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Rubella infection during first trimester of pregnancy, is it always termination of pregnancy? a case report

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Abstract. The clinical diagnosis of acute rubella infection in pregnancy is extremely difficult because the symptoms are not very specific nor particularly apparent, and most infectious cases are subclinical and therefore seroconversions and presence of high IgM titres is the primary mode of diagnosis of acute rubella in pregnancy. But a positive IgM doesn't means she had acute rubella infection because there were false positive with IgM antibody positive. More other confirmation test should be done such as include isolation of rubella virus from an appropriate clinical specimen. Decision for termination of pregnancy should not solely base on IgM antibody finding. In case that the family keen to continued her pregnancy should offer amniotic fluid or cord blood PCR for detection and diagnostic of perinatal infection. In this case, we report a 42-years old pregnant woman at 7 weeks' gestation complains acute onset of generalized maculopapular rash suspected of rubella infection with positive of IgM anti rubella and positive for IgG. Patient is informed that she has acute rubella infection and risk of perinatal infection and discussed about an option of termination of pregnancy. After families counselling they decided to continue the pregnancy because of a specific condition (baby will adopted by her younger brother). At 18 weeks of pregnancy we do amniotic fluid for rubella PCR RNA, and the result was negative. The pregnancy is continued with routine prenatal care. Unfortunately, she has very early preterm premature rupture of the membrane at 23 weeks and fetal death caused by umbilical cord compression, and the baby was do induction of labor and born a fetal death baby of 400 grams. A new protocol was made for management of acute rubella infection in early pregnancy.

1. Introduction

Rubella (initially known as German measles) is high seropositivity. A study was to determine how many pregnant women are at risk of primary infection with rubella in a rural and urban area found that an overall seropositivity rate of 95.0%. The high overall seropositivity rate in the absence of routine immunization suggests a continuous transmission of endemic rubella [1].

Rubella infection was associated with a 80% risk of usually multiple congenital abnormalities if acquired in the first 12 weeks of pregnancy, especially the first 8-10 weeks, and leads to fetal growth problems or stillbirth. It is transmitted via respiratory airborne droplets. The virus initially replicates in the nasopharyngeal mucosa and local lymph nodes, and in pregnancy infects the placenta and developing fetus [2]. If primary rubella infection occurs during pregnancy, the rubella virus will cross the placenta and induce fetal infection depending upon the time of gestation. Infection occurring in the first 12 weeks of pregnancy causes congenital rubella infection in 90%, with almost a 100% risk of congenital defects

[3]. Congenital rubella syndrome characterized by growth retardation, cataracts, chorioretinitis, deafness, cardiac anomalies, hepatosplenomegaly, jaundice, thrombocytopenia, microcephaly and mental retardation [4], [5], [6].

The incubation period (prior to appearance of symptoms) is 12-23 days, with an average of 18 days. The infectious period commences 7 days prior to the onset of symptoms and continues until 4 days after the onset of the rash. In the second week following exposure symptoms of fever (usually mild and <39.0°C), malaise and mild conjunctivitis may be present, and a characteristic lymphadenopathy is typically found in the neck and behind the ears (sub occipital and post auricular). These symptoms generally precede a maculopapular, erythematous, and pruritic rash by about 5-10 days. The rash occurs in 50-80% of infected people and usually lasts 1-3 days, commencing on the face and neck before spreading down the body [2].

A case with or without symptoms who has laboratory evidence of rubella infection confirmed by one or more of the following laboratory tests: isolation of rubella virus or detection of rubella virus specific nucleic acid by polymerase chain reaction or IgG seroconversion or a significant rise between acute and convalescent phase titers in serum rubella IgG antibody level by any standard serologic assay or positive serologic test for rubella IgM antibody [7]**.**

For that reason in our hospital if mother has rubella infection based on suspicion on clinical finding and positive serologic test for IgM anti rubella we counsel the woman regarding relevant risk to fetus in relation to timing of maternal infection and options for management including termination of pregnancy should be offered if maternal infection occurs in the first trimester [5]. In our hospital we did not have a confirmation test after IgM positive and termination decisions based solely on the results of the examination of IgM serologic result.

In this case report we will report a case of rubella infection in first trimester who showed symptoms of rubella infection and positive rubella IgM serology and after counseling the patient's for pregnancy termination, patients refuse and wait for the confirmation for rubella infection, and if the baby is proved to be infected, the mother is willing to do the pregnancy termination.

2. Case Report

A 42-year-old pregnant woman at 7 weeks' gestation complains acute onset of generalized maculopapular rash and fever temperature of 38,0°C and arthralgia. No arthritis, lymphadenopathy, or conjunctivitis and no epidemiologic linkage of rubella in her village. She did not have rubella vaccination before. Based on her clinical suspicion of rubella infection we did a serologic test for Rubella and the result was positive for IgM anti rubella antibody and also positive for IgG anti rubella antibody. Patient was informed that she has acute rubella infection and discussed about an option of termination of pregnancy base on epidemiologic data about risk of transmission and risk of congenital rubella syndrome because the pregnancy affected in the first trimester. She was also give counseling about a high risk pregnancy because of her age and two times of previous caesarian section. After families counseling they decided to continue the pregnancy because of a specific condition (baby will adopted by her younger brother because of 10 years infertility). She want to wait because about 10 percent the baby will not affected and keen to do other examination like ultrasound and invasive perinatal testing include amniocentesis or chordocentesis and noninvasive perinatal testing to screen of genetic disease and if the baby is proved to be infected, the mother is willing to do the pregnancy termination.

Base on resources in our institutions and possibilities for other examination outside the laboratory hospital we planned for follow up the pregnancy base on her symptoms, ultrasound for prenatal screening of Down’s syndrome and congenital cardiac defect with measurement of nuchal translucency (NT), screening for other structural anomaly especially CNS defect, eyes scan and screening of cardiac anomaly as early as 12 weeks using detection of tricuspidal

regurgitation. We also offer noninvasive perinatal testing for free fetal DNA for screening of trisomy 21, 13 and 18. For risk of transmission of rubella to the fetus we plan do the amniocentesis and PCR for rubella virus from amniotic fluid at 16-18 weeks of pregnancy. The antenatal result is the mother is in good condition after fever and rush, nuchal translucenchy (NT) was 1.0 mm (normal), ultrasound from 12 and 16 weeks of pregnancy showed normal structural of the fetus (no fatal fetal anomaly), targeted sonography for eyes and fetal cardiac show no cardiac defect and no congenital cataract. NIPT result is 46 XY and no trisomy 21, 13 and 18. Amniocentesis do in 18 weeks of pregnancy and the amniotic fluid is sent to Division of Microbiology University of Indonesia Jakarta. The PCR RNA result is negative for rubella. The patient is given counseling about the result and continued to do antenatal care and plan for cord blood examination after delivery. Unfortunately, she has very early preterm premature rupture of the membrane at 23 weeks and fetal death caused by umbilical cord compression, and the baby was do induction of labor and born a fetal death baby of 400 grams.

3. Discussion

In our patient diagnosis of recent rubella infection is base on clinical suspicion and rubella specific IgM, and the discussion and counseling for termination of pregnancy is solely base on epidemiologic data that a high possibility of perinatal infection from rubella if the infection occur in first trimester of pregnancy. This is base on our local institution clinical practice guidelines and lack of resources to do other further test for confirmation diagnosis of rubella infection.

The clinical diagnosis of acute rubella infection in pregnancy is extremely difficult. The rash is not very specific nor particularly apparent, and most infectious cases are subclinical. Therefore, demonstration of seroconversion and presence of high IgM titres the primary mode of diagnosis of acute rubella in pregnancy [3].

Guidelines by Public Health Laboratory Service (PHLS), investigation of pregnant woman for rubella with significant exposure to rash should consist of Rubella IgG and IgM. If rubella specific IgG is detected, and rubella specific IgM is not detected, women should be reported as no evidence of recent primary rubella. In a pregnant patient with onset of a rash in the previous 10 days, if a low concentration (<10 iu/ml) of rubella-specific IgG is detected, a further serum should be requested even if a rubella specific IgM is not detected. If rubella-specific IgM reactivity is detected then she should be further tested for rubella. No woman in the first 20 week of pregnancy should have rubella diagnosed based on a positive rubella specific IgM alone. Results must be interpreted in relation to full clinical and epidemiological information. Unless seroconversion has been shown, further testing by alternative rubella specific IgM tests and measuring the strength of binding of specific IgG (avidity) is advised [4], [7].

To made the critical decisions to do or not to do termination of pregnancy should be done by a highest modality for diagnostic and the possibility of a false positive should be taken account. Even for this case the diagnostic is appropriate as per Manitoba's Public Health and Primary Health Care Communicable Disease Control that consistent clinical illness with laboratory confirmation of infection in the absence of recent immunization with rubella containing vaccine. Laboratory confirmation includes at least one of positive test for rubella IgM antibody using a recommended assay in a person with an epidemiologic link to a laboratory confirmed case or who has recently travelled to an area of known rubella activity or by others confirmation test include isolation of rubella virus from an appropriate clinical specimen (e.g., nasal or throat swab, urine) or detection of rubella virus by nucleic acid amplification test (NAAT) (e.g., throat swab or urine specimen) or seroconversion or a significant rise in rubella

IgG titre between acute and convalescent sera by any standard serologic assay or clinical illness in a person with an epidemiologic link to a laboratory confirmed case [8].

IgM serology may be a false positive. If the clinical presentation is inconsistent with a diagnosis of rubella or in the absence of recent travel/exposure history, IgM results must be confirmed by another listed confirmatory method. Rubella avidity serology is recommended for IgM positive results in pregnant women [8]. In this case the clinical presentation is not specific. She just complaint of malaise, and low grade fever, upper respiratory symptoms followed by generalized rush with arthralgia but there is no arthritis or lymphadenopathy found. Clinical infection is usually mild characterized by a generalized erythematous maculopapular rash, lymphadenopathy and slight fever. Up to 50% of infections are subclinical. Signs and symptoms are nonspecific and rubella may be mistaken for other rash infections such as measles, dengue, parvovirus, adenoviruses, enteroviruses or human herpesvirus. In older children and adults, there is often a one to five day prodrome with low-grade fever, malaise, lymphadenopathy and upper respiratory symptoms preceding the rash. The rash starts on the face, becomes generalized within 24 hours, and lasts approximately three days. Lymphadenopathy commonly involves the post auricular, posterior cervical and sub occipital nodes and lasts five to eight days. Adult infection is often accompanied by transient polyarthralgia or polyarthritis, especially in females [8]. CDC also made their confirmation of diagnosis of rubella base on clinical symptoms and epidemiologic status of patients that includes an illness characterized by all of the following: acute onset of generalized maculopapular rash, temperature greater than 99.0°F or 37.2°C, and arthralgia, arthritis, lymphadenopathy or conjunctivitis, and epidemiologic linkage to a laboratory confirmed case of rubella. In this patient not fulfill all the criteria since there is no epidemiologic linkage to a laboratory confirm case of rubella [7]**.** False-positive rubella IgM tests have been reported with other viral infections (e.g., measles, Epstein-Barr virus, parvovirus and cytomegalovirus, or in the presence of rheumatoid factor. When a false positive rubella IgM is suspected, consider the following tests rheumatoid factor, parvovirus IgM, and heterophile testing. Other confirmatory rubella testing (i.e., avidity tests or cultures) [9].

Fetal infection with rubella has a devastating effect including either death or long term neurological disability. In developing countries, where rubella vaccination is not compulsory, all pregnant women should ideally be screened for the rubella antibody. The detection of rubella RNA directly in clinical specimens is a critical factor in early laboratory diagnosis in addition to detection of rubella specific IgM. Prenatal diagnosis in form of amniocentesis in 2nd trimester of pregnancy and fetal blood sampling with testing of rubella specific IgM or rubella specific RNA PCR can be offered to pregnant women who have positive maternal rubella IgM or increased IgG avidity which was done as in our patient. However, there have been reports of false negative amniotic fluid rubella RNA or false positive amniotic fluid RNA in some pregnant women as was seen in the patient where amniotic fluid RNA PCR was negative and neonatal blood for rubella IgM was positive at birth and child clinically had congenital rubella syndrome. In fact, Tang *et al* found that optimal sample for prenatal diagnosis is fetal blood. In our case there was negative result from amniotic fluid rubella RNA that means that she may not had rubella infection or in a smaller possibility she had a false negative that still need to do more follow up for perinatal infection and do the cord blood RNA PCR after delivery [4].

In Indonesia, there were not an universal screening for rubella infection in pregnancy. As per the UK National Screening Committee (NSC) antenatal subgroup, all pregnant women should be screened for rubella antibody at least in the first pregnancy irrespective of previous

immunization history, although they indicate that testing may be considered unnecessary if there is documented evidence of the presence of rubella antibody from two prior tests [4].

In this case she has IgG antibody positive, that means she had exposure from rubella before but she was not vaccinated before since there are no vaccination program for rubella as national guidelines in Indonesia. The European WHO therefore issued a plan for eliminating congenital rubella with the aim of having less than one case of CRS per 100,000 live births by 2010. In order to reach this goal, it was planned to ensure at least 95% vaccine coverage among children aged 2 years, with at least one dose of vaccine in all administration units [10], [11], [12].

4. Conclusion

The clinical diagnosis of acute rubella infection in pregnancy is extremely difficult because the symptoms is not very specific nor particularly apparent, and most infectious cases are subclinical and therefore seroconversion and presence of high IgM titers is the primary mode of diagnosis of acute rubella in pregnancy. But a positive IgM does't means she had acute rubella infection because there were false positive with IgM antibody positive. More other confirmation test should be done such as include isolation of rubella virus from an appropriate clinical specimen (e.g., nasal or throat swab, urine) or detection of rubella virus by nucleic acid amplification test (NAAT) (e.g., throat swab or urine specimen). Decision for termination of pregnancy should not solely base on IgM antibody finding. In case that the family keen to continued her pregnancy should offer amniotic fluid or cord blood PCR for detection and diagnostic of perinatal infection. We proposed a new algorithm to manage of suspicion of acute rubella infection in early pregnancy to replace of our previous clinical practice that termination of pregnancy is offer only base on positive IgM rubella result.

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Appendix

Proposed new Algorithm for Serologic Evaluation of Pregnant Women Exposed to Rubella