Did the fetus catch it?
The role of ultrasound in perinatal infections
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1. Mother has known infection- did it affect the fetus in a "sonographically recognizable" way?

2. Sonographic fetal findings- were they caused by transmission of maternal (possibly unrecognized) infection?

Disclaimer
I have no conflict of interest with respect to any of the material presented in this lecture. I am on the Ob/Gyn Board of advisors of Philips Healthcare and Siemens. I will not discuss off-label or unapproved uses of drugs or devices.

In utero infection
- Congenital syndrome
- Congenital infection

Intrapartum infection

Post partum infection

Congenital syndrome
CMV
Parvovirus B19
Rubella
Varicella (Chickenpox) and Herpes Zoster
Toxoplasma
HIV (?)
**Congenital infection**

- Syphilis
- GBS
- Listeriosis
- HSV
- HIV

**Limitations**

- Most infected fetuses will be sonographically normal
- Ultrasound findings may change with time
- No strong correlation with neonatal outcome

**Neonatal infection**

- GBS
- Hep B
- Hep C
- Gonorrhea
- Condylomata Acuminata
- Chlamydia trachomatis
- Candida
- HIV

**Did the fetus catch it?**

**Diagnosis**

1. Direct: PUBS (Amniocentesis)
2. Indirect: sonographic findings
In utero infection

Congenital syndromes

**CMV**

- Double stranded DNA herpes virus
- Emerged in recent years as the most important cause of congenital infection in the developed world
- Approximately 1% (range, 0.5-2.5%) of all newborns are congenitally infected with CMV

CMV

- Approximately 10% of congenital CMV occur in women with primary infection during pregnancy, and 90% of these infants have neurological sequelae.
- Preexisting immunity (eg, maternal recurrent infection) protects against severe disease, but sequelae in approximately 15% of these infants, particularly sensorineural hearing loss.

CMV

- Route of congenital infection: presumably transplacental.
- May also be transmitted perinatally (aspiration of cervicovaginal secretions in the birth canal and/or breastfeeding).
- More than 50% of infants fed with breast milk that contains infectious virus become infected with CMV.

CMV

- Most common congenital infection (1% of live births)
- 10% of infected neonates demonstrate clinical manifestations that could be identified, theoretically, by prenatal ultrasound
  - Ventriculomegaly, intracranial calcifications, IUGR, oligohydramnios
**CMV**

Chaoui et al.: Marked splenomegaly in fetal CMV infection: detection supported by 3-D power Doppler ultrasound. UOG 2002;20:299-302

**Parvovirus infection**

B19 Non-immune hydrops (NIH)

**Parvovirus**

- Most infected fetuses are sonographically normal
- Findings may change with time
- No direct correlation with infant outcome

**Rubella**

- Single-stranded RNA virus of the togavirus family
- Mild exanthematous disease of childhood
- In pregnant host, can have catastrophic effects on fetus (first described by Gregg in 1941).
- Last epidemic in prevaccine era (1964-1965): approx. 11,000 miscarriages, abortions, stillbirths, and approx. 20,000 cases of congenital rubella syndrome in newborns

Indirect evidence:
- Fetal anemia
- PUBS
- MCA Doppler (PSV)
- Sens: 94%
- Spec: 93%
- PPV: 94%
- NPV: 93%

(Caumi et al. AJOG, 2002;187:1290-3)
**RUBELLA**

- Incidence: < 1:100,000 live births
- Prenatal diagnosis by sonographic findings never reported
- Potential detected abnormalities: cardiac anomalies, microcephaly, hepatosplenomegaly, IUGR, cataract, microphthalmia

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**Varicella and Herpes Zoster**

- Incidence: 0.7/1000 pregnancies
- Infection until 28 weeks can lead to intrauterine infection
- 1-2% risk of developing congenital varicella syndrome (CVS):
  1. Virus-specific deformation sequence: limb hypoplasia, skin scarring, microcephaly, microophthalmia, cataract, cerebellar dysplasia, GI or/and GU malformations.
  2. Non-specific NIH-like syndrome

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**Varicella and Herpes Zoster**

- Most common reported ultrasound finding: polyhydramnios
- Also reported: intrahepatic calcifications, hepatomegaly, hydrops, limb malformations, ventriculomegaly, IUGR

Toxoplasmosis

Infection:
1. Contact with cat feces (gardening or cleaning litter box).
2. Eating contaminated food (lamb, pork and venison).
3. Unpasteurized dairy products and even water can also become contaminated.
4. Unwashed produce and not properly cleaned utensils or cutting boards.
5. Very rare cases, may be acquired through organ transplant or blood transfusion.

Incidence of congenital toxoplasmosis: 1/1000-1/10 000 live births. 50% of fetuses infected, 1/3 sub clinical infection, 1/10 severe infection. Risk of congenital toxoplasmosis: lower if infection occurs during the first trimester (10% to 25%) than during the third trimester (60% to 90%). But severity of congenital infection is substantially higher if infection occurs during the first trimester.

Typical triad: hydrocephalus, chorioretinitis, and intracranial calcifications. Does not always occur.

- Hepatosplenomegaly, thrombocytopenia, microcephaly, convulsions, fever, and SGA
- Most neonates: asymptomatic at birth on routine examination but deafness, mental delay, learning difficulties often detected later in life.
**HIV+ mother**
- Dysmorphic syndrome in children exposed to HIV in utero: IUGR (75%), microcephaly (70%), and craniofacial abnormalities [hypertelorism (50%), prominent forehead (75%), flat nasal bridge (70%), obliquity of the eyes (65%), long palpebral fissures (60%), short nose (65%), and patulous lips (60%)]

Marion et al., 1986-87

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**In utero infection**

**Congenital infection**

- Reduced left ventricular size (but no altered function)
- Shorter femurs

Hornberger et al. Am Heart J, 2000;140:575-84

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**Syphilis**

- Treponema pallidum

Nearly half of all fetuses infected with syphilis die shortly before or after birth.

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**Group B Streptococcus (GBS)**

- Most frequent sonographic manifestations: hepatomegaly, placentomegaly
- Less common: ascites, hydrops and polyhydramnios
- Resolution of sonographic signs reported with maternal therapy

- GBS: most common cause of life-threatening infections in newborns
- Maternal infection at conception or within the first two weeks of pregnancy may lead to:
  - Hearing loss
  - Vision loss
  - Mental delay
Listeriosis

*Listeria monocytogenes*: gram-positive, motile bacillus with aerobic and facultative anaerobic characteristics. Found in soil and water and can be carried by animals that do not appear ill, leading to contamination of food of animal origin, particularly ready-to-eat foods such as meats and dairy products. Other potential sources: unpasteurized raw milks or foods.

Placental transfer: can cause amnionitis, resulting in spontaneous septic abortion or PTL with delivery of infected baby. Fetal infection may manifest as septicemia, meningoencephalitis, or disseminated granulomatous lesions with microabscesses. Twenty-two percent of perinatal infections result in neonatal death or stillbirth.

Herpes simplex (HSV)

- Congenital infection: often severe, high morbidity and mortality.
- Most cases acquired during delivery.
- Intrauterine infection: transplacental passage or ascending, local infection.
- Transplacental infection may result in a neonate born with skin lesions, multisystem organ failure and CNS lesions consistent with destruction of developing brain tissue (microcephaly,hydranencephaly, multicystic encephalomalacia), as well as microophthalmia, chorioretinitis, NIH.
HSV

- 100 reported cases of intrauterine infections resulting in clinical signs
- Only sonographic sign reported antenatally: hydranencephaly
- Potentially detectable: microcephaly, intracranial calcifications, IUGR

Sonographic findings: a sign of intrauterine infection?

Ventriculomegaly

- Measured at the posterior aspect of the choroid plexus (atrium)
- Almost always symmetric
- Only about 5% of cases can be attributed to fetal infection
Intracranial Calcifications

- Rare: 10-15% of affected, scanned fetuses
- Main cause: Intrauterine infection
- Hallmark: periventricular hyperechoic foci
- May also be located in the thalami and basal ganglia
- Small with no acoustic shadowing
- Most frequent etiology: CMV and Toxoplasmosis (also Rubella and Tri 13)

Hydranencephaly

- Most severe (end-stage) manifestation of destructive process
- Cerebral hemispheres replaced by fluid
- Brain stem preserved, posterior fossa structures can be identified
- Falx present, absent or deviated
- Think: CMV, Toxoplasmosis, Herpes simplex, Rubella
- (Tri 13, neoplasms, bleeding disorders, syndromes)

Microcephaly

- Rarely isolated. Often associated with other CNS anomalies
- Diagnosis: HC >3SD below mean for GA
- Abnormal HC/AC and HC/FL ratios
- Isolated microcephaly: documented in CMV, Rubella and Herpes simplex
Cardiac anomalies

- Cardiomegaly: mostly in CMV (Check cardiothoracic ratio)
- VSD, ASD, Pulmonic stenosis and coaractation of the aorta: Rubella

Intra-abdominal Calcifications

- Typical appearance: echogenic foci with acoustic shadowing
- Peritoneum, intestinal lumen, organ parenchyma, biliary tree and vascular structures
- Different from echogenic bowels
- Think: CMV and Toxoplasmosis

Hepatosplenomegaly

- Documented in all TORCH infections
- Often transient finding
- Nomograms are available

Hydrops, Placenta and Amniotic fluid

- Hydrops reported in most TORCH but may be transient
- Placentomegaly: usually associated with intrauterine infection, but small placentae have also been reported
- Hydramnios and oligohydramnios have been reported with similar frequency

Fetal growth restriction

- EFW< 10th percentile
- Common feature in early infection with almost any infection (Syphilis in particular)
Controversies

- Influenza
- Measles
- Mumps
- Echoviruses
- Coxsackie viruses

Major (common) sonographic findings

- IUGR
- Ventriculomegaly
- Hydrops
- Intracranial calcifications
- Intraabdominal calcifications
- Echogenic bowels

Less common

- Hepatosplenomegaly
- Cardiac anomalies
- Hydranencephaly
- Microcephaly

IUGR

Common in:
- CMV
- Rubella
- HSV
- Varicella

Ventriculomegaly

5% of cases can be attributed to fetal infection

Intracranial calcifications

- CMV
- Toxoplasmosis
- Rubella
- HSV
Mechanisms
Cardiovascular failure
Chromosomal anomalies
Fetal anemia
Chest compression
Twinning

Possible mechanisms in infections:
- Fetal anemia, myocarditis, hepatitis
- May be transient
- Placentomegaly may be early or only sign

Intra-abdominal (hepatic) calcifications

Echogenic focus with acoustic shadowing
- Peritoneal (meconium peritonitis)
- Parenchymal (infection, tumor)
- Vascular (calcified portal or venous clots)

Intrahepatic calcifications

HSV
Varicella-Zoster
Rubella
CMV
Echovirus 11
Syphilis
Toxoplasmosis

Echogenic bowels

Definition: bowels as echogenic as bone (decrease overall gain to check)

CMV
Toxoplasmosis
Echogenic bowels

Severe malformations: 9%
Multifetal pregnancy: 9%
Bowel obstruction: 6%
Abnormal karyotype: 6%
Intrauterine infection: 6%
CF: 2.5%
Unknown: 38%

Yaron et al. Fetal Diag Ther, 1999;14:176-80. n=79

Pearls

- Ultrasound is not a sensitive test for fetal infection
- Normal sonographic fetal anatomy does not predict favorable outcome
- Multiple organ systems affected in 50% of cases

Ventriculomegaly, intracranial and hepatic calcifications:
CMV

Ocular and cardiac anomalies:
Congenital rubella syndrome

Limb contractures and cerebral anomalies:
Varicella zoster virus

Thank you