CHORIOAMNIONITIS (I.E. INTRA-AMNIOTIC INFECTION)

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Goals and Objectives

• I.C.3a Know the significance of a maternal temperature increase during labor
• I.C.3b Know the complications and effects of chorioamnionitis in the mother and the fetus.
• XVII.A.3f Mycoplasma and ureaplasma 1. Know the epidemiology pathogenesis and prevention of perinatal infection with mycoplasma and ureaplasma
• Know the clinical manifestations diagnostic features, management and complications of perinatal infection with mycoplasma and ureaplasma
You have a 31 yo G3P2 mother who is A+, GBS unknown, serology negative mother who is 38 weeks who has been in labor. She had an epidural placed 1 hour ago and has rapidly progressed to fully dilated. The patient’s nurse reports that she has developed a fever of 100.6 degrees Fahrenheit, HR is 110, and the fetal baseline HR is 165 with good beat to beat variability.

Based on current guidelines what do you do next?

A. Allow patient to push and monitor for further signs of infection
B. Start Ampicillin/Gentamicin and allow patient to start to push
C. Start Ampicillin/Gentamicin and take back for an urgent C/S
D. Start Ampicillin/Gentamicin/Clindamycin and allow to push
E. Start Erythro and co-amoxiclav and take for an urgent C/S
The infant is born and is well appearing. The physical exam is unremarkable. Based on current guidelines what do you do?

A. Draw a blood culture, CBC, CRP, and start Ampicillin and Gentamicin
B. Draw a blood culture, CBC, CRP, and start Ampicillin and Cefotaxime
C. Draw a blood culture, CBC, CRP and monitor for signs and symptoms
D. The baby is well appearing, continue to monitor closely for 48 hours
Chorioamnionitis (Intra-amniotic Infection)

• Acute chorio is the most frequent diagnosis in placental pathology reports.
• Cause of neonatal and maternal morbidity and mortality
• Associations with
  – Preterm birth
  – EOS
  – BPD
  – ROP
  – PVL
• Lack of complete understanding due to lack of precision in the diagnosis
Epidemiology

• 1-5% of all pregnancies
• Histologic chorioamnionitis ranges from 50-70% in VLBW to 10-15% in term infants
• 30% in PTL have histologic chorio
• 80% with PPROM
Placental Anatomy

- 3 major structures
  - Placental disc
  - Chorioamnionitic membranes
  - Umbilical cord
Types of Chorioamnionitis

Clinical Chorio
- Divided into:
  - Acute Chorio (symptomatic mother)
    - Strongly associated with EOS (RDS, CV instability)
    - Assoc w/ GBS, E. Coli, Strep viridans
  - Subclinical Chorio (PTL or asymptomatic)
    - May contribute to CLD and PVL
    - Assoc w/ Ureaplasma, Mycoplasma, Gardnerella

Histologic Chorio
- 3x as common as clinical chorio (confirmed by amniotic fluid culture)
- Typically ascending infection
- Difficult to identify
  - Chronic and can be silent
  - Organisms are difficult to culture
Histologic Definition

- Neutrophil invasion into the
  - Chorio decidual space (between maternal and fetal membranes) OR
  - Fetal membrane OR
  - Placenta OR
  - Amniotic fluid OR
  - Umbilical cord OR
  - Fetus
Pathogenesis

- Ascending – typical
- Retrograde through abdominal cavity
- Hematogenous from placenta
- Iatrogenic via amniocentesis
Protective barriers

• Cervical mucus plug
  – Anatomic barrier
  – Contains numerous antibacterial peptides with bactericidal activity
• Fetal membranes
• Placenta
Chorioamnionitis: Visual

Acute chorioamnionitis

Normal placenta
Pathology

- Maternal neutrophils migrate from the Decidua to the Amniotic Cavity
- Maternal inflammatory response
- 90% of neutrophils derived from the membranes are maternal
Grading and Staging of Histologic Chorioamnionitis

• Amniotic Fluid Infection Nosology Committee
  – Stage – progression based on anatomical regions infiltrated by neutrophils
  – Grade intensity of the acute inflammatory process at a particular site.

• Maternal inflammatory response vs fetal
Maternal inflammatory response

• Stage I – neutrophils in chorion or subchorionic space
• St. 2 0 chorionic connective tissue and/or amnion or the chorionic plate
• St. 3 – necrotizing chorioamnionitis with amnion epithelial necrosis
• Grade 1 (mild to mod) – individual or small clusters of maternal neutrophils that infiltrate the chorion laeve, chorionic plate, subchorionic fibrin, or amnion
• Grade 2 (severe) – presence of 3 or more chorionic microabscesses (confluence of neutrophils)
Funisitis

- St. 1 in umbilical vein (phlebitis)
- St. 2 when they are seen in the artery (arteritis)
- St 3 when they progress to the Wharton jelly (funisitis)
Fetal Inflammatory response

- Staging – refers to the location of neutrophil infiltration
  - More important than grading in the assessment of the severity.
Clinical Chorioamnionitis (Diagnosis)

- Fever
- AND 2
  - Maternal Leukocytosis (>15,000 cells)
  - Uterine fundal tenderness
  - Maternal tachycardia (>100 bpm)
  - Fetal tachycardia (>160 bpm)
  - Purulent amniotic fluid
  - Foul smelling amniotic fluid
Risk Factors

• Clinical Chorio
  – GBS colonization or bacteriuria
  – Nulliparity
  – Internal monitoring devices
  – Meconium stained amniotic fluid
  – Serial vaginal digital exams
  – Duration of active labor
  – Duration of ROM
  – Chorio in prior pregnancy
  – Single nucleotide PMNS in immunoregulatory genes (IL-10, IL-16)
Sensitivity and Specificity of Diagnostic Criteria

• Much variation
• Fever – 42-95% sensitivity, 85% specificity and 61% accuracy
• Fever, maternal tachycardia and fetal tachycardia – 18% sensitivity, 98% specificity, and 52% accuracy.
• Leukocytosis in 70-90% of patients with clinical chorio.
Microbiology

• Usually polymicrobial.
• Culture proven Chorio –
  – Ureaplasma (47%)
  – Mycoplasma (30%)
• Other organisms found include:
  – Gardnerella (25%)
  – Bacteroides (30%)
  – GBS (15%)
  – E. coli (8%)
• Anaerobes more in Pre term delivery
Microbiology

• PCR techniques identify 30-50% more organisms than culture-based methods

• 5 phyla commonly present
  – Firmicutes, Actinobacteria, Bacteroidetes, Proteobacteria, Fusobacteria

• Differing patterns in PTL vs. PPROM
Microbiology

• Ureaplasma commonly found in asymptomatic women (16-20 wk gestation undergoing amniocentesis).

• Many of these women developed a robust inflammatory response and went on to develop adverse pregnancy outcomes.

• May cause a much more robust inflammatory response than other pathogens.
Treatment
Treatment

• Obstetric Management
  – Broad spectrum antibiotics (A/G).
  – Prompt delivery reduces both maternal and fetal morbidity

• Controversies
  – Length of treatment
  – Mycoplasma and Ureaplasma are not covered.
  – Antibiotic administration in PTL w/ intact membranes
  – Antibiotics in some circumstances may be harmful.
Outcomes

- 2 fold increase in abnormal progression of labor, increased risk of C/S, postpartum hemorrhage, poor cervical dilation, and placental abruption.

- Surgical complications after c/s and chorio include endometritis, pelvic abscess, wound infection, thromboembolism, and bacteremia
Neonatal Treatment

• CDC and Committee on Fetus and Newborn (2012):
• Full sepsis evaluation and initiation of antimicrobial therapy (even in well appearing infants)
Fetal Outcomes

- Depend on timing of the inflammatory process.
- Chorio is a risk factor for early-onset sepsis and hemodynamic instability.
- Subclinical infections have been associated with PVL, BPD, ROP, NEC, and thymus involution.
Chorio and Preterm Birth

• Important cause of Preterm birth.
  – Up to 25% of preterm births are caused by an intrauterine infection.

• The evidence includes:
  – Intrauterine infection in animals results in preterm delivery
  – Extrauterine infections (pyelo) are associated with preterm labor
  – In animal models, antibiotic treatment of intrauterine infections can prevent prematurity
  – Treatment of asymptomatic bacteriuria prevents prematurity
  – Administration of antibiotics to women with preterm premature rupture of membranes prolongs gestation
  – Microorganisms can be cultured from the placenta in a high percentage of women with preterm labor
Chorio and Preterm Birth

• ? Adverse effects due to chorio versus prematurity
• Alabama Preterm Birth Study
  – PMN infiltrations in the free membranes, chorionic plate, and umbilical cord associated with positive intrauterine cultures and a fetal inflammatory response, but not with mortality or intraventricular hemorrhage.
  – Decreased incidence of RDS.
  – At 6 years there was strong association of neurodevelopmental outcomes with gestational age at delivery and caregiver IQ but not with in utero exposure to acute inflammation.
Chorio and CLD

– Inflammation and CLD
– Association is indirect and based on experimental observations.
– Incidence of RDS is increased with clinical chorio but decreased with histologic chorio.
– Animal studies show bacterial cell wall products (LPS) and inflammatory mediators (IL-6) accelerate surfactant production.
Clinical chorio and white matter disease

- Controversial
- Increased Cytokine levels in cord blood – Increased PVL
- ? Chorio and CP
- ELGAN study
  - 900 placentas were cultured and biopsied.
  - The Odds Ratios for ventriculomegaly and echolucent lesions were significantly increased with recovery of any aerobic or anaerobic organism.
  - Dose-response relationship between the number of species found and the risk of ventriculomegaly, echolucent lesions, quadripareisis, and diaparesis.
  - Those associations did not persist if there was only histologic chorioamnionitis without recovery of an organism.
Acute chorio and neonatal sepsis

- Guidelines of antibiotics were based data that stated in newborns greater than or equal to 37 weeks with EOS, histologic chorioamnionitis was present in 90%.

- Adoption of intrapartum antibiotic prophylaxis in 1990s
  - 85% reduction in the rate of culture proven EO GBS sepsis
  - 0.2-0.25% of EOS in 1980s-90s to 0.08-0.1% in 2005 and 0.05-0.06% in infants greater than or equal to 35 weeks.
Acute chorio and neonatal sepsis

• Risk is dependent on gestational age.
  – In 3 studies with 1892 pts. Infants greater than or equal to 35 weeks born to mothers with chorio the rates of EOS (culture proven) was only 0.47-1.24% (NNT 80-210)
  – In preterm infants 4.8-16.9% (NNT 6-21)
Acute chorio and neonatal sepsis

• In 1 study of 1413 clinically well infants – no cases of EOS GBS sepsis.
• 1662 at-risk infants 1 instance of a positive blood culture (in a preterm infant).
• “These data make it apparent that it is time to abandon the policy of treating well-appearing infants greater than or equal to 34 weeks’ gestation because of chorioamnionitis alone”
What is coming?

• Changes to definition and treatment
• Continued research
  – Healthy maternal-fetal microbiome
  – Abnormal colonization of the lower genital tract
  – Immune responses to specific pathogens
  – Risk factors that put women at increased risk for infectious complications of pregnancy
  – Preventive strategies