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(RESEARCH ARTICLE)

One-point evaluation of children exposed to rubella infection *In Utero* in Maiduguri, North-Eastern Nigeria: A follow-up Study

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Abstract

Background: Rubella is a disease caused by a virus, rubella virus. Major obstetrics concerns are profound effects of the virus on developing fetuses, which may result in multiple congenital malformations. Although vaccination has reduced the incidence of rubella virus substantially; the World Health Organization (WHO) estimated that more than 100,000 cases of congenital rubella syndrome occur each year worldwide, most of them in developing countries. Diagnosis of rubella cannot be made on clinical grounds alone due to lack of specific symptoms or signs that are unique to the disease. Women infected with rubella during pregnancy are at increased risk of developing complication for the women and their fetuses. Some of these complications may not present at birth, but several years during childhood and later in life.

Methodology: The main rubella sero-prevalence study was conducted in 2013, at the Department of Obstetrics and Gynaecology of the University of Maiduguri Teaching Hospital (UMTH), Maiduguri, Borno State, North-Eastern Nigeria. This is a follow-up descriptive study. The children of women who had significant titres of Immunoglobulin M antibodies, and who were negative for Immunoglobulin G antibodies were followed during their pregnancies and childbirth. The children born to these women who acquired rubella virus infection in mid pregnancy were reviewed at 10-11 years of age, and their current state of health is reported. Their biodata, educational status, rubella serostatus, state of health, and history of vaccination with measles were obtained.

Results: There were 459 pregnant women who consented and participated in the main sero-prevalence study. Four hundred twenty-one women (91.7%) women tested positive for rubella-specific IgG antibodies, and of the remaining 38 women, 6 (15.8%) were positive for IgM rubella-specific antibody. All the patients with positive IgM antibodies were followed up till birth. All the pregnancies were carried to term and delivered in hospital. None of the neonates was found to have any congenital malformation at birth.

At 10 years review of the six (6) children, 1 (16.7%) child developed cataract. None of the children developed cardiac, ear, or other complications of rubella. Five (5) children (83.3%) tested positive for both IgG, one (1) was negative (the child with cataract) for rubella antibodies. None had IgM rubella antibodies. All the children were enrolled in schools and their performance is at least average of their peers.

Conclusion: None of the known types of congenital rubella syndrome was found in this study, this may be as a result of smaller number of infected pregnancies. It is recommended that inclusion of rubella vaccination in the National programme on Immunization protocol will be cost effective in the prevention of rubella-associated complication in children.

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Keywords: Rubella; In utero rubella exposure; Child rubella; Rubella infection; Complications rubella

1. Introduction

Rubella virus is an enveloped RNA virus with a single antigenic type and the only member of the *Rubivirus* genus [1,2] that does not cross-react with other members of the *Togaviridae* group.[3] The virus contains an RNA with 9762 nucleotides [3] and has a simple architectural structure of single stranded RNA genome enclosed by an icosahedral nucleocapsid, protected by a lipid bilayer membrane.[3] It is relatively an unstable virus inactivated by liquid solvents, trypsin, formalin, low pH, heat, and amantadine.[2] Its ectodomains –E1 and E2, are organized into extended rows of density separated by 9*n*M spaces on the viral surface.[4] The nucleocapsids often form a roughly spherical shell which lacks high density at its centre.[3,5] Rubella exhibits a large degree of pleomorphism.[2,5,6]

Following infection with rubella, virus-induced cytopathic changes including cell detachments from monolayer and chromatin condensation occur on several cell lines.[4-7] Infected cells also exhibit acute and persistent alterations characteristic of apoptosis, including DNA fragmentation, reduced DNA content, and annexin V staining.[6]. The signals involved in the RV-associated apoptosis are independent of *P53* and the *Bcl*-2 gene family.[6] The cytopathic effects have been shown to be due to caspase-dependent apoptosis in the susceptible cells.[4,8] Infection is also associated with citron-K kinase (CK) functional perturbations and development of tetraploidy state in specific cell types.[9]

Rubella has a worldwide distribution.[3,10-16] Following introduction of vaccination against rubella in 1969, congenital rubella syndrome has become rare in industrialized countries,[11-17] due to massive immunization of children and vulnerable non-immunized women of reproductive age.[10,11,15] Outbreaks are seen commonly due to vaccine failure or missed vaccination[14,18,19] in children between the ages of 3-10 years.[16] The sero-positivity of rubella antibodies increases with age,[15] and has been reported to be higher in rural than in urban communities[13] and in people of low socio-economic status.[20]

Rubella is a human disease.[3,15] There is no known evidence that animals can transmit the disease or act as reservoir.[15] Although infants with CRS may shed rubella virus for an extended period, a true carrier state has not been described.[15,21-23] Rubella is transmitted by the respiratory route via airborne transmission or droplets shed from the respiratory secretions of infected persons,[10-12,14,21-24] There is no evidence other agents of transmission exist.[14,23] Transmission has been successfully minimized via mass vaccination programmes.[25,26] Vertical transmission has been well documented and associated with embrayopathy,[10,19,20,27-30] prevention of which has been the target of vaccination against rubella.[10,27]

Rubella is moderately contagious.[10,12,19,21-24] The disease is most contagious during the three days (3-days disease) when the rash first appears, but the virus may continue to be shed from 7 days prior, to 5–7 days or more after rash onset.[3,12,15] Children usually recover from the infection more quickly [10,11,15] but may continue to shed large quantities of virus from body secretions.[7] The World Health Organisation (WHO) has since recommended that all countries should consider universal rubella vaccination of children, and ensure immunity of women of childbearing age.[10,19]

This study is a reports the state of the health of six (6) children at 10 years of age, whose mothers acquired infection with a wild rubella virus, during first trimesters of the pregnancies that resulted in the delivery of the studied children.

2. Methodology

This study reviews the health status of children at 10-11 years of age, who were exposed to rubella virus *in utero*. It is a follow up descriptive study. The main rubella sero-prevalence study was conducted in 2013, at the Department of Obstetrics and Gynaecology of the University of Maiduguri Teaching Hospital (UMTH), Maiduguri, Borno State, North-Eastern Nigeria.[1] Their mothers had significant titres of Immunoglobulin M (IgM) antibodies during pregnancies, and were negative for Immunoglobulin G (IgG) antibodies. Their mothers were followed during the respective pregnancies and childbirth. The delivery records of these babies were also reviewed.

The children born to these women were reviewed at ten 10-11 years of age, and their current state of health is reported. Their biodata, educational status, and history of vaccination with measles, rubella serostatus, and the general state of health were obtained. Their various schools were contacted and assessment of their performance in class was requested. All the children were tested for IgG and IgM rubella antibodies, using ELISA technique, in a similar fashion with the main study.

Institutional ethical clearance was obtained from the Ethical Committee of the hospital. The parents consented on behalf of the children.

3. Results

A total 6 children were studied. Their age ranges between 10.6-11.6 years with mean of 11.1±0.4 years. All the children were enrolled in Primary Schools, with 3 (50%) at grade III, and the other half at grade IV. Their biodata, and school performance are as presented in Table II.

Table 1 Socio-demographic characteristics of the children

Description	**Number**	**Percentage**
Religion		
Islam	4	66.7
Christianity	2	33.3
School Grade		
Primary School Grade III	3	50.0
Primary Sch Grade IV	3	50.0
School Performance		
Very Good	3	50.0
Excellent	3	50.0

All the children were evaluated and reviewed by medical specialist (Paediatrician, Otorhinolaryngulogist, Psychiatrist) and were found to have no features of congenital physical, cardiac, or ear problems, and none had other complications of rubella at birth. One child (16.7%) was found to have developed cataract and was referred for treatment.

Five (5) children (83.3%) tested significantly positive for IgG, with serum titres of 150-200U/mL, one (16.7%) was negative for rubella antibodies. None had IgM rubella antibodies. All the children were enrolled in schools and their performance is at least above average of their peers. All the children have received full courses of vaccination for their age, but rubella vaccine was not given. Their Intelligence Quotient Level was found to range from 40-50.

4. Discussion

All the IgM sero-positive pregnant women were diagnosed during antenatal booking in the third trimester (26-32 weeks).[1] Generally, after 20 weeks of gestation, acquired rubella infection in pregnancy is not associated with increased risk of CRS or malformations in the fetus,[1,11] but the fetuses may suffer variable degree of growth restriction, fetal death or mental retardation.[1,31,32] The high incidence of IgM sero-positivity could be as a result of an asymptomatic outbreaks, which occurs in a seasonal pattern, with epidemics every 5-9 years.[1,18,20] The delivery records of the pregnancies that resulted in the delivery of these children revealed that all the children were delivered at term and the babies had normal birth weights.[1] The Paediatrician's review reported normal findings in the babies.

The IgM sero-prevalence of 15.8% found in the primary study[1] among the pregnant women who were sero-negative for IgG antibodies was significantly higher than rates reported from Benin (10%),[34] Jos (6.8%),[35] and Makurdi (3.9%).[36] This indicated that the mothers acquired new recent infection with rubella virus, [1] as none of the women had a recent history of vaccination prior to presentation.

Five of the children (83.3%) had tested positive for rubella IgG antibodies. This is slightly lower than the sero-prevalence of rubella-specific IgG antibodies (rubella immune) found in the primary study (91.7%).[1] This indicates that the children have had previous infection with wild rubella virus.[1] The current prevalence rate compares well with those reported from Zaria (97.9%)[37] but higher than those reported from Benin (53%),[34] Nigeria. Although all the children were vaccinated against measles, history of measles vaccination has not been shown to be significantly associated with the presence of rubella-specific IgG antibodies.[1] Previous studies showing this relationship may have resulted from false positive tests due to cross-reacting specific IgG produced following infection with other non-

common viruses, such as Cytomegalovirus (CMV), Epstain Barr Virus (EBV), and human parvovirus B19.[38-42] Generally, when infection with rubella is clinically suspected, laboratory tests should include those for the CMV, EBV, herpes simplex virus (HSV), toxoplasmosis, syphilis and Zika virus.[15,47]

One of the children (16.7%) tested negative for both IgG and IgM rubella antibodies. This percentage, when placed in the population is still large. These are the group of children that are at risk of acquiring rubella infection and therefore will require rubella immunization. [43,44] It is important and desirous to vaccinate all sero-negative children with a potent rubella vaccine, together with all women of reproductive age.[1,16,19]

Serum IgG titers in the children were found to be in the range of 150-200U/mL in the sero-positives in this study. These titers are comparable to those reported from Ibadan with a median titer of 165U/mL,[46] and those reported from India, with serum IgG titers above 200U/ml.[36] This blood antibody titre level profer strong protection against re-infection with the wild type rubella virus.[1,15]

Most of the complications known to result in children exposed to rubella infection during pregnancy were not seen in the majority of these children. This may be as a result of the size of the study population. However, one child was found to have developed bilateral cataracts at age 11 years. This was not diagnosed at birth.

Other complications seen in other studies include sensorineural hearing loss, cardiac abnormalities, skeletal defects, mental retardation, and reduced intelligence quotients when compared with results obtained in unexposed peers.[15,46-49] None of these was seen in these children. Following childhood infection, survivors have increased risk of developing insulin-dependent diabetes mellitus later in life.[15]

5. Conclusions

Rubella infection during pregnancy can significantly exposed children to increased risk of developing diseases such as cataract early in life. As such children that are exposed to rubella in utero should benefit from life time follow up. This is to enable developing conditions are diagnosed early and managed.

Limitation

It is a limitation of this study that IgM antibodies to other viruses such as EBV, CMV, or parvovirus B19, that could cross-react with rubella antigens were not screened.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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