Diagnosis and Management of Perinatal Infections

While not a threat in most cases, certain micro-organisms can have significant effects on fetal/neonatal morbidity and mortality, and pregnant women should be monitored for possible infections.

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Exposure to infectious agents is a relatively common reason for pregnant women to consult their obstetrical-care providers. Although in the majority of cases there is no real threat to fetal health, certain micro-organisms can have very significant effects on fetal/neonatal morbidity and mortality. This article will address issues of diagnosis and management in cases of exposures to toxoplasmosis and group B *streptococcus* (GBS).

Toxoplasmosis

Toxoplasma gondii, an intracellular parasite, is found in many mammalian species. The parasite

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exists in several forms: the trophozoite, which is the actively replicating and invasive form found in blood, body fluids and tissue during primary infection; the tissue cyst, which is a dormant form seen in tissues (*i.e.,* brain and retina) during chronic infection; and finally, an oocyst which is found only in the intestinal tract of cats and shed for approximately two weeks after the primary infection.

The most common mode of transmission is direct contact with an oocyst from the feces of an infected cat. Consumption of cysts in undercooked meat of infected animals, most often lamb, is the second most common mode of transmission, followed by receiving blood products or organ transplants.

Epidemiology. The prevalence of seropositivity varies greatly between countries. In the U.S., 20% to 30% of women have serological evidence of a prior infection, and about two per 1,000 pregnant women will seroconvert during pregnancy. In European countries, such as France, 80% to 90% of women are seropositive.[1,2]

Clinical manifestations. Acute infection in adults is unrecognized in up to 90% of cases, either because it is subclinical or its symptoms are nonspecific.[3] The most common manifestations are nontender lymphadenopathy, fever, fatigue, headache and myalgia. Occasionally, patients develop a sore throat, maculopapular rash or hepatosplenomegaly.

In healthy adults, clinical toxoplasmosis is a mild and self-limited disease requiring no treatment, however, in immunosuppressed patients, it may lead to serious pulmonary and central nervous system involvement.[4]

Fetal risk. Acute toxoplasmosis complicates one to five per 1,000 pregnancies, with a risk of fetal infection of only one per 10,000 live births.[1] Fetal infection occurs during the parasitemia period of a primary infection.

The risk of maternal-fetal transmission is directly related to the gestational age at the time of maternal infection, whereas the severity of con-

Summary

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• In the U.S., 20% to 30% of women with toxoplasmosis have serological evidence of a prior infection, and about two per 1,000 pregnant women will seroconvert during pregnancy. Acute toxoplasmosis complicates one to five per 1,000 pregnancies, with a risk of fetal infection of only one per 10,000 live births. Fetal infection occurs during the parasitemia period of a primary infection.

• Isolation of the toxoplasma gondii from blood or body fluids establishes that the infection is acute. Detailed ultrasonography is an essential tool in the search for evidence of *in utero* infection, such as ventriculomegaly, hydrocephalus, microcephaly, intracranial calcifications, hepatosplenomegaly, ascites, hydrops and placental thickening.

• The incidence of neonatal GBS infection is 1.8 per 1,000 live births, of which 80% are early-onset GBS disease. Approximately 25% of neonatal deaths occur in premature infants, with a case fatality rate ranging from 5% to 20%.

• Vaccines are currently being developed to induce antibodies against the polysaccharide capsule of GBS. The current primary strategy for preventing GBS disease, however, is chemoprophylaxis using antibiotics.

Table 1

Toxoplasmosis: Outcome by Trimester of Acquisition

Trimester Acquired	Infants Infected (Serologic) (%)	Clinically Severe Disease (%)	Clinically Mild or Absent Disease (%)
1	17	13	87
2	25	10	90
3	65	0	100

Adapted from: Desmonts G: Congenital toxoplasmosis. N Engl J Med 1974; 291:366.

genital disease is inversely related to gestational age (Table 1).

Approximately 90% of congenitally infected neonates are asymptomatic at birth, but if left undiagnosed and untreated, up to 85% will develop sequelae such as chorioretinitis, visual impairment, or learning disabilities.[5-7] Clinically apparent infection may be manifested in the neonate as low birth weight, intracranial calcification, hydrocephalus, microcephaly, seizures, chorioretinitis, anemia, thrombocytopenia, jaundice and hepatosplenomegaly.[8]

Diagnosis. Isolation of the toxoplasma gondii from blood or body fluids establishes that the infection is acute. The classic Sabin-Feldman dye test has been used, although other techniques have become available, including enzyme-linked immunosorbent assay (ELISA), double sandwich ELISA (DS-ELISA), indirect fluorescent antibody (IFA), indirect hemagglutination and agglutination tests and complement fixation. Although diagnosis usually relies on serologic testing, these assays, unfortunately, currently are not well standardized, leading to a high false-positive rate.

Immunoglobulin M (IgM) can be detected within one or two weeks of infection and the patient may remain positive for several months or even years. IgG can be detected two months after infection, and levels decline gradually thereafter. Low levels of IgG may persist for life. Although the presence of IgM antibodies generally represents a recent infection, the possible persistence of IgM after the acute infection must be taken into account.[9,10]

The presence of a high titre of IgG with IgM, supports the diagnosis of a recent infection and additional testing is required to confirm the diagnosis. A fourfold or more rise in serum antibody titers in parallel specimens, collected three to four weeks apart, confirms an acute infection.

Polymerase chain reaction (PCR) or cultures are also available to test directly for organisms in the blood and other body fluids.
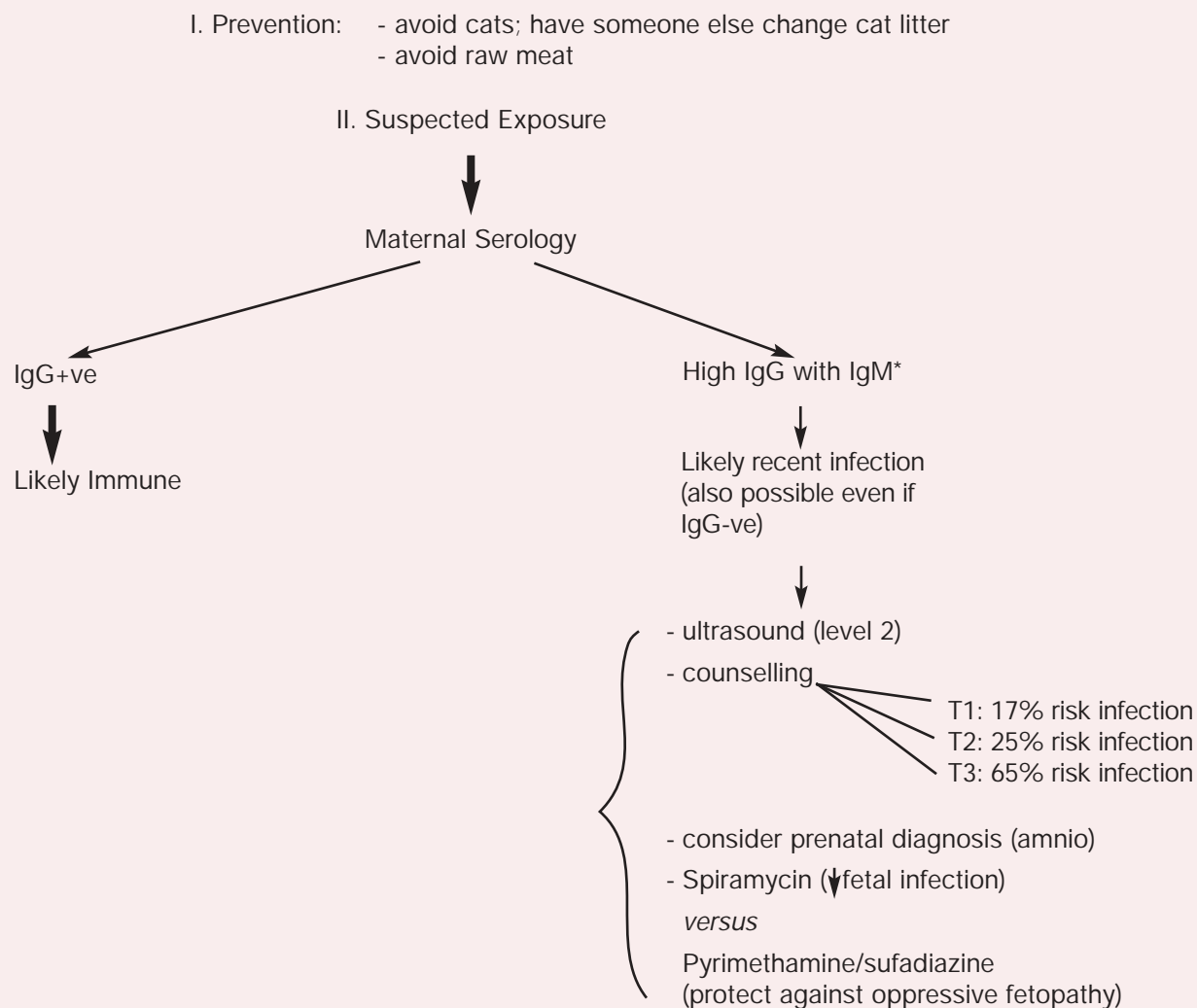
Fetal diagnosis and monitoring. Detailed ultrasonography is an essential tool in the search for evidence of *in utero* infection, such as ventriculomegaly, hydrocephalus, microcephaly, intracranial calcifications, hepatosplenomegaly, ascites, hydrops and placental thickening. In 30% to 40% of cases of congenital toxoplasmosis, ultrasound abnormalities are found.[11]

If no evidence of infection is seen in an ultrasound, fetal blood sampling can be offered after

Perinatal Infections

Suggested Approach to
Management of Perinatal Exposure to Toxoplasmosis

I. Prevention: - avoid cats; have someone else change cat litter
                  - avoid raw meat

II. Suspected Exposure

↓

Maternal Serology

IgG+ve   High IgG with IgM*

↓   ↓

Likely Immune   Likely recent infection
                                          (also possible even if
                                          IgG-ve)

                                          ↓

                                          - ultrasound (level 2)
                                          - counselling

                                                    T1: 17% risk infection
                                                    T2: 25% risk infection
                                                    T3: 65% risk infection

                                          - consider prenatal diagnosis (amnio)

                                          - Spiramycin (↓fetal infection)

                                          versus

                                          Pyrimethamine/sufadiazine
                                          (protect against oppressive fetopathy)

   * Remember IgM may remain (+) up to months/years.

IgG = immunoglobulin G; IgM = immunoglobulin M

20 weeks of gestation to detect toxoplasma-specific IgM, IgA and IgE, as well as toxoplasma gondii isolation in tissue culture. Although antibody production may be delayed in the fetus, other nonspecific indicators of fetal infection, such as white blood cell and differential counts, platelet count, and a liver function test, also can be assessed.[12,13]

Fetal infection can be ascertained with PCR testing of amniotic fluid, allowing for earlier diagnosis than fetal blood sampling, while carrying a sensitivity of 97% and a negative predictive value of 99%.[14]

Prevention and treatment. Universal screening cannot be recommended (with the exception of immunocompromised hosts) given the low frequency of seropositivity in Canadian women (Figure 1). Toxoplasmosis in pregnancy can be prevented by improving hygiene and dietary habits, such as avoiding undercooked meat, washing all fruits and vegetables before eating them, avoiding consumption of raw eggs and unpasteurized milk, washing one's hands after handling a cat and avoiding contact with cat feces. One European study demonstrated a 63% reduction in maternal infections after institution of an educational program focusing on these interventions.[9]

The recommended treatment for acute toxoplasmosis in pregnancy is spiramycin — a macrolide antibiotic, concentrated in the placenta, which can reduce the risk of fetal transmission by 60%.[15] Whenever a primary maternal infection is confirmed, spiramycin should be started at a dose of 1 g every eight hours and continued throughout the pregnancy. In the second trimester, amniocentesis can be performed for evaluation of fetal infection.

Since spiramycin is ineffective in treating an infected fetus, once fetal infection is confirmed by amniotic fluid PCR, pyrimethamine and sul-fadiazine are required to reduce the severity of congenital infection and increase the proportion of infants asymptomatic at birth, as well as reduce long-term sequelae. Because of the folic acid antagonist effect of these agents, folic acid rescue must be added.[8]

Group B Streptococcus Infection

Over the past two decades, group B beta-hemolytic *streptococcus* or *Streptococcus agalactiae* has emerged as an important cause of perinatal morbidity and mortality. This gram-positive *diplococcus* organism can colonize the lower gastrointestinal tract, and secondary spread to the genitourinary tract is common. It is the most common cause of neonatal bacterial sepsis and meningitis.

Approximately 15% to 20% of pregnant women are colonized with the organism in the lower vagina or anorectal areas, and only 1% to 2% of infants delivered to GBS-colonized women will develop early onset disease.[12] The incidence of neonatal group B *streptococcus* infection is 1.8 per 1,000 live births, of which 80% are early-onset GBS disease. Approximately 25% of neonatal deaths occur in premature infants, with a case fatality rate ranging from 5% to 20%.[13,14]

Risk factors. Obstetric factors associated with an increased likelihood of early onset GBS disease in the newborn include:
- Premature delivery;
- Prolonged rupture of the membranes greater than 18 hours;
- Maternal intrapartum temperature of over 37.5°C; and
- Having had a previous infant with GBS disease as well as maternal GBS bacteriuria.[15]

Perinatal Infections

Other risk factors include maternal age (under 20); black race; diabetes; heavy colonization; low level of anti GBS capsular antibodies; and low birth weight.[16] An apparent increased risk in twins may be attributable to the increased frequency of prematurity and low birth weight with multiple gestations.[17]

Maternal clinical significance. GBS has been implicated in several adverse outcomes, including urinary tract infection, chorioamnionitis, endometritis, premature delivery, premature rupture of the membranes, puerperal sepsis, as well fetal and neonatal infection. Postpartum, it can

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Intrapartum maternal administration of antibiotics has been shown to reduce early-onset neonatal GBS disease.

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cause wound infection, osteomyelitis and mastitis.

Neonatal clinical significance. Colonization of the infant before, during or after birth is a prerequisite to invasive GBS disease and the risk is related to inoculum size.[12,18]

Although premature infants are at a substantially higher risk for GBS disease, term infants still account for 75% of early onset infection.[19] Early-onset GBS disease usually develops within six to 12 hours of birth. Manifestations include respiratory distress, pneumonia, septicaemia and shock. The mortality rate is approximately 20%. It is not uncommon for survivors to exhibit neurological sequelae from sepsis.

Late-onset GBS disease may result from vertical, nosocomial or community-acquired infection. It generally develops after the baby is seven days of age. In the majority of infants, meningitis is the predominant clinical manifestation. The mortality rate is less than early-onset sepsis, but again, neurological sequelae are common in survivals.

Diagnosis. Maternal colonization can be assessed by culturing the lower vagina and anoractum. Selective media must be used, as they increase yield by 50%. Rapid tests are also available, but their low sensitivity (15% to 74%) has so far precluded their clinical use.

Prevention. Vaccines are currently being developed to induce antibodies against polysaccharide capsule of GBS. The current primary strategy for preventing GBS disease, however, is chemoprophylaxis using antibiotics.

Antepartum chemoprophylaxis is of no benefit to neonatal morbidity and mortality since re-colonization occurs in up to 70% of patients within three weeks after treatment. Immediate postnatal treatment also has been found generally ineffective in preventing disease or mortality in the neonate. Conversely, intrapartum maternal administration of antibiotics has been shown to reduce early-onset neonatal GBS disease. A recent review demonstrated intrapartum antibiotic treatment reduces the rate of infant colonization (odds ratio 0.10, 95% confidence interval (CI) 0.07:0.14) and early-onset neonatal infection with GBS (odds ratio 0.17, 95% CI 0.07:0.39).[20]

Identification of carriers. Maternal colonization status may vary considerably during gestation and tends to be unpredictable. For instance, 7.4% of women with a negative culture at 26 to 28 weeks were found in one study to be carriers at delivery.[12] Furthermore, the positive predictive value of a single positive culture at any time during pregnancy is 67% and, therefore, screening for GBS in early pregnancy cannot be recommended.[12] Other studies, however, have suggested culture status remain essentially unchanged within a five-week period, therefore, supporting the practice of obtaining samples in the late third trimester.

Table 2

Risk Factors for Which Intrapartum Chemoprophylaxis is Recommended

1. Pre-term labour (< 37 weeks gestation)

2. Term labour (> 37 weeks gestation)

   a. Prolonged rupture of membranes. Chemoprophylaxis should be given if labour and/or ruptured membranes are likely to continue beyond 18 hours (neonatal benefits are optimally achieved if antibiotics are given at least 4 hours prior to delivery).

   b. Maternal fever during labour (> 38°C orally).

3. Previous delivery of a newborn with GBS disease regardless of current GBS colonization status

4. Previously documented GBS bacteriuria:

   • Recommended: Penicillin G 5 mU IV load, then 2.5 mU IV every 4 hours until delivery. Alternative: Ampicillin 2 g IV Load, then 1 g IV every 4 hours until delivery.

   • If allergic to penicillin: Recommended: clindamycin 900 mg IV every eight hours until delivery. Alternative: erythromycin 500 mg IV every six hours until delivery.

GBS = group B *streptococcus*
Adapted from: Center for Disease Control and Prevention: Prevention of early onset Group B Streptococcal Disease: A Public Health Perspective. MMWR 1996; 45 (RR-7):16-7.

Approaches for antibiotic prophylaxis. There currently are two suggested approaches consisting of either universal screening with culture followed by selective intrapartum chemoprophylaxis for women identified as GBS carriers, or intrapartum chemoprophylaxis for pregnant women with risk factors for GBS infection in the newborn.

To date, these strategies have not been evaluated within the context of a randomized controlled trial to compare their efficacy, since at least 100,000 pregnant women would be needed in each arm of such a trial.[16] Although both strategies can lead to significant reductions (70% to 85%) in neonatal morbidity and mortality from early onset disease, neither is expected to completely prevent group B *streptococcal* disease in the newborn.

The Society of Obstetricians and Gynaecologists of Canada recommends the following:

Until more specific information is available, identification and management of women whose newborns might be at increased risk of GBS disease are acceptable by either of two methods:

• Universal screening of all pregnant women at 35 to 37 weeks gestation with a single combined vaginal-anorectal swab and the offer of intrapartum chemoprophylaxis to all GBS-colonized women; and

• No universal screening, but intrapartum chemoprophylaxis for all women with identified risk factors (Table 2). This strategy should also be used in cases where universal screening is the policy, but either was not done or the test results are not available.[21] CME

Perinatal Infections

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