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Rubella Infection In Pregnancy

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A B S T R A C T

Rubella is a systemic viral disease that is mild, non-specific, rarely diagnosed, and easily transmitted. Rubella virus easily crosses the placenta, so infection in pregnancy, especially in the first trimester, has the risk of transmitting to the fetus and potentially causing abortion, fetal death, and congenital rubella syndrome (CRS). CRS includes auditory, sensorineural, cardiac, and ocular abnormalities, and is an irreversible congenital disorder. Rubella can be prevented by the administration of antirubella vaccination.

Serology tests are still the most reliable diagnostic test today, although these immune reactions appear later than the appearance of the rash. Analysis of serology test results can provide information on whether you are in acute infection, infected, and are still active, or chronic infection and are currently active or inactive.

Management of rubella infection in pregnancy is symptomatic, nothing can be done for CRS in pregnancy. Postpartum CRS management is multidisciplinary and supportive

I. INTRODUCTION

Rubella is a mild systemic viral infection(Mawson and Croft, 2019) that mainly occurs in childhood (Bouthry et al., 2014). Although most cases of infection lead to a mild, self-limiting measles-like disease, the real threat arises when the rubella virus infects the fetus - particularly during the first trimester (Lambert et al., 2015), when infection can lead to abortion, fetal death, or congenital rubella syndrome (CRS) (Grant et al., 2019; Taku et al., 2019) and autism (Mawson and Croft, 2019). CRS includes auditory, sensorineural, cardiac, and ocular abnormalities (Bouthry et al., 2014). CRS has its own challenge, not only because of the supportive management and long-term multidisciplinary care (Kurniawan, 2019), but also causes psychological and social burdens on parents, families, and society.

Early diagnosis of rubella infection is difficult as more than 50% of cases are asymptomatic (Bouthry et al., 2014). In addition to its mild appearance, there are no specific markers before the rash (rush) appears that can be a reference for diagnosis. Serology test (RV-IgM) as the main reference for the diagnosis of rubella infection only yields positive results in 50% of cases when performed at the time of rash appearance (Lambert et al., 2015); while the disease has been infectious since 8 days before the rash appears (Bouthry et al., 2014). This makes rubella morbidity

and transmission difficult to control. It is not surprising that rubella cases are still reported to be high in Indonesia and are one of the public health problems that require effective prevention efforts (Kurniawan, 2019).

The commitment of WHO, as well as the Indonesian government to control or eliminate rubella through vaccination (Kurniawan, 2019) is the right choice because this disease is indeed vaccine-preventable (Abdulkadir and Gebrehwot, 2019) and humans are the only hosts of rubella (Lambert et al., 2015). However, its implementation requires careful consideration and caution. The theoretical teratogenic risk of rubella vaccine makes vaccination during pregnancy or pregnancy in the first month after immunization is not recommended (Bouthry et al., 2014); while on the other hand rubella infection in pregnancy especially in the first trimester is very risky for CRS (Abdulkadir and Gebrehwot, 2019).

II. DISCUSSION

II.1 RUBELLA

Rubella, also known as German measles, is a mild systemic viral infection (Mawson and Croft, 2019) that mainly occurs in childhood (Bouthry et al., 2014). It is caused by the Rubella virus (RV), is a *self-limiting disease*, and is *vaccine-preventable* (Abdulkadir and Gebrehwot, 2019). The only known host of rubella infection is humans and VR is transmitted by direct airborne human contact (Lambert et al., 2015).

Rubella virus (RV) easily crosses the placenta (Bouthry et al., 2014), so the result of conception can be subject to infection with this virus. Rubella infection that occurs early in pregnancy can lead to abortion, fetal death, or birth of a fetus with congenital rubella syndrome (CRS) (Grant et al., 2019; 5.Taku et al., 2019) and autism (Mawson and Croft, 2019). CRS includes auditory, sensorineural, cardiac and ocular abnormalities (Bouthry et al., 2014). The sequelae of CRS are permanent, so the management is only supportive and long-term multidisciplinary care (Kurniawan, 2019).

Rubella is globally distributed. The incidence depends on geography. In industrialized countries, it is estimated that there is 1.3 cases/100,000 population (Bouthry et al., 2014). CRS occurs in more than 80% of rubella-infected pregnancies in the first trimester (Tushabe et al.,2019). In 2008 there were more than 110,000 babies born with CRS, with the highest rates in Southeast Asia (48%) and Africa (38%) (Bouthry et al., 2014). In Southeast Asia in 2017, there were 754 cases of rubella. In Indonesia, out of 11,000 suspected measles cases, (16-43) % were rubella (Kurniawan, 2019). The incidence of CRS ranges from 0.1-0.2/1,000 live births when not endemic and between 0.8-4.0/1,000 births during rubella endemic periods (Lambert et al., 2015).

Living in *crowded* places, having large families, not getting vitamin A in the last 6 months, and contact with rubella patients are risk factors for rubella *outbreaks* (Abdulkadir and Gebrehwot, 2019).

II.2 VIRUS

RV is the only member of the Rubivirus genus, and belongs to the Togaviridae family. RV is spherical with a diameter of 50-85 nm, has a core surrounded by two layers of lipid membrane. The core consists of a protein capsid (nucleocapsid/ protein C) and a copy of the genomic RNA with a length of 9.8 kb (Lambert et al., 2015). On the lipid membrane are attached and protrude two glycoproteins, namely protein E1 and protein E2.

The core also has two nonstructural proteins, p90 and p150 (George et al., 2019). The E1 protein contains antigenic determinants that induce major immune responses and a hemagglutination-inhibiting and hemagglutination-neutralizing epitope.

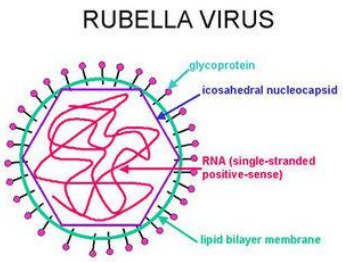


Fig 1: (Rubella Virus (http://id.images.search.yahoo.com/)

E1 proteins mediate VR *attachment* to host cells and membrane fusion in endosomal compartments. The main receptor of E1 protein on hosts is *myelin oligodendrocyte glycoprotein (MOG)*, which is abundant in the central nervous system (George et al., 2019).

Some host proteins interact with viral proteins to produce teratogenic effects. Some host proteins that regulate cell division and growth are associated with the viral protein p90. Host cell proteins directly or indirectly affect the expression of genes involved in sensory organ development. Thus, the lifelong effects that RV has on the developing fetus are cumulative with those arising from RV host protein interactions (George et al., 2019).

II.3 PATHOGENESIS

The only known source of rubella infection is humans, and VR is transmitted through direct air-to-human contact (Lambert et al., 2015). Once inhaled, the virus replicates in the respiratory mucosa and in the cervical lymph nodes, before reaching the taget organ via systemic circulation. The infectious period ranges from 8 days before to 8 days after the appearance of the rash (Bouthry et al., 2014). Immunity resulting from rubella infection is lifelong (Lambert et al., 2015).

Congenital infection of the fetus occurs transplacental during the maternal viremia phase, usually 5-7 days after inoculation (Kurniawan, 2019). CRS is thought to occur on average 24 weeks after maternal VR infection (Lee et al., 2019).

Symptoms and signs of rubella may be due to impaired vitamin A (retioid) metabolism in the liver, which is triggered in the acute phase of infection. Infection causes hepatic dysfunction, and spillage of vitamin A components into the circulation causes endogenous hypervitaminosis A. Various manifestations of CRS and autism are thought to be the manifestations of this form of hypervitaminosis A (Mawson and Croft, 2019). The pathogenesis is summarized in the next figure.

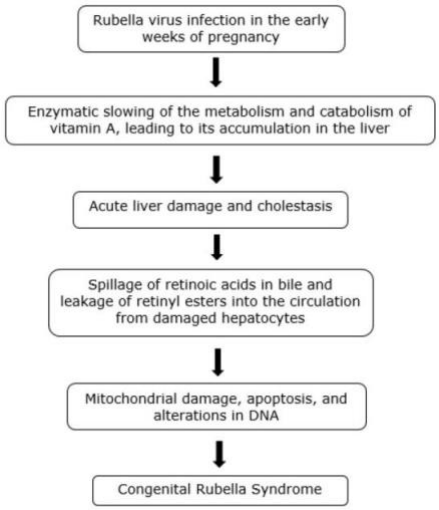


Fig 2: (Pathogenesis of CRS (Mawson and Croft, 2019))

II.4 VACCINATION.

The antibody response rate to a single dose is higher than 95%. After two doses, the response rate is close to 100%, and immunity can be detected at ages over 21 years, despite the fading of the VR immunoglobulin G (RV-IgG) titer. In most countries, the rubella vaccination schedule is two doses before 24 months, which is identical to the measles vaccination schedule (Bouthry et al., 2014).

The rubella vaccine is generally well tolerated, and most side effects are benign. Fever, rash, transient lymphadenopathy or parotiditis may be present. Moderate to severe sequelae such as febrile seizures, anaphylaxis, thrombocytopenic purpura or encephalitis are very rare. Due to the theoretical teratogenic risk of the rubella vaccine, vaccination during pregnancy or becoming pregnant in the first month after immunization is not recommended (Bouthry et al., 2014).

II.5 SIGNS AND SYMPTOMS

More than 50% of cases are asymptomatic. In clinically manifest cases, after an incubation period of 13-20 days, prodromal symptoms appear in the form of: fever, malaise and adenopathy, especially in the postauricular lymph nodes, occurring with viremia. A maculopapular rash develops which usually lasts 1 to 3 days and is characterized by small pinkish papules. It is sometimes atypical, scarlatiniform, or purpuric. The rash alone of rubella is not reliable as similar rashes occur also in some other viral infections, toxoplasmosis, or allergic reactions (Bouthry et al., 2014).

Polyarthritis and polyarthralgia are the most common complications, occurring mainly in adult women and usually lasting 3 to 4 days; these symptoms sometimes persist for 1 month. Other manifestations, although rare, include post-infectious encephalitis, thrombocytopenia, hemorrhagic manifestations and Guillain-Barré syndrome (Bouthry et al., 2014).

II.6 RUBELLA RE-INFECTION

Rubella re-infection is a rubella infection in someone who already has rubella antibodies (resulting from natural infection or from immunization). Rubella re-infections are usually subclinical and often difficult to diagnose; however, significant elevations in antibody titers (IgG and/or IgM) can be found. The incidence of re-infection during pregnancy is unknown, and the risk of transmission to the fetus is difficult to determine (Bouthry et al., 2014).

II.7 DIAGNOSIS OF RUBELLA INFECTION

Rubella in the general population presents in a mild degree, hence most of the diagnostic tools developed are focused on diagnosing rubella in pregnancy, fetus and newborn (Bouthry et al., 2014). Laboratorial diagnostics are more trusted to establish the diagnosis of Rubella. Specimens examined are throat swabs, saliva, nasopharyngeal secretions or serum (Lambert et al., 2015). The principles of diagnosis proposed by Bouthry et al. are as follows (Bouthry et al., 2014):

1. Natural immunity

RV-IgM appears within 3 days after the rash and generally disappears within 4 to 12 weeks (IgG levels decrease to half in every 3 weeks), mainly depending on the assay used. Detection of RV-IgG by ELISA is slower (5-8 days after rash onset) and persists throughout life. RV-IgG reaches stable levels after a few days to weeks, and maximal and residual RV-IgG levels vary widely, depending on the patient tested and the assay used. A high RV-IgG titer is not necessarily a marker of recent primary infection.

2. Rubella immune status assessment

In epidemiologic situations, it is recommended to check rubella serology at the first prenatal visit, unless previous immunity is known or two doses of rubella vaccine have been received. Patients who are serologically negative should have their serology repeated at 20 weeks gestation; women who remain seronegative at 20 weeks are recommended to be vaccinated after delivery.

Immunity to rubella is usually determined by measuring RV-IgG using an enzyme immunoassay method that gives quantitative results in international units (IU) per milliliter. RV-IgG results and interpretation may be confusing, depending on the assay used.

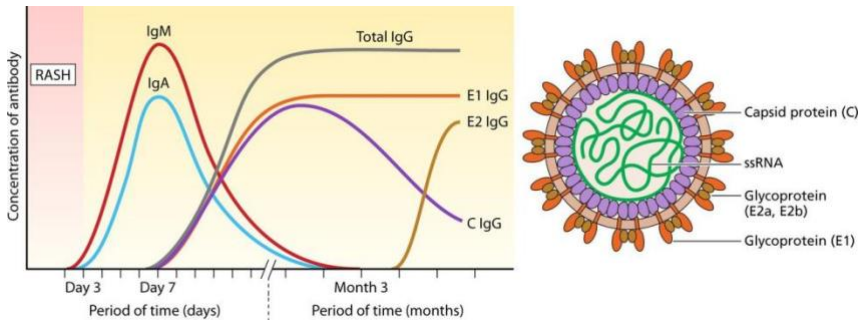
The avidity test is performed under certain conditions. Low RV-IgG avidity indicates current infection (Lambert et al., 2015).

3. Diagnosis of maternal rubella infection

The clinical diagnosis of rubella is difficult to confirm due to its inconsistent and non-specific clinical symptoms. Laboratory diagnosis is essential to confirm recent rubella infection, which is based on the observation of RV-IgG, RV-IgM seroconversion and RV-IgG avidity and on the detection of rubella virus in nasopharyngeal secretions by *reverse transcription/polymerase chain reaction (RT-PCR)*.

In cases where a pregnant woman comes into contact with a suspected rubella case, RV-IgG should be checked as soon as possible (<12 days). An RV-IgG-positive result indicates that the patient has been infected. For at-risk cases, examination of RV-IgG and RV-IgM titers is recommended 3 weeks later to exclude the presence of asymptomatic primary rubella infection. RV-IgG can reach a steady state within a few days or weeks after the onset of infection. Therefore, in cases of ultrasound abnormalities (including intrauterine growth retardation), RV-IgM, RV-IgG avidity and amniotic fluid (AF) rubella RT-PCR should be tested.

RV-IgG avidity can describe how long the primary infection has been established. A low RV-IgG avidity index indicates that the primary infection has not long occurred (<1-3 months); a high RV-IgG avidity index indicates that the primary infection has long occurred (>3 months).



Rubella Antibody (http://id.images.search.yahoo.com/)

II.8 CONGENITAL RUBELLA SYNDROME

Pathogenesis

Rubella infection can affect all organs. The pathogenesis of CRS is multifactorial (Bouthry et al., 2014).

- Non-inflammatory necrotic cells of the endothelium and chorion epithelium are transported to the fetal circulation and fetal organs such as the eyes, heart, brain, and ears, triggering thrombosis and ischemic lesions.

- Actin formation is inhibited directly or indirectly, resulting in inhibited cell mitosis and development of organ precursor cells.
- Upregulation of interferons and cytokines leads to impaired cell development and differentiation, resulting in congenital abnormalities.
- In children with CRS, rubella virus persists and is detected in urine, saliva and cerebrospinal fluid for several months; this suggests that the immune defect is cell-mediated.

Incidence of fetal infection

The risk of infection and congenital defects depends on the gestational age at the time of infection (Bouthry et al., 2014).

- Before 11 weeks of pregnancy, the congenital infection rate is close to 90%, decreases to 30% between 24 and 26 weeks, and increases to almost 100% after 36 weeks.
- During the first 12 weeks of pregnancy, the risk of a major defect approaches 85%; approximately 20% of cases experience spontaneous abortion in the first 8 weeks.
- The risk of fetal infection in cases where conception occurs after the onset of the rash is likely to be very low, and the onset of the rash usually coincides with the appearance of antibodies and the end of viremia.
- No intrauterine infection has been detected in children or fetuses whose mothers developed the rash before or within 11 days of the last menstrual period.
- Teratogenic infection may occur in pregnancy where the rubella rash appears 3 to 6 weeks after the last menstrual period.

Fetal manifestations

Rubella virus infection during embryogenesis causes the classic triad (i.e. cataracts, heart defects and sensorineural deafness) and other defects that may be detected. These abnormalities are classified as transient, permanent or late onset (Bouthry et al., 2014).

- Transient abnormalities are found in newborns such as low birth weight, thrombocytopenic purpura, hemolytic anemia, hepatosplenomegaly and meningoencephalitis.
- Permanent abnormalities include ophthalmic abnormalities (microphthalmia, cataracts and retinopathy), hearing loss (sensorineural deafness), cardiac defects (patent ductus arteriosus and pulmonary artery hypoplasia), central nervous system manifestations (mental and psychomotor retardation and language delay), and craniofacial malformations/microcephaly). Deafness is the most common defect and can be the only defect found, especially in cases where infection occurs at 12 to 18 weeks of pregnancy.
- Late onset abnormalities include endocrine, cardiovascular and neurological abnormalities.

Diagnosis of congenital rubella infection

1. Prenatal diagnosis

   Prenatal diagnosis of congenital infection is recommended in rubella-infected mothers,through detection of RV-IgM in fetal blood or detection of the viral genome in amniotic fluid, fetal blood, or chorionic villus biopsy. The specificity of prenatal diagnosis is about 100%, and the sensitivity is greater than 90% if the following conditions are met (Bouthry et al., 2014):

   - at least a 6-week period elapses between infection and sampling;
   - sample collection is done after 21 weeks of pregnancy; and
   - samples for RT-PCR were stored and transported frozen (fetal blood for RV-IgM detection was stored and transported at 4°C).

Although not easy, prenatal diagnosis of fetal infection is necessary when primary rubella infection occurs during the first 4 months of pregnancy (Bouthry et al., 2014).

2. Diagnosis of congenital infection from birth

   The diagnosis of congenital infection from birth is based on the detection of specific RV-IgM by ELISA method, which has a sensitivity and specificity close to 100% in infected newborns (<3 months of age). In cases where the RV-IgM test is positive, congenital infection may be confirmed by isolating rubella virus or by detecting the viral genome in nasopharyngeal swabs, urine and oral fluid using RT-PCR (Bouthry et al., 2014).

II.9 Management Of Rubella Infection In Pregnant Women

1. General management

Management of rubella infection depends on the gestational age at the onset of infection (Bouthry et al., 2014):

- Infection before 18 weeks of pregnancy:

  The fetus is at high risk of infection and severe symptoms. Termination of pregnancy may be discussed and accepted, according to local laws, especially if infection occurs before 12 weeks. A detailed ultrasound examination and assessment of viral RNA in the amniotic fluid is recommended, especially for infections occurring between 12 and 18 weeks of gestation. If prenatal diagnosis is not performed, special pediatric examinations should be performed on the newborn, including RV-IgM testing.

- Infection after 18 weeks of pregnancy:

  Pregnancy can be continued with simple ultrasound monitoring. Specific pediatric screening of the newborn and RV-IgM testing is recommended.

Ultrasound findings

The most common ultrasound abnormalities are cardiac (septal defect) and ocular (cataract and microphthalmia) defects. Microcephaly, hepatomegaly, splenomegaly and intrauterine growth retardation are less common. No descriptive series of fetal ultrasound semiology has been reported that can determine the frequency of these abnormalities (Bouthry et al., 2014).

PREVENTING CRS

The proven primary prevention strategy for CRS is, and will continue to be, the vaccination of young women (Mawson and Croft, 2019). In a population covered by universal childhood rubella immunization, antenatal rubella seronegativity was associated with increased pre-eclampsia and perinatal loss only in multiparas, suggesting that the rubella seronegativity in these women served as a proxy for some form of altered immune response which increases adverse pregnancy outcomes (Lao et al., 2022).

Some women, mainly those who were not vaccinated, will continue to acquire rubella infection in the first trimester of pregnancy, so their unborn fetus will be at risk of CRS. In many countries, this is an indication for elective abortion. For those who do not wish to take this step, the following simple measures could be taken by the mother to reduce the expression of excess retinoids and hence lower the risk of fetal CRS (Mawson and Croft, 2019):

1. stopping all alcohol for a period of at least 4 weeks;
2. stopping all liver-damaging drugs that are not essential to life (e.g., anabolic steroids, recreational drugs, antidepressants, anxiolytics and hypnotics);
3. maintaining good hydration by drinking plain, non-fluoridated water (and not through drinking coffee or tea, both of which are dehydrating);

4. eliminating vitamin A from the diet for one month (the main dietary source is liver, but vitamin A is also found in milk, cheese, egg yolks and fish oils);
5. (optional) reducing circulating retinoids, under medical supervision, through phlebotomy, plasmapheresis or hirudotherapy.

III. CONCLUSION

- Rubella is a mild and contagious systemic viral infectious disease.
- CRS is a very severe complication of a mild preventable disease, which can only be managed with supportive therapy.
- Serology tests and DNA testing are still the most trusted diagnostic tests today.
- Rubella vaccination in Catin to reduce the incidence of CRS is a plausible option.

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