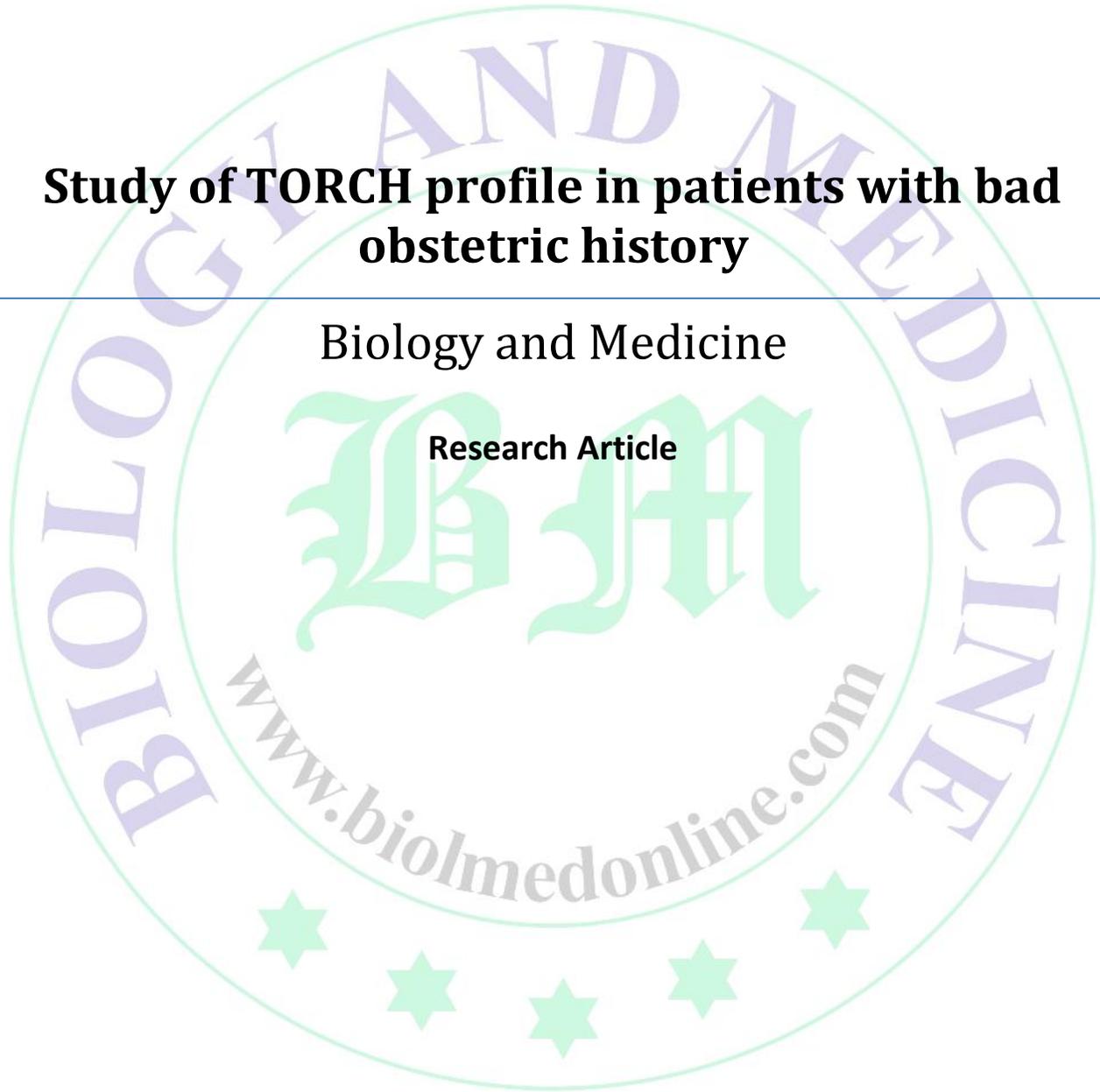


Study of TORCH profile in patients with bad obstetric history

Biology and Medicine

Research Article



Study of TORCH profile in patients with bad obstetric history

MS Sadik, H Fatima, K Jamil*, C Patil

Bhagwan Mahavir Medical Research Centre, Hyderabad, Andhra Pradesh, India.

*Corresponding Author: kj.bmmrc@gmail.com

Accepted: 24th May 2012, Published: 1st Jul 2012

Abstract

Infections caused by TORCH complex - *Toxoplasma gondii*, Rubella virus, cytomegalovirus (CMV), and herpes simplex virus (HSV) - are causes of bad obstetric history (BOH). TORCH infections are generally mild in the mother but can prove disastrous to the fetus. The degree of severity depends on the gestational age of the fetus; when infected, the virulence can damage the fetus in the developmental stages and also increase the severity of maternal disease. The aim of this study was to evaluate the incidence of TORCH infections in pregnancy wastage in women with BOH in south Indian population. This study reports the prevalence of *Toxoplasma*, Rubella, CMV, and HSV-II infections in randomly selected 86 pregnant women by demonstrating the presence of immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies using ELISA kits. Immunoglobulin M antibodies were positive in six patients (6.97%) for *Toxoplasma*, four (4.65%) for Rubella, Nil for CMV, and one (1.69%) for HSV-II. Immunoglobulin G antibodies were positive in 18 patients (20.93%) for *Toxoplasma*, 25 (29.06%) for Rubella, 20 (23.25%) for CMV, and 16 (18.60%) for HSV-II. It was evident that among the TORCH pathogens, our study group did suffer from *Toxoplasma* and Rubella to a larger extent compared with CMV and HSV-II viruses. Hence, from this study, we conclude that all antenatal cases with BOH should be routinely screened for TORCH for early diagnosis so that appropriate intervention at early stages can help in proper management of these cases.

Keywords: TORCH; bad obstetric history; ELISA; IgG; IgM

Introduction

Bad obstetric history (BOH) implies previous unfavorable fetal outcome in terms of two or more consecutive spontaneous abortions, history of intrauterine fetal death, intrauterine growth retardation, stillbirth, early neonatal death, and/or congenital anomalies (Kumari *et al.*, 2011). The causes of BOH may be genetic, hormonal, abnormal maternal immune response, and maternal infection (Turbadkar *et al.*, 2003).

The prenatal and perinatal infections, falling under the designation of TORCH complex (Nickerson *et al.*, 2012) (also known as STORCH, TORCHES, or the TORCH infections), are a medical acronym for a set of perinatal infections (Maldonado *et al.*, 2011), i.e., infections that are passed from a pregnant woman to her fetus. The TORCH infections 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 transplacentally via the chorionic villi. Hematogenous transmission may occur at any time during gestation or occasionally at the time of delivery via maternal-to-fetal transfusion (Kumar *et al.*, 2009). Primary infections caused by TORCH—*Toxoplasma gondii*, Rubella virus, cytomegalovirus (CMV), and herpes simplex

virus (HSV)—are the major causes of BOH (McCabe and Remington, 1998).

These infections usually occur before the woman realizes that she is pregnant or seeks medical attention. The primary infection is likely to have a more important effect on fetus than recurrent infection and may cause congenital anomalies, spontaneous abortion, intrauterine fetal death, intrauterine growth retardation, prematurity, stillbirth, and live born infants with the evidence of disease (Maruyama *et al.*, 2007). Most of the TORCH infections cause mild maternal morbidity but have serious fetal consequences (Stegmann and Carey, 2002). The ability of the fetus to resist infectious organisms is limited and the fetal immune system is unable to prevent the dissemination of infectious organisms to various tissues (Mladina *et al.*, 2000).

An attempt is being made in this work to find out the correlation of TORCH infection during pregnancy in the south Indian population. TORCH infections in the mother are transmissible to fetus in the womb or during the birth process and cause a cluster of symptomatic birth defects. Many sensitive and specific tests are available for serological diagnosis of TORCH complex (Stern and

Tacker, 1973); however, ELISA test is more routinely used for its sensitivity. Details of the infections caused by various organisms are as follows:

- (i) *Toxoplasma*: Most of the information on toxoplasmosis in India is on pregnancy wastage. Toxoplasma is a parasitic infectious disease caused by a protozoan *T. gondii*, which is transmitted to humans through the infection of food or water contaminated with cat faces or eating undercooked meat of the infected sheep, goat, cow, or pig and other avian species (Richard *et al.*, 2006). Identification of positive titer of immunoglobulin G (IgG) and immunoglobulin M (IgM) during pregnancy in women with previous negative titers of antitoxoplasma IgG antibodies suggests a proliferative disease condition dangerous to the fetus.
- (ii) *Rubella*: Rubella is caused by RNA virus of paramyxovirus group. It spreads mainly through family. Approximately 30%–50% fetuses of women who contact with Rubella during the first 3 months of pregnancy will be adversely affected by the virus. The Rubella virus readily invades the placenta and fetus during gestation (Coulter *et al.*, 1999). In the case of Rubella, a woman in the first 2 or 3 months of pregnancy who is exposed may develop the infection and give birth to child with serious congenital defects such as deafness and blindness (Deorari *et al.*, 2000).
- (iii) *Cytomegalovirus (CMV)*: This infection is caused by DNA virus of herpes group. The common modes of infection are through saliva (kissing), urine, stool, breast milk, and unscreened blood transmission. Cytomegalovirus is a leading cause of congenital infections and long-term neurodevelopmental disabilities among children. High maternal sero-prevalence rates have been consistently associated with high congenital infection rates. Primary CMV infection in the mother results in a substantially higher risk of congenital CMV infection in the newborn (30%–40% risk) when compared with maternal CMV reactivation infection (1%–3% risk in the newborn) (Stagno *et al.*, 1982). Fetal damage is more likely to be severe when maternal infection occurs early in pregnancy (Boppana *et al.*, 1993).
- (iv) *Herpes simplex virus (HSV)*: It is a DNA virus of the same group as CMV. Infection

in the neonate is commonly acquired by contact with the mother's infected birth canal. Incubation period for herpes virus is between 4 and 21 days (Fleming *et al.*, 1997). Primary infection of HSV enters a latent state in the nerve ganglia and may emerge later to cause recurrent active infection (Corey and Spear, 1986). Latency in nervous tissue is caused by HSV-I (Hutto *et al.* (1987). Neonatal HSV infection is usually acquired at birth, although a few infants have had findings suggestive of intrauterine infection.

Materials and Methods

The present study was conducted from January 2010 to December 2011. About 86 patients were randomly selected and included in this study on BOH. The study was approved by the institutional ethics committee, and informed consent from participants was obtained. Generally, BOH is found in pregnant mothers where her obstetric outcome is likely to be affected adversely by the nature of previous obstetric disaster. Further, it also applies to previous unfavorable fetal outcome in terms of two or more consecutive spontaneous abortion, history of intrauterine fetal death, intrauterine growth retardation, stillbirths, early neonatal death, and/or congenital anomalies. Causes of BOH may be genetic, hormonal, abnormal maternal immune response, and maternal infection. Each patient who entered the study as a case of BOH had suffered two or more consecutive pregnancy losses and was registered at anti-natal clinic with regular follow-up by their attending gynec doctors. These patients were also diagnosed for anemia, syphilis, diabetes, and chronic liver diseases by the pathologist and gynecologist.

TORCH testing using ELISA kits

After obtaining consent from each woman, 3 mL of venous blood was collected in a container with strict aseptic precautions. Serum was extracted from the blood samples by centrifugation and the sample thus obtained was used for serological evaluation of TORCH infections. TORCH IgG and IgM antibodies were detected from the serum by ELISA test kit (Cal Biotech Inc., Canada) following the instructions of the manufacturer. The optical density was read in the spectrophotometer at the peak absorbance wavelength of the substance using micro samples (200–300 μ l) (Voller *et al.*, 1978).

Interpretation of TORCH test (as defined by encyclopedia of medicine)

Results are presented as positive or negative for the antibody titer, indicating the presence or absence of IgG and IgM antibodies for each of the infectious agents tested with the panel. Generally "normal" implies a negative/ or undetectable, IgM antibody in the blood of the mother. Presence of IgM antibodies indicates either a current or recent infection. The following observations for all patients were also recorded:

Post-history: history of operation, fever, and other associated symptoms.

Personal history: habits, smoking, and alcohol.

Menstrual history: age of menarche, obstetric history, previous abortion, first trimester, second trimester, third trimester, and fourth trimester.

Family history: previous treatment.

Clinical investigation: Hb (gm %), BSL-1 (Biosafety Level Test-1 for pathogenic microorganisms) HIV, blood grouping and typing, VDRL (Venereal Disease Research Laboratory test for Syphilis), and CBP (Complete Blood Picture).

Results

Results obtained from TORCH study for Toxoplasma, Rubella, CMV, and HSV (IgG and IgM) are presented in Table 1 with respect to the age of the women. All tests have been evaluated against the reference range in the reports of the laboratory. The normal result would be normal levels of IgM antibody in the serum samples. Immunoglobulin M is one of the five types of protein molecules found in blood that function as antibodies. Immunoglobulin M is a specific class of antibodies that seeks out virus particles and it is the most common type of immunoglobulin. It is, therefore, the most useful indicator of the presence of a TORCH infection.

Demographic parameters and age distribution

It was found that incidence of Toxoplasma, Rubella, CMV, and HSV infection was more common in 25- to 30-year age group and the results are presented in Table 1. We also found that incidence of HSV was more common in the age group of 25–30 years.

Table 1: Showing Toxoplasma, Rubella, CMV, and HSV infections in various age groups.

Age in Years	IgG No. (%)		IgM No. (%)	
	Positive	Negative	Positive	Negative
Toxoplasma				
19–24	7 (8.13)	29 (33.72)	3 (3.48)	30 (34.88)
25–30	11 (12.79)	36 (41.86)	3 (3.48)	47 (54.65)
31–35	Nil (0)	3 (3.48)	Nil (0)	3 (3.48)
Rubella				
19–24	12 (13.95)	21 (24.41)	2 (2.32)	31 (36.04)
25–30	13 (15.11)	37 (43.02)	2 (2.32)	48 (55.81)
31–35	Nil (0)	3 (3.48)	Nil (0)	3 (3.48)
CMV				
19–24	9 (10.46)	24 (27.90)	Nil (0)	33 (38.37)
25–30	11 (12.79)	39 (45.34)	Nil (0)	50 (58.13)
31–35	Nil (0)	3 (3.48)	Nil (0)	3 (3.48)
HSV				
19–24	7 (8.13)	26 (30.23)	Nil (0)	33 (38.37)
25–30	9 (10.46)	41 (47.67)	1 (1.16)	49 (56.97)
31–35	Nil (0)	3 (3.48)	Nil (0)	3 (3.48)

The obstetric outcome results are presented in Table 2A–D. Results presented in Table 2A show that preterm delivery rate and stillbirth rate were mostly associated with Toxoplasma-positive (IgG and IgM) cases. It is seen from the results presented in Table 2B that preterm delivery rate and spontaneous abortions

were more associated with Rubella (IgG and IgM) cases. We found that spontaneous abortion rates were also associated with CMV (IgG positive) cases (Table 2C) as seen in cases of Rubella viruses. Herpes simplex virus (IgG positive) cases were also responsible for

preterm delivery and spontaneous abortion rates as seen in the results presented in Table 2D.

We present here the comparative studies on 86 BOH cases for TORCH; these results are presented in Table 3 (IgG and IgM titers).

Comparative studies on the outcome of BOH cases and TORCH

Table 2: Obstetric outcome of patients with TORCH infection.

Obstetric Outcome	IgG No. (%)		IgM No. (%)	
	Positive	Negative	Positive	Negative
<i>(2A) T. gondii</i>				
Full-term delivery	8 (9.30)	25 (29.06)	4 (4.65)	29 (33.72)
Preterm delivery	3 (3.48)	10 (11.62)	2 (2.32)	12 (13.95)
LSCS	4 (4.65)	14 (16.27)	Nil (0)	18 (20.93)
Stillbirth	3 (3.48)	4 (4.65)	Nil (0)	6 (6.97)
Spontaneous abortion	Nil (0)	6 (6.97)	Nil (0)	6 (6.97)
Follow-up	Nil (0)	9 (10.46)	Nil (0)	9 (10.46)
<i>(2B) Rubella</i>				
Full-term delivery	12 (13.95)	20 (23.25)	1 (1.16)	30 (34.88)
Preterm delivery	3 (3.48)	9 (10.46)	Nil (0)	12 (13.95)
LSCS	4 (4.65)	13 (15.11)	1 (1.16)	18 (20.93)
Stillbirth	1 (1.16)	6 (6.97)	Nil (0)	7 (8.53)
Spontaneous abortion	5 (5.81)	1 (1.16)	2 (2.32)	4 (4.65)
Follow-up	Nil (0)	12 (13.95)	Nil (0)	11 (12.79)
<i>(2C) CMV</i>				
Full-term delivery	9 (10.46)	23 (26.74)	Nil (0)	32 (37.20)
Preterm delivery	3 (3.48)	10 (11.62)	Nil (0)	11 (12.79)
LSCS	2 (2.32)	16 (18.60)	Nil (0)	20 (23.25)
Stillbirth	1 (1.16)	6 (6.97)	Nil (0)	8 (9.30)
Spontaneous abortion	3 (3.48)	3 (3.48)	Nil (0)	5 (5.81)
Follow-up	2 (2.32)	8 (9.30)	Nil (0)	10 (11.62)
<i>(2D) HSV-IV</i>				
Full-term delivery	5 (5.81)	27 (31.39)	1 (1.16)	30 (34.88)
Preterm delivery	2 (2.32)	10 (11.62)	Nil (0)	12 (13.95)
LSCS	4 (4.65)	15 (17.44)	Nil (0)	20 (23.25)
Stillbirth	Nil (0)	7 (8.13)	Nil (0)	7 (8.13)
Spontaneous abortion	1 (1.16)	5 (5.81)	Nil (0)	6 (6.97)
Follow-up	4 (4.65)	6 (6.97)	Nil (0)	10 (11.62)

LSCS – Lower Segment Caesarian Section

Table 3: Comparative results of TORCH.

	IgG No. (%)		IgM No. (%)	
	Positive	Negative	Positive	Negative
Toxoplasma	18 (20.93)	68 (79.06)	6 (6.97)	80 (93.02)
Rubella	25 (29.069)	61 (70.93)	4 (4.65)	82 (95.34)
CMV	20 (23.25)	66 (76.74)	Nil	86 (100)
HSV Ig	16 (18.60)	70 (81.31)	1 (1.69)	85 (98.83)

In Table 3, 86 BOH cases with the TORCH antibody (IgG and IgM) titers showed the following results:

(i) In Toxoplasma, 20.93% IgG positive, 6.97% IgM positive, 79.06% IgG negative, and 93.02% IgM negative.

(ii) In Rubella, 29.069% IgG positive, 4.65% IgM positive, 70.93% IgG negative, and 95.34% IgM negative.

(iii) In CMV, 23.25% IgG positive, 76.74% IgG negative, and 100% IgM negative.

(iv) In HSV, 18.60% IgG positive, 1.69% IgM positive, 81.31% IgG negative, and 98.83% IgM negative.

These data showed a significant statistical correlation between BOH and positive

TORCH (IgG and IgM) titer. The infections caused by TORCH organisms are grouped together because they all result in serious birth defects when transmitted from an infected mother to her fetus during pregnancy. In most healthy persons exposed to *T. gondii*, the organism causes an asymptomatic infection or mild self-limiting illness resembling infectious mononucleosis. The same pattern occurs for CMV infection. Rubella causes an acute infection with fever and rash but is self-limiting with symptoms subsiding in 2–3 days. Besides women, children and young adults are typically infected. HSV-I typically causes fever blisters. These results are presented in Table 4.

Table 4: Blood and urine profiles of patients with TORCH infections.

	IgG No. (%)		IgG No. (%)		IgM No. (%)		IgM No. (%)	
	Positive		Negative		Positive		Negative	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Toxoplasma	20 (23.25)	1 (1.16)	65 (75.5)	Nil (0)	6 (6.97)	Nil (0)	80 (93.02)	Nil (0)
Rubella	23 (26.74)	2 (2.32)	61 (70.93)	Nil (0)	4 (4.65)	Nil (0)	82 (95.34)	Nil (0)
CMV	19 (22.09)	1 (1.16)	66 (76.74)	Nil (0)	Nil (0)	Nil (0)	86 (100)	Nil (0)
HSV	5 (5.81)	1 (1.16)	80 (93.02)	Nil (0)	1 (1.16)	Nil (0)	85 (98.83)	Nil (0)

Discussion

Infections acquired *in utero* are a significant cause of fetal and neonatal mortality and an important contributor to early and later childhood morbidity (Binnicker *et al.*, 2010). In general, abnormal, or positive, findings are high levels of IgM antibody. The TORCH screen, however, can produce both false-positive and false-negative findings. We can measure the IgM levels in the blood for further confirmation of the TORCH results. Women affected with any of these diseases during pregnancy are at high risk for miscarriage, stillbirth, or for a child with serious birth defects and/or illness and also a hazard to attending staff nurses (Young *et al.*, 1983). Thus, this test is performed before or as soon as pregnancy is diagnosed to determine the mother's history of exposure to these organisms.

Primary infection with TORCH complex in pregnant women can lead to adverse outcome, which is initially unapparent or asymptomatic and thus difficult to diagnose on

clinical grounds (Devi *et al.*, 2008). This is a prospective study on 86 patients with BOH. In this study, BOH was comparatively bad for those patients with TORCH-positive titer. When a woman is infected with a pathogen during pregnancy, the normal immune response results in the production of IgM antibodies followed by IgG antibodies. Immunoglobulin M antibodies against TORCH organisms usually persist for about 3 months, while IgG antibodies remain detectable for a lifetime, providing immunity and preventing or reducing the severity of reinfection. Thus, if IgM antibodies are present in a pregnant woman, a current or recent infection with the organism is predicted.

It is evident that maternal infections play a critical role in pregnancy wastage and their occurrence in patients with BOH is a significant factor. Persistence of encysted forms of Toxoplasma in chronically infected uteri and their subsequent rupture during placenta leads to infection of the baby in the first trimester and often results in recurrent miscarriages.

Follow-up of TORCH cases

In this study, Toxoplasma was associated with 9.30% (8/86) IgG-positive and 4.64% (4/86) IgM-positive full-term deliveries, whereas 3.48% (3/86) IgG-positive, 2.32% (2/86) IgM-positive preterm delivery, and 16.67% IgG positive had stillbirth respectively. Out of these preterm deliveries, two fetuses born to the mothers with toxo IgG-positive titers had hydrocephalus, one fetus had undeveloped eyes with spongy head, and one fetus had small size head. Congenital transmission of Toxoplasma is known to occur during the acute phase of maternal infection, and the IgM antibodies were found in high levels in the maternal sera.

In Rubella, 13.95% (12/86) were IgG positive and 1.16% (1/86) were IgM positive at full-term delivery, whereas 3.48% (3/86) IgG positive and 1.16% (1/86) IgM positive preterm delivery had stillbirths. And 5.81% (5/86) IgG positive and 2.32% (2/86) IgM positive had spontaneous abortions. The rate of spontaneous abortion was more in patients with Rubella-positive titers; Rubella is a mild viral illness in children but can occasionally infect adults. Primary virus infection during pregnancy caused fetal damage.

About 10% of CMV patients with IgG positive went for full-term delivery and 3.48% (3/86) with IgG positive went for preterm delivery. 1.16% IgG positive had stillbirths and 3.48% IgG positive had spontaneous abortions.

Herpes simplex virus-positive titer was associated with 5.81% IgG positive, 1.16% IgM went for full-term, 2.32% IgG positive had preterm deliveries, and 1.16% IgM positive had spontaneous abortion. Both CMV and HSV are known to have an intrauterine route of transmission with significant mortality and morbidity.

Infections caused by TORCH — Toxoplasma, Rubella virus, CMV, and HSV — are the major cause of BOH (Sharma *et al.*, 1997). This study determined the incidence of preterm deliveries, and congenital malformation was more in patients with Toxoplasma-positive titers, while the incidence of spontaneous abortion was more in patients with Rubella-, CMV-, and HSV-positive titers. It was also found that in these patients, fever, pain in stomach, cough, and loss of appetites screen for TORCH infection In BOH, fetuses born had hydrocephalus, omphalocele, anencephaly, and multi-congenital anomalies. These patients with positive titers for TORCH were treated with antibiotics like Spiramycin, Rovamycine, and

Siflox during pregnancy by the attending gynecologist and the outcome was good.

Conclusion

In this study, we have shown the prevalence of Toxoplasma, Rubella, CMV, and HSV-II infections in pregnant women by demonstrating the presence of IgM and IgG antibodies using ELISA test. In this kind of scenario/setup, it may not be possible to screen all pregnant patients with BOH for TORCH as it is economically not possible, but all the patients with previous history or recurrent pregnancy miscarriage should be subjected to TORCH screening. In cases where antibodies are positive, the patient should be advised and counseled about the adverse effect of the TORCH infection on the fetus, due to this the complications such as congenital, malformation, abortion, stillbirth, and preterm deliveries may occur, and the affected female should be counseled with her husband regarding continuation of pregnancy and treatment. TORCH infections are associated with recurrent abortion, intrauterine growth retardation, intrauterine death, preterm labor, early neonatal death, and congenital malformation. Previous history of pregnancy wastages and positive serological reactions during the current pregnancy help to manage these cases in order to reduce adverse fetal outcome. Based on the findings of the study, it is concluded that a previous history of pregnancy wastage and the serological reactions for TORCH infections during current pregnancy must be considered while managing BOH cases to reduce the adverse fetal outcome. If an infection occurs, it needs to be treated aggressively to prevent transmission to the fetus. Hence, all antenatal cases with BOH should be routinely screened for TORCH as early diagnosis and appropriate intervention will help in proper management of these cases.

Ethical Approval

The patients' consent was obtained before this study.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgement

The authors thank all the participants/patients who cooperated with them to undertake this study.

References

- Binnicker MJ, Jespersen DJ, Haring JA, 2010. Multiplex detection of IgM and IgG class antibodies to *Toxoplasma gondii*, Rubella virus, and cytomegalovirus using a novel multiplex flow immunoassay. *Clinical and Vaccine Immunology*, 17(11): 1734–1738.
- Boppana SB, Pass RF, Britt WJ, 1993. Virus-specific antibody responses in mothers and their newborn infants with asymptomatic congenital cytomegalovirus infections. *The Journal of Infectious Diseases*, 167(1): 72–77.
- Corey L, Spear PG, 1986. Infections with herpes simplex viruses (1). *The New England Journal of Medicine*, 314: 686–691.
- Coulter C, Wood R, Robson J, 1999. Rubella infection in pregnancy. *Communicable Diseases Intelligence*, 23: 93–96.
- Deorari AK, Broor S, Maitreyi RS, Agarwal D, Kumar H, Paul VK, *et al.*, 2000. Incidence, clinical spectrum, and outcome of intrauterine infections in neonates. *Journal of Tropical Pediatrics*, 46(3): 155–159.
- Devi KS, Devi YG, Singh NS, Singh AM, Singh ID, 2008. Seroprevalence of TORCH in women with still birth in RIMS hospital. *Journal of Medical Society*, 22: 2–4.
- Fleming DT, McQuillan GM, Johnson RE, Nahmias AJ, Aral SO, Lee FK, *et al.*, 1997. Herpes simplex virus type 2 in the United States, 1976–1994. *The New England Journal of Medicine*, 337: 1105–1111.
- Hutto C, Arvin A, Jacobs R, Steele R, Stagno S, Lyrene R, *et al.*, 1987. Intrauterine herpes simplex virus infections. *The Journal of Pediatrics*, 110(1): 97–101.
- Kumar V, Abbas AK, Fausto N, Aster J, 2009. Robbins & Cotran, *Pathologic Basis of Disease* (8th Edition). Philadelphia, PA: Elsevier, p. 480.
- Kumari N, Morris N, Dutta R, 2011. Is screening of TORCH worthwhile in women with bad obstetric history: an observation from eastern Nepal. *Journal of Health, Population, and Nutrition*, 29(1): 77–80.
- Maldonado YA, Nizet V, Klein JO, Remington JS, Wilson CB, 2011. Current concepts of infections of the fetus and newborn infant. In *Infectious Diseases of the Fetus and Newborn Infant* (7th Edition). Eds., Remington JS, Klein JO, Wilson CB, Nizet V, Maldonado YA, Philadelphia, PA: Elsevier Saunders, pp. 1–23.
- Martin RJ, Klaus MH, Fanaroff AA, Walsh MC, 2006. *Neonatal and Perinatal Medicine: Disease of the Fetus and Infant* (8th Edition). Mosby and Elsevier, Philadelphia, pp. 993–995.
- Maruyama Y, Sameshima H, Kamitomo M, Ibara S, Kaneko M, Ikenoue T, *et al.*, 2007. Fetal manifestations and poor outcomes of congenital cytomegalovirus infections: possible candidates for intrauterine antiviral treatments. *Journal of Obstetrics and Gynaecology*, 33(5): 619–623.
- McCabe R, Remington JS, 1988. Toxoplasmosis, the time has come. *The New England Journal of Medicine*, 318: 313–315.
- Mladina N, Mehikic G, Pasic A, 2000. Torch infections in mothers as a cause of neonatal morbidity. *Medical Archives*, 54(5–6): 273–276.
- Nickerson JP, Richner B, Santy K, Lequin MH, Poretti A, Filippi CG, *et al.*, 2012. Neuroimaging of pediatric intracranial infection, Part 2: TORCH, viral, fungal, and parasitic infections. *Journal of Neuroimaging*, 22(2): e42–e51.
- Sharma P, Gupta T, Ganguly NK, Mahajan RC, Malla N, 1997. Increasing toxoplasma seropositivity in women with bad obstetric history and in new borns. *The National Medical Journal of India*, 10(2): 65–66.
- Stagno S, Pass RF, Dworsky ME, Henderson RE, Moore EG, Walton PD, *et al.*, 1982. Congenital cytomegalovirus infection: the relative importance of primary and recurrent maternal infection. *The New England Journal of Medicine*, 306(16): 945–949.
- Stegmann BJ, Carey JC, 2002. TORCH infections. Toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), Rubella, cytomegalovirus (CMV), and herpes infections. *Current Women's Health Reports*, 2(4): 253–258.
- Stern H, Tacker SM, 1973. A prospective study of cytomegalovirus infection in pregnancy. *British Medical Journal*, 2(5861): 268–270.
- Turbadkar D, Mathur M, Rele M, 2003. Seroprevalence of torch infection in bad obstetric history. *Indian Journal of Medical Microbiology*, 21: 108–110.
- Voller A, Bartlett A, Bidwell DE, 1978. Enzyme immunoassays with special reference to ELISA techniques. *Journal of Clinical Pathology*, 31: 507–520.
- Young AB, Reid D, Grist NR, 1983. Is cytomegalovirus a serious hazard to female hospital staff? *The Lancet*, 321(8331): 975–976.