Infection of Rubella Virus in Pregnancy

Herdiman T Pohan

Rubella is belonging to togavirus family with single band RNA strand on its nucleus.[1] The biggest jeopardy of rubella virus is infection in pregnancy, which may cause congenital rubella syndrome/CRS of newborn. Before we had any vaccine, thousand of CRS cases were reported annualy in United States. The given vaccine has been very effective, so that there are only 2 cases of CRS every year.[2]

EPIDEMIOLOGY

Man was known as the only natural host of rubella virus.[3] Viral transmission may though droplet inhalation, which came from the patient respiratory tract. Occasional exposure to patient relatively ineffective to transmite disease, and generally it needs long-term contanct.

The Incubation period is 14-21 days (mean 16 days). The virus may be found in nasopharyngeal secrete since 13 days before up to 21 days after rash. In this period disease could be transmitted to other person. Patient with atipical or sub clinical infection may transmit virus. Though generally it is regarded as children disease, rubella is not very infectious, and frequently children were avoided from this disease. In United State, intensive vaccination effort has reduced susceptible adolescence. Insidence of rubella infection usuall increase locally, in campus, hospitals, prison, and millitary instantion.

On 1944, Gregg an Australian ophthalmologist has associated child's cataract to epidemi of maternal rubella infection. Long term study of children that was born in United States when rubella epidemi occured reveals there was congenital rubella syndrome. Eyes, heart and nervous system easily affected on birth.

Division of Tropical-Infectious, Department of Internal Medicine, Medical Faculty of The University of Indonesia-Dr. Cipto Mangunkusumo National Central General Hospital, Jakarta

The study has proven that fetal infection on first trimester may cause congentinal damage on 50-80% cases. Infection on second trimester on 25% cases may cause hear loss (deafness) and mental retardation whereas infection on third trimester usually does not cause any structural damage.[4]

Rubella tends become endemic in industrial countries. Wide endemic may occured in 6-9 years cycle, but massal vaccination can reduce that cycle in many countries. There is no data about characteristic of this disease in tropical area and in area of sparse inhabitants.

PATHOPHYSIOLOGY

Rubella is respiratory tract disease which develop 2-3 weeks after togavirus infection. The viral infection usualy found in nasopharyngeal and upper respiratory tract 1 week before clinical manifestation. Clinical manifestation of acute infection is signed by pink maculo-papule rash on face, neck, head, breast and extremity in 3 days period. There are some other symptoms that may be found i.e. post-auricular and sub-occipital lymphadenopathy, fever and joint-ache. Twenty five up to fifty percent of all rubella infection is sub-clinical infection.[4] Whereas, skin rash that seen on rubella patient may also caused by adenovirus, enterovirus, and infection by other respiratory virus. Laboratory test was needed in order to prove diagnosis.

Direct effect of rubella is decreased cell replication which cause mental retardation and defect of cell differentiation process on embryogenesis. Inflamation reaction to infection of autoimunity reaction cause tissue damage, and this process may cause myocarditis, pneumonitis, liver and spleen enlargement (hepatosplenomegaly), and vascular stenosis. Further complication occured in about 20% patient, such as endocrinopathy (diabetes mellitus type-1, abnormal thyroid, hypoadrenalism), hearing defect or occular damage and the rare progresive rubella panecephatlitis, develop in 10-20 years of age.

There are 4 mechanism which cause malformation after intrauterine infection has been occured:

1. Persistent infection on fetal tissue cause mitotic process and inhibit cell multiplication, so that the organ development was disturbed.
2. Vasculopathy of fetal blood vessel, which cause proliferation of arterial wall fibromuscular and inhibit blood flow to the growing tissue.
3. Tissue necrosis
4. Elevation of chromosomal damage.

The absent of rubella clinical manifestation on birth will not negate possibility of sub clinical damage or further damage. So that baby with sub clinical rubella infection in pregnancy period still need long-term evaluation.

CLINICAL DIAGNOSIS

Rubella is generally known as German Measles or 3-days measles. Clinical manifestation of rubella is difficultly differ form other viral disease such as infectious mononucleosis, echovirus infection, and infection of c*oxsackie-virus,* even arthritis is more dominant of rubella. Definitive diagnosis is only by viral isolation or serology.

Clinical manifestation may include : fever, mild weakness, head ache, myalgia, influenza, polyarthritis (25% of adult case), lymphadenopathy (*cervical posterior, post-auricular*), erythema palatum and throat, which is famous as *Forchheimers sign*, Pink maculopapule raseh with 1-4 mm diameter of face, nect, head, breast, extremity, which is occured fast (2-3 days for every location).

Complication rarely occured in rubella. There could be arthritis, and thrombocytopenia and encephalitis are more unusual. The more frequent complication in pregnancy is c*ongenital rubella syndrome* (CRS).

The most common manifestation of CRS are defect in the ear, eyes, heart and central nervous system. Hearing defect / deafness is the most frequently occured. The most common of eye problem are cataract, glaucoma, micro-opthalmia, and corioretinitis. Heart defect including peripheral pulmonic stenosis, patent ductus arteriosus (PDA), and heart septal defect. The central nervous system defect including mental retardation, microcephal, and the rarely occured, encephalitis.[2]

LABORATORY DIAGNOSIS

Sub clinical rubella infection that are found in newborn and adults cause unimportancy of laboratory confirmation in the found clinical cases. Even virus isolation may be done through nasopharyngeal secretion, only a few of laboratory provide this service and it usually takes time up to 4-6 weeks. Serology test only proves new infection of immunity response. In most case, rubella antibody proves that there is immunity reaction of systemic infection eventhough there is re-infection in pregnancy. Rubella hemaglutination inhibiton test, which has been standard serology teset by clinical laboratory, has been covered by aglutination test and commercial enzyme immunoassay, which is easier and less expensive. [5]

In most of cases, Rubella spesific IgG both caused by natural infection or vaccination will stay still in the patient's body forever. Almost 95% of all patient after vaccinantion by RA27/3 reveal positive antibody through *enzyme immunoassay* after seroconvertion for 18 years. In new infection of Rubella, confirmation reveals positive spesific IgM antibody of rubella, which emerge fast and reach peak within 1-1.5 weeks after it was started. IgM can be detected for one month or more depend on sensitivity of examination.

Recent study has reported 19 cases of rubella congenital among women with rubella antibody, and re-infected during pregnancy. The cause of that cases remain unclear, but laboratory error on antibody test, negative IgG antibody as protetion, antigene of different kind of virus, and sub clinical maternal immunocompromize may become good explanation causes of the above rubella congenital cases.

Spesicfic Rubella IgM in fetal blood that is taken through funipuncture indicate intra-uterine infection in second trimester. Fetal seroreactivity may be seen early in 19th weeks of gestation. Study on 93 cases reported reveals 95% concordation within fetal and neonatal serology test in funipuncture, which has been done over 2 weeks after clinical infection and 22 weeks after gestation using rubella spesific IGM. But, the optimal period to detect intrauterine infection by using this system is uncertain. Instead fetal immunity reaction was develop during 20th up to 24th weeks of gestation, minimal one false negative was found relatedl to congenital subseguent infection when the serology test was done on 20th weeks. RT-PCR (reverse transcriptase-nested polymerase chain reaction amplification) which detect viral RNA has substitue the chorion villi sampling which is usually used to diagnose rubella intrauterine infection in first trimester. Eventhough a retrospective study reported 85% concordation within viral culture and RT-PCR, both of methodes may detect the undetected cases by other alternative method.

Clonning hibridization, DNA probing and rubella complement by using radioactive labelling are more sensitive in detecting first trimester infection compare to chorion villus sampling. However, false negative may occured on both of methodes.[6]

TREATMENT

There is no spesific treatment, usually symptomatic treatment.

PREVENTION

Rubella vaccine has been available in United States since 1969. Vaccination gives long-term sero-convertion on 95% infection cases. Rash, arthropathy, and lymphadenopathy are limited complication that rarely occured on vaccination. Symptoms of transient peripheral nerves is also rarely occured.

On 1994, The Committee on Immunization Practices revised general recommendation and recommended that all children should have MMR (measles-mumps-rubella) vaccination on 12-15 months with re-vaccination on 12-15 years. Woman on age productive who has no rubella IgG antibody was also recommended to have immunization, with prerequisites that they are not pregnant when receiving the vaccine and will not pregnant at least 3 months after receiving vaccine. Failure of primary vaccination rarely occured in rubella case and rubella congenital syndrome, sub clinical immunocompromize, and defect on active immunization, which is caused by blood transfusion or immunoglobuline therapy (except RhoGAM) that recently done, are the causes of vaccination failure.

Rubella vaccination was not recommended during pregnancy based on opinion that it will occur fetal damage. The risk of rubella congenital syndrome that is caused by 3 months vaccination after conception usually very small. Therefore if rubella vaccination was given during pregnancy, it is not indication for pregnancy termination. CDC states that patient and doctor need to decide final determination about the pregnancy continuation.

Routine laboratory screening examination is not important to perform before giving vaccine. Doctors need to recommend rubella vaccinantion against women with risk of rubella infection and there is no contraindication of vaccination. Rubella vaccinatiion is contraindicated in pregnancy, immunodeficiency or immunocompormized (except on HIV patient), and patient with history of immunoglobuline administration less than 3 months.

As has been discussed above, in most cases, the vaccination failure is one of causes of rubella and rubella congenital syndrome in United States. High-people density area and narrow and closed area enhance the transmission. The other important epidemiology factors are sosial, politic, economic, ethic and religion factor affect national success in eradicating rubella.

CDC recommend some of following strategies to assist rubella prevention and evaluation:

- Enhancing vaccination in children
- Legal aspect that requires all of children at school receive two doses of MMR vaccine.
- Encouraging doctors to perform vaccination on high-risk individual including woman in reproductive age that came to family practice clinic.
- Make vaccination as compulsory task for university student acceptance.
- Start the prevention and evaluation program of rubella in all correctional facilities.
- Encourgage individual of certain religion group to receive vaccination.
- Targeting special vaccination program with adolescens as target, who has high unvaccination possibility an they are contact to the person who infected by rubella, who came from other countries, which is not routinely give rubella vaccination.

COMPLICATIONS

Complication of Acute Rubella Infection

Acute rubella infection may cause complications:

- Thrombocytopenia
- Otitis media
- Post-infection encephalitis

In 1 of 6000 cases, there could be encephalitis 1-6 days after rash. The mortality rate is about 20% but sequelle is rarely occured. The mechanism of complication is uncertainly known.

Complication of Rubella Infection in Pregnancy

- Exposure During Pregnancy

In the early pregnancy, we should know the antibody status against rubella. On pregnant women, who has been suspected having rubella infection or exposed to rubella, immediatelly examine the rubella antibody level. If the examination result is negative, we need further clinical and serological evaluasion. If the result shows acute rubella infection, then conseling to related pregnant mother is done, it is about the possibility risk of

congenital defect of baby inside. If there is some proof that there is acute rubella infection on first trimester pregnancy, theurapeutical abortion may be considered.[4,7] But this alternative must be carefully considered in keeping with patient's personality, religion / belief and the legal ascpect.

- Congenital Rubella Syndrome/CRS)

The most severe complication is congenital rubella syndrome (CRS). Frequency of CRS is 50% if rubella infection occured in first 12 weeks of pregnancy and 25% if infection occured within 13-24 weeks of pregnancy. The characteristic of this syndrome generally: deafness, congenital cataract and patent ductus arteriosus.

REFERENCES

1. Wright PF. Respiratory diseases. In: Nathanson N, Ahmed R, Gonzalez-Scarano F, et al, editors. Viral pathogenesis. Philadelphia: Lippincott-Raven Publishers. 1997. p. 703-11.
2. Reef SE, Plotkin S, Cordero JF, Katz M, Cooper L, Schwartz B, et al. Preparing for elimination of congenital rubella syndrome (CRS): summary of workshop on CRS elimination in US. Clin Infec Dis. 2000;31:85-95.
3. Amor S, Mehta S. Virus infecti ons of the central nervous system. In: Cook GC, editor. Manson's tropical diseases 20th ed. London: WB Saunders Co. 1996.p.785-7.
4. Collins TM, Saltzman RL, Jordan MC. Viral infection. In: Burrow GN, Ferris TF, editors. Medical complications during pregnancy 4th ed. Philadelphia : WB Saunders Co. 1995.p. 381-403.
5. Herrmann KL. Available rubella serologic tests. Rev Infect Dis 1985:7;S108
6. Bosma TJ. Use of PCR for prenatal and postnatal diagnosis of congenital rubella. J Clin Microbiol 1995:33;2881.
7. Grossman III JH, Rubella in pregnancy. In: Mad PB, Hagen WD, Faros, eds. Protocols of infectious diseases in obstetrics and gynecology. 2nd ed. Malden, Blackwell Science Inc. 2000; 195-201.