Congenital Rubella Syndrome in Iran

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Abstract

**Background:** Congenital Rubella Syndrome (CRS) can be prevented with appropriate vaccination program. Incidence of rubella disease and CRS is unknown in Iran; therefore the risk of exposure in the pregnant women and Importance of implementation of rubella vaccination in national vaccination program is not clear. Incidence of CRS in the pre-vaccine era can be obtained by estimating the proportion of children in the population with sensori-neural hearing loss attributable to rubella.

**Objective:** To estimate prevalence of congenital rubella syndrome in Iran by determines Attributable Risk of congenital rubella syndrome in hearing impaired children.

**Design:** Case-Control study.

**Setting:** Tehran (Iran), 1995 - 1996

**Subjects:** 225 children aged 1 to 4 years. 113 cases with diagnosed sensori-neural hearing loss who were attended to deaf educational centers were compared with 112 controls who were attended to surgery ward of Amirkabir hospital.

**Results:** Of the 113 children in the case group, 22 (19.5%) were sero-positive, whereas only 10 (8.9%) of 112 children in the control group were sero-positive. This difference was statistically significant. The Odds Ratio was 2.47 (95% confidence interval: 1.04-5.97).

Attributable risk was estimated about 12%. Therefore vaccination of rubella can prevent about 12% from sensori-neural hearing loss in children. Prevalence of CRS is estimated 0.2/1000.

**Conclusions:** Congenital Rubella Syndrome (CRS) can be prevented with appropriate vaccination program.

Regarding experience in rubella vaccination in developed countries can help us to initiate rubella vaccination program. A serosurvey of handicapped especially hearing-impaired children after rubella vaccination can help us to follow the impact of vaccination to the incidence of congenital rubella syndrome.

The strategic planning is needed for implementation rubella vaccination, because inappropriate program can transfer virus circulation from children population to
reproductive age group. Therefore a surveillance system must follow the pattern of virus circulation with registration of rubella and CRS incidence and epidemic intervals.

**Key words**: Congenital Rubella Syndrome, Vaccination, Case-control study, Children.

**Introduction**
Rubella is a common communicable viral disease of childhood. Rubella in pregnancy may cause abortion, still birth and congenital anomalies or Congenital Rubella Syndrome (CRS).

The rubella pandemic in 1960’s demonstrated clearly extraordinary teratogenic potential of the rubella virus. In spite of 80% of pregnant women were immune to rubella in the United States, it is estimated that more than 12,500,000 cases of rubella occurred. Congenital rubella occurred in on estimated 30,000 pregnancies, 10,000 resulting in fetal death or therapeutic abortion and 20,000 resulting infants born with CRS (1).

The estimated cost of the US economy was approximately $ 2 billion (2). Rubella Vaccination program in the United States has been initiated in 1969 and has caused reduction in 90% of rubella and CRS cases (3). Rubella cases have recently increased in the US mainly because of the unvaccinated special ethnic groups and foreign immigrant (4).

Incidence of congenital rubella is various in different populations and depends on the number of susceptible pregnant women, circulation of rubella virus and rubella vaccination coverage. According to WHO (world health organization) report, at least 236,000 CRS cases occur every non-epidemic year in developing countries, which this number increases up to 10 fold in the epidemic years (5). CRS cases are rarely reported in these countries and the extent of problem has still remained unknown. However, the indiscriminate introduction of rubella vaccine without epidemiological data and adequate monitoring program should be avoided because of the occurrence of rubella cases can shift to higher ages and increasing the incidence of CRS. Retrospective studies on the children with the similar abnormality to complications of CRS in the developing countries can specify the rate of congenital rubella risk in these children. Cases of rubella-related deafness in children have been identified by comparing the prevalence of rubella antibody in children with and without sensori-neural deafness. Therefore, reduction in the number of deaf children has been used as an indication of reducing maternal rubella infection after the introduction of rubella vaccination program (6).

Sensori-neural hearing loss is one of the most common abnormalities (50%) associated with congenital rubella syndrome (7) and it is the most common complication (80%) with the late onset (8). In the other words, sensori-neural hearing loss in these children
could be with delay beginning and progressive. Moreover, up to 50% of infections during pregnancy is sub-clinical and many are unrecognized. Thus, the incidence of rubella-related deafness (like the other CRS defects) is estimated less than the true incidence (5). Hearing impairment can result from fetal rubella not only during the first trimester but also in the second and third trimester of pregnancy (7).

Rubella serology is useful in epidemiological studies to examine the role of rubella as a cause of sensori-neural hearing loss, because the number of acquired infections can be estimated from data gathered from controls and cases of rubella-related deafness in populations of children. It has been identified by comparing the prevalence of rubella antibody in children with and without sensori-neural hearing loss.

**Methods**

An unmatched case-control study of 225 children aged 1-4 years, were conducted from Nov. 22 1995 to May 1996 in Tehran. This study compared the frequency of positive rubella antibody titer in children with and without sensori-neural hearing loss and tested the hypothesis that congenital rubella are associated with an increased risk of sensori-neural hearing loss.

The case group consisted of 113 deaf children who were admitted to deaf educational centers. Their deafness was sensori-neural which their medical records confirmed. The control group consisted of 112 children with the normal hearing which were selected from the surgery ward of Amirkabir hospital in Tehran.

Data collected through blood sampling and completing questionnaire. Information was collected on maternal (prenatal and delivery) and neonatal history. The blood samples were taken from children and antibody titer in the case and control groups. The serological technique employed was the hemagglutination inhibition (HI) test. Children with rubella HI antibody titers of 1:8 or greater regarded as sero-positive and those with titers of < 1:8 as sero-negative. The virology department of public health school (Tehran
University) has done HI test. Sero-positive children in the case and control groups were compared, and their significant difference was assessed by Odds Ratio.

It is considerable that children under one and over four years were excluded from the study. In infants (mainly under 6 months), high level of rubella antibody which has passively transferred from mother to fetus make us to mistake in comparing and in the over four years old children, rubella antibody is usually acquired from postnatal infection. Detection of antibody in children 1 to 4 years of age was used to make a retrospective diagnosis of congenital rubella infection. It is also considerable that rubella is most frequent among children 5 to 14 years of age (9).

Results

There were 113 children in case group and 112 children in control group. The case and control groups consisted of 53% and 47% male subjects, retrospectively. This difference was not statistically significant (P= 0.2). No statistical difference was found with regard to age distribution of cases as compared to controls (P = 0.12). Mean of age in case group was 2.94 years (Standard Deviation = 1.1) and mean of age in control group was 2.6 years (SD = 1.3). This difference was not statistically significant.

Of the 113 children of the case group, 22 (19.5%) were Sero-positive, whereas only 10 (8.9%) of 112 children of the control group were sero-positive (table 1). This difference was statistically significant (p = 0.02). The Odds Ratio was 2.47 (95% confidence interval: 1.04- 5.97). Therefore, congenital rubella was associated with significantly increased (greater than two times) sensori-neural hearing loss in children.

Attributable Risk (AR) was estimated about 12% and that means 12% decrease in the incidence of sensori-neural hearing loss if pregnant women were no exposed to rubella infection.

According the results of this study, the prevalence of congenital rubella syndrome (CRS) in Tehran estimated about 0.2 /1000 children.

This prevalence is estimated according following data:
B= prevalence of hearing loss in children in Iran: 1/1000
A*B= children born with hearing loss: 207 children
C= attributable risk to rubella (due to this study): 12%
A*B*C= hearing impaired children born with CRS: 25 children
D= frequency of sensori-neural hearing loss following CRS: 50%
A*B*C*1/D= children born with CRS = 50
Therefore:
Prevalence of CRS= 50/ 207115 = 0.2/ 1000
We conduct this study when immunity to rubella was 80-85% among reproductive aged women (non-epidemic years). We estimate that this prevalence will increase in the epidemic years.

Table 2 shows the birth weights distribution of the sero-positive and sero-negative hearing- impaired (deaf) children (p = 0.02). In the deaf children, mean birth weight of sero-positive group was 2589 gr. (SD = 788) and mean birth weight of sero-negative group was 3137 gr. (SD = 628). This difference was statistically significant (p=0.001). In the sero-positive deaf group, 3 children had a birth weight of less than 1501 gr. or very low birth weight (VLBW) who were considered to be full-term, and had no maternal history of rubella or rubella exposure during pregnancy. Four children had a birth weight of 1501 to 2500 gr. or low birth weight (LBW), who were considered to be full-term, and three of them (four) had maternal history of rubella infection during pregnancy. In the sero-negative deaf group, eight children were LBW and two children were VLBW. All of VLBW children were premature. In LBW children, one was premature and the others were full-term, and their mothers reported history of prenatal problems (disease, x-ray exposure, and trauma). However, it seems that congenital rubella as a cause of intrauterine growth retardation had caused LBW children, and VLBW children were mainly due to prematurely or prenatal problems.
The birth month distribution of the sero-positive and sero-negative deaf children was compared, and there was no statistical significant difference. This finding reflects no seasonal pattern of the incidence of rubella in the deaf children.
Table 3 shows that nine mothers (41%) of 22 deaf sero-positive children reported history of rubella or rash or rubella exposure during pregnancy whereas none of 91 sero-negative deaf children mother reported above history (p = 0.000).

**Discussion**

Prevalence of bilateral sensori-neural hearing loss is 0.5-1 new born/ 1000 live births. In addition, onset of hearing loss can occur at any time throughout childhood. Thus, it is estimated that the prevalence of bilateral hearing loss increases to 1.5-2/ 1000 children under the age of 6 yr. (9).

Considering prevalence of sensori-neural hearing loss and computed AR in this study (12%) and concerning birth rate in Tehran, it could be estimated that congenital rubella causes annually 12-50 births with hearing loss in Tehran. It is supposed that these results are extrapolated in all the country and it could be estimated that annually 80-340 deaf children are born in Iran and their deafness could be prevented by rubella vaccination. Recent investigation in Iran showed that the rubella immunity in women of childbearing age from 1968 through 1995 (time of this study) has fluctuated between 95% and 80% (10), which has recently reached about 80% and it probably indicates that is non-epidemic years of rubella. So this computed numbers of children birth with deafness would increase in epidemic years.

Congenital rubella was estimated 15% of sensori-neural hearing loss causes before the vaccination in England and Wales and according to analysis, it was specified that 98-250 children birth with deafness could be prevented in non-epidemic years by rubella Vaccination (11).

It could also be argued that some of sero-negative cases were also caused by intrauterine rubella but had lost antibody. A study reported loss of antibody in an about 10% of their cases of congenital rubella (12).

Mean birth weight of the sero-positive deaf children was less than the sero-negative deaf children whom this conclusion has been confirmed by some studies (13). It seems that congenital rubella as a cause of intrauterine growth retardation in the sero-positive deaf
group and VLBW as a main factor in the sero-negative deaf group can reduce mean birth weight in children. In this study, intrauterine growth retardation more than prematurity have caused low birth weight in the sero-positive deaf group.

There was not significant difference between birth season of sero-positive and sero-negative deaf children. In the most of studies it has been recognized that the sero-positive deaf children were born during the winter and the trimester of pregnancy of their mother have passed in the spring and seasonal incidence of rubella has been confirmed (13). The results of this study are justifiable by two theories. Firstly, sample size was not enough and secondly, mother’s infection has not perhaps been mainly in the first trimester. Hearing impairment can result from fetal rubella not only during the first trimester of pregnancy but also in the second and even third trimester, in spite of the mother infection in the first trimester is more harmful (7).

Nine mothers (41%) of 22 deaf sero-positive children reported history of rubella or rash or rubella exposure during pregnancy, which other studies also reported 40% and sometime 75% of deaf sero-positive children had such maternal history (12).

In this study, the degree of hearing loss in children who were attended to deaf educational centers was often higher than 50 dB (sever to profound hearing loss), and their hearing loss were bilateral. Thus, children with low severity of deafness were not included in this study the relation between severity of deafness and congenital rubella could not be estimated.

About 20% of the children in deaf educational centers were not included because of vaccination history of MMR (Measles, Mump and Rubella), so perhaps odds ratio has been underestimated. Meanwhile regarding the other country experiences, if MMR vaccination coverage is less than 60%-70%, it may actually increase the age of infection and therefore the incidence of congenital rubella syndrome (14). If we entertain this dangerous fact that MMR vaccination coverage is about 20% in our community, prompt planning about amendment of the existence policy in rubella vaccination is mandatory.

After comparing vaccination records with parents reports about vaccination history, it was found out five children in studied deaf cases had history of MMR vaccination, and consequently they were excluded from study. Contrary to expectation, rubella antibody
titer had been negative in two of these children. Therefore it is necessary to investigate the efficacy of MMR vaccine (at least in rubella) in the future studies.

This study showed not only the Odds Ratio for sensori-neural hearing loss in relation to congenital rubella but also importance and risk of rubella infection in our community. According to researches done in our country, the rate of rubella immunity has reached about 80% (10) and that is to say, the rate of immunity in more countries had been about 80% in the rubella pandemic in 1960’s which had thousands victims (1-2). However, recent epidemiological evidence has shown that while rubella virus continues to circulate among children, there is the risk of infection in pregnant women, even when only 3% of them are non-immune, and there is no prospect of eliminating congenital rubella syndrome (11-14).

Regarding 26 years of experience in rubella vaccination* in developed countries, we must do extensive study and serious action about rubella vaccination program.

**Comments on the future studies:**

1) Study of MMR vaccine efficacy
2) The same research about the group of children with congenital heart disease or eyes problems (e.g. congenital cataract).
3) The same research about the deaf students in the first grade of primary deaf schools and random sample selection of the first grade healthy students for control group (to obtain control indicator of congenital rubella syndrome incidence before and after rubella vaccination). Then, serological survey of hearing-impaired children after rubella vaccination can help us to follow the impact of vaccination to the incidence of congenital rubella syndrome.

**What is already known on this topic**

1. Rubella is a common communicable viral disease of childhood.
2. Rubella in pregnancy may cause congenital rubella syndrome.

*The recommended age for routine MMR vaccination is 12-15 months of age. The second dose of MMR vaccine should be administered either at 4-6 years or at 11-12 years of age (11-15).
3. Sensori-neural hearing loss is the most common abnormality associated with congenital rubella syndrome and it is the most common complication with the late onset.

**What this paper adds**

1. Prevalence of CRS is estimated 0.2/1000 in capital city of Iran.
2. Rubella vaccination can prevent 12% of sensori-neural hearing loss in Iranian children.
3. Rubella vaccination (two doses) must add to national vaccination program in Iran. Appropriate surveillance system is needed because introduction of rubella vaccine without epidemiological data and adequate monitoring program should be avoided because of the occurrence of rubella cases can be shifted to higher ages and increasing the incidence of congenital rubella syndrome.
Table 1  Rubella antibody status in hearing impaired (Case) and Control children aged 1-4 years, Tehran, Iran, 1995-96

<table>
<thead>
<tr>
<th>Rubella antibody status</th>
<th>Groups</th>
<th></th>
<th></th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Case</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N. (%)</td>
<td>N. (%)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Sero-positive</td>
<td></td>
<td>22 (19.5)</td>
<td>10 (8.9)</td>
<td>2.47 (1.04-5.94)</td>
</tr>
<tr>
<td>Sero-negative</td>
<td></td>
<td>91 (80.5)</td>
<td>102 (91.1)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>113 (100)</td>
<td>112 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2  Birth weight in hearing- impaired children aged 1-4 years according to rubella antibody status, Tehran, Iran, 1995-96

<table>
<thead>
<tr>
<th>Birth weight (gr.)</th>
<th>Sensorinoural hearing-Impaired children</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seropositive</td>
<td>Seronegative</td>
</tr>
<tr>
<td></td>
<td>N. (%)</td>
<td>N. (%)</td>
</tr>
<tr>
<td>&lt;1501</td>
<td>3 (13.6)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>1501- 2500</td>
<td>4 (18.2)</td>
<td>8 (9.5)</td>
</tr>
<tr>
<td>2501 – 3500</td>
<td>15 (68.2)</td>
<td>58 (69)</td>
</tr>
<tr>
<td>&gt; 3500</td>
<td>0 (0)</td>
<td>16 (19.1)</td>
</tr>
<tr>
<td>Total</td>
<td>22 (100)</td>
<td>84 (100)</td>
</tr>
</tbody>
</table>
Table 3: Maternal history in sensori-neural hearing impaired children age 1-4 years according to rubella antibody status. Tehran, Iran, 1995-96

<table>
<thead>
<tr>
<th>Maternal history</th>
<th>Sensorinoural hearing-Impaired children</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seropositive N. (%)</td>
<td>Seronegative N. (%)</td>
</tr>
<tr>
<td>Diagnosed rubella / Rubella exposure</td>
<td>9 (41)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Without above history</td>
<td>13 (59)</td>
<td>91 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>22 (100)</td>
<td>91 (100)</td>
</tr>
</tbody>
</table>
References


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