ORIGINAL ARTICLE

Seroprevalence survey of rubella infection in pregnancy at the University of Benin Teaching Hospital, Benin City, Nigeria

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Abstract

Objective: To determine the serosusceptibility of rubella infection in pregnancy and the feasibility of establishing an organized prevention program in a tertiary hospital in Nigeria.

Materials and Methods: This prospective, cross-sectional, laboratory-based study involved 300 consecutive pregnant women who gave informed consent and were screened for rubella immunoglobulins G (IgG) and M (IgM), using the ELISA-based quantitative assay at the University of Benin Teaching Hospital, Nigeria. Of the cohort, 30 women later withdrew. IgG seropositive samples were screened for IgM antibodies.

Results: The mean age and parity of the women were 30.0 ± 4.8 years, 95% CI 29.727-30.873 and 2.0 ± 1.4; 95% CI 1.317-1.661, respectively. IgG seroprevalence was 53%, while 10.0% of all IgG seropositive women were IgM seropositive. Most infections were acquired before the age of 35. None of the women ever had previous rubella vaccination. Rubella vaccine is scarce in Nigeria.

Conclusions: Prevalence of rubella seromarkers for previous and current infection is high. Facilities for routine diagnosis and vaccination are lacking. Initiation of organized screening and vaccination programs is limited by lack of vaccine. We recommend immunization of children and women of child-bearing age as a cost-effective public health intervention strategy for managing the sequelae of the congenital rubella syndrome.

Key words: Rubella, pregnancy, sero-markers, vaccination

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Introduction

The burden of infectious diseases is great. Infectious diseases inflicted a new magnitude of suffering after the world entered the last millennium. They are among the biggest disablers and killers of the young.[1] According the World Health Organization,(WHO), as diseases continue to catch the world off guard, near misses are on the increase and the future is uncertain. Medicines are losing their effectiveness and the world is becoming a smaller place for microbes.[1] Fortunately, however, most of these diseases are affordable to prevent, avoidable at a low cost, and controllable in any country.[1-4] Among the cases of death, at least half, and in some cases nearly all, could be avoided by simply using affordable interventions, most of which cost no more than US $5 per person, on an average.[1,2]

Several viruses and bacteria belong to the dreaded group of infectious diseases, some of which, although preventable, are transmitted vertically and horizontally.[4,5] In pregnancy, they either cross the placenta to cause congenital infections in the fetus, abortion, intrauterine death, preterm labor or infect the baby perinatally as it passes through the birth canal of the mother or in postnatal life, through breast milk, as in HIV.[5] Rubella virus is among the microorganisms

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that can be transmitted from mother to child (MTCT).[2-4] It is a non-sexually transmittable viral infection with mild febrile symptoms and a rash in adults and children,[2] and occasional outbreaks.[6] In pregnancy, it may lead to serious congenital anomalies, still births and increased perinatal mortality.[6-10] As the rubella virus was first isolated in 1962 by Parkman, Beuscher, and Arenstein, and independently by Weller and Neva[11] as co-discoverers, a syndrome of severe bilateral sensorineural deafness, cataracts, mental retardation, microcephaly, and congenital heart defects among others, known as the congenital rubella syndrome (CRS), was recognized over 50 years ago.[7-12]

In the United States of America (USA), approximately 20,000 cases of CRS were reported in the mid-1960s, during an outbreak, from 1964 to 1965.[11] The associated economic cost for medical attention was astronomical, costing at least US $220,000 per case.[11,12] To eliminate this ugly scenario, significant efforts were made to prevent further outbreaks by massive immunization campaigns across the USA, Latin America, and Europe, while the year 2010 was targeted for the elimination of rubella infection and new cases of CRS across these regions.[13-19] Despite the potentially devastating effects of CRS, many developing countries are yet to embrace prevention and immunization programs against rubella, and where such programs exist the immunization rates are sub-optimal.[2,4,11] Consequently, rubella infections in pregnancy still occur with CRS often diagnosed in postnatal life.[4,9,14]

Inadequate response, poor investment in health development, and many developing countries not using the World Health Organization (WHO) recommended policies have encouraged the spread of the infection. Sporadic outbreaks of rubella infection, with its associated significant harm, makes full immunization in childhood and in women of child-bearing age, imperative.[1,3,6] As the development of new drugs and vaccines continue and the need for research intensifies, the products are often out of reach of the majority of persons in poor or developing countries.[1] In an era of scarce resources, the need for the rational use of resources has become imperative and establishment and implementation of new prevention programs must be evidence-based. In other words, the task of furthering health and development begins by identifying achievable and cost-effective interventions that provide substantial benefits to communities. In spite of the high perinatal mortality rate in Nigeria, screening for and vaccination of women and children against rubella is neither part of antenatal care nor among the diseases recommended for vaccination, in the National Program on Immunization (NPI).[4,13] Rubella infection and CRS are not reportable diseases in Nigeria. Fortunately, however, rubella is a vaccine-preventable disease.

In Nigeria, the national prevalence of rubella infection, whether in- or out-of pregnancy, and CRS is unknown. In the last two decades, there have been scanty reports of rubella infection from few centers across Nigeria,[13,20-22] but information from the Nigerian Niger Delta is scarce. Also, no assessment of combined IgG and IgM seromarkers for previous and current rubella infections has been reported in a single study in the country. The feasibility of establishing a screening and vaccination program has not been addressed. In a low-income country like Nigeria, where rationalization of available scare resources is needed, obtaining a government political will for positive interventions requires evidence-based advocacy. The need to provide this information through the determination of sero-susceptibility of rubella infection in pregnancy and the feasibility of establishing an organized prevention program in Nigeria, including vaccination against rubella, is the justification for this study.

Materials and Methods

Three hundred women were counseled and volunteers had their biodata recorded in a standard questionnaire and then they were screened for rubella IgG and IgM antibodies using the ELISA-based quantitative assay, at the Virology Laboratory of the Hospital. Of the cohort, 270 women volunteered and were recruited for the study. Ten milliliters of blood was collected by an aseptic technique from the antecubital veins of the volunteers into bottles containing ethylene diamine tetra-acetic acid (EDTA) anti-coagulant. The sera obtained after centrifugation were quantitatively analyzed for IgG antibodies using the RUB IgG Test kit (Dia Pro. Diagnostic Bioprobes SrI, Columella Milano, Italy), according to the manufacturer's instructions.[23] Samples with IgG antibody ≥10.0 IU/ml were considered positive and further subjected to IgM antibody analysis, using the RUB IgM Test kit, according to the manufacturer's instructions.[23] The IgG seropositive cases were regarded as exposed (previous or current), while the IgM seropositive cases were regarded as acute or active infection.

This study had the Hospital Ethical Committee's approval.

The laboratory protocol

The antibody assay

Antibodies of immunoglobulins G (IgG) and M (IgM) were assayed by the Plate ELISA Method. Quantitative IgG results were expressed in international units (IU), with calibration performed against reference standards of 10, 20, 50, 100, and 250 IU/mL for IgG, according to the manufacturer's instruction.[23] The confirmation of IgM was performed by an indirect ELISA assay and expressed as a qualitative result.

Specifically, with the aid of a Stat Fax Auto Washer and Stat Fax Microplate Reader 2600 ELISA machine (Awareness Technology USA) the specimens were analyzed for Rubella

IgG and IgM antibodies, using RUB IgG and RUB IgM test kits by the quantitative and qualitative methods, respectively.[23]

Discrimination between IgG seronegative and seropositive samples

The concentration of 10 IU/ml was used to discriminate between negative and positive samples after standardization of the equipment in accordance with the Manufacturer's Instructions Manual for IgG.[23] Samples with IgG antibody concentration ≥10 IU/ml were regarded as seropositive or exposed cases (previous or current), while samples <10 IU/ml were considered seronegative and unexposed.

Confirmation tests for IgM antibodies

The IgG seropositive samples were further analyzed for IgM using RUB IgM according to the manufacturer's instructions for IgM.[23]

Principles of the IgM assay

The microplates were coated with a monoclonal anti-human IgM (hIgM) antibody that in the first incubation specifically 'captured' this class of antibodies. After washing out all the other components of the sample, in the second incubation, bound anti-Rub IgM were detected by the addition of purified and inactivated Rub antigens, complexed with a specific monoclonal antibody, and labeled with peroxidases (HRP). The enzyme captured on the solid phase, acting on the substrate/chromogen mixture, generated an optical signal that was proportional to the amount of IgM antibodies present in the sample and could be detected by an ELISA reader.[23]

Criteria for the validity of the assay[23]

The assay was considered valid:

1. When the OD450nm of the A1 blank well was <0.100
2. After blanking on A1, the OD450 nm mean value of the Negative Control (NC) was <0.200
3. The OD450 nm mean value of the positive control (PC) was >1.00.

The test assay meant that all these criteria with our NC were 0.068.

The cut off value was NC + 0.250 = 0.318

Calculation of results

Samples with an OD450 nm value lower than the cut-off were classified as negative for Rub IgM. Samples with an OD450 nm value within the cut-off +20% were considered to be in the gray zone. Samples with an OD450 nm value higher than the upper limit of the gray zone were classified as positive.[23]

Sensitivity and specificity of the IgM assay

The Sensitivity and Specificity of the IgM assay using RUB IgM are both known to be >98% when compared with the FDA (Food and Drug Administration, USA) approved kits present in the market.[23] The presence of a positive IgM antibody test is an evidence of current or active infection.

Data analysis

The data were expressed as percentages and differences between groups were assessed by the Chi-square (χ^2) test using GraphPad Instat3, version 3.06, 32 bit for windows, 2003 software (GraphPad Software Inc. San Diego, USA). A *P* value of <0.05 was considered statistically significant.

Results

The mean age and parity of the study population [Table 1] were 30.3 ± 4.8 (range 16-45) years, 95% CI 29.727-30.873 and 1.5 ± 1.4; 95% CI 1.317-1.661 (range 0-7), respectively.

Table 1: Age distribution and marriage status of the study population

Indicator	Frequency	Percentage
Age range		
≤19	3	1.1
20-24	21	7.7
25-29	96	35.6
30-34	96	35.6
35-39	44	16.3
≥40	10	3.7
Total	270	100.0
Marriage status		
Single	5	1.8
Married	265	98.2
Total	270	100.0

Table 2: Frequency of sero-positive and negative tests for IgG and IgM antibodies

Test category	Total number screened	Number positive	Gray zone/ borderline	Number negative	Percent positive
IgG antibody: Quantitative assay/test: (≥10.0 IU/ml = positive; <10.0 IU/ml = negative)	270	143	0	127	53.0
Confirmatory test using IgM:					
Positive IgG test	143	14	2	127	9.7
IgG negative test, but with samples titers 8.5 to 9.9 IU/ml	10	0	1	9	0.0
Total	153	14	3	136	9.2

The majority, 57.0 and 91.3%, were seronegative for IgG and IgM antibodies, respectively. The borderline results could not be confirmed further [Table 2].

Nulliparous women were 84 (31.1%), while women with parity ≥1 were 186 (68.9%). The relationship of parity with IgG serostatus is as shown Figure 1.

One hundred and eleven (51.4%) women with positive IgG seromarkers were less than 35 years of age, while 32 (59.2%) were above 35 years of age. There was no statistically significant difference between the age groups; $P = 0.36$, RR 1.19; 95%CI 0.84-1.69. Similarly, of the 84 nullipara, 63 (75%) were seropositive, while 44.1% of the women who were para 1 or more were IgG seropositive. Nulliparous women were more likely than parous women to have rubella infection, $P < 0.000$, RR 0.4897; 95%CI 0.3379-0.7097 [Figure 1]. The IgG serostatus of the study population is as shown in Table 2 and Figure 2.

The IgM seropositivity was 9.7% in the IgG seropositive samples. When combined with the IgG seronegative samples near the discriminatory zone, the IgM prevalence dropped to 9.2% [Table 2, Figures 2 and 3]. The samples whose titers were near the discriminatory zone were IgM seronegative.

Discussion

This study has shown that rubella is quite common and active among the pregnant population. None of the women was symptomatic. This was probably due to the mild nature of the infection, which could easily be confused with the malarial fever endemic in Nigeria. Asymptomatic carriers of 20 to 50% have been reported in other studies.[2,6,7]

The mean age of 30.3 ± 4.8 years is comparable with 28.1 ± 1.7 years reported by Pena *et al.*[20] from the middle belt of Nigeria. A majority of 80% of the women was younger than 35 years[Table 1]. The mean parity was 1.5 ± 1.4, while over 31% of the study population was nulliparous. Although women less than 35 years, or more, did not significantly differ in the risk of infection, $P = 0.36$, RR 1.19, nulliparity was associated with rubella infection, $P < 0.000$, RR 0.4897 [Figure 1]. A woman's risk of acquiring the infection should expectedly increase with increasing age and parity, due to the longer duration of interaction with an infectious environment. The non-significant difference associated with the age below ≥35 years in this study, could suggest that most infections were probably acquired before that age. In a study to determine the prevalence of rubella antibodies and age of exposure to rubella among 323 Yemeni schoolgirls of age 11-21 years, Sallam *et al.*[24] reported 91.64% rubella IgG antibody seropositivity, indicating that a majority of the girls were naturally immune by age 11-21 years.

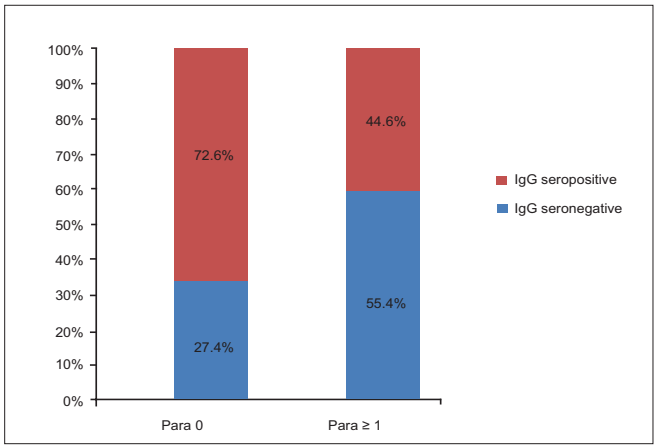

Figure 1: 100% stacked cylinder relationship of parity and IgG serostatus

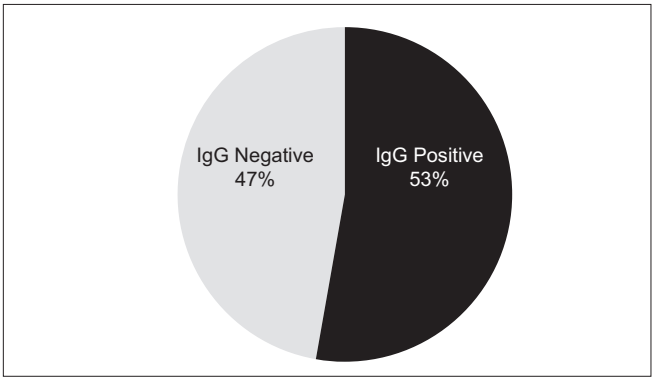

Figure 2: IgG seropositive and seronegative sub-populations

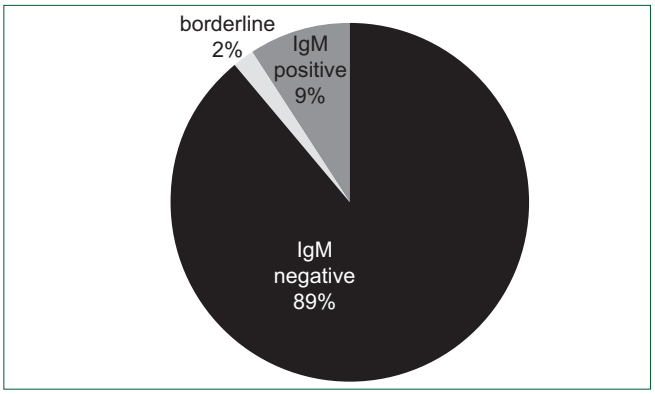

Figure 3: IgM seromarkers for previous and current rubella infections

The association of nulliparity with the risk of rubella infection might be a chance finding as pregnancy is not known to be protective against rubella infection. Alternatively, the intentional delay in marriage and child bearing due to a quest for higher education could have led to prolonged exposure to the virus from various environments, as students are generally more mobile than married women. In this study, 1.8% of the women were single ladies, more than 31% nulliparous, and approximately 20% had children

at relatively older ages (35-45years). Single motherhood, no doubt, can exert some physical, psychological, and financial strain on the mothers, especially in this environment where there is no social security. The social status of women is low, poverty is high, and single parenthood is viewed with derision.[25,26]

The reported prevalence of rubella IgG of 53% in this study is much lower than 85-90% in European women[11] and 91.64% in Yemini adolescents, but about 54-76% has been reported from other parts of Nigeria.[13,20-22]

The IgM seropositivity was 9.7% in IgG seropositive samples and 9.2% when combined with samples near the discriminatory zone [Table 2, Figures 2 and 3], but the later samples were also IgM negative, thus confirming the high sensitivity and specificity of the test kits.[23]

The IgM prevalence rate of 9.7% is about three-fold, with 3.9% reported for the middle belt of Nigeria,[21] and is comparable to the 11.4% reported for Cord blood in children of Costa Rica.[27] Sporadic outbreaks of rubella, every four to seven years, have been reported in America, various European countries, Japan, Costa Rica, Panama, and Brazil.[11,16,17,19,27-30] Outbreaks, which may go unrecognized due to the mild nature of the infection, could account for variation in prevalence of rubella IgG and IgM antibodies in various populations.

None of the women, including the infected patients, had ever had prophylactic vaccination. Antenatal health-talks in Nigeria routinely do not incorporate information on Rubella infection. Vaccination against rubella is also not part of the Nigerian national or local immunization programs.[4,21] Preconception counseling of women of reproductive age about rubella is also not routine in Nigeria. Concerted efforts to combat the spread of HIV/AIDS through seminars, workshops, outreaches, and electronic and print media is yielding dividends resulting in the decline of the national prevalence of HIV, but the campaigns do not include rubella.[26] General knowledge about rubella may thus be poor. In developed countries of North and Latin America and Europe, the goal taken in 2003, to eliminate rubella and CRS by 2010, is being pursued with vigor, after having met the goal that eliminated polio by 1991, and eradicated measles in 2000, with the introduction of the combined MMR (Measles, Mumps, Rubella) vaccination in pediatric vaccination schedules.[11] In an attempt to eliminate rubella infection and prevent new cases of CRS, Brazil in September 2008, targeted adolescents and adults and vaccinated 70 million men and women across the country; one of the greatest rubella vaccination campaign in history.[11,17] Unfortunately many developing countries including Nigeria is yet to learn from these experiences.

It is desirous to vaccinate the seronegative women and all the infants in this study in the puerperium. This initiative could not be realized, as Rubella vaccine was not available. All attempts to secure the vaccine failed. Generally, vaccine procurement and distribution is the responsibility of the Federal Government of Nigeria, occasionally supported by international partners. The lack of vaccine is a reflection of the poor attention paid to rubella infection. Poverty has been noted to be a major constraint in poor or developing countries in getting the products needed for prevention and control of infectious diseases,[1] and Nigeria is still entangled in this dilemma. The serious congenital anomalies of CRS[7,14,16,17] are preventable, and all efforts by stakeholders to achieve this goal would be noble.

Rubella vaccination was earlier believed to be contraindicated during pregnancy and for women intending to get pregnant within three months of vaccination, because of theoretic concerns about fetal damage with the live-attenuated vaccine. In spite of this, no real risk of CRS after rubella vaccination during pregnancy has been reported in scientific literature.[6,11,33-35] The overall theoretical risk of severe malformations attributed to the RA 27/3 vaccine against rubella varies from 0 to 1.6%.[11,17] Thus, a window of opportunity exists during antenatal care, to counsel women for vaccination, at best in the immediate partum period, if risk of vaccine-associated fetal malformation is a concern. The period of vaccination of children in the NPI is another opportunity for women's vaccination, as women are mostly involved in getting their children to immunization centers. The routine vaccination of girls in early teens was a major contribution to the prevention of rubella infection in pregnancy, in developed countries.[17,30-35] Extension of immunization to non-pregnant women of reproductive age and men is a key element in maintaining the current high immunization rates that ensured high herd immunity.[17] Missed opportunities for vaccination are responsible for new cases of rubella and CRS.[11]

We are aware of the possible cross-reaction of rheumatoid IgG complexes mimicking IgM antibody. Due to logistic constraints, we were unable to exclude other sources of potential IgM cross-reacting antibodies, such as CMV, EBV, Toxoplasma, and Parvovirus infections. However, the presence of rubella-specific IgM or a significant rise in rubella-specific IgG is indicative of recent infection.[7] Unfortunately, there are no medications for mothers with active infections. Even so, routine antenatal testing for rubella antibody is a good practice irrespective of a woman's seronegative status in a previous pregnancy.[7]

Where a woman was immunized to rubella and she had contact with rubella in early pregnancy, the CDC recommended that the patient and her physician make the final decision regarding continuing the pregnancy.[6] Termination of pregnancy could be offered, if infection was confirmed. Except for proven medical reasons of life-incompatible malformations, induced abortion is illegal

and litigious in Nigeria. For religious and cultural reasons, discussing induced abortion can tear members of the same family apart in Nigeria.[36]

Conclusions

We have not only provided evidence of high previous and current rubella infections in pregnancy, but this study has also highlighted the difficulties associated with initiating organized routine screening and vaccination programs in antenatal clinic settings in this country, due to the scarcity of rubella screening kits, vaccine, and immunization schedules. These are serious critical issues that should be addressed before the establishment of such programs. The incorporation of the triple MMR vaccine into the NPI and integration of rubella prevention program into the antenatal care services will be a cost-effective intervention, rather than to wait and treat the sequelae of CRS.

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