Toxoplasmosis & Pregnancy

Razieh Vanda

MD, Perinatologist

Introduction

- *Toxoplasma gondii* is a **ubiquitous** protozoan parasite .
- Mainly acquired during childhood and adolescence .
- **Immunocompetent** humans are able to **limit** spread of parasite and associated tissue damage, parasite remains in **latent form** in **neural and muscle tissue** for the life .
- In **immunosuppressed patients**(AIDS) can **reactivate** and cause disease.
- In **primary infection** during pregnancy or reactivated, the parasites can be **transmitted** from mother to fetus, resulting in **congenital toxoplasmosis**.
- The **frequency** of congenital toxoplasmosis **increases** with **gestational age** , but frequency of **severe sequelae** is greater when infection is **early in pregnancy**.

Sources of infection

- ***T. gondii*** is **obligate intracellular parasite** in three forms: **sporozoite** (oocysts) is shed only in cat feces; **tachyzoite** (a rapidly dividing form observed in acute phase of infection); and **bradyzoite** (a slow-growing form observed within tissue cysts) .
- Cats are only animals in which *T. gondii* can complete its reproductive cycle
- The main source of maternal infection is ingestion of bradyzoites contained in raw, undercooked meat or meat products.
- Maternal ingestion of sporozoites from contaminated soil or water or soil-contaminated fruit or vegetables
- Drinking unpasteurized goat's milk and eating raw seafood from contaminated water .
- Infected organ transplant or blood transfusion is a rare source .

Incidence of acute primary infection in pregnancy

- **Incidence** of acute maternal infection during pregnancy is range from **1 to 8 per 1000** pregnancies, with **highest rates in France** (rate in France has significantly decreased in the past decade)

Clinical manifestations

- **Acute maternal infection is usually asymptomatic.**
- Symptoms are typically **nonspecific and mild**:
- Fever, chills, sweats, headaches, myalgias, pharyngitis, hepatosplenomegaly, and/or a diffuse nonpruritic maculopapular rash.
- **Common and more specific symptom** of acute toxoplasmosis is bilateral, symmetrical, nontender **cervical adenopathy**.
- 20 to 30 percent of patients develop generalized lymphadenopathy.
- **Ocular disease** (chorioretinitis , posterior uveitis) may occur with acute disease but is **more common with reactivation**. (visual loss or floaters)

Screening

- **Should all pregnant women be screened?**
- ACOG and Society of Maternal-Fetal Medicine recommend against routine serological screening for toxoplasmosis for several reasons:
- Prevalence of disease is relatively low
- Standardized serologic assays are not available except in a few reference laboratories
- Highly effective treatment is not available
- Screening is costly.

Fetal Infection

- Fetal infection results from **transplacental** transmission of tachyzoites following primary maternal infection
- **Risk factors for fetal infection from recent maternal infection**:
- Maternal infection at advanced gestational age
- High-virulence *T. gondii* strain
- High parasite load
- Maternal parasite source (risk is higher when source is sporozoites in oocysts [cat feces] than bradyzoites in tissue cysts [meat]).
- Maternal immunocompromise

Fetal Infection

- **Risk of fetal infection from reactivation or reinfection** :
- **Congenital toxoplasmosis** secondary to maternal infection from **reinfection** with a different *T. gondii strain* is a **rare**.
- **Reactivation** of latent toxoplasmosis during pregnancy leading to congenital infection could occur in HIV-infected pregnant women, particularly in severely immunocompromised.

  (very low risk of maternal-fetal transmission in this population approximately 4 percent)

Ultrasound findings in congenital toxoplasmosis

- One or more of the following sonographic findings may be observed :
  - Intracranial calcifications/densities
  - Hydrocephalus
  - Echogenic bowel
  - Hepatosplenomegaly
  - Intrahepatic calcifications/densities
  - Intrauterine growth restriction
  - Ascites
  - Pericardial and/or pleural effusions
  - Hydrops fetalis
  - Fetal demise
  - Placental densities and/or increased thickness
- **The most common sonographic findings** in fetal toxoplasmosis are **intracranial hyperechogenic foci or calcifications** and **cerebral ventricular dilatation** (poor prognostic signs)
- Generally bilateral and symmetrical

Goals of prenatal diagnosis

- Main purpose of prenatal diagnosis of fetal infection is to guide **choice of drug therapy**
- In some , prenatal diagnosis is **important to aid in decision** to terminate the pregnancy.
- Exclusion of fetal infection by prenatal diagnosis can **prevent unnecessary postnatal treatment** in children without clinical signs of toxoplasmosis .

Termination of pregnancy

- Termination only by **definite evidence** of fetal infection based on PCR **and** evidence of intracranial abnormalities on fetal ultrasound
- **Most infected infants** have **good prognosis** and do not differ in their development at three to four years from uninfected children

Timing pregnancy after maternal infection

- Immunocompetent women who become pregnant **at least three months after** acute infection unlikely to transmit the infection to the fetus.

Toxoplasma in Pregnancy

DX , TX

Dr. davarpanah

Toxoplasma DX

- Indications : clinical evidences of acute toxoplasmosis in pregnant mother , sonograghic evidence of fetal anomaly
- In some countries such as france routine serial toxoplasma serologic test in seronegative pregnant mothers are done
- Serology : IgM positive within first week and continue for few months, IgG positive within second week of acute infection and persist long life
- No correlation between IgG titer and time of acute infection

Toxoplasma DX

- IgM+, IgG-: Indicative of acute infection especially if IgG become positive thereafter.
- IgM+ , persistent –IgG : false positive IgM (Autoantibodies such as ANA, RF). IgM capture ELISA or IgM ISAGA is needed.
- IgM +, IgG +: usually acute infection. But IgM may persist for few months or years. IgG Avidity test or IgM capture assay or IgM ISAGA is recommended.
- High avidity indicative of infection at least 4 months ago, low avidity usually in less than 4 months and other tests are needed for final decision

Toxoplasma DX

- Agglutination assay (IgM, IgG) : new antibodies react with acetone and old types react with formalin.
- PCR : on blood, CSF, Amniotic fluid , lymph node , brain tissue, BAL fluid.
- PCR sensitivity 15-85% , specificity 95% .
- Histopathology : parasite visualization or pathologic evidences.
- In GA <16 weeks : IgM ,IgG, IgG avidity tests
- In GA >16 weeks : IgM , IgG, IgG avidity(or Differential agglutination test)
- Acute pattern in AC/HS test is in favor of infection during last one year but non acute pattern is seen in infections older than one year.

Toxoplasma TX

- In GA<18 wks : spiramycine 1 gr Tid and PCR of amniotic fluid after 18 wks and fetal sonography .
- If PCR is negative and fetal sonograghy is normal , continue spiramycine till delivery time
- If PCR is positive or fetal sonography is abnormal, change spiramycine to pyrimethamine +sulfadiazine + folinic acid and continue them till delivery time
- In GA>18 wks: If PCR is positive pyrimethamine +sulfadiazine + folinic acid till delivery. But if PCR is negative , pyrimethamine + sulfadiazine + folinic acid or spiramycine as monotherapy continue till delivery time.

Toxoplasma TX

- Co-trimoxazole is the second line of therapy.
- Azithromycin or clarithromycin can be used instead of spiramycine
- Clindamycin or azithromycin can used instead of sulfadiazine
- Termination may be done for positive PCR and fetal brain anomaly.
- Contraception for 3 months in women with acute toxoplasmosis.

Toxoplasma in neonate

Dr. Mehrdad Rezaei

Neonatologist - SUMS

Introduction:

The rate of **mother-to-child transmission** during pregnancy is:

- mothers not treated: **50% to 60%**
- those treated: **25% to 30%**.

Congenital infection

- is **most** commonly secondary to acute maternal infection during pregnancy
- less commonly due to reactivation of previous infection in an immunocompromised mother.
- It should also be considered in women infected within **3** months prior to conception.

↑ Gestational age → ↑ Risk of intrauterine infection

risk of transmission to the fetus: 6% at 13 wks,
40% at 26 wks,
72% at 36 weeks.

earlier in pregnancy → more severe

clinical manifestations: 61% at 13 weeks' gestation
9% at 36 weeks.

- Infection early in pregnancy → intrauterine fetal demise, spontaneous abortion.
- third trimester → asymptomatic (nearly all infants)
  (accounting for 67% to 80% of prenatally infected infants.)

Clinical manifestations in neonate:

4 recognized patterns of presentation for congenital toxoplasmosis.

1. Subclinical/asymptomatic infection. **Most** infants with congenital toxoplasmosis (70% to 90%) do not have overt signs of infection **at birth**.

If untreated, a large proportion will later demonstrate **visual**, central nervous system (**CNS**) deficits, including **hearing impairment, learning disabilities, or mental retardation** several **months to years** later.

congenital disease

- **2. Neonatal symptomatic disease:** Signs at birth:

- **maculopapular rash,**
- **lymphadenopathy,**
- **hepatosplenomegaly,**
- **jaundice,**
- **pneumonitis,**
- **diarrhea,**
- **hypothermia,**
- **petechiae,**
- **thrombocytopenia.**
- **CNS disease symptoms** include **cerebral calcifications**, **hydrocephalus**, seizures, cerebrospinal fluid (CSF) abnormalities, meningoencephalitis, and **chorioretinitis**.

- **3. Delayed onset** is most often seen with **premature infants** and occurs within the first 3 months of age. It can behave like neonatal symptomatic disease.

- **4. Sequelae or relapse** in **infancy through adolescence** of a previously untreated infection. **Chorioretinitis** develops in up to 85% of adolescents/young adults with previously untreated congenital infection.

CSF **eosinophilia** and/or **elevated protein** can be seen.

Ophthalmology exam:

- **at birth**
- **every 3 months** until **18** mo/o
- **every 6 to 12 months** until **18** y/o.

Screening for hearing loss:

- **3** mo/o **(ABR) auditory brainstem response** or **(OAE) otoacoustic emissions**.
- **24** mo/o **Full audiologic evaluation:**.

- **Routine labs**: Abnormal CBC, liver enzymes, and bilirubin levels can also be seen with **disseminated disease**.

- Brain imaging. **Head computed tomography** (CT) scan without contrast. One study reported a clear relationship between the lesions on CT scan, neurologic signs, and the date of maternal infection.

  a. **calcifications:** (not seen by ultrasonography) single or multiple.

  b. **Hydrocephalus:**

is usually due to periaqueductal obstruction.

Massive hydrocephalus may develop in 1 week.

Differential diagnosis:

- **Congenital infections** caused by rubella, cytomegalovirus, syphilis, neonatal herpes simplex virus, HIV, and lymphocytic choriomeningitis virus (LCMV). Other disorders to be considered include hepatitis B, varicella, bacterial sepsis,
- **hemolytic diseases**,
- **metabolic disorders**,
- **immune thrombocytopenia**,
- **histiocytosis**,
- **congenital leukemia**.

OUTCOMES:

Treatment for 1-year duration **significantly improved outcomes** for many congenitally infected children.

All children who **died** had severe infection at birth.

A. Chorioretinitis:

After treatment: new or recurrent eye lesions **did not** develop

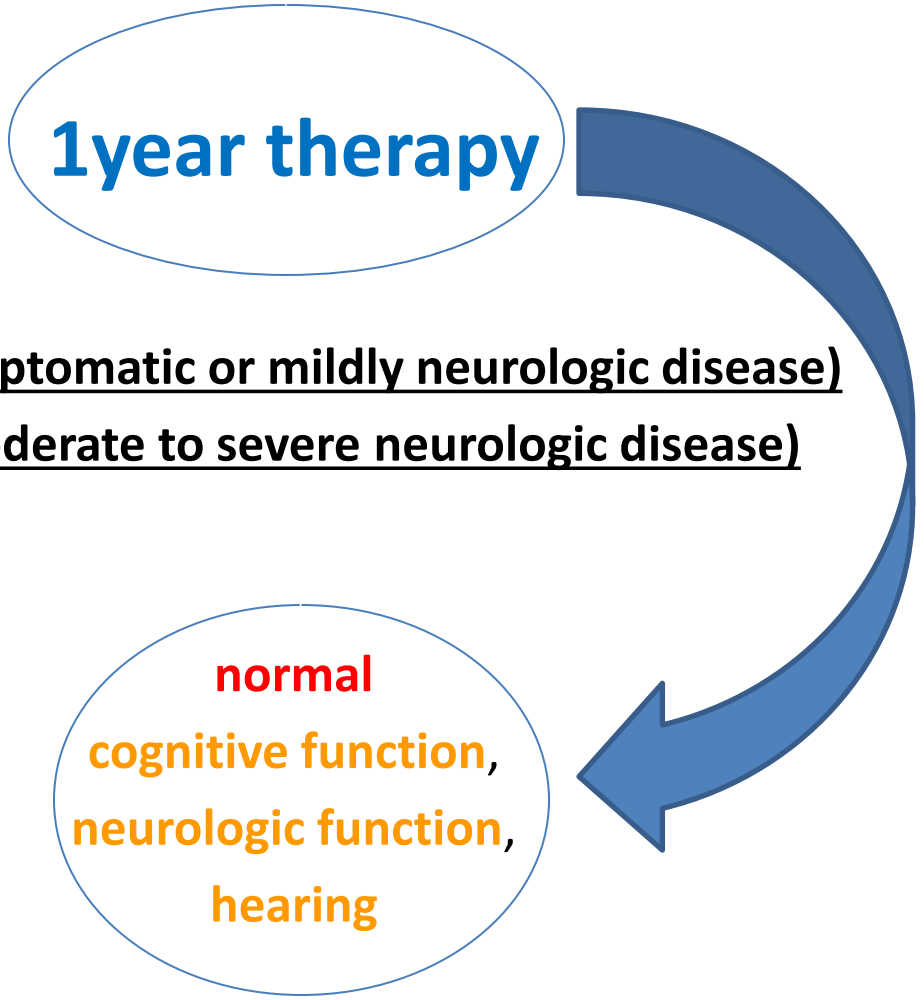
91% of asymptomatic or mild neurologic disease at birth.

64% of moderate or severe neurologic disease at birth.

chorioretinitis usually **resolved within 1 to 2 weeks** & did not relapse during Tx.

- **Relapse after treatment** may occur, often during adolescence.
- **Visual impairment** is a prominent sequela, even with treatment, in **85%** of patients who had severe disease at birth and **15%** of neonates with mild or asymptomatic disease.

B. Neurologic outcomes:



Congenital toxoplasmosis: diagnosis

Dr Gholamreza Pouladfar

EVALUATION AND DIAGNOSIS

- **Clinical suspicion**
- **Eye examination (20%) (**Chorioretinitis)
- **Neurologic evaluation (3**0%)
  - Detailed neurologic examination
  - Lumbar puncture
  - Neuroimaging.
- **Hearing evaluation**
- **Laboratory evaluation**
  - **Serology**
  - **PCR**
  - **Other tests**

Serology

- The usual method of diagnosis
- Interpretation: Complicated
- **Initial testing**
  - *Toxoplasma* (IgG
  - *Toxoplasma*-specific IgM
  - *Toxoplasma*-specific IgA
  - not always necessary, often useful, routinely performed

- Timing:
  - In the first 5 to 10 days of life
    - repeat testing may be necessary to exclude false positives.

- Both the infant and the mother
  - Immunologically normal women: typically positive *Toxo.* IgG and IgM

Reference laboratories

- the IgG enzyme-linked immunosorbent assay (ELISA) or dye test
- the *Toxoplasma* IgM ELISA or immunosorbent agglutination assay (ISAGA)
- The *Toxoplasma* IgA ELISA or ISAGA

- Negative toxoplasma IgM from testing performed at a commercial laboratory does not exclude the diagnosis of congenital toxoplasma infection [4].

Issues that complicate interpretation of serologic results in the newborn include :

- *Toxoplasma* IgG in the newborn
  - may reflect past or current infection in the mother (because IgG crosses the placenta).
- The fetal/newborn antibody response to *T. gondii* is variable.
  - Depending on the timing of maternal infection, *Toxoplasma*-specific IgM may disappear before birth, may be demonstrated within the first few days of life, or may be delayed for months.
- Antenatal treatment may affect the serologic profile of the infant;
  - IgM is rarely present in infants exposed to anti-*Toxoplasma* therapy with pyrimethamine and sulfadiazine in utero .
  - Data regarding the effects of antenatal treatment on other antibodies are lacking.
- Placental leakage of maternal IgM or IgA
  - may result in low positive IgM or IgA in an uninfected infant shortly after birth.

PCR

- PCR of CSF
  - should be performed if there is strong clinical suspicion for congenital toxoplasmosis.
- other samples
  - peripheral blood
  - Urine
  - vitreous fluid (ocular *Toxoplasma*),
  - bronchoalveolar lavage fluid
  - Cord blood
  - or placenta.
- Neonatal testing should be performed only at reference laboratories

Congenital toxoplasmosis:

Management

A. Sanaei

Professor of Pediatric Infectious Diseases

Toxoplasmosis

Antiparasitic therapy is Indicated for infants (<12 months old) in whom a diagnosis of congenital toxoplasmosis is confirmed or highly likely, including :

- When there is the increased risk of late sequelae in untreated congenital toxoplasmosis,
- for asymptomatic infants with equivocal newborn serology, pending definitive diagnosis (which may take months)

- The preferred antiparasitic regimen includes pyrimethamine plus sulfadiazine (or sulfamerazine or sulfamethazine) and folinic acid (leucovorin

- Infants with suspected congenital toxoplasmosis who have confirmation serology or polymerase chain reaction (PCR) performed by a reference laboratory.
- Infants with evidence of recent maternal T. gondii infection in conjunction with clinical findings compatible with congenital toxoplasmosis in the infant (eg, chorioretinitis, intracranial calcifications, hydrocephalus); in these infants T. gondii infection should be confirmed (with maternal and infant serology, infant cerebrospinal fluid PCR) and in the absence of confirmative tests alternative etiologies should be excluded (eg, congenital cytomegalovirus, Zika virus if maternal exposure risk is identified).

The End