RUBELLA IN PREGNANCY

Background

1. Definition
   o Single stranded RNA/rubivirus from togavirus family
     - 3 major viral polypeptides: C, E1 and E2
     - E1 polypeptide has hemagglutination capabilities
   o Humans are the only natural hosts

2. General information
   o Also known as German measles / 3-day measles
   o History
     ▪ 17th century - described as different form of measles by Arabian doctors
     ▪ 1814 - recognized as a mild childhood illness in Germany
     ▪ 1941 - Australian ophthalmologist (Sir Norman Gregg)
       - Clinical correlation between early rubella infection in pregnancy and congenital anomalies
     ▪ 1962 - rubella virus isolated
     ▪ 1964-1965 rubella epidemic led to congenital rubella syndrome (CRS) and pregnancy abortions
     ▪ 1969 - 1st live attenuated rubella vaccine licensed

Pathophysiology

1. Pathology of disease
   o Transmitted airborne - respiratory droplets
   o Viral replication occurs in upper respiratory tract and local lymph nodes
   o Target organs infection
     ▪ Placenta, skin and joints
   o Fetal infection
     ▪ Occurs in first 16 weeks of pregnancy
   o Fetal damage is secondary to an immunopathologic process:
     ▪ Slow cell division
     ▪ Unorganized cell differentiation
     ▪ Small vessel damage

2. Incidence, prevalence
   o After 1969 (rubella vaccination program)
     ▪ Infection and congenital rubella syndrome have been reduced to record levels
     ▪ No longer considered endemic
   o US incidence - decreased
     ▪ 0.45/100,000 in 1900
     ▪ 0.1/100,000 in 1999
   o Risk still present in the US
     ▪ Esp pregnant women born outside US (vaccination programs at early stages or don't exist)
   o US trend
     ▪ Most cases in the Hispanic community
   o Worldwide prevalence
• Higher than US due to inadequate universal immunization programs\textsuperscript{4,5,6}
  • Only 64\% of European Countries have national immunization programs\textsuperscript{6}
  • In Europe, Asia and other developing nations the prevalence of seronegative childbearing women ranges from 2.7 to 29.2\%\textsuperscript{7,8,9,10,11,12,13}
  • 1996 - 110,000 cases of CRS occurred in developing countries\textsuperscript{14}
    o Women residents of developing countries
      • Positive rubella antibody screen may indicate active rubella infection rather than immunity

3. Risk factors
  o Unvaccinated status
  o Lack of universal vaccination programs at pre-school age
  o Childbearing mothers living in or immigrants from developing countries\textsuperscript{14}
  o Risk for CRS:\textsuperscript{14}
    • 90\% if infection occurred in first 11 weeks of gestation
    • 33\% in weeks 11-12
    • 17.5\% in weeks 13-16
    • 0\% after 16 weeks

4. Morbidity / mortality \textsuperscript{16}
  o Congenital defects incidence is 80-85\% (rubella related)
  o Spontaneous miscarriages occur in 20\% of cases

Diagnostics
  1. History
    o Symptoms include\textsuperscript{2,17}
      • Low grade fever >99.0\° F
      • Generalized rash\textsuperscript{17}
        • 1-5 days prior to most other symptoms
      • Coryza
      • Conjunctivitis
      • Cough
      • Sore Throat
      • Headache
      • General Malaise
      • Vaginal Bleeding
      • Arthralgia/arthritis\textsuperscript{18,19}
        • 1/3 of rubella infected adult women affected with arthritis
        • Evidence rubella virus - grows in the synovial fluid
        • Arthritis may begin at onset of the rash and lasts up to 1 month
    o Atypical sequelae\textsuperscript{20,21}
      • Pericarditis and myocarditis
      • Hepatitis
      • Hemolytic anemia
      • Hemolytic uremic syndrome
• Encephalitis
• Thrombocytopenia
  o Clinical characteristics of CRS:16,22
    • Deafness
      • Rubella virus persists in the middle ear beyond neonatal period causing hearing damage22
    • Ophthalmic defects:
      • Cataracts
      • Pigmentary retinopathy (not a serious complication itself but assoc with more serious defects)23
      • Congenital glaucoma assoc with Fuchs heterochromic uveitis with glaucoma risk of 15 to 59%24
    • Cardiac defects
      • PDA and pulmonary artery stenosis
    • Neurological deficits including mental retardation, behavior problems, and meningoencephalitis
  o Late CRS manifestations:
    • Insulin dependent diabetes mellitus in as high as 40% of cases25,26
    • Progressive encephalopathy18
    • Idiopathic thrombocytopenic purpura20
    • Pneumonitis
    • Thyroid problems

2. Physical examination
  o Mildly pruritic erythematous maculopapular rash
    • Rash classically begins on face and moves to trunk / extremities (resolution in ~3 days)
  o Forchheimer spots
    • Rose spots on soft palate before the rash
  o Lymphadenopathy
    • Sub occipital, post auricular and cervical areas
  o Congenital rubella infection leads to:
    • Fetal malformations- may be detected during prenatal ultrasound surveillance
      • IUGR and cardiac anomalies
    • Cataracts
    • Pigmentary retinopathy/uveitis
    • Low weight for gestational age
    • Postnatal hearing impairment
      • Difficult to diagnose in young children

3. Diagnostic testing during pregnancy
  o Laboratory evaluation15,20,28,30,31,32
    • Complete Blood Count
    • Rapid plasma reagin
      • R/o secondary syphilis
    • If rubella screen positive / if active rubella suspected:
      • Antenatal rubella IgG and rubella specific IgM ELISA
        o Obtain serum sample 7-10 days after rash onset & repeat 2-3 wks later
Rubella in Pregnancy

4x rise in IgG titer (acute vs convalescent serum specimens)

- Rubella viral culture
  - Virus isolated from pharynx 1-2 wks post rash
  - Virus also found in nasal mucosa, blood, urine & CSF
- Antenatal PCR on Chorionic villous sampling & amniotic fluid
  - CVS /PCR - more sensitive than amniotic fluid/ PCR

- Diagnostic imaging
  - Fetal ultrasound - evaluate IUGR / other congenital anomalies
  - Lacks specificity to dx congenital rubella infection

4. Diagnostic "Criteria" for maternal rubella 28, 29
- Acute onset of rash
- Temp > 99.0 F
- Arthralgias/arthritis, lymphadenopathy or conjunctivitis
- Isolation of rubella virus or ↑ rubella titers (from acute to convalescent state) or positive rubella IgM antibody

5. Diagnostic "Criteria" for congenital rubella syndrome 28, 29
- Pigmentary retinopathy, congenital heart disease, congenital cataracts/glucoma & hearing loss
- Jaundice, microcephaly mental retardation, meningoencephalitis, enlarged spleen, purpura and radiolucent bone disease
- Laboratory criteria for diagnosis:
  - Rubella virus isolation OR positive IgM antibody for rubella OR persistent rubella antibody in the infant
- Any 2 signs/symptoms + laboratory criteria is diagnostic for congenital rubella infection
- 2 signs/symptoms without positive laboratory criteria represent "probable" cases

Differential Diagnosis

1. Maternal differential diagnoses
   - Measles
   - Scarlet fever
   - Secondary syphilis
   - Erythema infectiosum (Parvovirus B19)
   - Mononucleosis
   - Coxsackievirus infections

2. Perinatal differential diagnoses
   - TORCH (5 infections with similar presentations) 34
     - Toxoplasmosis
     - Other: Syphilis
     - Rubella
     - Cytomegalovirus
     - Herpes simplex virus
Maternal therapeutics

1. Acute treatment
   o Supportive
   o Increase fluid intake and tylenol for relief of symptoms

2. Further management
   o Patients with thrombocytopenia or encephalopathy
     o Glucocorticoids
       ▪ Prednisone (1 mg/kg/day)
       ▪ High dose Dexamethasone (40 mg/day)
       ▪ High dose Methyl prednisone (1,000 mg)
       ▪ IV Immunoglobulin (0.4-1 g/kg)
     o Platelets transfusions
       ▪ Not indicated in pts w/ thrombocytopenia caused by peripheral destruction
       ▪ Unless severe bleeding and thrombocytopenia occurs
     o Supportive therapy

3. Long-term Care
   o Benefits of IVIG controversial in women rubella positive and decide against elective abortion
     ▪ Intramuscular Immune globulin (IG) 20 ml within 72 hours of rubella exposure
       ▪ May reduce-but will not eliminate-the risk for rubella
     ▪ IG is not recommended for
       ▪ Routine post exposure prophylaxis of rubella early pregnancy or any other circumstance
     ▪ Infants with CRS have been born to women who received IG early after exposure
     ▪ IG should be considered only if a woman who has been exposed decides continue with the pregnancy

Maternal Follow-Up

1. Return to office
   o Early and regular prenatal visits
   o Consider CVS between 10 to12 weeks of gestation
     ▪ For early detection in woman with positive rubella screen
   o Time frame for return visit 4 wks until 28 wks
     ▪ And then every 2 wks until 36 wks and weekly thereafter
   o Recommendations for earlier follow-up:
     ▪ Early Rubella infection or exposure during pregnancy
     ▪ Preexisting medical illness
     ▪ Previous poor pregnancy performance
       ▪ Bleeding, Intrauterine growth restriction, placental accidents and congenital defects
     ▪ Maternal malnutrition

2. Refer to specialist
   o Refer all cases to maternal fetal specialist for adequate prenatal surveillance
   o Recommendations / urgency
- Discuss risks and benefits of continuing pregnancy vs elective abortion

3. Admit to hospital
   - Severe maternal infection with evidence of thrombocytopenia or neurological symptoms
   - Maternal bleeding to monitor fetal status
   - Abortion for dilatation and curettage

**Infant follow up**
1. Watch for extended rubella syndrome
   - Consists of type 1 diabetes mellitus and pan encephalitis which develop during 2nd & 3rd decade of life
2. 1/3 of infants who are asymptomatic at birth
   - May present later in life with developmental sequelae
3. Infants born with rubella infection may shed the virus for several months
   - Responsible for other adults/infants infection

**Prognosis**
1. Pregnant women have excellent clinical prognosis

**Prevention**
1. General public education and health-care workers of dangers of rubella infection
2. Identification and vaccination of unimmunized women immediately after abortion
3. Rubella vaccination (RA27/3)
4. Universal vaccination program
   - All children between 12 to 15 months
   - Postpartum in seronegative women
   - Vaccination of nonpregnant susceptible women identified by premarital serology
   - Vaccination of susceptible hospital employees exposed/contact with pregnant women/rubella patients
   - Advisory Committee on Immunization Practices (ACIP) recommends
     - Avoidance of pregnancy 28 days after vaccination to prevent theoretical risk of rubella infection
   - Advisory Committee on Immunization Practices (ACIP) recommends
     - No supportive data showing correlation between Autism and MMR immunization

**Patient Education**
1. Pre-pregnancy evaluation to coordinate adequate preventive care
2. Mothers with confirmed rubella infection before 16 weeks
   - Can be oriented about maternal fetal transmission
   - Offered pregnancy interventional abortion
3. Rubella vaccine contraindications:
   - Pregnancy
   - Febrile illness
   - Neomycin allergy
   - Immunodeficiency condition
   - Breast feeding is not a contraindication
4. Rubella vaccine side effects:
   - Fever
   - Rash
   - Arthritis/Arthralgia
   - Lymphadenopathy

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