

Causal Relationship Between Rubella Virus Infections and Bad Obstetric History in Pregnant Women

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Abstract

Background: The aim of present study was to know if the rubella virus infection demonstrated via IgG and IgM seroprevalence in pregnant women with adverse reproductive outcome had any adverse relationships in these women **Materials and Methods:** A case control study was conducted in Baghdad, IRAQ, which included 143 women with age range from 15 to 46 years. Hundred normal age matched pregnant women were also included. Structured questionnaires were used to gather sociodemographic and risk factors data. Qualitative and quantitative IgG and IgM ELISA tests were used to detect rubella seroprevalences. **Results:** Out of the 143 women, 129 (90.2%) were rubella IgG positive and none were IgM positive. Women with normal pregnancy showed significantly lower rates of Rubella virus IgG seropositivity. Women age, occupation and residence were significantly associated with Rubella virus seropositivity. **Conclusion:** This study provides important and highly useful information on baseline seroprevalence data on rubella in Iraq. A 9.8% of our women study population were non-rubella immune and were susceptible for rubella infection. In addition, rubella seroprevalence clearly were associated with BOH manifestations.

Keywords: BOH; Rubella; IgG; IgM; ELISA; Pregnant women; Socio-demographic variables; Iraq,

1. Introduction

Rubella is a common cause of rash and fever during childhood. However, its public health importance relates to the teratogenic effects of primary rubella infection occurring in pregnant women, which can lead to fetal death with spontaneous abortion or to congenital defects in surviving infants. Most of the cases are asymptomatic and difficult to diagnose on clinical grounds.

Primary rubella infection is associated with congenital infection in 80% of the conception (1). The risk of development of anomalies depends on the gestational age. The risk is 90% when infection occurs before 11 weeks and falls to 25% at 16 weeks. When infection occurs between 16 and 20 weeks, congenital defects are rare, and seem to be confined to deafness. No congenital defects have been documented when maternal infection occurs after 20 weeks gestation (1).

Maternal infections with this virus have been considered a significant factor in causing poor pregnancy outcome, has not, however assumed much significance in IRAQ. Their prevalence and effects on pregnancy outcome have only partially explained in the literature (2,3,4). Hence the present study was undertaken to establish the

seroprevalences of Rubella virus infections during pregnancy in women with Bad Obstetrical History (BOH) aiming to try to establish reasons behind the unexplained high IgG seropositivity in BOH women. Further, some basic knowledges for future pregnancy care in IRAQ, and the study of the possible risk factors for acquiring these infections for Iraqi women was also hoped.

2. Material and Methods

Study Population

This descriptive case-control study was conducted at the antenatal clinic of Baghdad gynecology Hospital and Primary Health Care Centre in Al-Yarmouk PHC. Pregnant Women with bad obstetric history were recruited from those attending outpatient Gynecology Clinic, Baghdad or the antenatal Clinic at Al-Yarmouk. The study population was divided into two group, the women with bad obstetric history (n=143) and women with non-BOH normal pregnancy (n=100). Women were recruited only if they developed two or more consecutive abortions, intrauterine fetal death (IUFD) or neonatal deaths (NND), stillbirth (SB) or low birth weight (LBW) infants or off springs with multiple congenital malformations (CM). All women were interviewed to ascertain of

their demographic, medical and obstetric information. Data were recorded in a specially constructed questionnaire after taking consent and full history. women were thoroughly examined by trained gynecologists for the probable factor(s) responsible for their past reproductive losses. Blood samples were obtained, and serum was separated and stored at -20°C until processing. The following kits were made available:

A. Rubella IgG ELISA from BIOTEC Laboratories Ltd. (UK).

B. Rubella IgM ELISA from BIOKIT, S.A. SPAIN

Qualitative and quantitative evaluation of maternal serum for ant-Rubella virus IgG and IgM antibodies were done according to the instruction provided by the manufacturer. Data obtained in this study were analyzed using SPSS statistical package. To determine possible association, every variable was compared to Rubella virus seroprevalence in 2 x 2 table using chi- square (x2) test and Fisher's exact test. Effects were considered significant if P-value of less than 0.05 (p<0.05) is obtained.

3. Results

A Total of 143 pregnant women with bad obstetric history attending Gynecology and Obstetrics

department in Baghdad hospital over a period of six months were recruited for this cross-sectional study to estimate the prevalence of IgM and IgG antibodies specific to Rubella virus. Hundred (100) normally pregnant women as control were also included in this study. Serum samples were collected from them and assayed using Rubella virus IgG and IgM ELISA techniques.

Current rubella seropositivity were 90.2% (129 /143) in BOH group compared to71% (71/100) in normal pregnancy group in our study population. Differences between seropositivity levels obtained in the BOH and normal pregnant groups were significant (<0.05).

The demographic characteristics of the recruited patients were presented in Table (1).

Rubella virus IgG seropositivity were significant for the age groups of 28-36 and 37-46 years in comparison with seronegative women. The overall IgG Seropositivity rates of the BOH group were significantly different compared to the normal pregnancy controls (90.8% versus 71.0 %). The table depict also the relationship between occupation and residency of the chosen ladies which demonstrated a significant influence on rubella virus IgG seropositivity.

Table 1: Rubella IgG antibodies and demographic characteristics

| Dem. Charact. | No. of Patient | Positive | | Negative | | P-Value |
|-------------------------|----------------|-----------|-----------|-----------|------------|----------------|
| | | No. | % | No. | % | |
| Age 18-27 | 12 | 9 | 75 | 3 | 25% | >0.05 |
| Age 28-35 | 66 | 59 | 89.4 | 7 | 10.6% | <0.05* |
| Age 36-48 | 65 | 61 | 93.8 | 4 | 6.2% | <0.05* |
| Total No. | 143 | 129 | 90.2 | 14 | 9.8% | |
| Residency | | | | | | |
| Urban | 100 | 93 | 93 | 7 | 7% | <0.05* |
| Rural | 43 | 36 | 83.7 | 7 | 16.3% | <0.05* |
| Total No. | 143 | 129 | | 14 | | |
| Occupation | | | | | | |
| Employee | 55 | 47 | 85.5 | 8 | 14.5% | <0.05* |
| Non-Employee | 88 | 82 | 93.2 | 6 | 6.8% | <0.05* |
| Total No. | 143 | 129 | | 14 | | |
| Normal pregnancy | 100 | 71 | 71 | 29 | 29% | ≤ 0.05* |

Risk factors participation to the rubella virus positivity is depicted in Table-2.

Small numbers of BOH women gave a history of diabetes, hypertension, use of immunosuppressive

drugs and cat possession. History of blood transfusion and soil exposure were exerted a significant effect on the IgG seropositivity (16(69.7%) out of 23 and 45(88.2% out of 51, respectively).

Table-2: Risk factors of BOH women

| Risk factor | Total Number (%) | No. positive (%) | No. negative(%) | P value |
|----------------------------|------------------|------------------|-----------------|---------|
| Diabetes | 7 | 3 (42.8%) | 136 | ND |
| Hypertension | 13 | 5 (38.4%) | 130 | ND |
| Immunosuppressive drug use | 3 | 3(100%) | 140 | ND |
| Cat possession | 15 | 7(46.6%) | 136 | ND |
| Blood transfusion | 23 | 16(69.7%) | 127 | <0.05 |
| Soil exposure | 51 | 45(88.2%) | 98 | <0.05 |
| Other medical problems | 13 | 8(61.5%) | 135 | ND |

BOH features are depicted in Table (3). Out of 143 serum samples, a total of 129(90.2%) were Rubella virus IgG positive. None of the recruited women was

seropositive to RV IgM antibodies. One hundred and seventeen (117) of women were given a history habitual abortion; mostly during the first trimester, of

which 106(90.6%, were IgG seropositive. Twelve had history of intrauterine fetal death; of them, two gave history of more than one intrauterine fetal death. Twenty-six and six women gave history of neonatal death and stillbirth respectively. Twenty-three women gave history of child with congenital malformations; six of them have more than one child with congenital malformation. Twentyfour women

gave history of delivering a child with low birth weight (LBW), of them 23 (95.8%) were IgG seropositive. Differences in relationship between BOH presentation and anti-Rubella virus IgG levels were statistically significantly (Table 3).

Table 3: Rubella IgG antibodies and bad obstetric history.

| Bad obstetric history | No. | Positive | | Negative | | P-Value |
|---|-----|----------|------|----------|------|---------|
| | | No. | % | No. | % | |
| Habitual abortion (HA) | | | | | | |
| Yes | 117 | 106 | 90.6 | 11 | 9.4 | <0.05* |
| No | 26 | 23 | 88.5 | 3 | 11.5 | <0.05* |
| Total No. | 143 | 129 | | 14 | | |
| Intrauterine fetal deaths (IUFD) | | | | | | |
| Yes | 12 | 12 | 100 | 0 | 0 | <0.05* |
| No | 131 | 117 | 89.3 | 14 | 10.7 | <0.05* |
| Total No. | 143 | 129 | | 14 | | |
| Neonatal deaths (NND) | | | | | | |
| Yes | 26 | 23 | 88.5 | 3 | 11.5 | <0.05* |
| No | 117 | 106 | 90.6 | 11 | 9.4 | <0.05* |
| Total No. | 143 | 129 | | 14 | | |
| Congenital malformations (CM) | | | | | | |
| Yes | 23 | 19 | 82.6 | 4 | 17.4 | <0.05* |
| No | 120 | 110 | 91.7 | 10 | 9.3 | <0.05* |
| Total No. | 143 | 129 | | 14 | | |
| Low birth weight (LBW) | | | | | | |
| Yes | 24 | 23 | 95.8 | 1 | 4.2 | <0.05* |
| No | 119 | 106 | 89.1 | 13 | 10.9 | <0.05* |
| Total No. | 143 | 129 | | 14 | | |
| Stillbirths (SB) | | | | | | |
| Yes | 6 | 5 | 83.3 | 1 | 16.7 | <0.05* |
| No | 137 | 124 | 90.5 | 13 | 9.5 | <0.05* |
| Total No. | 143 | 129 | | 14 | | |

In table (4), Low Levels ranged between 20 -250 IU/ml were detected in 40(27.9%) women whereas moderate levels between 250-500IU/ml were demonstrated in 29(20. 4%) women, whereas strong concentrations of (500-100 IU/ml) were detected in

60 (41.9%) women. Women with moderate and strong responses counted 89 women (62.2%). The remaining seronegative and low titer seropositivity represented 54 (37.7%) women only. Differences between these 2 figures were statistically significant (<0.05).

Table 4: RV IgG antibodies expressed quantitatively (IU/ml).

| RV IgG conc. IU/ml | Number | Total % |
|---------------------------------|--------|---------|
| Negative <15 | 14 | 9.8 |
| Weak Positive (20-250) | 40 | 28.0 |
| Intermediate Positive (250-500) | 29 | 20.3 |
| Strong Positive (500-1000) | 60 | 42.0 |
| Total | 143 | 100.0 |

Table (5) demonstrated that: 47(78.3%) of the strong positive cases suffered habitual abortion compared to 26(89.6) showed moderate concentrations compared to 28(70%) out of 40 in the low-levels group. In women with congenital malformation (CM), moderate and strong rubella IgG seropositivity were

occurred in 14 women compared to 3 negative and 2 showed low concentrations. In respect to those gave a history of low birth weight, 12 out of the total 21 presented with strong IgG seropositivity.

Table 5: High, low, intermediate and negative concentrations RV IgG and bad obstetric history.

| RV IgG conc. IU/ml. | No. of cases with different bad obstetric history manifestations (%) | | | | | | |
|---------------------|--|----------|---------|----------|---------|---------|---------|
| | Total | HA | IUFD | NND | C.A | SB | LBW |
| <15 Negative | 14 (9.8) | 12(85.7) | 0 | 1(7.1) | 3(21.4) | 1 (7.1) | 1(7.1) |
| 20-250 Weak | 40(27.9) | 28 (70) | 4 (10) | 4 (10) | 2 (5) | 0 | 5(12.5) |
| >250-500 Moderate | 29(20.4) | 26(89.6) | 3(10.3) | 3(10.3) | 6(20.7) | 3(10.3) | 3(10.3) |
| 500-1000 Strong | 60(41.9) | 47(78.3) | 3 (5%) | 13(21.7) | 8(13.3) | 4 (6.7) | 12(20) |

4. Discussion

Bad obstetrical history (BOH) could be due to environmental factors, genetic predisposition,

infections, radiations, occupational hazards, addiction and habits (6) This study tried to confirm if

there is significant association between Rubella virus infections and BOH manifestations. In susceptible pregnant women, especially when the virus is contracted during the first trimester, maternal viremia frequently infects placental tissues and the fetus (The virus then spreads through the vascular system of the developing fetus causing damage to blood vessels and developing organs. (7)

Rubella virus, which is a recognized teratogen to the fetus. In adult, infections are usually innocuous except when occur during early pregnancy. Fetal infections can lead to devastating congenital abnormalities (8). The most important factor during primary rubella infection is the gestational age of the fetus. The chance of fetal infections causing severe congenital inflammation is 50-80 % in the first month of gestation and reduced to 10% in the third month. This risk is reduced to approximately 5% in the second and third trimesters. No congenital defects have been documented when maternal infection occurs after 20 weeks of gestation (9).

Rubella is a preventable disease with various national schemes of immunization-practiced worldwide. Vaccination program for rubella was implemented in the USA by 1969 and in UK in 1970, where live attenuated rubella vaccine is offered to all preschool children of both sexes. A sharp decline associated with mass immunization has led to low rate of reported cases of congenital rubella in 1981 and later (9)

In Iraq, rubella vaccine was first introduced in late eighty's as single dose at one and half years. Now it is given within the mumps, measles and rubella (MMR) vaccine supplied to children at one, one and half year age as recommended by the primary health administration. The new policy of two shots of MMR is only practiced since 2006. However, this does not cater for seronegative teenagers and mothers. There have been many reports on the prevalence rate of rubella antibodies in Iraq indicated that 80% of the population had enough immunity against infection (10)

RV seroprevalence rates ranged from 22.2% to 100% was shown for Iraqi children from infancy to 12 years old in the one reported study (11). In their study, the probable age when significant proportion of Iraqi contract RV infections for the first time is around 3-5 years. Most of the Iraqi women become exposed to primary rubella infection at a very early age in their life quite far from childbearing age.

Rubella infection is best documented by IgM and IgG seroconversion. IgM antibodies can be detected at onset of rash. Their levels peak at 7-10 days and persist for up to 4-6 weeks. If the IgM is not detected, this does not exclude the infection because there may be early waning of antibodies (12). Statistical analysis showed that pregnant women age was directly related with anti-rubella IgG level and finding consistent with the results of most other studies that antirubella IgG positive rate increased by age (13,14). The older age group are remained unprotected from rubella infection and weakling

immunity seen in more than 30 age and older. This is agreed with the present data indicating that increased age of women result in decline of protecting immune responses in vaccinated populations (15). The occurrence of reinfection during pregnancy is reported (16). Furthermore, in Iraq the incidence of congenital malformation and repeated abortion in Eastern area of Baghdad is more than middle of Baghdad and this is due to either educational level or vaccination program. Prevalence also is more in eastern area of Baghdad, probably due to higher population growth and spread of rubella infection, poor immunization coverage or did not apply routine rubella vaccination program in childhood (17, 18). Rubella Reinfection or unprotective immunity during pregnancy can be followed by transmission to the Fetus as shown in the present study. Moreover, the current data as well many other reports documented that rubella reinfection during pregnancy in a previously vaccinated woman with residual antibody titer to rubella of 15 IU/ml or more documented the possibility of reinfection following exposure to rubella virus. In their study Eilard and Strannegård (19) presented that contact with 6-year-old daughter with clinical rubella between the 7th and 10th week of pregnancy resulted in transmission of the virus to the fetus. Umbilical cord blood drawn by cordocentesis was found to be strongly positive for rubella IgM antibody. After termination of the pregnancy rubella virus was isolated in cell culture from fetal tissues. Proved the reinfection with rubella (19). This woman presented with high serum titers of rubella hemagglutination inhibition antibodies of the IgG class but no demonstrable neutralizing antibodies before reinfection. These data suggested that therapeutic abortion should be considered as reinfected pregnant women who lack neutralizing antibodies to rubella virus.

In the present piece of work, the real risk for fetus and newborn is not known, as are the incidences of rubella reinfection during pregnancy and congenital rubella infection after maternal reinfection.

The present study tried to assess the immunity status of BOH patients to RV and its role in intrauterine infections. High overall positivity rate (90.2%) of rubella IgG antibodies were observed in the recruited women. Data were comparable with that obtained among pregnant women in the Center and South-West regions of Cameroon and Nigeria (94.4% and 83.3 %, respectively) (20)

In Nigeria, reports (22) demonstrated that age of the women exerted significant variation in the prevalence rate s of anti-rubella IgG. Data obtained were as follows :85.7% in 15 -19year age group, 86.8% in 20-24year age group, 89.6% in 25-29year group, and 100% in greater than 40year age group. Identical significantly variable figures were shown in the present research data. It seems that, Rubella IgG seroprevalence were associated with age of the women, gestational age, gravidity, vaccination, residence, occupation and education as concluded

by one of south Africa reports (22). They showed an overall proportion of rubella seropositivity of 97.8%. The proportion of seropositive women increased with age group (18–25 years: 97.0%; 26–32 years: 97.7%; 33–40 years :99.3%.

Lower IgG seropositivity (31.6% - 54%) were obtained by a number of reports (23, 24,25)

Rubella immunity varies in different populations and geographical areas depending on the endemic rate of RV and rate of coverage of vaccination.

High seropositivity rate of RV IgG antibodies of the present study do not necessarily reflect the high levels of protective immunity against rubella among women of childbearing age in Baghdad-IRAQ. Although, the majority of recruited women appeared to possess high level of anti-Rubella IgG antibodies, but the ratio of the protective neutralizing high avidity immunity appears to be low as evidenced by the high rates of BOH manifestations. It is probably, essential for future protection against susceptibility or reinfection to screen for the high avidity neutralizing anti-rubella IgG in the women with BOH. In addition, rubella immunity seems to wane over time, a third dose of MMR may be a protective strategy for women who conceive later in life. Thus, the present applied vaccination scheme coupled with weak general hygiene and socioeconomic conditions seem to have not interrupted the major mode of transmission to mother through infected children. (26)

Furthermore, continuous analysis of RV immunity is required, since protection can be relative and related to the endemic rate of the disease and the level of herd immunity that should be always reinforced (27). The present study demonstrated a strong association between rubella infection and BOH in women. It is evident that maternal infection like rubella play a critical role in pregnancy wastage and their occurrence in women with BOH is a significant factor. A previous history of pregnancy wastage and a positive serological reaction during current pregnancy must be considered while managing BOH cases to reduce the adverse fetal outcome. Early detection and timely intervention can prevent morbidity and mortality of infants born to such mothers. All antenatal cases with BOH should be routinely screened for rubella, so that early diagnosis and appropriate intervention of these infections will help in proper management of fetal outcome. In addition to this, there is a need to modify vaccine strategies to immunize all adolescent girls and/or women of child-bearing age before conception to reduce incidence of congenital rubella syndrome and bad obstetric outcome.

Organized rubella vaccination campaigns do not exist in our country until late eighty's. This implies that large proportion of the included women contracted natural unprotective immunity to rubella that could be responsible for some of their bad obstetric history.

Susceptibility to rubella infection in the present

selected group of pregnant women and probably most of Iraqi individuals were high due the program of two vaccine shots during infancy (second and 4th year of age). Screening to pick up susceptible women is necessary so that rubella vaccine can be offered to such women postpartum for the protection of offspring's born in subsequent pregnancy and to judge on the vaccination coverage of the newly adapted immunization policy.

High susceptibility rates could be due to insufficient vaccination programs in areas from which these studies were published.

In the present study, we proved significant association between the selected risk factors and RV IgG seropositivity (tables2,3,4). RV antibody Prevalence tend to be higher in both urban areas and rural areas (28)

This was the case in the present study. In addition, significant differences observed in between employees and nonemployee. The similarity in rates may be because most of women were with identical exposure rates. The main source of maternal infection could be their children contracting the disease from other children at school. In Iraq, RV vaccination was first introduced in late eighty's; so, most of seropositivity reported in this study were induced by natural infections and not related to vaccinations policies.

Significant differences in seropositivity for RV IgG in relation to many bad obstetric history manifestations were obtained (table 3). This is probably because most of the patients acquired RV infections during their childbearing age.

Relationships between IgG concentrations to RV and any of the questioned bad obstetric manifestations were further investigated. (Table4). Forty women (27.9%) demonstrated low IgG responses compared to 89 (62.2 %) with high and moderate IgG levels. Similar bad obstetric manifestations, mainly habitual abortion profiles were noticed in both of the groups (70% and 78.8%). Those with moderate IgG titers and the negative ones showed similar figures 89.6% and 85.7% respectively. By this analysis, we aimed to find if those presented with high and moderate IgG titers are resulted because of re-infection before becoming pregnant or due to the presence of nonprotective low avidity IgG responses. However, none of the recruited women showed positive IgM results at the moment of testing proving that this assumption imposes the necessity for further search. We suggest, the need for follow-up by another IgG testing, two weeks from the first sample could be helpful.

In the present work, anti-rubella IgM seropositivity was null, indicating either the high rate of immunity against rubella in Iraqi women of childbearing age or the possibility of an unknown mechanism behind this finding is the time of the recruitment of patients. Acute infection manifested by the IgM responses was not demonstrated in recruited the current study group in contrast to the variable rates of IgM

seropositivity ranging between 0.4% to 28.6% that was reported in different countries (23). In one study from Egypt, it was 13% (29). These observations indicate less protection potential induced by immunization programs in these places caused this lagging behind the Iraqi situation.

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