Toxoplasmosis in pregnancy

Pr Laurent Mandelbrot
Service de Gynécologie-Obstétrique
Hôpital Louis Mourier, Colombes
Université Diderot Paris 7
Clinical scenarios

- Ultrasound screening  -> fetal toxo diagnosis
  - T toxoplasmosis
  - O other
  - R rubella
  - C CMV
  - H herpes

- Serological screening  -> maternal toxo diagnosis
National toxo screening policies in Europe
Toxo in pregnancy management, France

Serological screening

Primary infection

Spiramycin 3 M tid

Amniocentesis 4-6 weeks later (> 18 wks GA)

negative

Spiramycin until delivery
Monthly ultrasound
Neonatal work-up

positive

Prognostic evaluation

in utero therapy

Pyrimethamine 50g/day + sulfadiazine 1.5 mg bid
Folinic acid 50 mg/week + Weekly blood cell count
Ultrasound every 2 wks
Neonatal care

TOP

TOP
Estimated incidence: 3 p1000 pregnancies

Number of seroconversions/year: 2400

Number of prenatal diagnoses/year (22 certified labs): 1800

Number of positive prenatal diagnoses: 112

Number of TOP (46 CPDPN): 6 (4.3%)

(0.27% of total number of TOP in same centers)

Total number of congenital toxoplasmosis cases: 268

(3 / 10 000 births)
Prenatal diagnosis of toxoplasmosis

- Amniocentesis:
  - PCR toxo on amniotic fluid
  - At least > 1 month after seroconversion
  - After 18 wks

- Ultrasound: initial and monthly
Performance of state-of-art Toxoplasmosis PCR on amniotic fluid

Wallon et al, Obstet Gynecol. April 2010 - N=377

<table>
<thead>
<tr>
<th></th>
<th>First Trimester</th>
<th>Second Trimester</th>
<th>Third Trimester</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>75 (19–99)</td>
<td>97 (83–99.9)</td>
<td>88 (67–98.5)</td>
<td>92.2 (81–98)</td>
</tr>
<tr>
<td>Specificity</td>
<td>100 (97–100)</td>
<td>100 (95.4–100)</td>
<td>100 (66.4–100)</td>
<td>100 (98–100)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>100 (29.2–100)</td>
<td>100 (88.1–100)</td>
<td>100 (78.2–100)</td>
<td>100 (92.5–100)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>99 (96–99.9)</td>
<td>99 (93–99.9)</td>
<td>82 (48–98)</td>
<td>98.1 (95–99.5)</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of the Four Infected Children With Negative Polymerase Chain Reaction Results

<table>
<thead>
<tr>
<th>Case</th>
<th>Seroconversion</th>
<th>Spiramycin</th>
<th>Amniocentesis</th>
<th>IgM at Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>15.5</td>
<td>18</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>26</td>
<td>29</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>30.5</td>
<td>34</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>36</td>
<td>40</td>
<td>+</td>
</tr>
</tbody>
</table>

No false + Rare false -
A patient with 1st trimester infection

- At 12 wks: IgG+ IgM+ low avidity
- Amniocentesis at 19 wks
- Detection of *T.gondii* by PCR
Ultrasound follow-up at 20 SA +3 days

- Mild right ventriculomegaly 10 mm
- Ependyma 2 mm
- Placental thickness 25 mm
- No ascitis or hepatosplenomegaly
Outcome...

Termination of the pregnancy requested by patient, accepted by multidisciplinary committee (CPDPN), and performed at 21 wks

Pathology:
- Numerous zones of focal brain necrosis
- Ventriculomegaly
- Diffuse granulomatous placentitis

Photos AL Delezoide
Evaluating prognosis after 1st trimester congenital toxo

- One half of the fetuses will develop hydrocephalus
- Need for follow-up
- What is the risk for others?

36 children with congenital toxo from 1st trimester, without US abnormalities; mean follow-up 50 months, range 12–144 months
- 28 (78%) subclinical toxoplasmosis
- 7 (19%) chorioretinitis without major vision loss, normal intellectual development
- One (3%) developed severe congenital toxoplasmosis
Prognostic factors after positive prenatal diagnosis

- Timing of maternal infection
- Ultrasound signs
Prognostic factors:

1. time of maternal infection

Risk of cerebral signs or symptoms before 3 years of age

N = 473

SYROCOT. Lancet, 2007
Prognostic factors:
(2) quantitative PCR

Roman et al AJOG 2004
Prognostic factors:
(3) ultrasound signs
Ventriculomegaly

Example:
- Maternal seroconversion between 8 and 12 weeks
- Amniocentesis at 22 weeks: no abnormal US image
- PCR positive

25 weeks
27 weeks
Cerebral ultrasound abnormalities: pathophysiology

- Brain abnormalities due to necrosis
  - Ventricular dilatation
  - Intracerebral densities

- Hydrocephalus:
  - Obstruction of the aqueduct of Sylvius (and/or foramen of Monro)
  - Periventricular necrosis
Brain necrosis

31 weeks
Maternal infection during first trimester

One week later
Intracranial densities

- Less frequently observed than ventricular dilatation
- Underestimated by prenatal ultrasound because calcification is delayed
- Incidence not related to gestational age at maternal infection
- Due to focal necrosis
Intracranial densities

34 SA + 6j: 6 to 8 intracerebral densities
Toxo seroconversion at 22 wks
  => spiramycine
Amniocentèse at 29 wks: PCR+
  => Pyr/sulfadiazine
Ultrasound at 31 wks: nodules
MRI findings

- 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)
Prognosis of intracranial densities

- Difficult to establish during pregnancy
- When few and without hydrocephalus, not correlated with neurological sequelae
- Risk of seizures later in childhood?
- Relation with chorioretinitis:
  - Hohlfeld J Pediatr 1989
  - Jacquemard 2003
  - Kieffer 2008 (n=300, 7.3% with calcifications at birth, 12% with chorioretinitis): aOR 4.3
Other ultrasound signs

- Enlarged placenta
- Ascitis, pleural effusion, hydrops
- Enlarged liver & spleen
  - non specific
  - may be transient
  - Prognostic value uncertain
**Second trimester seroconversion**

- IgM+ : cross reaction or seroconversion?
- Higher transmission but lower risk of neurological damage
- Prenatal diagnosis: ultrasound, amniocentesis
- Discuss late TOP according to local laws
- Treatment issues ++: the main point of prenatal diagnosis is to allow for in utero therapy
Third trimester seroconversion

- High risk of transmission
- Low risk of severe neurologic disease, but chorioretinitis can occur
- TOP not a reasonable option

-> Treat as soon as possible with PYR/sulfa?
   But time to serologic diagnosis (exclude cross-reacting IgM)

-> Should amniocentesis be performed?
   Issue of sensitivity
Risk of transmission according to timing of maternal infection

SYROCOT. Lancet, 2007
Risk of clinical signs and symptoms in children with congenital toxo according to time of maternal infection

Risk of eye lesions before 3 years of age
N = 526

Wks gestational age at seroconversion

SYROCOT. Lancet, 2007
Therapy for toxoplasmosis in pregnancy

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

2) In utero therapy for infected fetus, following prenatal diagnosis
What do the studies show?

- No proof of efficacy of antenatal toxo treatment as prevention
  - No RCT
  - Historical cohort study: Desmonts & Couvreur NEJM 1974

- Is prevention with spiramycin too little or too late?
  - Too little because poor efficacy on T gondii vs Pyr/sulfa and other combinations
  - Too late after parasite has already infected the fetus: in Syrocot (transmission RR = 0.48 if therapy < 3 wks vs > 8 wks after serconversion)

- Observational studies will never be able to conclude
Can we prevent toxo transmission to the fetus?

Maternal primary infection

Parasitemie (tachyzoïtes)

Placenta

fetal infection

Tachyzoïtes

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

Toxo seroconversion

Eligibility / consent

Randomize

Pyrimethamine - sulfadiazine
spiramycine

Prenatal diagnosis

Conventional management

Outcome measures: transmission, tolerance
Conclusion

- Why screen for maternal infection, why perform prenatal diagnosis?

- Changing paradigm: from pessimism (TOP) to optimism (in utero therapy), but more evaluation is required

- Our ultimate objective should be to prevent mother-to-child transmission of T. gondii altogether
Take-home messages

- Toxoplasmosis seroconversion in pregnancy must not be considered as routine
- Diagnosis should be announced tactfully, and patient referred for specialized counselling and care
- Prenatal diagnosis is reliable and should be offered
- Children with congenital toxo require follow-up with specialists
- Research is required for the prevention of congenital toxo
Thank you for your attention