of abnormal fetal head ultrasounds. Infants with congenital toxoplasmosis also have an increased risk of cerebral palsy.

**Clinical Manifestations and diagnostic evaluation of the neonate**

Clinical manifestations of an active maternal Toxoplasmosis infection are misleading and frequently underdiagnosed. Up to 90 percent of women with acquired toxoplasmosis infection do not exhibit typical signs or symptoms. If at all present, clinical symptoms of active infection include low grade fever, malaise and lymphadenopathy (Paquet & Yadin, 2013). However, clinical implications of acquiring congenital toxoplasmosis encompass many fetal systems that could potentially have long term debilitating effects to the neonate. Many of these characteristics may not readily be discovered at delivery, especially if screening was not initiated. Most infants develop late manifestations months after delivery, such as chorioretinitis, seizures, mental retardations and motor or cerebellar dysfunction. Therefore, diagnosis at delivery does not always occur. Additional studies have related sensorineural hearing loss, congenital neprhosis, hematological abnormalities, hepatosplenomegaly, various endocrinopathies and myocarditis to congenital infection (Gomella, Cunningham & Eyal, 2013).

Diagnostic evaluation is imperative for early detection, prevention of transmission and if needed, treatment options. Although not routinely conducted in the United States, diagnostic testing includes obtaining maternal serum samples, conducting early fetal ultrasounds and if indicated, amniocentesis. In regions of high risk, particularly European countries, monthly maternal screenings are religiously performed. This is likely due to their cultural practices regarding food preparation and consumption. Dietary intake is a major component of maternal infection. Screening practices are exercised in order to prevent transmission to the fetus. Many European dietary and cultural implications are seldom practiced in the United States therefore routine screening is not a cost effective approach. Mothers who fall into the high risk category of obtaining toxoplasmosis should be screened to prevent congenital infection.

Serologic testing is usually the first diagnostic tool used. Serum markers identify the presence of IgG and IgM antibodies in maternal blood samples. The presence of these antibody markers in conjunction, indicate infection. Several types of testing available to detect these antibodies are the dye test, indirect florescent antibody test and enzyme immunoassay (Toxoplasma infection, 2013). IgM and IgG titers must carefully be analyzed to determine acute from chronic infection. Following an acute infection, IgM titers are sharply elevated 5 days to weeks after initial exposure. Peak elevations of IgM antibodies occur approximately 1 to 2 months thereafter. IgG antibodies are detectable usually 1 to 2 weeks after primary infection. IgG titers are elevated up to years after initial exposure. The presence of both serum antibodies predicts timing of maternal infection. If both IgG and IgM markers are not identified, then no indication of maternal infection exists. If testing reveals a positive IgG antibody marker with a negative IgM marker, then the presence of an old infection has been discovered. If both antibody markers are elevated, a recent infection is suspected. In the case of acute infection, repeat serum testing is recommended within 2 to 3 weeks of initial results. A dramatic increase in serum IgG antibody titers usually by at least 4 fold the initial level, indicate an acute infection (Paquet & Yadin, 2013). False positive results are fairly common, so confirmation of a positive test through laboratory results is necessary. In practicing countries, regardless if the mother tests negative on initial serum tests, blood samples for screening will continue to be drawn throughout the remainder of the pregnancy.

For maternal patients who test positive for toxoplasmosis, an amniocentesis is offered. Ideally, amniocentesis is conducted no earlier than 18 weeks gestation and after 4 weeks of suspected infection. Amniocentesis should not be performed earlier than 18 weeks due to high rate of false positive results and high risks of preterm labor. A prenatal diagnosis of congenital toxoplasmosis made by amniocentesis requires the detection of T. gondii parasite in amniotic fluid. Polymerase chain reaction (PCR) testing of the fluid is the preferred diagnostic method. Testing with PCR has a near 100 percent positive predictive value (Serranti et al, 2011). Traditionally, fetal blood sampling via cordocentesis was once thought to be the gold standard of diagnostic testing. Cordocentesis is no longer used due to associated higher fetal risks than amniocentesis.

Final diagnostic studies include the use of fetal ultrasound. Ultrasound is recommended for women with suspected or diagnosed acute infection. Fetal ultrasound monitors for abnormalities within the developing neurological, renal and hepatic systems. Ultrasound may reveal intracranial abnormalities such as hydrocephalus, ventriculomegaly and intracerbral calcifications. Additionally, splenomegaly, congenital nephrosis and ascites have been noted on ultrasound in conjunction with toxoplasmosis diagnosis (Montoya et al, 2008).

The infant diagnosed with congenital toxoplasmosis may not elicit any symptoms in the first 36 hours of life. Clinical manifestations usually occur months after birth. In an infant who is suspected to have congenital toxoplasmosis, but whose mother did not receive screening, a MRI is useful in detection of brain lesions. MRI is the preferred diagnostic tool, over computed tomography (CT) scan, due to its high sensitivity and resonance for smaller lesions. Laboratory evaluation must consist of evidence of T. gondii in blood, body fluids, or tissues (Brooks, 2013). Serum quantitative immunoglobulin testing will detect the presence of IgG and IgM antibodies in the newborn’s blood. A complete blood count (CBC) with differential should be ordered to monitor for infection or hematological abnormalities, particularly thrombocytopenia. A lumbar puncture may be required to detect the presence of T. gondii in the cerebrospinal fluid. Congenital nephropathy, along with hepatosplenomegaly is possible, therefore an abdominal ultrasound, along with liver function and urine studies are necessary. Anticipation of elevated liver function enzymes and serum creatinine is expected. An audiology screen should be performed prior to discharge to obtain baseline results, since hearing loss is possible.

**Therapeutic approaches and treatment options**

Although there is no cure, congenital toxoplasmosis is a treatable infection. Therapeutic agents are designed to destroy the tachyzoite, but are not capable of eradicating encysted bradyzoites (Gomella et al, 2013). Upon confirmation of a positive maternal toxoplasmosis screen, medical intervention is guided in two ways: prevention of transmission to the fetus and treatment. Gestational age of the infant is the determining factor of how to approach treatment therapy.

The ultimate goal of prevention therapy is to decrease the risk of mother-to-child transmission. Spiramycin is a macrolid antibiotic used to decrease the frequency of vertical transmission of T. gondii from the mother to the fetus. Spiramycin therapy is generally used if the pregnancy is less than 18 weeks gestation. Prevention therapy with Spiramycin may reduce congenital transmission but does not treat the fetus if in utero infection has already occurred. Spiramycin does not readily cross the placenta, and therefore is not a reliable treatment for the fetus. Reports show that the use of Spiramycin has decreased the rates of vertical transmission in the first trimester (Gomella et al, 2013). Spiromycin is not teratogenic. Prevention therapy is initiated with the first positive serum screen until delivery, even in mothers who have tested negative by amniotic PCR (Montoya & Remington, 2008). Theoretically, prophylaxis prevention therapy is continued throughout pregnancy in order to prevent the development of a later gestational fetal infection from an earlier maternal infection.

Antiparasitic treatment is indicated in infants with confirmed case of toxoplasmosis through serology, PCR, in utero ultrasound or by maternal clinical symptoms. This treatment plan is useful for pregnancies that are greater than 18 weeks gestation. Sulfadiazine is an antibiotic used in conjunction with antiparasitic medication to treat toxoplasmosis. Sulfadiazine 50 mg/kg twice daily along with tapered doses of pyrimethamine and folinic acid 10 mg, three times a week are prescribed for a minimum of 12 months. Pyrimethamine is given as 2 mg/kg/day for 2 days, then 1 mg/kg/day for 2-6 weeks, then 1 mg/kg/day 3 times a week (Gomella et al, 2013). Pyrimethamine is an antiparasitic drug that prevents the growth and reproduction of T. gondii in the cells. Pyrimethamine is not used in the first trimester due to its potentially teratogenic properties toward the fetus. Increased use of Pyrimethamine causes reversible bone marrow depression. Folinic acid prevents hematological toxicities of pyrimethamine. Due to the severe side effects of medication regimen, complete blood counts must be monitored during the course of treatment.

**Pertinent theories and evidenced based practice**

Theoretically, it was first believed that the primary transmission of toxoplasmosis was solely though cats. Several epidemiologic studies have found that cats are not the only risk factor to acquiring toxoplasmosis. These studies uncovered that cat ownership by its self is not linked to toxoplasmosis (Gomella et al, 2013). Instead, an increased risk of acquiring toxoplasmosis is attributed to consuming raw or undercooked meat, fruits and vegetables. Additional risk factors identified are exposure to sandboxes, soil, and travel outside of the United States, Europe or Canada. A recent study identified that eating raw oysters, clams or mussels has also contributed to maternal infection (Gomella et al, 2013). Avoiding cleaning the litter box should be emphasized to expectant mothers as well as counseling on the importance of cooking meat to a safe temperature of at least 152 degrees Fahrenheit, washing fruit and vegetables before eating and avoiding unfiltered water. Meat that has been cooked to a lesser degree has been found to withstand contamination. In addition, undercooked meat should not be fed to pets and keeping cats indoors prevents acquisition of the infection by eating prey.

Evidenced based practice is a driving force behind treatment modality in the infant with congenital toxoplasmosis. A study conducted by Cortina-Borja et al. (2010) evaluated the effectiveness of prenatal treatment in preventing serious neurological sequelae and post natal death (SNSD). The study followed a group of 293 children who were diagnosed with congenital toxoplasmosis, from birth to four years of age, and their subsequent neurological outcomes. From the sample size, two thirds of children received treatment by either spiramycin or by a combination of pyrimethamine-sulfonamide. Approximately one third of children did not receive any treatment. The neurological outcomes of the two groups were analyzed over the remaining years. Neurological deficits were defined as microcephaly, insertion of an intraventricular shunt, seizures or abnormal neurodevelopment. The researchers concluded that prenatal treatments of congenital toxoplasmosis reduced the risk of obtaining SNSD by three quarters (Cortina-Borja et al, 2010). Furthermore, the study goes on to state the effectiveness of pyrimethamine-sulfonamide and spiramycin was similar. In essence, the study provided that initiating proper treatment was beneficial in decreasing the severity of neurological impairment in the neonate.

**Economic, emotional and social implications on the family unit**

The diagnosis of congenital toxoplasmosis may inflict anxiety and feeling of guilt in future parents. Parents’ may place blame knowing that the diagnosis may have been preventable. Educating the family, utilizing resources and allowing the family options will best facilitate transition to life with their new baby. Counseling the family, assessing physical status of the mother and infant will provide anxious parents with guidance and allow them to cope with the diagnosis. The role of the practitioner involves assessing the risk, knowledge and plan of action for the infant with congenital infection (Serranti et al, 2011). With well-known neurologic damage in early gestation, families may be provided an option such as termination of pregnancy. Other options include undergoing repeated invasive testing along with a stringent medication regimen in order to keep the pregnancy healthy. These choices alone may provide a serious economic, as well as emotional strain on the family unit. With congenital infection, severe irreversible neurologic damage, along with other delays remains possible. Severe neurologic impairment may adversely affect the child’s growth and largely impact future schooling and social settings. After birth, the infant may require close developmental, as well as neurological follow up for years depending on the effects of the disease. The lasting effects of congenital toxoplasmosis may create a crisis situation, thus interrupting the family unit.

**Conclusion**

In conclusion, congenital toxoplasmosis is a preventable infectious disease that may cause life-long detrimental effects to the developing fetus. Maternal education, along with proper hand hygiene, adequate prenatal care and routine screening tools can provide mothers with a relatively healthy pregnancy. In the case of congenital toxoplasmosis, treatment modalities are essential for minimizing risk to the fetus.

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