Seroprevalence and pregnancy outcome in Rubella infection in antenatal women with bad obstetric history: A case control study

Divya Pandey[1], Monika Gupta[2,*]

[1]Associate Professor, [2]Associate Professor, Dept. of Obstetrics and Gynecology, VMMC and Safdarjung Hospital, Delhi, India

***Corresponding Author: Monika Gupta**
Email: drmonikagupta@hotmail.com

Received: 15th November, 2018 **Accepted:** 28th December, 2018

Abstract

Objective: To evaluate seroprevalence of Rubella infection in antenatal patients with bad obstetric history (BOH), pregnancy outcome of seropositive cases and incidence of congenital malformations in maternal Rubella infection.

Materials and Methods: This was a prospective case control study done at a tertiary teaching institute over duration of one year. One hundred and seventy four antenatal women with BOH were studied against one hundred and six control cases. Their serum sample was subjected to ELISA test for Rubella IgG and IgM antibodies estimation at their first antenatal visit. Interconception interval i.e. the time interval between the previous pregnancy loss and current pregnancy was noted. All women were followed to know the pregnancy outcome. Apparent congenital anomalies in the newborns were evaluated. Chi square test was applied for statistical analysis.

Result: Seropositivity for Rubella IgG antibodies, IgM antibodies and both IgG and IgM was 48.3%, 25% and 3.5% respectively in study group. Abortions, preterm delivery and stillbirths were seen in 56.8%, 18.3% and 4.5% of IgM positive cases. 2.24% with IgG positive had abortion while 4.5% with both IgG and IgM antibodies had fetal congenital malformation. Incidence of congenital anomalies in the form of Neural Tube Defects was 4.48%. Abnormal pregnancy outcome in present pregnancy was seen in 59.1% of women with interconception interval less than 3 months.

Conclusions: Seropositivity of IgM Rubella antibodies was significantly higher in women with Bad Obstetric History. Incidence of Neural Tube Defects was higher with Rubella infection if exposure occurs in first few weeks of pregnancy. There is need for immunization against Rubella, of adolescent girls and seronegative prospective mothers. A proper (more than 3 months) interconception interval should be recommended after acute Rubella infection in pregnancy causing obstetric loss in that pregnancy.

Keywords: German measles, Rubella in pregnancy, Pregnancy loss, Interconception interval.

Introduction

Bad obstetric History (BOH) implies previous unfavorable fetal outcome in terms of two or more consecutive spontaneous abortions, history of intrauterine death, intrauterine growth retardation, still births, early neonatal death and/or congenital anomalies. Amongst other causes of BOH viz. genetic, hormonal, abnormal maternal immune response and maternal infection, infections are important cause of increasing perinatal morbidity and mortality.

Recurrent pregnancy wastage due to maternal infection transmissible in utero at various stages of gestation can be caused by a wide array of organism which include *TORCH (Toxoplasmosis, Rubella, Cytomegalovirus and Herpes)* complex also. According to World Health Organization, 10-25% of women of developing countries have been tested to be seronegative.[1] It has been observed that susceptibility rate of 10% among adult women can lead to CRS outbreaks.[2]

Infection with Rubella during pregnancy may lead to congenital malformation in 10-54% cases.[2,3] These infections are disastrous particularly if contracted during first three months of gestation. Risk of Rubella infection is highest to fetus if it occurs in first two months of pregnancy (40-60%) and progressively decreases during the fourth and fifth months (10-20%). The first humoral immune response to infection is the synthesis of specific anti-rubella virus IgM antibody which reaches high serum levels two weeks after the rash and lasts for about 2 to 3 months. Specific IgG antibody generally appears a few days after the onset of rash, about 1 week after IgM develops, rapidly rises to reach a plateau in 6-10 weeks after onset of symptoms and then progressively decreases to a level (15-200 IU/ml) lasting for whole life. Reinfection, is accompanied by moderately increased levels of specific IgG and nil or mild clinical symptoms. Correct detection of IgG, provides an essential test for diagnosing and following up acute infection, for assessment of immune status in fertile women and therefore, for adopting suitable prophylaxis in susceptible women of child bearing age.

Congenital Rubella Syndrome (CRS) in newborns which occurs when infection is contracted during first trimester of pregnancy is the most important concern.[3] Congenital Rubella causes a wide range of severe defects, many of which are permanent and adversely affect later development of child e.g., cataract, deafness, hepato-splenomegaly, physcho motor retardation, nueromotor deficits, diabetes mellitus, bone lesions, interstitial pneumonitis, meningoencephlalitis, cardiopathies, neuropathies.[4] Infact spectrum of Rubella infection is much wider and is known as *Extended Rubella Syndrome*.[3] It can lead to spontaneous abortions, fetal infection, fetal growth restriction and still births in addition to congenital malformation.[4] With the availability of Rubella vaccine, this infection becomes a preventable cause of congenital malformations in the fetus. So as a whole in view of these

disastrous consequences of Rubella in mothers and neonates, there is high need to assess the seroprevalence of the infection. The knowledge thus attained can help us in planning our vaccination strategies by focussing on target groups.

This study was thus conducted to know the seroprevalence of Rubella infection in antenatal women with bad obstetric history (BOH), to know the pregnancy outcome in affected women and to know the incidence of congenital malformations in the seropositive women.

Materials and Methods

This prospective case control study was conducted on one hundred and seventy four antenatal women (study group I) with bad obstetric history (BOH) (two or more abortions, still births, intrauterine death or neonatal deaths) attending outdoor and indoor antenatal clinics in the department of Obstetrics and Gynecology of a tertiary teaching institute over duration of one year. Another 106 women (Study group II) without any obstetric losses were taken as control. In addition to a thorough systemic and obstetric examination routine antenatal tests were done in all cases. Enzyme linked Immuno Sorbent Assay (ELISA) was done for estimating IgM and IgG levels at their first antenatal visit and all patients were followed to know the pregnancy outcome. Apparent congenital anomalies in the newborns were also evaluated. Pregnant women below 20 years and more than 45 years, those who underwent in-vitro fertilization, immune-compromised, those with autoimmune disorders and with other recognizable causes of BOH like cervical incompetence, uterine anomaly, endocrine disorders etc were excluded from the study.

The presence or absence of Rubella antibodies is defined by comparing the sample absorbance with the absorbance of the cut-off control (threshold value). Samples with absorbance lower than the threshold value were considered non-reactive for anti-Rubella antibodies and those with absorbance higher than the threshold value were considered reactive for anti-Rubella antibodies. The test of significance applied was chi square test. P value of less than 0.05 was considered as significant.

Results

Table 1 shows antenatal women with BOH showing presence of Rubella infection in group I and group II. Out of 174 women in study group 77% (134/174) came out be seropositive in comparison to 50% (53/106) in control group. Both groups matched in age and parity. Table 1 shows that IgM, IgG and both IgG and IgM seropositivity was seen in 25%, 48.3% and 3.5% respectively in study group and the seropositivity for IgM (indicating the acute infection) and both IgG and IgM (indicating reinfection) was significantly higher in the study group ($p<0.05$).

The distribution of pregnancy outcome in women with rubella infection is shown in table 2. Adverse pregnancy outcome in form of abortions, preterm delivery and stillbirth was seen in 56.8%, 18.3% and 4.5% of IgM positive cases respectively. Of women with IgG antibody positive status, 2.24% had abortion while 4.5% with both IgG and IgM antibodies had congenital malformation in the baby.

The pregnancy outcome in 53 women with rubella seropositivity in control group is depicted in table 3. All women in this group had term delivery. The table 4 shows the interconception interval between the present pregnancy and the previous pregnancy wastage. It was seen that 59.1% (26/44) who conceived within 3 months of previous pregnancy loss had abortions (Table 2) while rest 40.9% (18/44) had adverse pregnancy outcome in the form of preterm birth, stillbirth and congenitally malformed fetus.

Incidence of congenital malformation in form of neural tube defects (NTDs) was 4.5% of IgM seropositive women (Table 5). Mothers whose fetuses had NTDs were already taking folate supplementation. Mean gestational age of detection of Rubella antibody where NTDs were found was 18 weeks (Table 5). All cases with IgM who aborted were detected in first trimester and all those who had preterm deliveries, stillbirths or baby with neonatal deaths were detected in mid trimester, mean gestational age of detection being 18.6 weeks.

Table 1: Antenatal women showing presence of Rubella infection in group I and group II

	Study Group I (n = 174)			**Control Group II (n = 106)**			**Test of Significance**
	n	%	Total% (N=174)	N	%	Total% (N=106)	
IgM	44	33	25	-	-	-	$P < 0.01^{*}$
IgG	85	63	48.3	52	98.1	49	$P>0.05^{\#}$
IgG & M	6	4	3.5	1	1.9	0.94	$P <0 .01^{*}$
Total	134	100	**77**	53	100	50	—
Mean Age(years)	25.6			25.4			$P>0.05^{\#}$
Mean parity	3.3			2.9			$P>0.05^{\#}$
$^{\$}$ 7 out of 44(16%) gave history of fever with rashes while 37 out of 44(84%) were asymptomatic. $^{*}P<0.01$-significant ; $^{\#}P>0.05$-non significant							

Table 2: Pregnancy outcome in women with Rubella infection in study group I (N=134)

	Antibody detected										
	IgG			IgM			IgG and IgM			Total	
Pregnancy outcome	n	%	total% (N=134)	N	%	Total % (N=134)	N	%	Total% (N=134)	N	%
Abortions	3	3.6	2.24	25	**56.8**	18.6	-	-	-	28	21
Congenital malformations	-	-	-	-	-	-	6	100	4.5	6	4.5
Preterm delivery	-	-	-	8	18.3	5.1	-	-	-	8	5.1
Macerated stillbirth	-	-	-	6	13.6	4.5	-	-	-	6	4.5
Fresh stillbirth	-	-	-	-	-	-	-	-	-	-	-
Fetal growth restriction	-	-	-	-	-	-	-	-	-	-	-
Neonatal death	-	-	-	3	6.8	2.24	-	-	-	3	2.24
Term deliveries	81	96.4	60.45	2	4.5	1.4	-	-	-	83	62
Total	84	100		44	100		6	100		134	100

Table 3: Pregnancy outcome in 53 women with Rubella infection in control Group II (N=53)

	Antibody detected										
	IgG			IgM			IgG and IgM			total	
Pregnancy outcome	n	%	total% (N=53)	n	%	Total% (N=53)	n	%	Total % (N=53)	N	Total % (N=53)
Abortions	-	-	-	-	-	-	-	-	-	-	-
Congenital malformations	-	--	-	-	-	-	-	-	-	-	-
Preterm delivery	-	-	-	-	-	-	-	-	-	-	-
Macerated stillbirth	-	-	-	-	-	-	-	-	-	-	-
Fresh stillbirth	-	-	-	-	-	-	-	-	-	-	-
IUGR	-	-	-	-	-	-	-	-	-	-	-
Neonatal death	-	-	-	-	-	-	-	-	-	-	-
Term deliveries	52	100	98.1	-	-	-	1	100	1.9	53	100
Total	52	100		-	-	-	1	100		53	100

Table 4: Interconception interval in antenatal women with Rubella Infection from last pregnancy to present pregnancy loss

Interconception interval (months)	Antibody Detected											
	Group 1 (n=134)						Group 2 (n=53)					
	IgM		IgG		IgG+IgM		IgM		IgG		IgG+IgM	
	n	%	n	%	n	%	N	%	n	%	N	%
1	-	-	-	-	-	-	-	-	-	-	-	-
2	25	**56.8**	-	-	-	-	-	-	-	-	-	-
3	1	2.3	-	-	-	-	-	-	-	-	-	-
>3	18	40.9	84	100	6	100	-	-	52	100	1	100
Total	44	100	84	100	6	100	-	-	52	100	1	100

Table 5: Congenital malformations in babies of women with acute Rubella infection in Group I

S. No.	Congenital malformations	No. of cases			IgG	IgM	IgG and IgM	
		N	%	Total % (N=134)	N	N	n	%
1	Anencephaly	4	66.7	2.99	-	-	4	66.7
2	Anencephaly with Meningocoel	1	16.7	0.75	-	-	1	16.7
3	Meningocoel	1	16.7	0.75	-	-	1	16.7
Total		6	100	4.48	-	-	6	100
Mean gestational age of detection rubella antibodies 18 weeks								

Discussion

In utero infections to the fetus are important cause of fetal and neonatal morbidity and mortality.[5] Moreover such infections contracted during antenatal period increase the rate of miscarriage, stillbirth, preterm labor and increased risk of congenital malformations.[6] When maternal infection occurs in the first trimester, fetal infection rates are about 80%, which reduce to 25% in late second trimester and rise again in third trimester from 35% at 27-30 weeks to almost 100% beyond 36 weeks of gestation.[7] The risk of congenital malformations has been reported to be 90% if infection occurs before 11 weeks, 33% at 11-12 weeks, 11% at 13-14weeks, 24% at 15-16 weeks and 0% after 16 weeks.[7] Therefore screening of such infections can be done in pre-conception and antenatal period so as to prevent such consequences.

In the present study, 25% antenatal women with BOH came out to be positive for IgM antibodies against Rubella which was statistically significant. Similar results were seen in the study of Turbadkar et al (2003), Fomda BA et al (2004) and Thapliyal et al (2005) where IgM seropositivity was seen in 26.8%, 26.12% and 28.6% respectively.[8-10]

Women who are seronegative for Rubella are at high risk of contracting infection. In present study, 48.3% women were found to be IgG seropositive (i.e. Rubella immune). This was lower than the seroprevalence of IgG antibodies in the study by Gandhoke et al (2005), Chandy et al (20110, Padmavathy et al (2013 and Chand et al (2017) with seropositivity in 86.9%, 87.5%, 90.8 and 84% respectively.[11-13,6] But it was higher than that according to the study by MS Sadik et al (2012) where IgG seroprevalence was 29.06%.[14] This difference in the seroprevalence may be attributed to the difference in the study population, different sample size and different methods of antibody detection in these studies. Low socio-economic status and poor hygiene may be contributory to exposure to and acquiring natural immunity against Rubella virus. On the other hand, good immunization coverage of rubella vaccine can also be a contributory factor for these impressive yet improvable figures.

Presence of IgG indicates natural immunity either after natural infection or post-vaccination. The present study demonstrated that about half of the antenatal women were seronegative in both study and control group, hence prone for Rubella infection. This is indicator of presence of rubella immunity in about half population which may either be due to previous rubella vaccination or history of rubella infection. This implies that we should make efforts to make rest of the population immune to Rubella by identifying the sero-negatives and vaccinating them preconceptionally. This also holds true in view of presence of significantly high number of IgM antibodies in antenatal women with Bad Obstetric History in this study.

Among viral diseases, Rubella is well known and manifests as a self-limiting disease with characteristic erythematous maculo-papular rashes, mild respiratory symptoms and low-grade fever. When occurs in an antenatal woman, it can lead to pregnancy loss, stillbirth, congenital defects, Congenital Rubella Syndrome (especially in first trimester infliction). 30-50% Infection is asymptomatic or mild in 30-50% cases thus likely to be clinically undetected or unreported.[2]

In present study 84% cases with Rubella infection were asymptomatic in the past with only 16% giving history of fever with rashes. This was similar to the result shown by Gong et al (1999).[15]

The interconception interval i.e. the interval from last pregnancy loss to the current pregnancy was within 2 months for majority of antenatal women i.e. 56.8% (25/44) in group 1,while 2.3% (1/44) conceived between 2-3 months and 40.9% (18/44) conceived after period of more than 3 months. This indicates that the acute rubella infection which led to previous pregnancy loss were again responsible for current pregnancy loss. Thus Rubella can be a cause of recurrent two pregnancy losses if the interconception interval is less than 8 weeks since during this time Rubella IgM antibodies are persisting in the body(rarely may persist for 3 months). So, acute Rubella can cause a second pregnancy loss, if interconception interval is less than 3 months.

In present study rest of 18 women with IgM and 6 women with both IgG and IgM antibodies where interconception interval was more than 3 months also had unfavorable pregnancy outcome. Here the cause of pregnancy loss was recently acquired Rubella infection in the corresponding pregnancy. The cause of previous bad pregnancy outcome in these cases must have been other than Rubella infection. Thus although statistically Rubella seroprevalence was high in BOH cases however when interconception interval was considered, it was inferred that Rubella can be cause of consecutive second pregnancy loss if the second conception occurs within 3 months of previous pregnancy loss which was due to acute rubella infection.

The pregnancy outcome shown by JB Sharma et al was in the form of spontaneous abortions in 50.73%, preterm delivery in 17.31%, stillbirths in 14.87% and neonatal deaths in 5.85% which was similar to the present study.[16] Primary Rubella infection occurring during early pregnancy leads to pregnancy loss. All women in control group had favorable pregnancy outcome as those with IgG antibody means immunity for Rubella while one women had both IgG and IgM which means it was reinfection which is milder in case of rubella.

It was seen that though wide array of congenital malformations are found with Rubella but in present study apparent congenital malformations were found in 4.48% antenatal women with both IgG and IgM positivity. These malformations were chiefly in the form of neural tube defects and the mean gestational age of detection of Rubella antibodies in these women was 18 weeks. Though limited studies are available which show association between neural tube defects and Rubella infection. TORCH complex as a whole has been implicated as a cause of neural tube defects. Hence neural tube defects is higher with rubella infection if exposure occurs in first few weeks of pregnancy.

Conclusion

The present study demonstrates a statistically significant seroprevalence of IgM rubella antibodies in women with BOH. This also reports incidence of neural tube defects in Rubella infection if it occurs in first few weeks of pregnancy. Since Rubella is a preventable viral illness, all women should have a preconception Rubella screening and seronegatives must be vaccinated against Rubella vaccine. In fact Rubella vaccination should be given to all adolescent girls in our community. A proper (more than 3 months) interconception interval should be recommended after acute Rubella infection in pregnancy causing obstetric loss in that pregnancy.

Conflict of Interest: None.

References

1. Gavin BG, Susan ER, Alya D, Gaci-Dobo M, Peter MS. Rubella and congenital rubella syndrome control and elimination-global progress,2000-2014. WHO weekly Epidemiological Record 2015;510-516.
2. Rubella vaccines: WHO position paper. *Weekly Epidemiol Rec* 2011;86:301-316.
3. BV Ramana, B Kailasanatha Reddy, DS Murty, KH Vasudevanaidu. Seroprevalance of Rubella in women with Bad Obstetric History. *J Family Med Prim Care* 2013;2(1):44-46. doi 10.4103/2249-4803.109943.
4. Lee JY, Bowden DS. Rubella virus replication and links to teratogenicity. *Clin Microbiol Rev* 2000;8(6):831-833.
5. Binnicker MJ, Jespersen DJ, Harring JA. Multiplex detection of IgM and IgG class antibodies to Toxoplasma Gondii, Rubella virus and cytomegalovirus using a novel multiplex immunoassay. *Clin Vaccine Immunol* 2010;17(11):1734-1738.
6. AE Chand, N Garg, S Rawat. Seroprevalence of Toxoplasma and Rubella infections in Bad Obstetric History patients at a tertiary care hospital. *Global J Res Analysis* 2017;6(4):711-712.
7. Gabbe SG, Niebyl JR, Simpson JL, eds. Obstetrics-normal and problem pregnancies.4th ed. New York: Churchill Livingstone, Inc 2002;1328-1330.
8. Turabadkar D, Mathur M, Rele H, Seroprevalence of TORCH infection in Bad Obstetric History. *Ind J Med Microbiol* 2003;21(2):108-110.
9. Fomda BA, Thokar MA, Farooq U, Sheikh A. Seroprevalence of rubella in pregnant women in Kashmir. *Indian J Pathol Microbiol* 2004;47(3):435-437.
10. Thapliyal N, Shukla PK, Kumar B, Upadhyay S, Jain G. TORCH infection in women with bad obstetric history-A pilot study in Kumaon region. *Indian J Pathol Microbiol* 2005;48(4):551-553.
11. Gandhoke I, Aggarwal R, Lal S, Khare S. Seroprevalance and incidence of Rubella in and around Delhi(1988—2002). *Indian J of Med Microbiol* 2005;23(3):164-167.
12. Chandy S, Abraham AM, Jana AK, Aggarawal I, Kekre A, Kaula G, Selvaraj K, Muliyil JP. Congenital Rubella syndrome and rubella in Vellore, South India. *Epidemiol Infect* 2011;139(6):962-966.
13. Padmavathy M, Mangala Gowri, Malum J, Umapathy BL, Navaneeth BV, Mohit Bhatia, Shruthi Harle. Seroprevalnce of TORCH infection and Adverse Reproductive outcome in current pregnancy with Bad obstetric history. *J Clin Biomed Sci* 2013;3((2):62-71.
14. MS Sadik, H Fatima, K Jamil, C Patil. Study of TORCH Profile in patients with bad obstetric history. *Biol Med* 2012;4(2):95-101.
15. Gong Z, Luo L, Xiao H. Preliminary study on TORCH epidemic laws in Wuhn region. *Zonghu Shi Yan He Lin Chuang Bing Du Xue Za Zhi* 1999;13(2):139-141.
16. JB Sharma, K Buckshee. Rubella Infection: a cause of fetal wastage. *J Indian Med Assoc* 1995;90(7)192:174-175.

How to cite this article: Pandey D, Gupta M. Seroprevalence and pregnancy outcome in Rubella infection in antenatal women with bad obstetric history: A case control study. *Indian J Obstet Gynecol Res* 2019;6(1):24-28.