Intrauterine Infections
Question

What is the differential diagnosis of a 3 year old girl with bilateral cataracts, ECHO confirmed PDA, PS and TOF
Intrauterine Infections

- Toxoplasmosis
- Rubella
- Cytomegalovirus (CMV)
- Human Herpes Simplex

Others
- Syphilis
- HIV
- Parvovirus B19
- Varicella-Zoster (VZV)
- Enteroviruses
- HTLV-1
- Hepatitis C
- Hepatitis B
- Lassa Fever
- Japanese Encephalitis
# Toxoplasmosis

<table>
<thead>
<tr>
<th>Causative</th>
<th>protozoan – Toxoplasma gondii</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive host</td>
<td>Cat</td>
</tr>
<tr>
<td>Transmission</td>
<td>Transplacentally, during vaginal delivery</td>
</tr>
<tr>
<td>High infectivity</td>
<td>3rd trimester (65%)</td>
</tr>
<tr>
<td>Higher mortality</td>
<td>1st trimester (17%), rare if infected before pregnancy</td>
</tr>
<tr>
<td>Clinical features</td>
<td>70-90% asymptomatic</td>
</tr>
<tr>
<td>Clinical triad</td>
<td>Chorioretinitis, Hydrocephalus and Intracranial calcifications</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>Fever, rash, HSM, microcephaly, seizures, jaundice, IUGR, MR thrombocytopenia, lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>Almost all congenitally infections not treated manifest signs or symptoms of infection, by adolescence e.g. chorioretinitis</td>
</tr>
</tbody>
</table>
Diagnosis
Culture from placenta, umbilical cord, infant serum

PCR testing on WBC, CSF, placenta IgM, IgA

Chorioretinitis of congenital toxo
Prevention and Treatment

- Treatment for pregnant mothers diagnosed with acute toxo
  - Spiramycin daily
    - Macrolide antibiotic
  - Small studies have shown this reduces likelihood of congenital transmission (up to 50%)
- If infant diagnosed prenatally, treat mom
  - Spiramycin, pyrimethamine (anti-malarial, dihydrofolate reductase inhib), and sulfadiazine (sulfa antibiotic)
  - Leucovorin rescue with pyrimethamine
- Symptomatic infants
  - Pyrimethamine (with leucovorin rescue) and sulfadiazine
  - Treatment for 12 months total
- Asymptomatic infants
  - Course of same medications
  - Improved neurologic and developmental outcomes demonstrated (compared to untreated pts or those treated for only one month)
# Syphilis

<table>
<thead>
<tr>
<th>Causative</th>
<th>Treponema pallidum (spirochete)</th>
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<tbody>
<tr>
<td>Definitive host</td>
<td>Sexually transmitted through direct contact with sore or rash</td>
</tr>
<tr>
<td>Transmission</td>
<td>Transplacentally</td>
</tr>
<tr>
<td>High infectivity</td>
<td>2nd trimester</td>
</tr>
<tr>
<td>Higher mortality</td>
<td>Rarely latent form</td>
</tr>
<tr>
<td>Clinical features</td>
<td>2/3 of affected live-born infants are asymptomatic at birth</td>
</tr>
<tr>
<td>Classification</td>
<td>Fetal effects, Early effects, Late effects</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>Fetal effects,: Still birth, Neonatal death, Hydrops fetalis, IUFD 25%</td>
</tr>
<tr>
<td></td>
<td>Early effects: Cutaneous lesions (palms/soles), HSM, Jaundice, Anemia, Snuffles, Periostitis and metaphysial dystrophy, Funisitis (umbilical cord vasculitis)</td>
</tr>
</tbody>
</table>
Radiograph of the extremities

Periostitis of long bones seen in neonatal syphilis

Preventable with appropriate treatment
Clinical Manifestations

• Late congenital:
  – Frontal bossing
  – Short maxilla
  – High palatal arch
  – Hutchinson teeth
  – 8th nerve deafness
  – Saddle nose
  – Perioral fissures

• Can be prevented with appropriate treatment
Diagnosis

• Primary syphilis confirmed with dark-field microscopy or direct fluorescent antibody to *T. pallidum* on skin lesions, placenta, or umbilicus specimens

• Polymerase chain reaction (PCR)

• Serologic tests for syphilis.
Diagnosis

• Available serologic testing
  – /VDRL: nontreponemal test all pregnant women in the 1st trimester and at birth
    • Sensitive but NOT specific
    • Quantitative, so can follow to determine disease activity and treatment response

  – TPHA/TPPA/FTA-ABS: specific treponemal test
    • Used for confirmatory testing
    • Qualitative, once positive always positive
      \[[T. pallidum\] hemagglutination assay (TPHA), Fluorescent treponemal antibody absorption (FTA-ABS) test
      \[T. pallidum\] particle agglutination (TPPA) test\]
CDC Definition of Congenital Syphilis

• Confirmed if T. pallidum identified in skin lesions, placenta, umbilical cord, or at autopsy

• Presumptive diagnosis if any of:
  – Physical exam findings
  – CSF findings (positive VDRL)
  – Osteitis on long bone x-rays
  – Funisitis (“barber shop pole” umbilical cord)
  – RPR/VDRL >4 times maternal test
  – Positive IgM antibody
Treatment

• Penicillin G is THE drug of choice for ALL syphilis infections
• Maternal treatment during pregnancy very effective (overall 98% success)
• Treat newborn if:
  – They meet CDC diagnostic criteria
  – Mom was treated <4wks before delivery
  – Mom treated with non-PCN med
  – Maternal titers do not show adequate response (less than 4-fold decline)
Characteristics of Rubella

• Single stranded RNA enveloped virus, member of the togavirus family

• Spread by respiratory droplets. maculopapular rash, lymphadenopathy, fever, arthropathy (up to 60% of cases)

• In the prevaccination era, 80% of women were already infected by childbearing age.
## Risks of rubella infection during pregnancy

<table>
<thead>
<tr>
<th>Preconception</th>
<th>minimal risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12 weeks</td>
<td>100% risk of fetus being congenitally infected resulting in major congenital abnormalities. Spontaneous abortion occurs in 20% of cases.</td>
</tr>
<tr>
<td>13-16 weeks</td>
<td>deafness and retinopathy 15%</td>
</tr>
<tr>
<td>after 16 weeks</td>
<td>normal development, slight risk of deafness and retinopathy</td>
</tr>
</tbody>
</table>
## Congenital Rubella Syndrome

Other abnormalities which may be transient, permanent and developmental.

<table>
<thead>
<tr>
<th>Category</th>
<th>Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient</td>
<td>low birth weight, hepatosplenomegaly, thrombocytopenic purpura bone lesions, meningoencephalitis, hepatitis, haemolytic anemia pneumonitis, lymphadenopathy</td>
</tr>
<tr>
<td>Permanent</td>
<td>Sensorineural deafness, Heart Defects (peripheral pulmonary stenosis, pulmonary valvular stenosis, patent ductus arteriosus, ventricular septal defect) Eye Defects (retinopathy, cataract, microophthalmia, glaucoma, severe myopia) Other Defects (microcephaly, diabetes mellitus, thyroid disorders, dermatoglyptic abnormalities)</td>
</tr>
<tr>
<td>Developmental</td>
<td>Sensorineural deafness, Mental retardation, Diabetes Mellitus, thyroid disorder</td>
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</table>
Prevention/Treatment

• Testing for immune status against rubella available

• Highly effective live attenuated vaccine has been available with 95% efficacy

• MMR regimen for schoolgirls/ mother before pregnancy/immediate post partum period

• Hard immunity for efficiency of vaccination

• Treatment mainly preventive
“Blueberry muffin” spots representing extramedullary hematopoiesis
Diagnosis

- Maternal IgG may represent immunization or past infection - Useless!
- Can isolate virus from nasal secretions
  - Less frequently from throat, blood, urine, CSF
- Serologic testing
  - IgM = recent postnatal or congenital infection
  - Rising monthly IgG titers suggest congenital infection
- 15 IU/ml is regarded as the cut-off for immunity
Cytomegalovirus

• Member of the herpesvirus

• Primary infection usually asymptomatic. Virus then becomes latent and is reactivated from time to time.

• Transmitted by infected saliva, breast milk, sexually and through infected blood
Congenital Infection

• Defined as the isolation of CMV from the saliva or urine within 3 weeks of birth, CMV IgM from the blood of the neonate, Cytomegalic Inclusion Bodies from affected tissue (rarely used)

• Commonest congenital viral infection, affects 0.3 - 1% of all live births. The second most common cause of mental handicap after Down's syndrome and is responsible for more cases of congenital damage than rubella.

• Transmission to the fetus may occur following primary or recurrent CMV infection. 40% chance of transmission to the fetus following a primary infection.

• May be transmitted to the fetus during all stages of pregnancy.

• No evidence of teratogenecity, damage to the fetus results from destruction of target cells once they are formed.
Cytomegalic Inclusion Disease

- CNS abnormalities - microcephaly, mental retardation, spasticity CP, epilepsy, periventricular calcification.
- Eye - choroidoretinitis and optic atrophy
- Ear - sensorineural deafness
- Liver - hepatosplenomegaly and jaundice which is due to hepatitis.
- Lung - pneumonitis
- Heart - myocarditis
- Thrombocytopenic purpura, Haemolytic anaemia
- Late sequelae in individuals asymptomatic at birth - hearing defects and reduced intelligence.
Management

• Primary Infection
• 40% chance of the fetus being infected.
• 10% chance that congenitally infected baby will be symptomatic at birth or develop sequelae later in life.
• Severe sequelae associated with earlier acquisition
• Therefore in case of primary infection, there is a 4% chance (1 in 25) of giving birth to an infant with CMV problems.

• Vaccination - may become available in the near future.
Ventriculomegaly and calcifications of congenital CMV
Treatment

• Ganciclovir x 6wks in symptomatic infants
  – Studies show improvement or no progression of hearing loss at 6mos
  – No other outcomes evaluated (development, etc.)
  – Neutropenia often leads to cessation of therapy

• Treatment currently not recommended in asymptomatic infants due to side effects
Herpes Simplex (HSV)

• HSV1 or HSV2
• Primarily transmitted through infected maternal genital tract
  – Rationale for C-section delivery prior to membrane rupture
• Primary infection with greater transmission risk than reactivation
Clinical Manifestations

• Most are asymptomatic at birth

• 3 patterns of ~ equal frequency with symptoms between birth and 4wks:
  – Skin, eyes, mouth (SEM)
  – CNS disease
  – Disseminated disease (present earliest)

• Initial manifestations very nonspecific with skin lesions NOT necessarily present
Presentations of congenital HSV
Diagnosis

• Culture of maternal lesions if present at delivery
• Cultures in infant:
  – Skin lesions, oro/nasopharynx, eyes, urine, blood, rectum/stool, CSF
• CSF PCR
• Serologies again not helpful given high prevalence of HSV antibodies in population
Treatment

• High dose acyclovir 60mg/kg/day divided q8hrs
  – X21days for disseminated, CNS disease
  – X14days for SEM
• Ocular involvement requires topical therapy as well
Neonatal Herpes Simplex (1)

• Incidence of neonatal HSV infection varies inexplicably from country to country e.g. from 1 in 4000 live births in the U.S. to 1 in 10000 live births in the UK.

• The baby is usually infected perinatally during passage through the birth canal.

• Premature rupturing of the membranes is a well recognized risk factor.

• The risk of perinatal transmission is greatest when there is a florid primary infection in the mother.

• There is an appreciably smaller risk from recurrent lesions in the mother, probably because of the lower viral load and the presence of specific antibody.

• The baby may also be infected from other sources such as oral lesions from the mother or a herpetic whitlow in a nurse.
Neonatal Herpes Simplex (2)

- Neonatal HSV infection varies from a mild disease localized to the skin to a fatal disseminated infection.
- Infection is particularly dangerous in premature infants.
- Where dissemination occurs, the organs most commonly involved are the liver, adrenals and the brain.
- Where the brain is involved, the prognosis is particularly severe. The encephalitis is global and of such severity that the brain may be liquefied.
- A large proportion of survivors of neonatal HSV infection have residual disabilities.
- Acyclovir should be promptly given in all suspected cases of neonatal HSV infection.
- The only means of prevention is to offer caesarean section to mothers with florid genital HSV lesions.
Parvovirus

- Causative agent of Fifth disease (erythema infectiosum), clinically difficult to distinguish from rubella.
- Also causes aplastic crisis in individuals with haemolytic anaemias as erythrocyte progenitors are targeted.
- Spread by the respiratory route, 60-70% of the population is eventually infected.
- 50% of women of childbearing age are susceptible to infection.
Congenital Parvovirus Infection

- Known to cause fetal loss through hydrops fetalis; severe anaemia, congestive heart failure, generalized oedema and fetal death.
- No evidence of teratogenicity.
- Risk of fetal death highest when infection occurs during the second trimester of pregnancy (12%).
- Minimal risk to the fetus if infection occurred during the first or third trimesters of pregnancy.
- Maternal infection during pregnancy does not warrant termination of pregnancy.
- Cases of diagnosed hydrops fetalis had been successfully treated in utero by intrauterine transfusions and administration of digoxin to the fetus.
Varicella-Zoster Virus

• 90% of pregnant women already immune, therefore primary infection is rare during pregnancy
• Primary infection during pregnancy carries a greater risk of severe disease, in particular pneumonia

First 20 weeks of Pregnancy

up to 3% chance of transmission to the fetus, recognised congenital varicella syndrome;
• Scarring of skin
• Hypoplasia of limbs
• CNS and eye defects
• Death in infancy normal
Neonatal Varicella

- VZV can cross the placenta in the late stages of pregnancy to infect the fetus congenitally.
- Neonatal varicella may vary from a mild disease to a fatal disseminated infection.
- If rash in mother occurs more than 1 week before delivery, then sufficient immunity would have been transferred to the fetus.
- Zoster immunoglobulin should be given to susceptible pregnant women who had contact with suspected cases of varicella.
- Zoster immunoglobulin should also be given to infants whose mothers develop varicella during the last 7 days of pregnancy or the first 14 days after delivery.
MOTHER TO CHILD TRANSMISSION OF HIV (MTCT)

- The number of HIV-positive infants born annually in Nigeria ranges from 64,900 to 103,840
- Also referred to as vertical or perinatal transmission.
- It is the major route of HIV transmission in children under 15 years.
- MTCT accounts for over 90% of the global 800,000 annual pediatric HIV infection
- 90% of these infections occur in sub-Saharan Africa.
- Nigeria is estimated to account for the largest number of AIDS orphans.
MOTHER TO CHILD TRANSMISSION OF HIV (MTCT)

• Transmission rate:
  15-25% in developed countries.
  25-40% in developing countries
• The transmission may occur during pregnancy, labour/delivery and breastfeeding.

• About 60-65% transmission appears to occur during delivery.

• The risk of MTCT increase if a woman becomes infected or re-infected with HIV during pregnancy or when she become ill with AIDS (high viral load).

• Concurrent parasitic, bacterial or viral infections.

• Exposure to maternal blood or cervical secretion during delivery.
HIV Diagnosis

• Presence of HIV virus (antigen) rather than antibody (persisting maternal antibody)

• Use of virological tests DNA PCR

• Ideally: @ birth, 6/52, 3-6/12

• If resources are limited; @ 6 -8/52 (98% sens @ 4/52)

• Dry Blood Spot (DBS) can be used

• Repeat virology on different specimen or antibody test >18 months
<table>
<thead>
<tr>
<th>Scenario</th>
<th>Infant prophylaxis</th>
</tr>
</thead>
</table>
| Mother continues on HAART, with or without breastfeeding | If BW > 2500 g:  
  • AZT 15 mg twice daily OR  
  • NVP 15 mg once daily  
  • Until 6 weeks of age  
|                                               | If BW < 2500 g:  
  • AZT 10 mg twice daily OR  
  • NVP 10 mg once daily  
  • Until 6 weeks of age  |
| Mother does NOT get postnatal ART, does NOT breastfeed | Same as above                                           |
| Mother does NOT get postnatal ART, does BF   | Infant prophylaxis with NVP until 1 wk after BF stops  
  • Birth to 6 wk:  
    • 15 mg once daily if BW > 2500g  
    • 10 mg once daily if BW < 2500g  
  • 6 wk to 6 mo: 20 mg once daily  
  • 6-9 mo: 30 mg once daily  
  • 9 mo to end of BF: 40 mg once daily |
Thank You