RUBELLA IN PREGNANCY

Background

1. Definition
    - Single stranded RNA/rubivirus from togavirus family[1,2]
        - 3 major viral polypeptides: C, E1 and E2[3]
        - E1 polypeptide has hemagglutination capabilities [3]
    - Humans are the only natural hosts[1]
2. General information
    - Also knows as German measles / 3-day measles[1]
    - History
        - 17th century - described as different form of measles by Arabian doctors[1]
        - 1814 - recognized as a mild childhood illness in Germany[2]
        - 1941- Australian ophthalmologist (Sir Norman Gregg)
            - Clinical correlation between early rubella infection in pregnancy and congenital anomalies[2,3]
        - 1962 - rubella virus isolated[2,3]
        - 1964-1965 rubella epidemic led to congenital rubella syndrome (CRS) and pregnancy abortions
        - 1969 - 1st live attenuated rubella vaccine licensed[2]

Pathophysiology

1. Pathology of disease
    - Transmitted airborne - respiratory droplets
    - Viral replication occurs in upper respiratory tract and local lymph nodes
    - Target organs infection
        - Placenta, skin and joints
    - Fetal infection
        - Occurs in first 16 weeks of pregnancy
    - Fetal damage is secondary to an immunopathologic process:
        - Slow cell division
        - Unorganized cell differentiation
        - Small vessel damage
2. Incidence, prevalence
    - After 1969 (rubella vaccination program)
        - Infection and congenital rubella syndrome have been reduced to record levels
        - No longer considered endemic[1,2,3]
    - US incidence - decreased
        - 0.45/100,000 in 1900
        - 0.1/100,000 in 1999[1]
    - Risk still present in the US
        - Esp pregnant women born outside US (vaccination programs at early stages or don't exist)[1]
    - US trend
        - Most cases in the Hispanic community[1]
    - Worldwide prevalence

        - Higher than US due to inadequate universal immunization programs[4,5,6]
            - Only 64% of European Countries have national immunization programs[6]
            - In Europe, Asia and other developing nations the prevalence of seronegative childbearing women ranges from 2.7 to 29.2%[7,8,9,10,11,12,13]
            - 1996 - 110,000 cases of CRS occurred in developing countries[14]
    - Women residents of developing countries
        - Positive rubella antibody screen may indicate active rubella infection rather than immunity
3. Risk factors
    - Unvaccinated status
    - Lack of universal vaccination programs at pre-school age
    - Childbearing mothers living in or immigrants from developing countries [14]
    - Risk for CRS:[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 [16]
    - Congenital defects incidence is 80-85% (rubella related)
    - Spontaneous miscarriages occur in 20% of cases

Diagnostics

1. History
    - Symptoms include[2,17]
        - Low grade fever >99.0° F
        - Generalized rash[17]
            - 1-5 days prior to most other symptoms
        - Coryza
        - Conjuntivitis
        - Cough
        - Sore Throat
        - Headache
        - General Malaise
        - Vaginal Bleeding
        - Arthralgia/arthritis[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
    - Atypical sequelae[20,21]
        - Pericarditis and myocarditis
        - Hepatitis
        - Hemolytic anemia
        - Hemolytic uremic syndrome

        - Encephalitis
        - Thrombocytopenia
    - Clinical characteristics of CRS:[16,22]
        - Deafness
            - Rubella virus persists in the middle ear beyond neonatal period causing hearing damage[22]
        - 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
    - Late CRS manifestations:
        - Insulin dependent diabetes mellitus in as high as 40% of cases[25,26]
        - Progressive encephalopathy[18]
        - Idiopathic thrombocytopenic purpura[20]
        - Pneumonitis
        - Thyroid problems
2. Physical examination
    - Mildly pruritic erythematous maculopapular rash
        - Rash classically begins on face and → moves to trunk / extremities (resolution in ~3 days)
    - Forchheimer spots
        - Rose spots on soft palate before the rash
    - Lymphadenopathy
        - Sub occipital, post auricular and cervical areas
    - 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
    - Laboratory evaluation[15,20, 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
                - Obtain serum sample 7-10 days after rash onset & repeat 2-3 wks later

        - 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/glaucoma & 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
    - Supportive
    - Increase fluid intake and tylenol for relief of symptoms
2. Further management
    - Patients with thrombocytopenia or encephalopathy
    - 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)
    - Platelets transfusions
        - Not indicated in pts w/ thrombocytopenia caused by peripheral destruction
            - Unless severe bleeding and thrombocytopenia occurs
    - Supportive therapy
3. Long-term Care[35]
    - 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
    - Early and regular prenatal visits
    - Consider CVS between 10 to12 weeks of gestation
        - For early detection in woman with positive rubella screen
    - Time frame for return visit 4 wks until 28 wks
        - And then every 2 wks until 36 wks and weekly thereafter
    - 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
    - Refer all cases to maternal fetal specialist for adequate prenatal surveillance
    - 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 live
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[35]
    - 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

References

1. Shoshana, Susan. Rubella. Dis Mon 2007:53 .p. 515-518
2. Rasmussen, Sonja A., Erickson, David J., Reef Susan E., Ross Danielle S. Teratology: From science to birth defects prevention. 2008.Volume 85 Issue 1 .p.82-92.
3. Cohen & Powderly. Infectious Diseases, 2nd ed. 2004. p. 1-6
4. Refef, SE Frey, TK, Theall, K, et al. The changing epidemiology of rubella in the 1990s:on the verge of elimination and new challenges for control and prevention. JAMA 2002; 287: 464.
5. Orenstein, WA, Bart, KJ, Hinman, AR, et al. The opportunity and obligation to eliminate rubella from the United States. JAMA 1984; 251:1988.
6. Aksit, S, Egemen, A, Ozacar, T, Kurugol, Z, et al. Rubella seroprevalence in an unvaccinated population in Izmir: recommendations for rubella vaccination in Turkey. Pediatr Infect Dis J 1999; 18:577.
7. Lin CC, Yang CY, Shih CT, Chen BH, Huang YL. Rubella seroepidemiology and catch-up immunization among pregnant women in Taiwan: comparison between women born in Taiwan and immigrants from six countries in Asia. Am J Trop Med Hyg. 2010 Jan;82(1):40-4.
8. Hardelid P, Cortina-Borja M, Williams D, Tookey PA, Peckham CS, Cubitt WD, Dezateux C.Rubella seroprevalence in pregnant women in North Thames: estimates based on newborn screening samples. J Med Screen. 2009;16(1):1-6
9. Oner N, Vatansever U, Karasalihoglu S, Tatman Otkun M, Ekuklu G, Küçükugurluoglu Y. Rubella seroprevalence among Turkish adolescent girls living in Edirne, Turkey. Turk J Pediatr. 2006 Oct-Dec;48(4):288-93.
10. da Silva e Sá GR, Camacho LA, Siqueira MM, Stavola MS, Ferreira DA. Seroepidemiological profile of pregnant women after inadvertent rubella vaccination in the state of Rio de Janeiro, Brazil, 2001-2002. Rev Panam Salud Publica. 2006 Jun;19(6):371-8.
11. Dayan GH, Panero MS, Urquiza A, Molina M, Prieto S, Del Carmen Perego M, Scagliotti G, Galimberti D, Carroli G, Wolff C, Bi D, Bellini W, Icenogle J, Reef S. Rubella and measles seroprevalence among women of childbearing age, Argentina, 2002.
    Epidemiol Infect. 2005 Oct;133(5):861-9.
12. Vargas-Leguás H, Campins Martí M, Juste Sánchez C, Martínez Gómez X, Hermosilla Pérez E, Cabero Roura L.[Rubella susceptibility of immigrant pregnant women in Catalonia]
    Med Clin (Barc). 2009 Mar 14;132(9):344-7. Epub 2009 Mar 5. Spanish
13. Désinor OY, Ansèlme RJ, Laender F, Saint-Louis C, Bien-Aimé JE. Seroprevalence of antibodies against rubella virus in pregnant women in Haiti.Rev Panam Salud Publica. 2004 Mar;15(3):147-50.
14. Cutts, FT, Vynnycky, E. Modelling the incidence of congenital rubella syndrome in developing countries. Int J Epidemiol 1999; 28:1176.

15. Mehta, NM, Thomas, RM. Antenatal screening for rubella-infection or immunity?. BMJ 2002; 325:90.
16. Gregg, NM. Congenital cataract following German measles in the mother. Trans Am Opthalmol Soc 1941; 3:35.
17. Cherry,JD.Rubella virus.IN:Textbook of Pediatric Infectious Diseases,5 th ed,Feigin,RD,Cherry,JD,Demmler,GJ, Kaplan,SL(eds),WB saunders,Philadelphia 2004.p2134.
18. Lund,KD,Chantler,JK.Mapping of genetic determinants of rubella virus associated with growth in joint tissue. J virol 2000;74;796.
19. Johnson,RE,Hall,AP.Rubella arthritis;report of cases studied by latex text.NEJM 1958;258:743
20. Ozsoylu, S, Kanra, G, Savas, G. Thrombocytopenic purpura related to rubella infection. Pediatrics 1978; 62:567.
21. Bayer, WL, Sherman, FE, Michaels, RH, et al. Purpura in congenital and acquired rubella. N Engl J Med 1965; 273:1362.
22. Cooper, LZ, Alford, CA. Rubella. In: Infectious Diseases of the Fetus and Newborn Infant, 6th ed, Remington, JS, Klein, JO, Wilson, CB, Baker, CJ (Eds), Elsevier Saunders, Philadelphia 2006. p. 893.
23. Peackham,Clinical and Laboratory study of Children Exposed in utero to Maternal Rubella, Archives of Disease in Childhood ,1972,47,571.
24. De Visser, Lenneke, Braaakenburg, Arthur, Rothova, Aniki and De Boer Joke H.Rubella Virus associate Uveitis: Clinical Manifestations and Visual Prognosis.2008.p292-297.
25. Forrest, JM, Menser, MA, Burgess, JA. High frequency of diabetes mellitus in young adults with congenital rubella. Lancet 1971; 2:332.
26. Ou, D, Jonsen, LA, Metzger, DL, Tingle, AJ. CD4+ and CD8+ T-cell clones from congenital rubella syndrome patients with IDDM recognize overlapping GAD65 protein epitopes. Implications for HLA class I and II allelic linkage to disease susceptibility. Hum Immunol 1999; 60:652.7
27. Chess,S, Fernandez,P,Korn,S. Behavioral consequences of congenital rubella. J Peds 1978;93:699
28. Bosma, TJ, Corbett, KM, O'Shea, S, et al. PCR for detection of rubella virus RNA in clinical samples. J Clin Microbiol 1995; 33:1075.
29. Bosma, TJ, Corbett, KM, Eckstein, MB, et al. Use of PCR for prenatal and postnatal diagnosis of congenital rubella. J Clin Microbiol 1995; 33:2881.
30. Ho-Terry, L, Terry, GM, Londesborough, P. Diagnosis of foetal rubella virus infection by polymerase chain reaction. J Gen Virol 1990; 71 (Pt 7):1607.
31. Tanemura, M, Suzumori, K, Yagami, Y, Katow, S. Diagnosis of fetal rubella infection with reverse transcription and nested polymerase chain reaction: a study of 34 cases diagnosed in fetuses. Am J Obstet Gynecol 1996; 174:578.
32. Tang, JW, Aarons, E, Hesketh, LM, et al. Prenatal diagnosis of congenital rubella infection in the second trimester of pregnancy. Prenat Diagn 2003; 23:509.17. Lund, KD, Chantler, JK. Mapping of genetic determinants of rubella virus associated with growth in joint tissue. J Virol 2000; 74:796.
33. Case definitions for infectious conditions under public health surveillance. Centers for Disease Control and Prevention. MMWR Recomm Rep 1997; 46:1.
34. Epps, RE, Pittelkow, MR, Su, WP. TORCH syndrome. Semin Dermatol 1995; 115:680.

35. Rubella prevention. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Recomm Rep1990; 39(RR-15):1-18
36. Loring Dales,MD: Hammer,RN,PHN,Smith,MD,MPH.Time Trends in Autism and in MMR Immunization Coverage in California. JAMA.2001;285:1183-1185.

Authors: Rafael Cortes & James Campbell, MD, *LSUHSC FPRP Kenner, LA*

Editor: David Wakulchik, MD, *Aultman FMRP, OH*