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Original Research Paper

Microbiology

SCREENING OF PREGNANT WOMEN FOR PRESENCE OF IGG ANTIBODIES FOR RUBELLA, MUMPS, MEASLES AND VARICELLA VIRUSES IN TERTIARY CARE HOSPITAL , JAIPUR

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ABSTRACT

Background : The aim of this study were assess the susceptible pregnant women for vaccine preventable infection like rubella, mumps, measles and varicella viruses. Infection of mothers with these viruses during pregnancy can be serious. They can cause congenital infections, miscarriage, stillbirth and death of fetuses.

Material and Method : This study is cross sectional. To determine the presence of IgG antibodies for rubella, mumps, measles and varicella viruses, blood samples were collected, stored at -700 c. Serum was separated for detection of IgG antibodies for these viruses by using enzyme linked immunosorbant assay.

Results : Of 277 samples evaluated for IgG antibodies. Susceptibility Of pregnant women for rubella, mumps measles and varicella viruses were 7.6%, 17.6%,7.2% and 19.5% respectively. Susceptibility rates for rubella and mumps were higher in rural population as compares to urban while for varicella urban population was more susceptible, but it was not statistically significant. No correlation could be observed in susceptibility to different to different viruses and their education status and age of patients, but youngest age group was most susceptible to varicella and oldest group to rubella. Primigravida were more susceptible to rubella and varicella while multigravida were more susceptible to mumps and measles.

Conclusion : Majority of the pregnant women had protective levels of IgG antibody although susceptibility to rubella, mumps measles and varicella were low. Intensification of MMRV immunization of all females of child-bearing age is advocated.

KEYWORDS : Rubella, Mumps, Measles, Varicella, IgG antibodies, Pregnant women, Immunization.

INTRODUCTION

Women are at an increased risk of acquiring certain transmissible diseases during pregnancy due to transient immunosuppression [1]. This may be enhanced due to missing vaccination, decreased uptake of the vaccine, reinfection of mothers and immigration from places where these viruses are endemic [2]. These infections can transmit to neonate transplacentally, perinatally or postnatally.The term congenital infection is used if the vertically transmitted infection persists after childbirth.Vertically transmitted infections are caused by various bacteria, viruses and parasites.

Many vertically transmitted viral infections have no effective treatment but some notably rubella, mumps, measles and varicella can be prevented by vaccinating the mother prior to pregnancy.

Rubella virus belongs to family *Togaviridae* and genus *Rubivirus*. Rubella causes maculopapular rash with fever in children which can occasionally infect adults. It is a mild self limiting disease of world wide distribution, however can be of serious consequences if contracted by a pregnant woman. Women contracting rubella infection during the first trimester of pregnancy may lead to miscarriage or stillborn baby. If the baby survives it can lead to Congenital Rubella Syndrome (CRS) in newly born with severe heart disorders, blindness, deafness, mental retardation or other life threatening disorders. With estimated ~30 million annual pregnancies, the assumed CRS load is ~29000 cases per year [3].

Mumps is caused by an RNA virus of family *Paramyxoviridae* and genus *Rubula*. Mumps is an acute infectious disease. Unilateral or bilateral parotid gland enlargement occurs 24 hours after initial symptoms. Typical acute parotitis occurs in only about 30–40% of cases, while 15–20% of infections are completely asymptomatic and up to 50% of infections are associated with nonspecific or primary respiratory symptoms. Although disease is generally mild and self-limited but occasional complications may ensue; like aseptic meningitis, encephalitis, permanent deafness, orchitis and pancreatitis [4].

Pregnant women with mumps have increased risk of embryonic and fetal death as well as spontaneous abortion but do not seem to have any relation to fetal congenital anomalies [5]. But one study revealed that like rubella, mumps in pregnancy can also give rise to fetal damage in the form of aqueductal stenosis leading to congenital hydrocephalus [6].

The burden of mumps remains high (100-1000 cases/100000 population) in countries which do not offer routine mumps vaccination, with epidemic peaks every 2-5 years [4,7]. Of late, there has been resurgence of mumps even in countries using mumps vaccine in their National Immunization Programs (NIPs) [8,9,10].

Measles virus is an RNA virus belonging to family *Paramyxoviridae* and genus *Morbillivirus*. The prodromal signs and symptoms include malaise, fever, conjuctival injection, cough and nasal discharge and rash appears after 3-4 days of prodromal illness. A day before the rash, Koplik's spots develop on the buccal mucosa and occasionally on the conjunctiva and intestinal mucosa. Complications are common and may be quite serious, many develop neurological sequelae, subacute sclerosing panencephalitis may also occur late. It is a leading cause of death among young children in many developing countries, accounting for 4% mortality in children aged less than 4 years. Prevalence of *measles virus* infection is approximately 98% in developing countries [11]. If measles occurs during the late stages of pregnancy, maternal and fetal morbidity are increased. Pregnant women have higher risk of miscarriage, severe respiratory distress, pneumonitis, hospital admission and death. Fetal death, prematurity and subacute sclerosing panencephalitis are seen more often in infants of these women [12]. The World Health Organization estimated in 2005 that there were 30–40 million measles cases and 530,000 deaths annually worldwide. Measles is the fifth leading global cause of mortality among children under 5 years of age and measles deaths occur disproportionately in Africa and Southeast Asia [13].

Varicella zoster virus belongs to subfamily *Alpha*

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herpesvirinae and genus *varicellovirus*. It's official name is *herpes* virus type 3 which causes chickenpox. Chickenpox in pregnancy can be dangerous for both mother and baby. It is characterised by fever, malaise and pruritic rash that develops into crops of maculopapules which become vesicular and crust over before healing [14].

In pregnant women chickenpox is associated with greater morbidity due to pneumonia, hepatitis and encephalitis. It may also cause fetal varicella syndrome (FVS) or congenital varicella syndrome in the newborn. FVS is characterised by one or more of the following: Skin scarring in a dermatomal distribution, microphthalmia, chorioretinitis, cataracts, hypoplasia of the limbs, dysfunction of bowel and bladder sphincters and neurological abnormalities eg microcephaly, cortical atrophy, intellectual disability [15]. Despite improvements in clinical care, varicella may be complicated by pneumonia in up to 28% of pregnant women and this remains associated with a risk of mortality. In a recent report of 198 cases of varicella in pregnancy, 16 deaths were reported, all in the group complicated by pneumonia [16]. Maternal varicella occurring five days before to two days after delivery is associated with severe neonatal varicella in 17% to 30% of infants and a case fatality rate as high as 31% [17].

Almost all studies on seroprevalence of rubella amongst Indian female revealed that 10-30% of adolescent girls and 12-30% of women in reproductive age group are susceptible [18,19]. Three studies revealed status of susceptibility in young children and adolescent against mumps and found susceptibility rate ranging from 32% to 80% in different age group [20-22]. The estimated global measles death in 2007 was 197,000 of which India contributed about 67%. Majority of these deaths occur in states like UP, Bihar, Rajasthan, MP, Jharkhand and the North Eastern States [23]. India reported 18,668 cases of measles in 2012, recording the second highest number in sub-Saharan Africa and the South East Asian region, according to WHO statistics [24]. Among vaccine preventable diseases, measles is the leading cause of death with an estimated 450 deaths each day world wide [25]. Average incidence of varicella in pregnant women is 1-3 per 1000 pregnancies. The incidence of pneumonia complicating varicella in pregnancy has been quoted at 10-14% [26].

Pregnant women are in contact with health care provider so it is best time to identify susceptible women and provide immunization postpartum. Moreover the antenatal women are the healthy population representing the community. Study of the immune status in antenatal mothers would be an indication of immune status in female population of the similar age group.

AIMS AND OBJECTIVES

To identify presence of IgG antibodies for *Rubella virus,Mumps virus Measles virus* and *Varicella zoster virus* in pregnant women attending Gangori Bazar Hospital, Jaipur.

MATERIAL AND METHODS

Study Area and Site: This study was conducted in ICMR Grade 1 Virology Lab , Advance Research laboratory, Department of Microbiology & Immunology of SMS Medical College, Jaipur.

Study Design: This was a cross sectional and descriptive type of study.
Study Period: This was completed in period of April 2014-June 2015.
Study Population: Pregnant women attending ANC clinic in Gangori Bazaar Hospital,Jaipur.

Sample Size : Available data from India suggest that 12-30% of the women in reproductive age group are susceptible to rubella. However, calculated sample size was 277(α error 5% and power of study (1-β) is 80% and confidence interval 95%) from the ANC attendees. It was assumed that sero-prevalance would be more for mumps, measles and varicella to rubella and the same sample size would suffice.

Inclusion Criteria: Healthy ANC attendees.

Exclusion Criteria: Ill subjects, those with bad obstetric history, history of diabetes, history of hypertension, immune-compromised patient were excluded.

Sample Collection: Informed consent was taken for taking blood samples and the use of personal data being collected using a specific form, 4-5 ml blood samples were collected from pregnant women attending antenatal clinics after filling the questionnaire which was specifically designed for study. Separated serum specimen in aliquots were stored at -20c until tested. Each specimen was given an unique identification number and a companion clinical proforma.

The questionnaire concerned socio-demographic data as name, husband name, age, residence, educational qualification, information about MMR /MR vaccination history and gravidity of women.

Ethical consideration

The implications of rubella, mumps, measles and varicella infection was clearly explained to the study participants for them to understand the disease under investigation and type of specimens to be collected. It was explained that congenital rubella syndrome, congenital varicella syndrome, mumps and measles infections affect individuals differently and there was no treatment but management was based on individual complications. Patients were given clear explanation of the disease and why it was mandatory for a blood sample to be collected so as to confirm virus infection as it was a notifiable disease.

Data analysis:

Data was summarized and classified in MS excel worksheet in the form of master chart. Data was analyzed and interfered with use of appropriate statistics.

Method

The concentration of human IgG antibodies for rubella, mumps, measles and varicella was determined using commercial ELISA test according to manufacturer's instructions. The calculation of results obtained by qualitative assay considered the optical density of each negative, positive and cut off control.

Interpretation of results

For mumps measles and varicella(calbiotech ELISA kit)

Antibody Index Interpretation

- <0.9 No detectable antibody
- 0.9-1.1 Borderline positive
- >1.1 Detectable antibody

For rubella (Diapro ELISA kit)

Samples with a concentration lower than 10 WHO IU/ml were considered negative for anti rubella virus IgG antibody by most of the international medical literature. Samples with a concentration higher than 10 WHO IU/ml were considered positive for anti rubella virus IgG antibody.

OBSERVATIONS AND RESULTS

Total 277 pregnant women attending antenatal clinic in the reproductive age group (15-45year) were included in our study. The demographic data included thier name, age, residence, education history of MMR vaccine and gravidity.

Majority of women 262/277(94.6%) did not know about their

immunization status both combined vaccine or any of the three single vaccines in the past. Only 15 /277 (5.4%) women knew their immunization status about combined MMR vaccination.

Table-1 Susceptibility of pregnant women to different viruses

Name of viruses	Number of susceptible women	Percentage
Rubella	21	7.6%
Mumps	49	17.6%
Measles	20	7.2%
Varicella	54	**19.5%**

Among the 277 pregnant women highest susceptibility was found against varicella (19.5%).

(A) Residence

Table-2 Showing susceptibility of participants to viruses in relation to residence

Residence	Rubella	Mumps	Measles	Varicella
Urban(193)	12 (6.2%)	33 (17.1%)	14 (7.2%)	39 **(20.2%)**
Rural(84)	9 **(10.7%)**	16 **(19%)**	6 (7.1%)	15 (17.8%)
P value	0.292	0.74	0.817	0.787

(P >0.05 not significant for rubella, mumps, measles and varicella)

Susceptibility rates for rubella and mumps were higher in rural population as compares to urban while for varicella urban population was more susceptible. But it was not statically significant.

(B) Age groups

Table-7 Showing susceptibility to different viruses in relation to age groups

Age groups (in years)	Rubella	Mumps	Measles	Varicella
15-19(13)	0 (0%)	1 (7.7%)	0 (0%)	5 **(38.4%)**
20-24(152)	9 (5.9%)	32 **(21.1%)**	16 **(13.2%)**	29 (19.1%)
25-29(83)	8 (9.6%)	13 (15.7%)	2 (2.4%)	15 (18.1%)
≥30(29)	4 **(13.7%)**	3 (10.3%)	2 (6.8%)	5 (17.2%)
P value	0.388	0.382	0.111	0.445

(P >0.05 not significant for rubella, mumps, measles and varicella)

No correlation was found between age of patient and susceptibility status to viruses, youngest age group was most susceptible to varicella and oldest group to rubella.

(C) Education

Table-8 Showing susceptibility of partcipants to different viruses in relation to their education

Education(n)	Rubella	Mumps	Measles	Varicella
Postgraduation(17)	1 (5.9%)	2 (11.8%)	0 (0%)	2 (11.7%)
Graduation(24)	1 (4.2%)	5 (20.8%)	1 (4.2%)	5 20.8%)
Higher secondary(29)	2 (6.8%)	1 (3.4%)	1 (3.4%)	10 **(34.5%)**
Secondary(52)	7 **(13.4%)**	11 (21.1%)	4 (7.6%)	6 (11.5%)
Primary(87)	5 (5.7%)	15 (17.2%)	7 (8%)	16 (18.3%)
Illiterate(68)	5 (7.3%)	15 **(22.1%)**	7 **(10.3%)**	15 (22.1%)
P value	0.740	0.348	0.769	0.220

(P >0.05 not significant for rubella, mumps, measles and varicella)

No correlation could be observed in susceptibility to different viruses and their education status.

D. Gravidity

Table-9 Showing status of susceptibility to viruses in relation to gravidity

Gravidity(n)	Rubella	Mumps	Measles	Varicella
Primigravida (125)	12 **(9.6%)**	20 (16%)	6 (4.8%)	27 **(21.6%)**
Multigravida (152)	9 (5.9%)	29 **(19.1%)**	14 **(9.2%)**	27 (17.7%)
P value	0.356	0.610	0.239	0.516

(P >0.05 not significant for rubella, mumps, measles and varicella)

Primigravida were more susceptible to rubella and varicella while multigravida weremore susceptible to mumps and measles. But it was not stastically significant.

DISCUSSION

The present study was done to assess immune status of pregnant women for rubella, mumps, measles and varicella attending a tertiary care center in Jaipur.

In our study susceptibility for rubella, mumps, measles and varicella was found to be 7.6%, 17.6%, 7.9% and 19.4% respectively.

In older Indian studies done during 1972-1982 the range of susceptibility for rubella were 12.7% to 32.5%[27-30]. While newer studies report lower susceptibility, 5.4% at Vellore by Black et al [31], 5.1% at Hyderabad by Bhaskaram et al [32]. Susceptibility rates were similar to our study in foreign countries also, 9.4% at U.S.by Hass et al[33], 9.4%% from Saudi arabia by Sharifa et al[34], 4% at Iran by Behman et al [35],3.4% at Nigeria by Obijimi et al[36] and 5% at Spain by Plans et al[37].

However higher susceptibility rates were reported from various studies from India than our study. Three studies from Delhi reported wide variation in susceptibility 12.8% by Ekta et al[38], 14.6% Gandhoke et al[39], 21% by Deka et al[40], 46% by Khare et al[41] and 24% by Rustugi[42]. Padmaja et al [43] from Kerala reported very high susceptibility of 37.3% and Thapliyal et al [44] from Haldwani 33.33%, a study from Karnataka done in Health science students susceptibility was 16.6%[22], 15.3% by Singh[45] from Chandigarh and 11.6% by Jain et al in Lucknow [46]. Even foreign studies reported high susceptibility, 22.1% from Italy [47] and 12.7% by Fadwa et al from Saudi Arabia[48]. Across the globe there is a considerable variation in susceptibility of rubella in childbearing age. European women have lower susceptibility (6.85%) as compared to women of Africa (13.3%)and Asian origin (21.6%)[49].

For mumps and measles no data is available on their susceptibility in pregnant women in India, one study done in health students by Kumar et al [22] in Karnataka, susceptibility for mumps and measles were 32% and 9.5% respectively and by Afgah et al in Iran [50] in health and dental student susceptibility were 24% and 48%. Another study conducted by Hass Dm in United state [33] in pregnant women reported susceptibility for mumps and measles to be 16.3% and 16.5% respectively and by Plans P et al from Spain [37] it was 19% and 11% respectively.

Similarly data on varicella in pregnant women is not

available, few studies done on students reported varicella susceptibility to be 25.8% by G Arun kumar et al from Karnataka [22],15% by Afgah et al at Iran [50], 3.7% by S kumakara et al at Japan[51].

In our study susceptibility in rural area was higher for rubella and mumps than urban. Susceptibility for rubella, mumps, measles and varicella in the participants which belonged to urban area were 6.2%, 17.1%, 7.2% and 20.2% respectively and those belonging to rural area were 10.7%, 19%, 7.1% and 17.8%.

A study conducted by Seth et al at Delhi observed the susceptibility for rubella to be 20.5% for urban population and 30% for rural population [52].

However there is no data available which show the susceptibility for mumps, measles and varicella in respect to urban and rural population.

In our study on the basis of their age groups susceptibility for rubella virus increased with age, age group 15-19 year (0%), for 20-24 year (5.9%), for 25-29 year (9.6%) and over the age of 30 year (13.7%).

Similar results were seen in a study done by Gupta et al [38] at Delhi, their susceptibility in age group 15-19 year was 7.5% and in 25-30 year the susceptibility was 13%. The possible explanation was more exposure of younger age group to rubella and other explanation was that higher immunity in the younger age group could also be due to persistence of immune response to MMR vaccination in childhood and waning of immunity with age.

Other studies showing similar results were by Kumakura et al in Japan[51] who reported susceptibility for rubella increase with increasing age.

For mumps highest susceptibility in age group 20-24 year was 21.7% followed by 25-29 year (15.7%) then over 30 year (10.3%) and lowest susceptibility for age group 15-19 year was 7.7%. A study conducted by Elisa langiano et al [52] in Italy showed that susceptibility for mumps was higher in age group 21-25 year and another study done by S. Kumakura [51] in Japan in HCW susceptibility was high in under 29 year age group(11%), compared to 30-39 year (7.4%) and for 40-49 year (5%).

In our study the result for measles was highest susceptibility in age group 20-24 year was 13.2% followed by age group over 30 year (6.8%) then age group 25-29 year (2.4%) and lowest susceptibility for age group 15-19 year was 0%.A study conducted by Langiano in Italy[52]showed that susceptibility for measles was higher in age group 21-25 year and over 31 year age groups. Another study done by Kumakura [51] in Japan in HCW susceptibility was higher in under 29 year age group (14.3%), compared to 30-39 year (7.8%) and for 40-49 year age group (0.8%).

In our study for varicella, highest susceptibility was seen for the age group 15-19 year (38.4%) followed by the age group 20-24 year (19.1%) and almost similar susceptibility in age group 25-29 year (18.1%) and over 30 year (17.2%). A study conducted by Kumakura in Japan [51] showed no age related significant difference in susceptibility for varicella. A study done by G.Gabutti [53] in Italy in reproductive age group susceptibility in age group 15-19 year was 17.2% and for 20-39 year was 9.2%.

Studies from Spain [54] in the period of 1996 -2003 showed that susceptibility for varicella in the 15-24 year age group was 6% followed by age group 25-29 year (5%) and for age group 30-49 year susceptibility was < 5%.

Several surveys investigated the rubella, mumps, measles and varicella susceptibility in different countries in similar setting and age specific profile of these viruses have wide variation. In places where the vaccine has been given in childhood, it is observed that immunity decreases with age while in others the pattern is variable depending on occurrence of natural infection and immunity achieved subsequent to it. However as the number of studies have documented decrease in immunity over the years, administration of booster dose at the time of the entry in health care system for health care worker and before marriage may be advocated for young women.

In our study no correlation was found in susceptibility to rubella, mumps, measles and varicella viruses and the education level of the pregnant women enrolled in the study. Other studies done by Maryam et al in Iran [55] and Obijimi et al from Nigeria [36] also observed no effect of education on susceptibility .

Though no correlation of susceptibility of different viruses with education was observed but to increase awareness it would be advisable to educate the high secondary students about the vaccine preventable viruses and need for immunization. Moreover it is important to carry out information, education and communication (IEC) activities for general public such that they can ask for immunization and help in prevention and control of infections by these viruses.

In our study susceptibility for rubella and varicella were higher in primigravida (9.6%,21.6%) compared to multigravida (5.9%,17.7%) women respectively. Susceptibility for mumps and measles were higher in multigravida (19.1%,9.2%) compared to primigravida (16%,4.8%) but were not significant statistically. A study done by Amita Jain et al at Lucknow also observed no relation of parity to their susceptibility to different viruses [46].

A study was conducted by Mahmoudi and his colleages in Mashad during years 2001-2004 for evaluating immune status against rubella of women before and after vaccination programme. They evaluated 1698 women before and 354 after vaccination. Immunity level achieved before vaccination were 67.19% and 77.4% post vaccination [56].

Choice of vaccines in National Immunization Schedule warrants careful decision and periodic reviews. In 1978, India adopted the Expanded Programme on Immunization (EPI) promoted by World Health Organization (WHO). In 1985, EPI was renamed as Universal Immunization Program (UIP). Four Union Territories (Delhi, Goa, Pudduchury and Sikkim) are already using MMR in their Universal Immunization Programme (UIP). The coverage of MMR vaccine has been reported as 42%, 30% and 5% from Delhi, Chandigarh and Goa, respectively [57]. Kerala became the latest entrant to start universal MMR vaccination in the state from 2014. By 2012, 132 of 194 WHO member states had also introduced rubella containing vaccine (RCV) in their National immunization programs (NIP), either as MR or MMR. Of these, 117 have RCV included in both routinely administered doses of measles-containing vaccine [58].

Nearly 45% females in the reproductive age group in India are susceptible to infections during pregnancy [59]. For control, the target age groups should be from 9 months to 15 years (following introduction in NIP). Further decision to expand is to be guided by the epidemiology of the disease (age distribution, sero-prevalence data, age-specific fertility rates, susceptibility data of women of child bearing age and maternal age distribution of CRS. For elimination, we must target all the above age groups along with expansion of target age of coverage beyond 15 years. They should include special

immunization activities targeting adults (up to 40 years of age). Further age groups for inclusion in target age for these activities will depend on sero-epidemiology data. Here, both the sexes, must be included for vaccination [60].

Pre-conceptional screening and immunization of pregnant women are not yet adequate in India. Its suggested that immunization should be part of preconception care. No specific programmes or initiatives have been endorsed so far by the WHO to promote varicella immunisation or prevention of congenital varicella [61].

It is important to educate women of child bearing age about the importance of vaccination against some of these diseases, as many of these congenital infections are preventable. Most of this education should be targeted toward teenaged girls, as many young women will not seek medical care outside their pediatrician until they are already pregnant.

Educating the pregnant patient to avoid contact with persons with viral infections and frequent hand washing when handling children can prevent infection. If exposure does occur, the patient should seek immediate assistance for postexposure prophylaxis with varicella immunoglobulin [62].

There is an urgent need to start MMR in the Universal immunization programme so as to reduce the disease burden. However states which have the ability to achieve and sustain routine immunization coverage of >80% should be considered first and other states to be encouraged to increase vaccination coverage. This would also provide a second opportunity for measles vaccination.

Moreover large scale well planned studies on CRS and CVS in India should also be carried out to know exact disease burden and areas where extra care is needed.

CONCLUSION

In our study we found that very high number of pregnant women were susceptible to varicella and lesser for rubella, mumps and measles. These viruses increase mortality and morbidity among the pregnant women and their unborn babies. In India MMR and varicella vaccine are being given as part of immunization programme in many states like Delhi, Goa, Puducherry, Sikkim and recently in Kerala but not in all states of the country. Minimum 80% coverage is required for control of these viruses which will not allow virus to circulate freely and infect women of child bearing age. In India the coverage of MMR and varicella vaccine has been reported to be very low. For control and elimination of these viruses. We should include special immunization activities targeting adults, adolescent girls and women of childbearing age.

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