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Original Article

Torch Infection among Females with Bad Obstetric History and its Association with Adverse Reproductive Outcomes in Current Pregnancy

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Abstract

Background: Maternal infections such as TORCH infections, syphilis, chlamydial infections, gonorrhea, and asymptomatic bacteriuria play a critical role in pregnancy wastage and their occurrence in patients with bad obstetric history (BOH) or a complicated pregnancy is a significant risk factor. At the same time, they contribute among the preventable factor. With immunoglobulin G antibody confirmed before pregnancy, there is no risk for a congenitally infected fetus. Congenital toxoplasmosis is suspected when sonography reveals findings such as hydrocephaly, intracranial, or hepatic calcifications, ascites, placental thickening, hyperechoic bowel, and growth restriction.

Objective: The aim of the study was to know the prevalence of TORCH infections in females with BOH and to find the association of TORCH infections with adverse pregnancy outcome.

Methods: Detailed clinical history, physical examination, and conventional laboratory investigations were conducted as per hospital protocol. History of any febrile illness or infections during previous pregnancies was also noted. All baseline investigations were done such as hemogram, kidney function test, liver function test, blood group, Rh type, coagulogram, urine analysis, blood sugar, thyroid stimulating hormone, triple serology, Venereal Disease Research Laboratory, antiphospholipid antibodies, antinuclear antibodies, anticardiolipin antibodies, Triple test, and TORCH test and was done in all patients included in the study. Ultrasonography obstetrics was done. ELISA is the most cost effective test to diagnose TORCH infections. 3–5 ml of blood sample was collected under aseptic precautions allowed to clot and centrifuged at 3000 rpm for 5 min.

Results: Out of 74 women studied, 63 were found to have TORCH infection of which 34 (54%) were aged between 31 and 35 years, 21 (33.3%) belonged to the age group of 36–40 years while only 8 (12.7%) women aged <30 years. History of the previous abortion was seen in 53 (84.1%) women with TORCH infection against 8 (72.7%) who did not have TORCH infection. The previous history of intrauterine death was observed in 10 (15.9%) women with torch infection against 1 (9.1%) women without any TORCH infection. The previous history of congenital anomaly was observed in 5 (7.9%) patients who had TORCH infection. The previous history of pre-term delivery was observed in 20 (31.7%) women with TORCH infection against only 3 (27.3%) who did not have any TORCH infection.

Conclusion: The present study demonstrates a strong association between the infectious agents (Toxoplasma, Rubella, and Cytomegalovirus) and BOH in women especially among young aged women.

Key words: Chlamydial infections, Gonorrhoea, Intrauterine death, Rubella, TORCH, Toxoplasma

INTRODUCTION

Pregnancy loss is a frustrating and challenging problem for couples and clinicians alike.[1] It is well realized that at least 12–15% of all recognized conceptions end in miscarriage and pre-clinical pregnancy loss rate is still higher - 22–30%.[2] The TORCH infections (Toxoplasmosis [TO], R- Rubella, C-Cytomegalovirus [CMV], and H-Herpes Simplex Virus [HSV]) can lead to severe fetal anomalies or even fetal loss. They are a group of viral, bacterial, and protozoan infections that gain access to the fetal bloodstream transplacental through the chorionic villi. Hematogenous transmission may occur at any time during gestation or occasionally at the time of delivery through maternal-to-fetal transfusion.[3] The ability of the

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fetus to resist infectious organisms is limited and the fetal immune system is unable to prevent the dissemination of infectious organisms to various tissues.[4] Early diagnosis and appropriate intervention will help in proper management of these cases.[5] The prevalence of TORCH infections varies from one geographical area to another.[6] In India, due to lack of national screening program, there are no baseline serological data regarding the presence of an antibody in TORCH infection during pregnancy.[7] Bad obstetric history (BOH) implies previous unfavorable fetal outcome in terms of two or more consecutive spontaneous abortion or history of intrauterine fetal death or intrauterine growth restriction or early neonatal deaths or congenital anomalies.[8,9]

Maternal infections such as TORCH infections, syphilis, chlamydial infections, gonorrhea, asymptomatic bacteriuria play a critical role in pregnancy wastage and their occurrence in patients with BOH or a complicated pregnancy is a significant risk factor. At the same time, they contribute among the preventable factor.[10,11] With immunoglobulin (Ig)G antibody confirmed before pregnancy, there is no risk for a congenitally infected fetus. The American College of Obstetricians and Gynecologists (2017) does not recommend prenatal screening for TO in areas of low prevalence, including the United States. Screening should be performed in immuno-compromised pregnant women, including those with HIV infection. In areas of high TO, the prevalence, for example, France and Austria-routine screening has resulted in diminished congenital disease.[12,13] Congenital *TO* is suspected when sonography reveals findings such as hydrocephaly, intracranial or hepatic calcifications, ascites, placental thickening, hyperechoic bowel, and growth restriction. Prenatal diagnosis of congenital TO is performed using PCR amplification of toxoplasma DNA in amniotic fluid.[14,15] The sensitivity of PCR varies with gestational age and is lowest before 18 weeks.[16]

CMV[17]

This DNA herpes virus eventually infects most humans. CMV is the most common perinatal infection in the developed world. There may be intrauterine or intrapartum infection or neonatal from breast feeding. Transplacental fetal infection is more likely during the first half of pregnancy. Maternal immunity does not prevent recurrences and maternal antibodies do not prevent fetal infection. Some seropositive women can also be reinfected with symptomatic congenital disease. Most infections are asymptomatic but 15% of infected adults have mononucleosis such as syndrome (fever, pharyngitis, lymphadenopathy, and polyarthritis). Immunocompromised women may develop myocarditis, pneumonitis, hepatitis, retinitis, gastroenteritis, or meningoenchephalitis.

HSV[18]

Two types of HSV have been distinguished based on immunological as well as clinical differences. Type 1 HSV accounts for the majority of non-genital herpetic infections, and Type 2 HSV is recovered almost exclusively from the genital the tract and is usually transmitted by sexual contact. More than half of the new cases of genital herpes in adolescents and young adults are now found to be caused by HSV-1 infection.[19] There is a large amount of DNA sequence homology between the two viruses, and prior infection with one type attenuates a primary infection with the other type. Approximately 70% of neonatal HSV cases are due to HSV-2 and 30% due to HSV-1.

Most primary and first-episode infections in early pregnancy are not associated with an increased rate of spontaneous abortion or stillbirth and there are no increased adverse fetal or neonatal effects after first trimester exposure. Late pregnancy primary infection results in an increased incidence of pre-term labor. Neonatal infection is acquired in three ways: Intrauterine (5%), peripartum (85%), or postnatal (10%).[20] The fetus becomes infected by virus shed from the cervix or lower genital tract. The virus either invades the uterus following membrane rupture or contacts the fetus at delivery.

Aims and Objectives

The objectives of the study are as follows:

1. To know the prevalence of TORCH infections in females with BOH
2. To know the specific TORCH infection that is more prevalent in Kashmiri women
3. To find the association of TORCH infections with adverse pregnancy outcome.

MATERIALS AND METHODS

The study entitled "Torch infection among females with BOH and its association with adverse reproductive outcomes in current pregnancy" was a prospective and cohort study that was conducted in the postgraduate Department of Gynaecology and Obstetrics, Lalla Ded hospital, Government Medical College, Srinagar, over a period of 1 ½ year after obtaining clearance from the Institutional ethical Committee and written informed consent from the patient.

Inclusion Criteria

Pregnant women with history of the previous unfavorable pregnancy outcome in terms of 2 or more consecutive spontaneous abortion, intra uterine fetal death, IUGR, congenital anomalies, in the age group of 19–36 years attending the antenatal clinic were taken for study.

Exclusion Criteria

Pregnant women with BOH of the same age group (19–36 years) attending the antenatal clinic with comorbidities which can contribute to BOH excluded, for example, (1) pregnancy-induced hypertension or chronic hypertension, (2) diabetes (Type 2 diabetes or gestational diabetes), (3) Rh incompatibility, (4) cervical incompetence, (5) antepartum hemorrhage (5a) placenta previa, (5b) abruptio placenta, and (6) syphilis.

Methodology

Detailed clinical history, physical examination, and conventional laboratory investigations were conducted as per hospital protocol. A preformed questionnaire was completed regarding parity of the patient, history of the previous abortions, gestational age at the time of abortions, history of IUGR or previous intrauterine death (IUD) or congenital malformations and type of congenital malformations or pre-term deliveries, mode of delivery and duration between pregnancies. History of any febrile illness or infections during previous pregnancies was also noted. All baseline investigations were done such as hemogram, kidney function test, liver function test, blood group, Rh type, coagulogram, urine analysis, blood sugar, thyroid stimulating hormone, triple serology, Venereal Disease Research Laboratory, antiphospholipid antibodies, antinuclear antibodies, anticardiolipin antibodies, triple test and TORCH test and was done in all patients included in the study. Ultrasonography obstetrics was done. Patients were followed till culmination of pregnancy which may be: Abortion, pre-term delivery, intrauterine death, still birth, or term delivery. Mode of delivery was noted in terms of vaginal delivery, instrumental delivery, or cesarean section and babies were followed in neonatal period. ELISA is the most cost-effective test to diagnose TORCH infections. 3–5 ml of blood sample was collected under aseptic precautions allowed to clot and centrifuged at 3000 rpm for 5 min. The serum samples were stored in small screw capped vials at 20°C. The samples were then tested for the presence of IgG and IgM antibodies against TO gondii, Rubella virus, CMV, and HSV using ELISA kits as per the kit instructions.

The recorded data were compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were express as Mean ± SD and categorical variables were summarized as frequencies and percentages. Graphically, the data were presented by bar and pie diagrams. Chi-square test or Fisher's exact, whichever appropriate, was employed for establishing association between various parameters. $P < 0.05$ was considered statistically significant. All *P*-values were two tailed.

RESULTS

In this study, a total of 74 patients were studied aged between 28 and 40 years. Majority of the patients, that is, 39 (52.7%) belonged to the age group of 31–35 years, 26 (35.1%) patients aged between 36 and 40 years, and 9 (12.2%) aged <30 years with a mean age of 34.5+3.12 years. Majority of the women were gravida 3 ($n = 36$), gravida 4 ($n = 18$), and >gravida 6 ($n = 11$) while 9 (12.2%) were gravida 5. History of the previous abortion was obtained from 63 (85.1%) women and the previous history of IUD in 11 (14.9%) the previous history of congenital anomaly in the baby were obtained from 5 (6.8%) women. Twenty-three (31.1%) women gave history of the previous pre-term delivery causing early neonatal death. Majority of women were found to have CMV, that is, 62 (83.8%) followed by rubella in 59 (79.7%), TO in 22 (29.7%) whereas herpes was observed in 5 (6.8%) patients. The prevalence of torch infection TO was observed in 4 (5.4%) patients with IgM positivity compared to 20 (27%) patients with IgG positivity. Rubella was observed in 4 (5.4%) women with IgM positivity against 58 (78.4%) women with IgG positivity. 7 (9.5%) women with CMV were positive for IgM against 61 (82.4%) women who were positive for IgG. Heperes was seen in 2 (2.7%) women with IgM positivity compared to 4 (5.4%) women with IgG positivity.

Out of 74 women studied, 63 were found to have torch infection of which 34 (54%) were aged between 31 and 35 years, 21 (33.3%) belonged to the age group of 36–40 years while only 8 (12.7%) women aged <30 years. When association of TORCH infection with age was observed, the difference was found to be statistically insignificant with p 0.733. Of the 63 women with torch infection, 29 (46%) were gravida 3, 16 (25.4%) were gravida 4, 10 (15.9%) were >gravida 6, and 8 (12.7%) women were gravida 5. The difference observed was statistically insignificant ($P = 0.756$). History of the previous abortion was seen in 53 (84.1%) women with TORCH infection against 8 (72.7%) who did not have TORCH infection. The previous history of IUD was observed in 10 (15.9%) women with torch infection against 1 (9.1%) women without any TORCH infection. The previous history of congenital anomaly was observed in 5 (7.9%) patients who had torch infection. The previous history of pre-term delivery was observed in 20 (31.7%) women with torch infection against only 3 (27.3%) who did not have any torch infection. Of the 74 studied women, term pregnancy was observed in 39 (52.7%) patients, 18 (24.3%) preterm, 10 (13.5%) had IUD, 5 (6.8%) had abortion while 2 (2.7%) delivered anomalous baby. Association of torch infection with pregnancy outcome was observed and found to be statistically significant with $P = 0.036$. Term pregnancy

Table 1: Age distribution of study patients

Patient characteristics	Number	Percentage
Age (years)		
≤30	9	12.2
31–35	39	52.7
36–40	26	35.1
Mean±SD (Range)=34.5±3.12 (28–40)		
Gravidity		
Gravida 3	36	48.6
Gravida 4	18	24.3
Gravida 5	9	12.2
≥Gravida 6	11	14.9
Obstetric history		
Previous history of abortion	63	85.1
Previous history of IUD	11	14.9
Previous history of congenital anomaly	5	6.8
Previous history of preterm delivery causing early neonatal death	23	31.1
TORCH infection		
Toxoplasmosis	22	29.7
Rubella	59	79.7
Cytomegalovirus	62	83.8
Herpes	5	6.8

IUD: Intrauterine death

Table 2: Prevalence of torch infections as per type of antibody among study patients

Type of torch infections	IgM		IgG	
	No.	% age	No.	% age
Toxoplasmosis	4	5.4	20	27.0
Rubella	4	5.4	58	78.4
Cytomegalovirus	7	9.5	61	82.4
Herpes	2	2.7	4	5.4

Table 3: Association of torch infections with age and gravidity in study patients

Patient characteristics	Torch infection		No torch infection		*P*-value
	No.	% age	No.	% age	
Age (years)					
≤30	8	12.7	1	9.1	0.733
31–35	34	54.0	5	45.5	
36–40	21	33.3	5	45.5	
Gravidity					
Gravida 3	29	46.0	7	63.6	0.756
Gravida 4	16	25.4	2	18.2	
Gravida 5	8	12.7	1	9.1	
≥Gravida 6	10	15.9	1	9.1	

was the outcome of 30 (47.6%) patients of TORCH infection, pre-term in 17 (27%) patients, IUD in 7 (14.3%) patients, abortion in 5 (7.9%) patients while as 2 (3.2%) with TORCH infection delivered anomalous baby. Of the 63 patients with TORCH infection, 30 (47.6%) had normal pregnancy outcome while of the 11 patients with no TORCH infection, 9 (81.8%) had normal pregnancy. The association between pregnancy outcome and TORCH infection was observed to statistically significant with *P* = 0.036. RR (95% CI) = 2.9 (0.804–10.32) [Tables 1-5].

Table 4: Association of torch infections with obstetric history

Obstetric history	Torch infection		No torch infection		*P*-value
	No.	% age	No.	% age	
Previous history of abortion					
Yes	53	84.1	8	72.7	0.359
No	10	15.9	3	27.3	
Previous history of IUD					
Yes	10	15.9	1	9.1	0.901
No	53	84.1	10	90.9	
Previous history of congenital anomaly					
Yes	5	7.9	0	0.0	0.752
No	58	92.1	11	100	
Previous history of preterm delivery					
Yes	20	31.7	3	27.3	0.767
No	43	68.3	8	72.7	

IUD: Intrauterine death

Table 5: Association of torch infections with pregnancy outcome

Pregnancy outcome	Torch infection		No torch infection		*P*-value
	No.	% age	No.	% age	
Normal	30	47.6	9	81.8	0.036*
Abnormal	33	52.4	2	18.2	
RR (95% CI)=2.9 (0.804–10.32)					
Term	30	47.6	9	81.8	
Preterm	17	27.0	1	9.1	
IUD	9	14.3	1	9.1	
Abortion	5	7.9	0	0.0	
Anomalous baby	2	3.2	0	0.0	

IUD: Intrauterine death, *Statistically Significant

DISCUSSION

History of the previous abortion was obtained from 63 (85.1%) women and the previous history of IUD in 11 (14.9%) and the previous history of congenital anomaly was obtained from 5 (6.8%) women. Twenty-three (31.1%) women gave history of previous preterm delivery causing early neonatal death. Singh M *et al.*, (2016)[20] did a study on 260 pregnant women in in which still births (17.4% vs. 3.8%; *P*=0.006), congenital abnormalities (8.7% vs. 0.5%; *P*=0.002), and abortions (17.4% vs. 2.7%; *P*=0.001) were more common in those positive for IgM antibodies compared to seronegatives. The IgG seropositives also showed adverse effects of abortion (31.4%), IUD (7.0%) congenital malformations (3.5%), and still birth (1.2%) in 37 out of the 86 cases (Bhatia M and Harle S, 2013)[21].

In the present study, majority of women were found to have Cytomegalovirus, that is, 62 (83.8%) followed by Rubella

in 59 (79.7%), Toxoplasmosis in 22 (29.7%) while Herpes was observed in 5 (6.8%) patients. Manjunathachar HV *et al.*, (2020)[22] found Rubella as the most prevalent infection (46.5%) followed by HSV 1 and 2 (41%), CMV (34.7%), and toxoplasmosis (6.3%). Tiwari S *et al.*, (2016)[23] conducted a study on 63 women admitted in obstetrics and gynecology ward with abortion as adverse pregnancy event in current pregnancy. Evidence of TORCH infection was seen in 66.7% of women positive for serum IgM antibodies. Maximum percentage was for HSV infection (30.10%) followed by rubella (14.2%), CMV (12.6%), and toxoplasma (9.5%). In the present study, the prevalence of TORCH infection Toxoplasmosis was observed in 4 (5.4%) patients with IgM positivity compared to 20 (27%) patients with IgG positivity. Rubella was observed in 4 (5.4%) women with IgM positivity against 58 (78.4%) women with IgG positivity. Seven (9.5%) women with cytomegalovirus were positive for IgM against 61 (82.4%) women who were positive for IgG. Heperes was seen in 2 (2.7%) women with IgM positivity compared to 4 (5.4%) women with IgG positivity. In a study by Turbadkar D *et al.*, (2003)[24], IgM antibodies were positive in 40 (10.52%) for Toxoplasma, 102 (26.8%) for Rubella, 32 (8.42%) for CMV. IgG antibodies were positive in 160 (42.10%) for Toxoplasma, 233 (61.3%) for Rubella, 346 (91.05%) for CMV. Based on the IgM positivity, Rubella is the most prevalent infection (46.5%) followed by HSV 1 and 2 (41%), CMV (34.7%), and TO (6.3%) in high-risk pregnant women having rash or any clinical signs. On the whole, the highest IgG seropositivity was recorded against CMV (88.6%), followed by Rubella (86.8%), HSV 1 and 2 (28.4%), and TO (15.2%) [Manjunathachar *et al.*,[22]

In India, the reported seroprevalence rate of TO is up to 80% (Nissapatorn *et al.*, 2011;[25] Shrivastava *et al.*, 2014).[26] In the present study, 15.2% and 6.3% pregnant women showed anti-toxoplasma IgG and IgM antibodies, respectively, whereas Shrivastava *et al.*[26] reported 9.37% and 29.68% toxoplasma IgG and IgM antibodies, respectively, in pregnant women from Indore, Madhya Pradesh. The seroprevalence of TO in different countries ranges between 7.7% and 76.7%.[25,27,28] The varying prevalence status between the geographical regions may be due to climate variability, hygiene and sanitization practices, and life standards of the people.[25-28] TO is a completely treatable infection in pregnancy with antibiotic therapy; hence, early antenatal detection and prompt treatment of infection may prevent the fetal complications. Out of 74 women studied, 63 were found to have TORCH infection of which 34 (54%) were aged between 31 and 35 years, 21 (33.3%) belonged to the age group of 36–40 years while only 8 (12.7%) women aged <30 years. When association of torch infection with age was observed, the difference was found to be statistically insignificant with $P = 0.733$. Tiwari *et al.*[23] conducted a study on 63 women admitted in obstetrics and gynecology ward with abortion as adverse pregnancy event in current pregnancy. When analyzed with respect to. age groups, in age group <20 years (18–20 years), toxoplasma IgM was found to be present in 5% suggestive of acute infection. In age group 21–25 years, toxoplasma IgM was 13.3% in age 26–30 years, IgM was 7.6%. Statistical analysis of the same has given the $P = 1.000$ (Fischer's exact test). It is a significant finding that the age group bears no relevance to IgM seropositivity if it is considered as evidence of infection responsible for adverse reproductive outcome. Similar findings have been reported by very few workers but one study by Mohammed *et al.*,[29] has very clearly shown that there is no relationship of IgM antibodies evidence in cases of abortion when TO is considered as an underlying cause 4. In an Indian study of Kaur *et al.*,[11] IgM antibodies were reported as 11.2% 5 while other studies across India, especially by Dar *et al.*[30] reported it in the range 0.7–3.1%.6 A relatively higher rate of resistance against the adverse effects of Toxoplasma infection appears to be due to improving environmental conditions and better personal habits, hygiene, and overall improving life styles of the people.

Tiwari *et al.*[23] conducted a study on 63 women. In age group <20 years, rubella IgM was found to be 5%, in 21–25 years age group, it was 20% while in age group 26–30 years, it was 15.3%. *P* value, in both the groups, is <0.05. It reflects that IgM serology status is very important as an evidence of primary Rubella infection in pregnancy. Primary Rubella infection has been reported as 4.5% by Yasodhra[31] while Surpam *et al.*[32] have reported IgM seropositivity 4.66%. Erstwhile, in Indian context, seropositivity has been reported in the range 4–17.7%. WHO estimates, across the globe, that more than 1 lakh children are born with congenital rubella syndrome each year, most of them in developing countries (Vijayalakshmi *et al.*, 2004).[33] Nearly 10–20% women in child bearing age are susceptible to Rubella and primary Rubella virus infection during pregnancy may cause fetal damage. Tiwari *et al.*,[23] also observed that in the age group <20 years, IgM seropositivity was 10% in group 21–25 years, it was 20% in age group 26–30 years, none was positive for IgM. On statistical analysis, *P* value is border line insignificant (0.055). IgM Seropositivity has been reported to be in the range 3–12.9 (Hossain *et al.*, 1986;[34] Seth *et al.*, 1971[35]). Primary CMV infection in pregnancy has a higher incidence of symptomatic congenital infection and fetal loss (Turbadkar *et al.*, 2003).[25] Demonstration of IgM antibodies is indicative of primary infection (Padmavathy *et al.*, 2013).[36] The transmission of CMV infection to fetus occurs in 40% of the cases with primary infection and results in the delivery of 10–15% symptomatic and 85–90% asymptomatic congenital-infected newborns (Singh *et al.*, 2009).[37]

CONCLUSION

TORCH series infection is one of the important causes of abnormal pregnancy outcomes. It is absolutely necessary to screen TORCH infection for women who had the histories of abnormal pregnancies to prevent birth defects and perinatal complications. TORCH testing being costly investigation cannot be done in all patient on antenatal care; therefore, selected patients with bad obstetric must be tested for TORCH. Knowledge of TORCH infection will help the clinician appropriately counsel mothers on preventive measures to avoid these infections and will aid in counseling parents on the potential for adverse fetal outcomes when these infections are present.

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