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Toxoplasmosis in pregnancy

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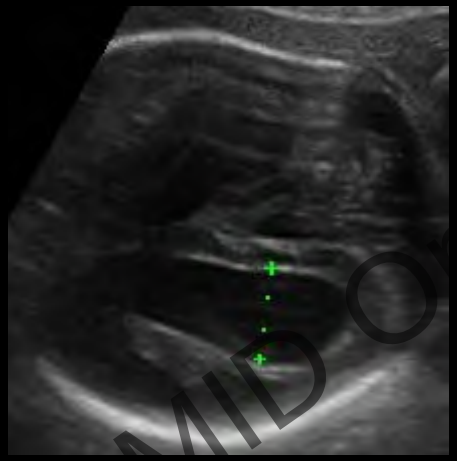
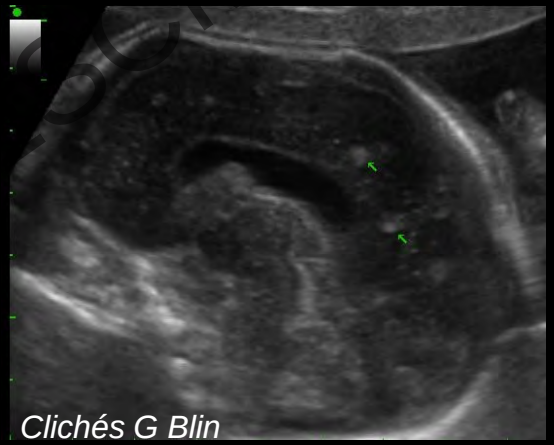
Congenital toxo : a potentially serious condition

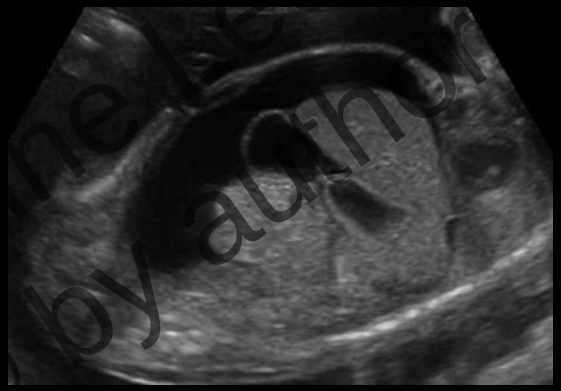
Neurological sequellae



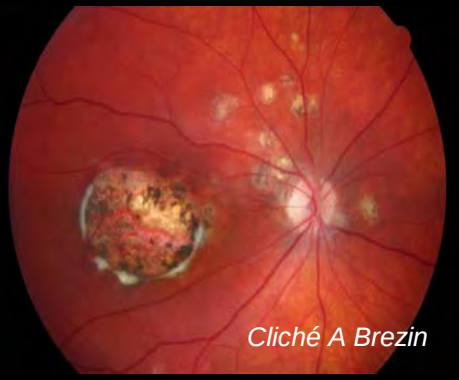


Clichés G Blin

Foetopathies



Chorioretinitis



Cliché A Brezin

The majority of children with congenital toxo are asymptomatic

Clinical scenarios

- Ultrasound signs -> fetal toxo diagnosis

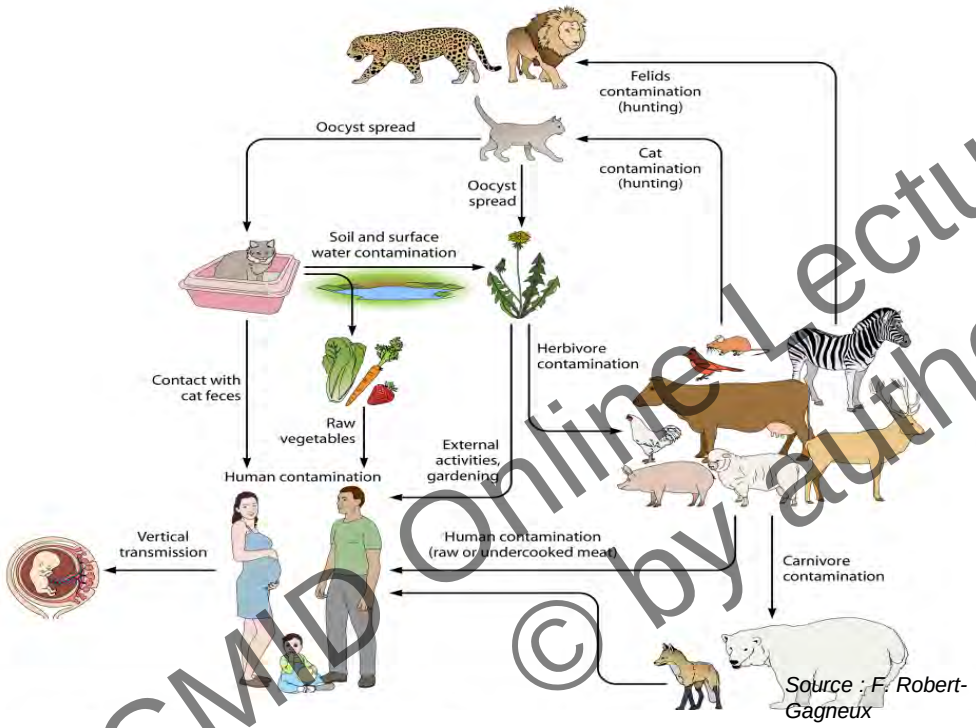
T	toxoplasmosis
O	other
R	rubella
C	CMV
H	herpes

- Serological screening -> maternal toxo diagnosis

Toxo screening issues

- Does the incidence justify a screening program ?
- Is primary prevention effective in seronegative women ?
- Is prenatal diagnosis reliable ?
- What is the efficacy of prenatal therapies ?

Primary prevention of toxoplasmosis

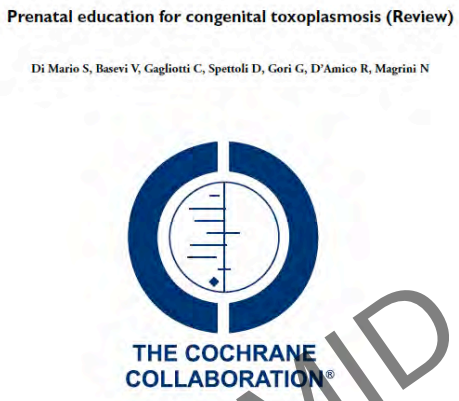


Source : F. Robert-Gagneux

No vaccine available

- Cook meat (well done) or use deep frozen meat,
- Wash hands and utensils before preparing and eating meals,
- Wash and/or peel fruit and vegetables,
- Avoid contact with cat litter (having a cat is OK)

Primary prevention : what is really the efficacy of prenatal education ?



Only 2 randomized studies

Carter AO, et al. Epidemiol & Infect 1989 (Canada)

Lyon thesis (dir. M Wallon) in Gollub EL, et al.EJOGBR 2008

Prenatal education on toxo not significantly associated with :

1. Seroconvertion rate : 13/2591(0.5%) vs 4/1358 (0.3%) in controls (P = 0.35);
2. Behaviors "no consumption of undercooked meat" (aOR 1.21; 95%CI 0.98-1.50); "handwashing after contact before meals" (aOR 1.01; 95% CI 0.83-1.22)

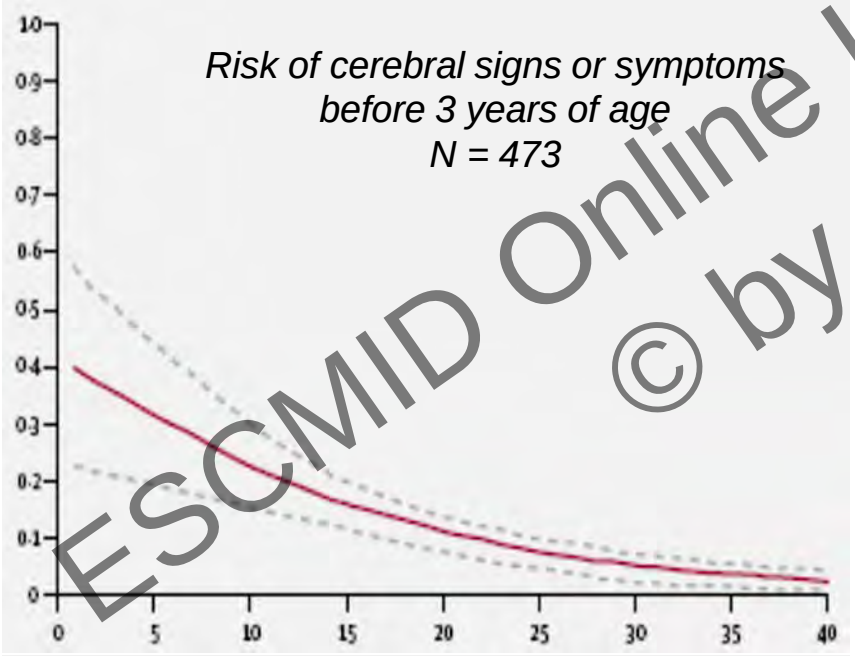
- High loss to follow-up ; low power

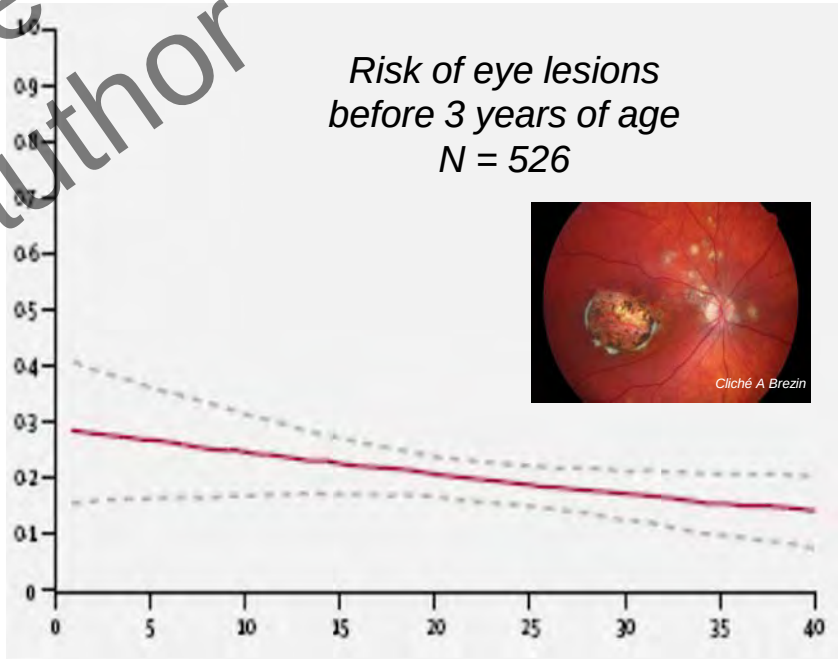
Background : the risk of congenital toxo depends on gestational age

Risk of transmission according to timing of maternal infection

SYROCOT. Lancet, 2007

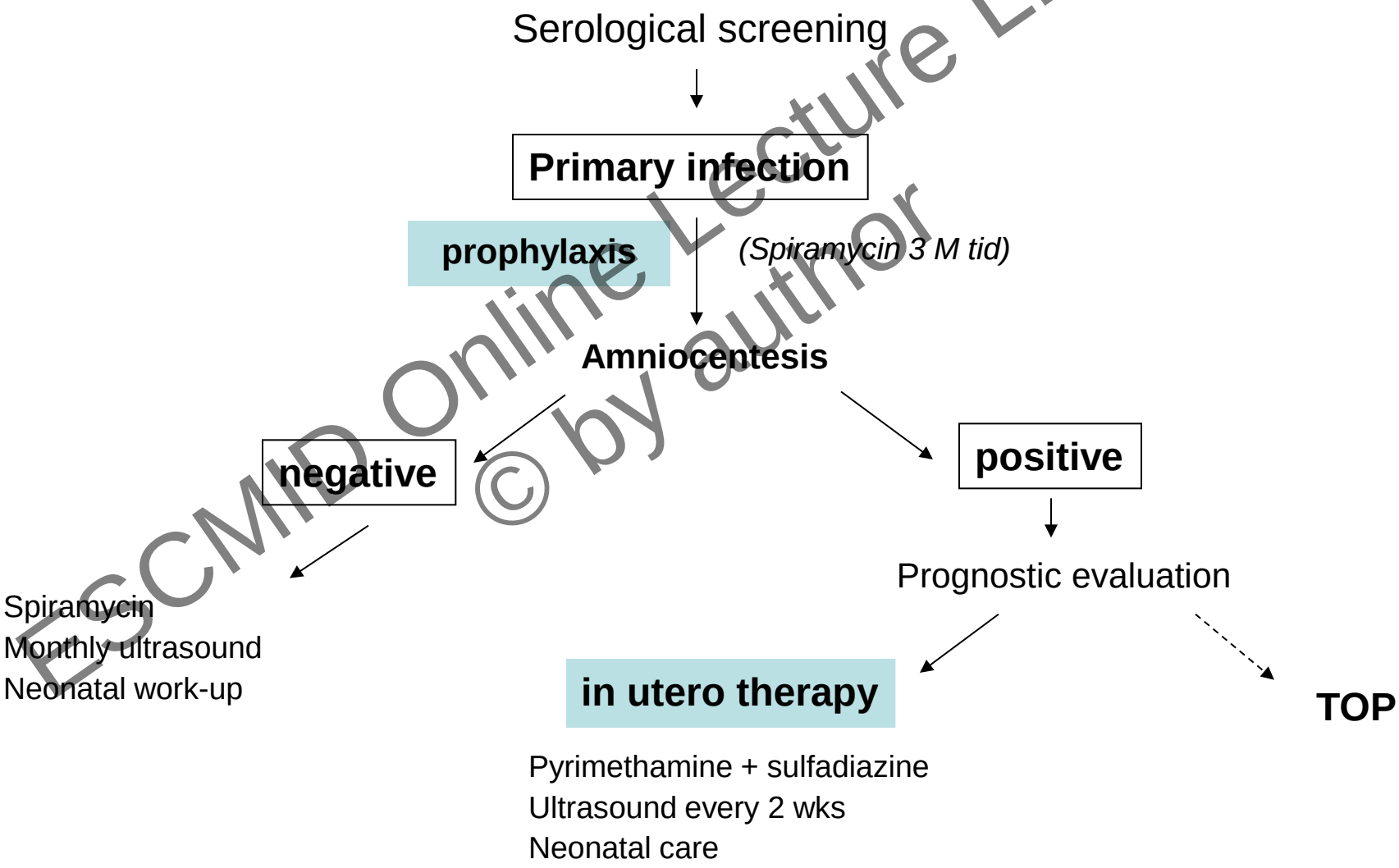
Risk of symptoms in congenital toxoplasmosis according to timing of infection





SYROCOT. Lancet, 2007

Toxo in pregnancy : conventional management in France



Therapy for toxoplasmosis in pregnancy

1) In utero therapy for infected fetus, following prenatal diagnosis

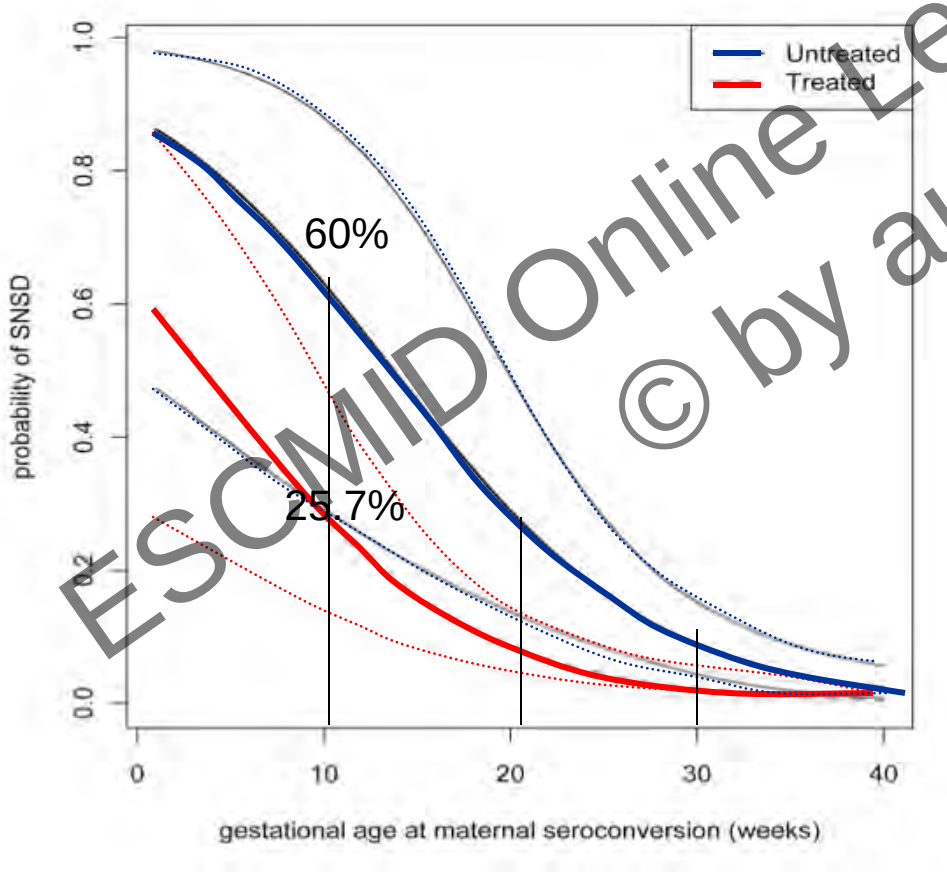
2) Treat seroconversion in order to :
   - Prevent mother-to-child transmission
   - Decrease risk of complications in case of congenital toxo

Antenatal therapy : does it improve outcome for infants with congenital toxo ?

- No randomized controlled trial (RCT) : numerous biaises
- No benefit of antenatal prophylactic therapy on symptoms *(SYROCOT, 2007)*
- Arguments in favor of therapy when amniocentesis PCR+ :
  - ✓ Analogy with post-natal therapy
  - ✓ Foulon, 1999 : early therapy reduced rate of severe sequellae
  - ✓ Kieffer, 2008 : treatment > 8 wks after seroconversion increased risk of chorioretinitis by age 2 yrs (OR 2.54)
  - ✓ Hotop, 2012 : treatment < 4 wks decreased risk of clinical manifestations
  - ✓ Wallon, 2013 : clinical signs of congenital toxo in infected children decreased after 1995 (17% vs 41%)

Antenatal therapy : EMSCOT re-analysis

Cortina-Borja, et al. (EMSCOT) Prenatal Treatment for Serious Neurological Sequelae of Congenital Toxoplasmosis: An Observational Prospective Cohort Study. PLoS Med 2010



14 european centres

Prenatal or neonatal screening

Follow up (median) 4 yrs

23/293 (8%) severe neurological symptoms (SNSD) including 9 TOP

Therapy associated with less sequellae (adjusted for gestational age at seroconversion)

OR = 0.24 (0.07-0.71)

Therapy for toxoplasmosis in pregnancy

1) In utero therapy for infected fetus, following prenatal diagnosis

2) Treat seroconversion in order to :
   - Prevent mother-to-child transmission
   - Decrease risk of complications in case of congenital toxo

What do the studies show ?

No proof of efficacy of antenatal toxo treatment as prevention

- No randomized controlled trial (RCT)
- Historical cohort study : *Desmonts &Couvreur NEJM 1974*
- Efficacy not demontrated in cohort studies : *Foulon et al (AJOG 1999), Gilbert et al (IJE 2001), EMSCOT (BJOG 2003), Peyron F (Cochrane 2005), SYROCOT (Lancet 2007)*
- Lyon cohort : decline in transmission rate after 1992 *(Wallon M, Peyron F et al. CID 2013)*
- Observational studies cannot conclude because of methodological bias : prescriptions differ according to gestational age, which is the major determinant of transmission

Prevention with spiramycin : is it too little or too late ?

- Too little because poor efficacy on T gondii
  - Pyrimethamine/sulfa may be more effective *(Hotop et al CID 2012)*
- Too late after parasite has already infected the fetus :
  - transmission RR = 0.48 if therapy started < 3 wks vs > 8 weeks after seroconversion *(Syrocot, Lancet 2007)*

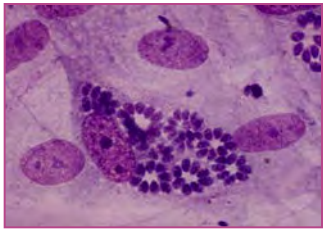
Can we prevent toxo transmission to the fetus ?

Maternal primary infection

↓

Parasitemia (tachyzoites)

↓



Placenta

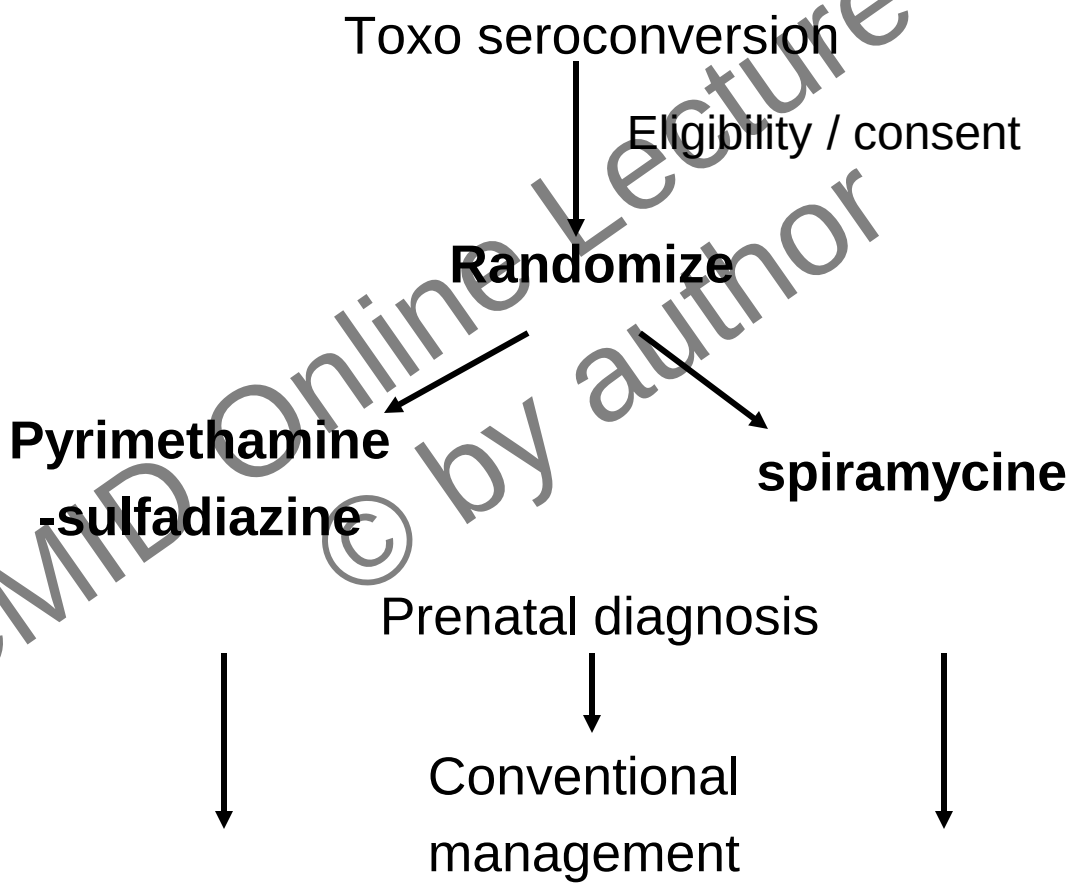
fetal infection

↙ ↘

Tachyzoites Cysts

TOXOGEST trial

Sponsor : Assistance Publique - Hopitaux de Paris
ClinicalTrials.gov Identifier : NCT01189448



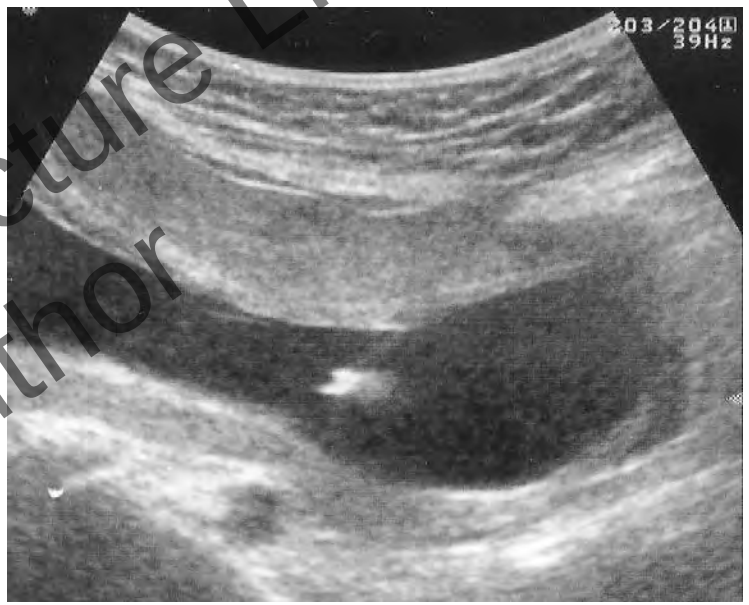
Outcome measures : transmission, tolerance

Clinical situations

1st-2d trimester primary infection

- Mme A :
  - At 16 weeks IgG and IgM negative
  - At 20 weeks IgG and IgM positive
  - What to do ?

Prenatal diagnogosis of toxoplasmosis



- **Amniocentesis :**
  - **PCR toxo on amniotic fluid**

    PPV 100% NPV 98%

    (Wallon Obstet Gynecol 2010)
  - **Not before :**
    - **18 wks GA**
    - **1 month after maternal primary infection**
- **Ultrasound : initial and monthly follow-up**

What to do in case of prenatal diagnosis of CT ?

- Mme A
  - Maternal primary infection between 16 and 20 wks
  - Amniocentesis at 23 weeks
  - Toxo PCR+

Prenatal therapy for infected fetuses

- Dosage
  - Pyrimethamine 50 mg x 1 / day
  - Sulfadiazine 1 mg x 3 / day
  - Folinic acid 50 mg/ week

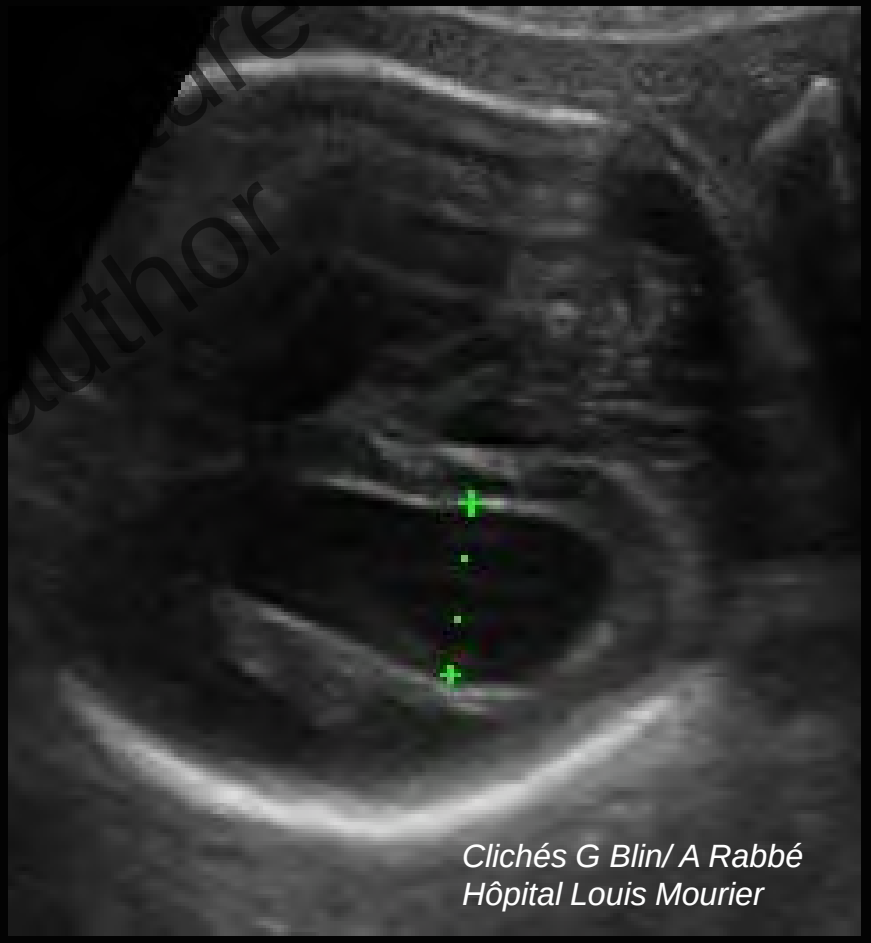
- Conditions
  - Inform women (couples) that no definite proof of benefit/risks
  - Weekly blood cell count
  - Ultrasound every 2 wks
  - Neonatal care

Prognostic factors : ultrasound signs

Ventriculomegaly

<u>Mme D</u> :

- **Maternal seroconversion between 19 and 23 weeks**
- **At 23 wks, ultrasound normal, spiramycin started**
- **At 26 weeks : enlarged ventricles**

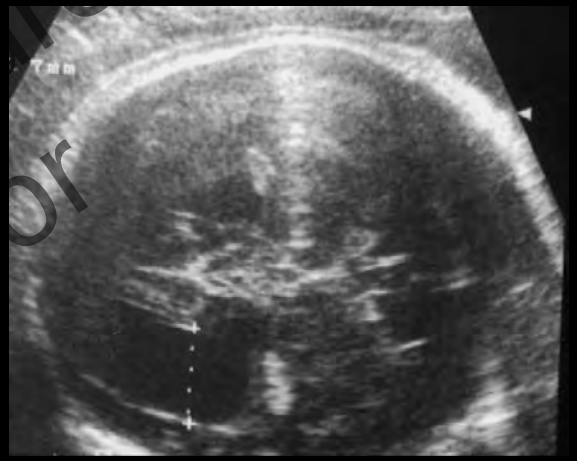


Clichés G Blin/ A Rabbé
Hôpital Louis Mourier

Ventricular dilatation : progression to hydrocephalus

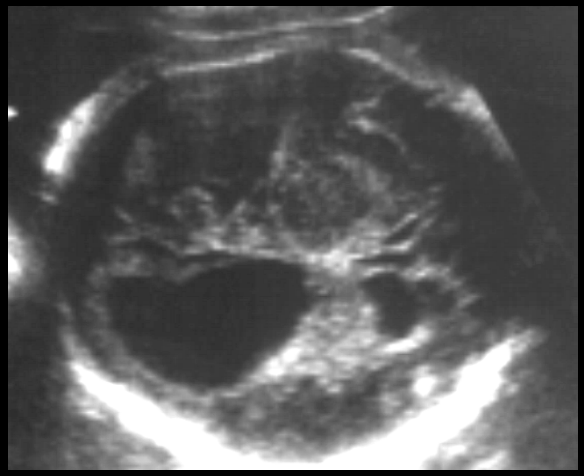
- seroconversion between 8 and 12 weeks gestation
- Amniocentesis at 22 weeks : normal ultrasound
- PCR positive

25 weeks

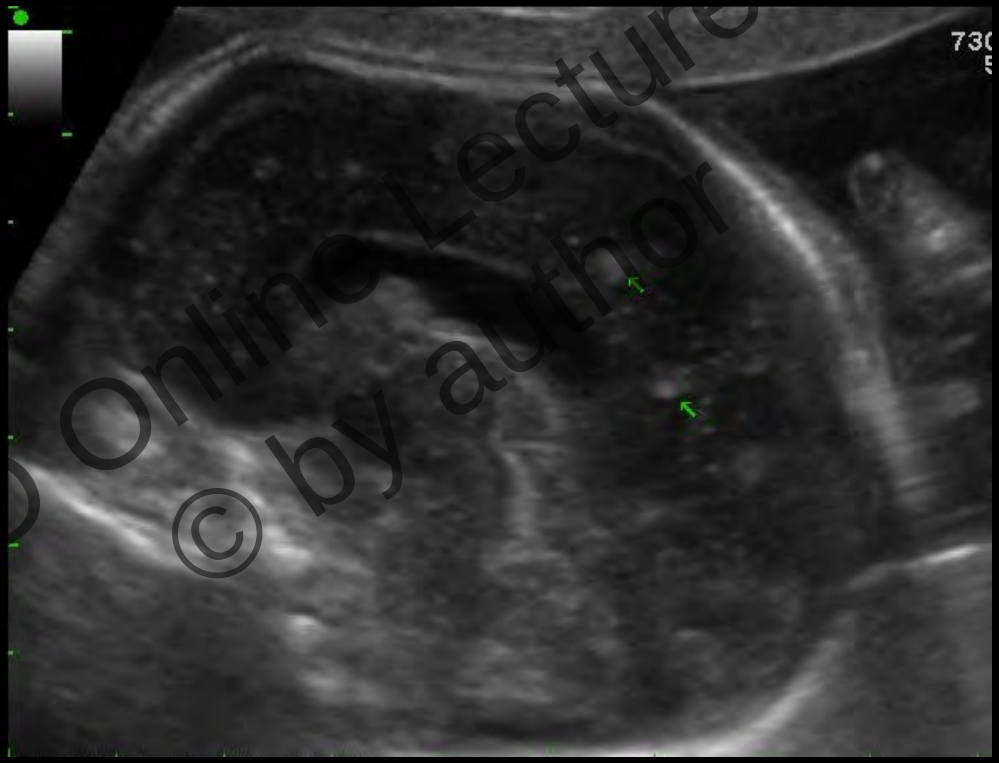


Clichés IPP

27 weeks

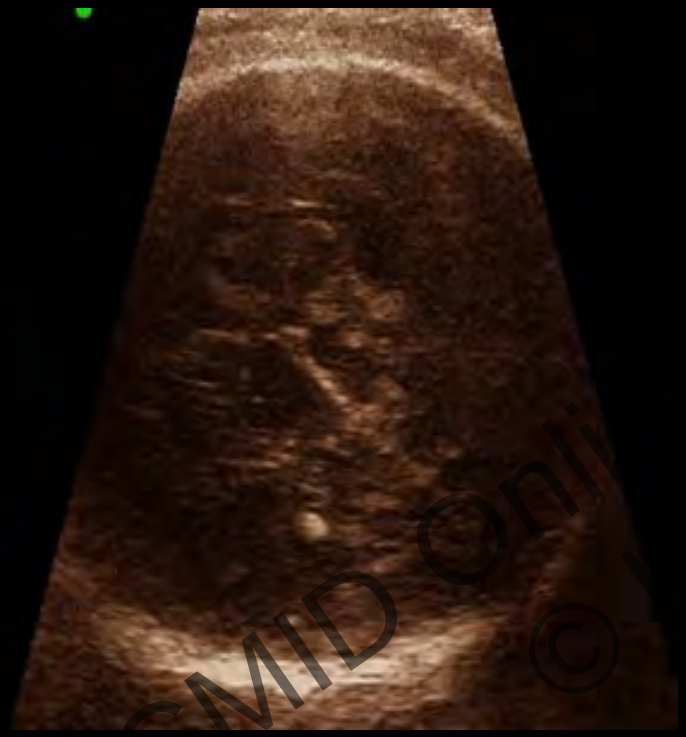


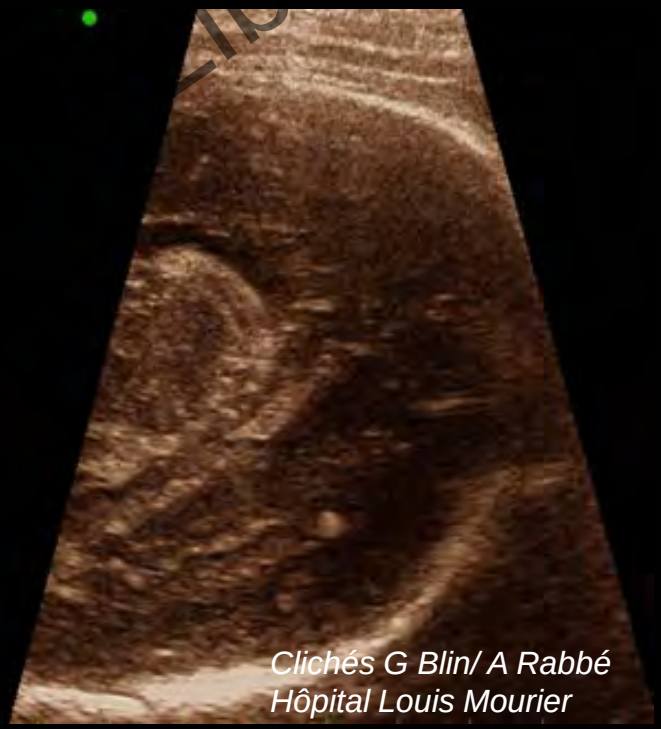
Intracranial densities associated with other cerebral signs



26 weeks, intracranial densities associated with ventricular dilatation and necrosis

Isolated intracranial densities



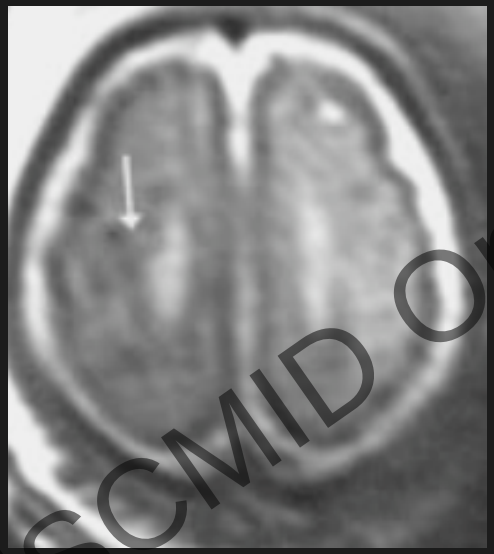


Clichés G Blin/ A Rabbé
Hôpital Louis Mourier

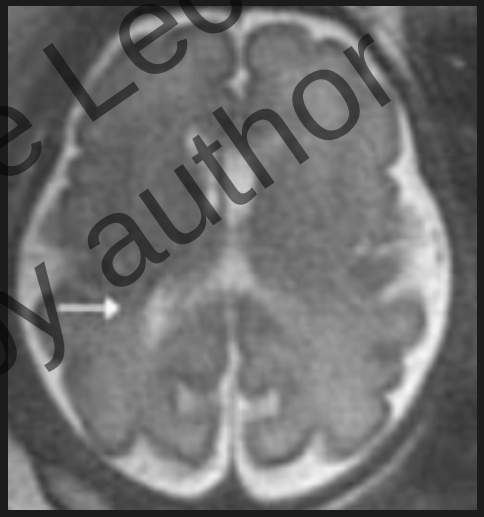
Prognosis difficult to establish
When few and without hydrocephalus, not correlated with neurological sequelae
Risk of seizures ?
Relation with chorioretinitis : aOR 4.3 (Kieffer 2008)

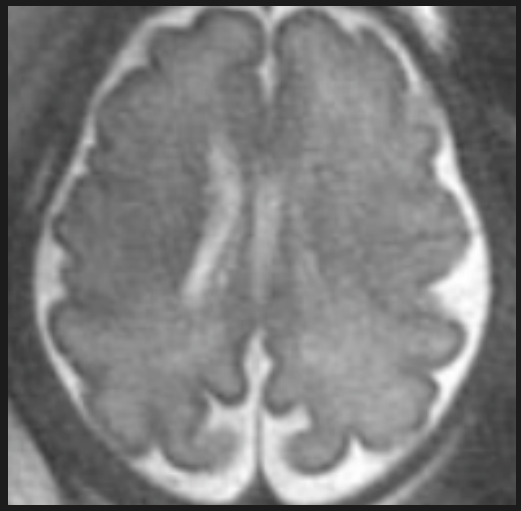
MRI in congenital toxo work-up ?

- Poor sensitivity for intracerebral densities
- Does not add to US for diagnosis of ventriculomegaly



26 weeks
small cystic cavity (bright signal) in frontal region
low signal intensity suggestive of calcifications (arrow)

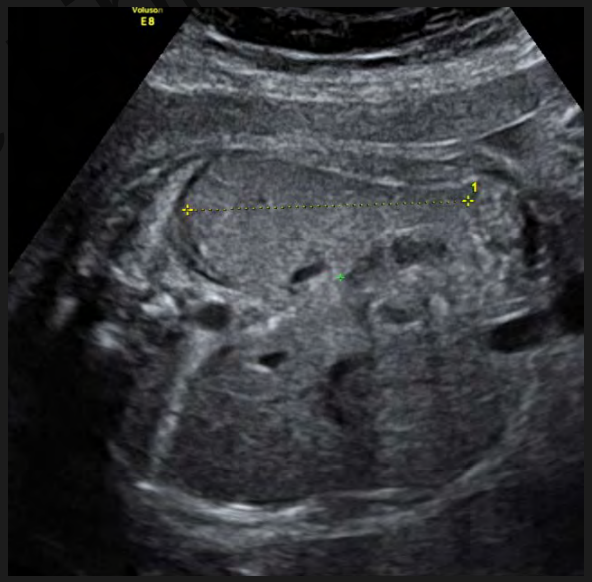


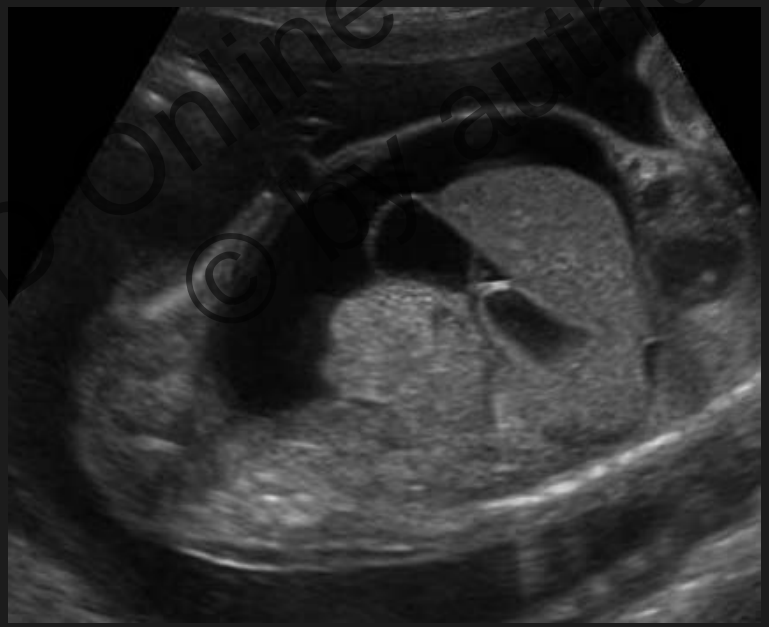


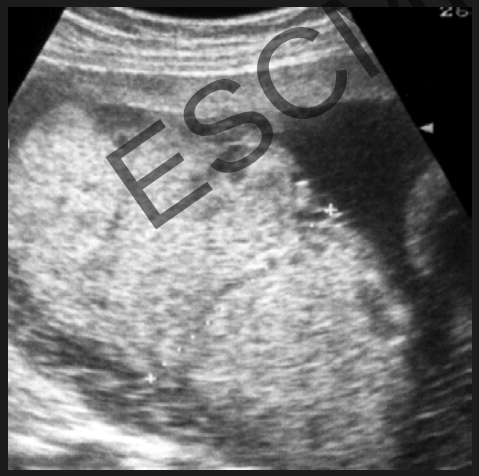
33 weeks
Unilateral ventriculomegaly
thickened ependymal/germinal zone (arrow)

Other ultrasound signs

- Enlarged placenta
- Ascitis, pleural effusion, hydrops
- Enlarged liver & spleen





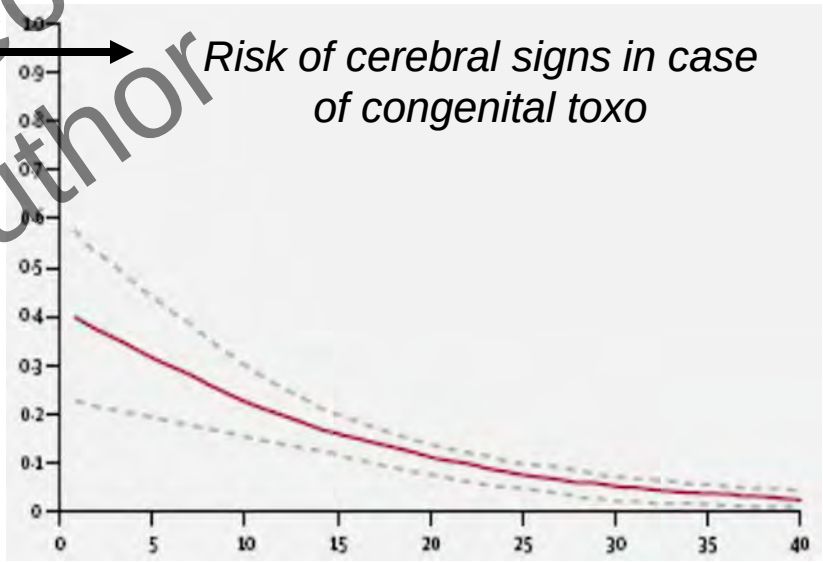


- non specific
- can be transient
- Prognostic value ?

The clinical questions differ according to timing of maternal seroconversion

Risk of transmission

Risk of cerebral signs in case of congenital toxo



Gestational age at primary infection

SYROCOT. Lancet, 2007

Periconceptional toxo : consider amniocentesis and therapy

- Main issue : determine whether toxoplasmosis likely occurred after conception (not true in most cases of positive IgM)
- If toxo is prior to pregnancy, reassure the couple
- If toxo is probably periconceptional :
  - Discuss prophylactic treatment
  - Ultrasound follow-up in all cases to detect severe lesions
  - Prenatal diagnosis option : benefit/risk of amniocentesis (objective to allow for therapy)

Third trimester seroconversion : offer amniocentesis and therapy

Background

- High risk of transmission
- Low risk of severe neurologic disease, but chorioretinitis can occur

Management options

-> Treat as soon as possible with spiramycine, with PYR/sulfa ?

- Time to serologic diagnosis : requires specific IgG to exclude cross-reacting IgM, immune response may be delayed by therapy
- Is the objective prophylaxis and/or for therapy

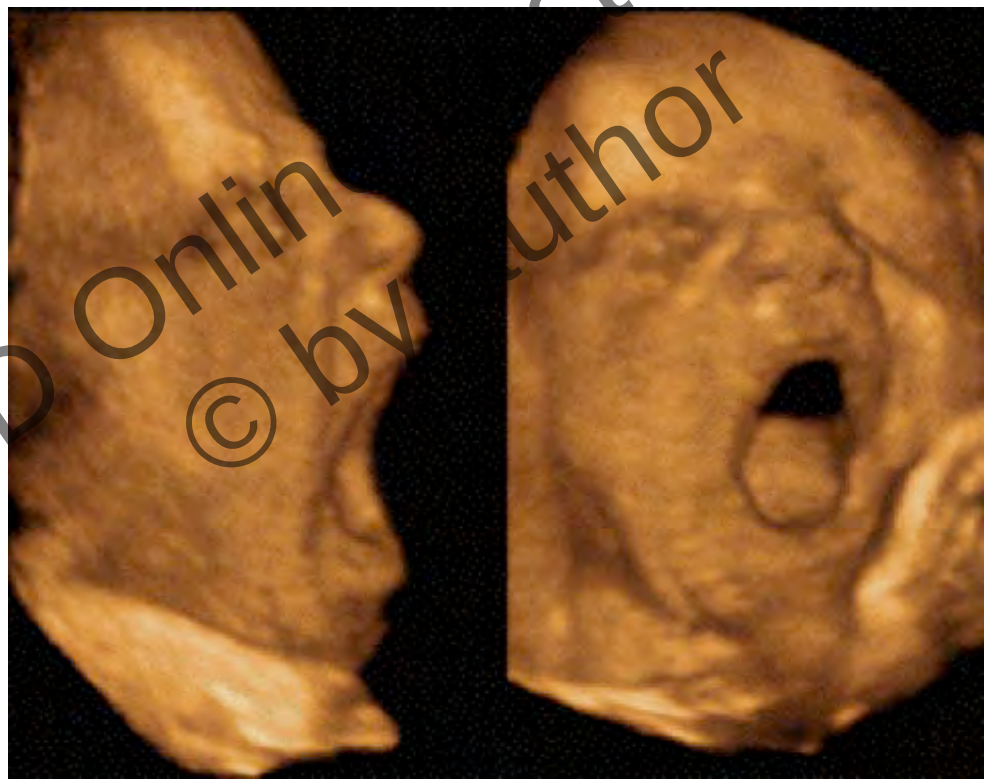
-> Should amniocentesis be performed ?

Useful for in utero therapy and timely postnatal care

Key points

- Diagnose and announce toxo seroconversion with care
- Prenatal diagnosis is reliable and should be offered
- The case for toxo screening depends on incidence and treatment efficacy
- Incidence is declining, treament efficacy is still unclear
- Changing paradigm : from pessimism (TOP) to optimism (in utero therapy), but more evaluation is required
- Main research issue today is prevention of mother-to-child tranmission of T. gondii

Thank you for your attention



A patient shows you the result of a toxoplasmosis screening test at 9 weeks gestational age : serology is IgG+ and IgM+. Which of the following statements are correct ?

A. She probably acquired primary toxoplasma infection in early pregnancy
B. The likelihood of congenital toxoplasmosis is about 5 %
C. Avidity testing should be used to determine whether she had toxoplasmosis before becoming pregnant
D. If preconceptional toxoplasmosis is diagnosed, an amniocentesis should be offered at about 15 weeks.

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Among the following, which are consequences commonly related to congenital toxoplasmosis which can be detected by prenatal ultrasound ?

A. Severe IUGR
B. Chorioretinitis
C. Ventricular dilatation
D. Ascitis
E. Intracerebral calcifications

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