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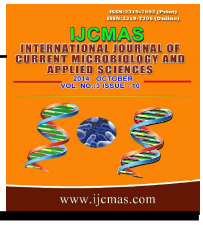

Original Research Article

Study of TORCH infections in women with Bad Obstetric History (BOH) in Kirkuk city

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Keywords

Toxoplasma, Cytomegalo-virus, Rubella, Herpes, Bad obstetric history, abortion

A B S T R A C T

Bad obstetric history(BOH) is specific to women specially during childbearing age, causes by TORCH group (*Toxoplasma gondii*, Rubella virus, Cytomegalovirus (CMV), Herpes simplex virus) and others agents like *Chlamydia trachomatis,Treponema pallidum, Neisseria gonorrhoeae, HIV,*etc. The present study was conducted to verify role of TORCH infections in women with bad obstetric history (BOH) in Kirkuk Province and to assess relationship between TORCH and women age, body mass index, contraception, drug use, number of family members in addition to type of laboratory tests. A total of 252 women with BOH were enrolled the study, they were aging from 15 to over than 46years. ELISA and rapid lateral immune-chromatography assay(RLICA) were applied on test group and on 65 sera of women without BOH. Results: the overall of TORCH was 71.82%. This rate contributed the following rates 34.92%, 26.68%, 21.03 %and 16.06 % for *CMV, Toxoplasma gondii, Rubella and HHSV-2* respectively, with high frequency of stillbirths 94.11 %, incomplete miscarriages74.07% specially (preterm labour 88.88%) P<0.05. Relationship between women age and TORCH distribution was significant specially women aging from 15 to 25 years with high occurrences of HHSV-2 and *Toxoplasma* 13.13 % and 7.14 % respectively. Frequency of TORCH positive according to gestational periods of pregnancy was significant especially high rate of *Toxoplasma* IgM 27.77% in first trimester and 66.66% of HHSV-2 IgM in third trimester of pregnancy. The efficacy of ELISA test was higher than RLICA in detecting TORCH infections P<0.05. Relationships between TORCH and Body mass index, use of contraception, women family number were not significant P>0.5, while it was significant with women use of fertility drugs prior to child conceiving p<0.05. Conclusions: The present study demonstrates a strong association between the infectious agents (Toxoplasma, Rubella and CMV) and BOH in women especially among young aged women. ELISA test is more efficacious than RLICA in demonstrating TORCH elements antibodies .

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; Sadik *et al.,* 2012). The causes of BOH may be genetic, hormonal, abnormal maternal immune response, and maternal infection. 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. Infections caused by TORCH (*Toxoplasma gondii, Rubella* virus, *Cytomegalovirus (*CMV), *Herpes simplex* virus (HSV), and others agents like *Chlamydia trachomatis, Treponema pallidum, Neisseria gonorrhoeae,* HIV, etc. are the major causes of BOH. (Turbadkar *et al.,* 2003; McCabe and Remington, 1988). These pathogens usually cause only asymptomatic or mild infection in mother, but can cause much more serious consequences in fetus (Kaur *et al.,* 1999).

The prevalence of these infections varies from one geographical area to another. These maternal infections can be established by demonstration of specific IgM antibodies. *Toxoplasma gondii*is an obligate intracellular parasite, which affects a wide-range of mammals including human. Based on serological studies, *T. gondii* is one of the most prevalent protozoan parasites (Kijlstra and Jongert, 2008). High prevalence of the infection have been reported among pregnant women and women of childbearing age from different foci in Latin America, parts of Eastern / Central Europe, the Middle East, parts of south-east Asia and Africa (Al-Tantawi, 2014). Most cases of toxoplasmosis are asymptomatic or mild and influenza-like, but immune-compromised patients often develop fulminating life-threatening symptoms as pneumonia and encephalitis (Weiss and Dubey, 2009) primary infection during pregnancy may cause spontaneous abortion or stillbirth. In utero infection may cause congenital toxoplasmosis with ocular and neurological manifestations (Montoya and Liesenfeld, 2004). Maternal CMV is the commonest viral infection in perinatal period and is the leading cause of congenital CMV infection (Padmavathy et al., 2013) .The incidence of congenital CMV ranges from 0.5- 3.0% in all live births. Primary HSV infection during first half of pregnancy is associated with increased frequency of spontaneous abortion, still birth, and congenital malformation (Hamdan et al., 2011).

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).

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 (Salman, 2014a). Neonatal HSV infection is usually acquired at birth, although a few infants have had findings suggestive of intrauterine infection.

Materials and Methods

1. Time and location: From 1st November 2013 to 30th June of 2014 a cross sectional study was carried on in Ibn-Nafies Private medical laboratory-Kirkuk city-Iraq.

2-Patients selection and blood sampling: Two groups of women were selected by obstetricians and gynaecologists in private clinics, they referred to laboratory. Prior to blood sampling a special questionnaire was completed for each patient, which contains all required informations. Women entire the study were classified into two groups: **first** group include 252 women with Bad Obstetrician History (BOH), whom they suffering from previous abortions, congenital abnormalities and some women included the group with recent abortion. **Second** group: involve 65 women without previous or recent abortion, or any signs BOH. All women participate the study, their age were from 15 years to 46 years over. For each woman in 2 groups; 5ml of venous blood samples were drawn. Sera were extracted after centrifugation and kept at -20 ^{0} C till to use. The serological tests were done using IgM and IgG ELISA kits purchased from BioCheck, Inc, 323 Vintage Park Dr, Foster City, CA 94404.

Table.1 Women descriptions enrolled the study

Informations	Number		Informations	Numbers
Total number examined with BOD	252		Type of delivery Normal delivery Lower Segment Caesarian Section No delivery (Pregnant)	 176 38 38
Control group without BOD	65		Other diseases Hypertension (HT) Diabetes Mellitus (D.M) D.M +HT	 18 8 3
Age ranges 16 up to 46 years	28.9 ± 1.2		Child conceiving state Gravida Parity	 717 273
Body mass index: Weight /kg Length /CM	 67.29± 2.6 159.19±1.8		Number of family average	2.91 ±0.39
Previous abortions Single abortion Double abortion Triple abortion More abortion Without abortion	183 56 76 43 8		Use of contraception Pills IUCD Protective condom No contraception use	56 19 7 28 198
Genital infections	16		Rhesus blood group	24

The kits were used to detect anti-IgM and IgG specific for *Toxoplasma gondii*, *CMV, Rubella and HHSV-2,* in accordance with the manufacturer's instructions ELISA procedures for *Toxoplasma*, and *HHSV* and according to (Salman, 2007). The sero-titers were interpreted as Non-reactive (<0.9), Equivocal (0.9-1.1) and Reactive (>1.1)as per the literature supplied along with the kits..Also rapid lateral immune - chromatography assay(RLICT) as a direct screen test for TORCH, (this test is rapid depending on the immune complex color line between the antigen present in serum with antigen coated on chromatography paper). Both ELISA and RLICT TORCH were applied also on 65 sera in control group.

Statistical analysis: The data processing was done by using Statistical Package of Social Science (SPSS) version16.Data description was presented as means with their standard errors (SE) and standard deviation (SD) were calculated to reflect the size and precision of the estimated values. The independent sample t-test of significance was used for the comparison between two groups. The lowest level of significance chosen to be when the probability (p) was less than or equal to 0.05($p \leq 0.05$).

Result and Discussion

The history of the 252 BOH consisted of incomplete miscarriages in 27(10.71 %), missed miscarriage in 86 (34.12 %), intrauterine fetal death (IUFD) in 34(13.49 %), threatened miscarriages in 31(12.30 %), Intrauterine growth retardation (IUGR) in 20 (7.93 %) and preterm labour in 18(7.14 %). Out of 252 BOH cases 181(71.82%) and out of the 65 healthy controls 6(8%) were serologically positive for one of the TORCH infections. Sero-positivity rate in women with BOH is significantly higher than in normal healthy controls, P<00.5 . It is obvious from the results in Table 1, that TORCH frequency were higher is sera of women with stillbirth and preterm labour, that contributed the following rates 94.11 % and 88.88 % respectively .While lower rate 63.15% was recorded in sera of women with congenital anomalies ,P>0.05.

Table.1 Frequency of positive TORCH according to types of presentations to obstetrician

Type of presentations	Number	Percentages %	TORCH		Torch negative	
			Positive	percentages	negative	percentages
Incomplete miscarriages	27	10.71	13	48.14	14	51.86
Threatened	31	12.30	22	70.96	9	29.03
Missed	86	34.12	61	70.93	25	29.06
IUGR	20	7.93	14	70.00	6	30.00
IUFD	34	13.49	27	79.41	7	20.61
Preterm labour (PTL)	18	7.14	16	88.88	2	11.11
Congenital malformation	19	7.53	12	63.15	7	36.85
Stillbirths	17	6.74	16	94.11	1	5.89
All total	252	100	181	71.82 *	71	28.18

*P<0.05

Regarding women ages in relation to TORCH infections: positive *Toxoplasma* IgM antibodies, *CMV, Rubella and HHSV-2* were highly observed in sera of women aging from 16 to 25 years, contributing the following rates 77.78 % 50 %, 75 % and48.58% for each respectively. P<0.05. Compare to high rates 83.34 %, 53.755 were recorded for HHSV-2 IgG antibodies among women aging from 36 to 46 years and for CMV IgG among women aging from 26 to 35 years respectively. While Toxoplasma gondii and Rubella positive IgG, 51.92 % and 46.93 % were recorded among women aging from16 to 25 years, Table 2.

Table.2 Distribution of *Toxoplasma gondii,Cytomegalovirus, Rubella* and Herpes simples virus type-2(HHSV-2) in relation to women age

Age in years	**IgG Number (%)**		**IgM Number(%)**		**All total positive(%)**
	Positive	**Negative**	**Positive**	**Negative**	
Toxoplasma gondii	**52(20.63) a**	**200(79.37) a**	**18(7.14) a**	**234(92.86) a**	**68(26.98)a**
16 to 25	27 (51.92)	45(22.5)	14 (77.78)	32(13.67)	41(16.26)
26 to 35	16 (30.76)	89 (44.5)	1 (5.55)	79 (33.76)	17(6.74)
36 to 46	9 (17.30)	66 (33.0)	2 (11.11)	123 (52.56)	11(5.36)
Cytomegalovirus	**80(31.74) b**	**172(68.34) b**	**8(3.17) b**	**244(96.83) b**	**88(34.92) b**
16 to 25	31 (38.75)	32(18.60)	4 (50)	43 (17.62)	34(13.49)
26 to 35	43 (53.75)	92 (53.48)	2 (25)	102 (41.80)	45(17.185)
36 to 46	6 (7.50)	48 (27.90)	2 (25)	99 (40.57)	8(3.17)
Rubella	**49(19.44) c**	**203(80.66) c**	**4(1.58) c**	**24**7(98.42) c	**53(21.03) c**
16 to 25	23 (46.93)	32 (15.76)	3 (75)	40(16.19)	26 (10.31)
26 to 35	19 (38.78)	97 (47.78)	1(25)	142(57.48)	20 (7.93)
36 to 45	7 (14.28)	74 (36.45)	Nil(0)	59 (23.88)	7 (2.77)
HHSV-2	**6(2.38) d**	**245(97.62) d**	**35(13.33) d**	**217(86.77) d**	**41(16.26) d**
16 to 25	1 (16.66)	37 (15.10)	17(48.58)	26 (11.98)	18(7.14)
26 to 35	Nil(0)	76 (31.02)	14 (40.00)	87(40.09)	14(5.55)
36 to 46	5 (83.34)	132 (53.88)	4 (11.42)	102 (47.00)	9 (3.57)

a,b,c,d : number examined from all total of 252 sera.

Considering role of laboratory tests for Detecting antibodies related to TORCH, Table 3 exerting that high rate of TORCH positive 29.76 % was recorded in sera of women by using ELISA technique, while rapid lateral immune-chromatography test reveal 8.0% of TORCH positive<0.05.

Table.3 Comparison between ELISA method and rapid lateral immune-chromatography assay (RLICA) in detecting TORCH IgM antibodies in sera of women with BOD

Type of tests	Total		Positive		Negative	
	No.	%	No.	%	No.	%
ELISA	252	100	75	29.76 *	177	70.24
RLICA	75	29.76	6.0	8.0	69	92.00

* P<0.05

Table.4 Frequency of TORCH positive according to trimesters of pregnancy

Period of gestations	Total No. (%)	Toxo. gondii		CMV		Rubella		HHSV-2	
		IgG	IgM	IgG	IgM	IgG	IgM	IgG	IgM
First trimester	18 (47.36)	3 (16.66)	5 (27.77)	5 (27.77)	1 (5.55)	3 (16.66)	0 nil	0 Nil	3 (16.66)
Second trimester	11 (28.94)	5 (45.45)	2 (18.81)	5 (45.45)	0 nil	5 (45.45)	1 (9.09)	1 (9.09)	5 (45.45)
Third trimester	9 (23.68)	5 (55.55)	2 (2.22)	3 (33.33)	1 (11.11)	5 (55.55)	1 (11.11)	0 Nil	6 (66.66)
Total	38	18 (47.36)	9 (23.68)	13 (34.21)	2 (5.26)	13 (34.21)	2 (5.26)	1 (2.63)	14 (36.84)

Table.5 TORCH positive and percentage according to contraception, infertility drugs use and number of family members

	TORCH +Ve	% +ve	Toxoplasma No.(%)	CMV No.(%)	Rubella No.(%)	HHSV-2 No.(%)
Contraception						
Pills	10	3.96	1 (10)	8 (80)	2 (20)	1 (10)
IUCD	10	3.96	3 (30)	5 (50)	4 (40)	3 (30)
Condom	0	Nil	nil	nil	nil	nil
Hypertension	2	0.79	1 (50)	1 (50)		
Diabetes	1	0.39	1			
Infertility drugs	32	12.69	11 (34.37)	15 (46.87)	7 (21.87)	7 (21.87)
Number of family member						
1	4	1.58	1 (25)	2 (50)	0 (nil)	1 (25)
2	30	11.90	6 (20)	13 (43.33)	5 (16.66)	6 (16.66)
3	43	17.06	12 (27.90)	18 (41.86)	6 (13.95)	7 16.27)
4	9	3.57	3 (33.33)	4 (44.44)	2 (22.22)	0 (nil)
5	6	2.38	1 (16.66)	3 (50)	1 (16.66)	1 (16.66)
6	2	0.79	1 (50)	1 (50)	nil	nil
7	2	0.79	1 (50)	1 (50)	nil	nil
8	1	0.39	nil	nil	nil	1 (100)

From a total of 252 sera examined for TORCH, only 38 women were pregnant, they contributed according to gestational periods as 18 women in first trimester,11 women in second trimester and 9 women in third trimester of gestation. The examination of their sera reveals the following results: for Toxoplasma antibodies 27 sera show positivity of 47.36% for IgG and 23.68 % for IgM with high frequency of IgG (55.55) in sera of women in third trimester of gestation, while high rate of Toxo-IgM

27.77% was recorded in first trimester of gestation , P<0.05. Regarding CMV high rates of IgG and IgM were recorded among women in second and first trimester of gestation respectively. Considering rubella high rate 55.55% of IgG was found among women in third trimester controversy to 16.66 % of IgM among women in first trimester of gestation. Statistically HHSV-2 IgM total rate 36.84% was significant to HHSV-2IgG that seen only in one sera with the rate of 2.63 % P<0.05 (Table 4).

Table 5 is showing distribution of Torch agents and Torch positive according to: contraception use prior to gestation and getting BOH later; the more common cause to BOH was CMV among women whom they were taken either oral pills or injections 80 %, followed by 50 % of CMV among women previously use IUCD, while wearing protective condom by women husbands not reveal any case of Torch positive. Relationship between number of family members and Torch agents and positivity were high among women their family consisting of 2, 3 and 4 member especially with CMV infections, the rates were:43.33%,41.86 %and 44.44 % respectively,P<0.05.

The rate of TORCH positive 71.82 % in sera of women is very high, this result is indicating, that infections by TORCH elements were 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). Specially stillbirths 94.11 %, incomplete miscarriage 74.04% and complete 48.14% miscarriages . The overall of TORCH in the present study is high comparing to 12% recorded by (Padmavathy *et al.,* 2013) in India. 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 placentation lead to infection of the baby in the first trimester and often to recurrent miscarriages (Surpam *et al.,* 2006). In the present study Toxoplasma antibodies which is a known etiological agent in recurrent pregnancy wastage was found in 26.83% of women sera with BOH. The all rate of *Toxoplasma* infection among women was high, this reflects degree of environment contamination with the oocysts of cat, the final host and water contamination with the infective especially in area when water chlorination and filtration process were not continuously used. Or might be due to fact that in most miscarriages or even during caesarian section cases, blood transfusion was applied without checking for *Toxoplasma* antibodies . In addition to chance of exposure to *Toxoplasma* during usage of syringes or blood lancets (Salman, 2007d). The overall rate of toxoplasmosis in present study is similar to what has been reported by (Al-Rawi *et al.,* 2012) in Ramadi-Iraq, while it was not agree with 38.98 % and 31.25 % of toxoplasmosis in Kirkuk city recorded by (Salman, 2014a,b) respectively. In other studies carried out in Iraq regarding toxoplasmosis were higher than the rate of the present study, the rates were 62.5 %,55.56 %, 36.57 % and33.42 % recorded in Kirkuk Province by (Noori, 2012, Ali, 2000, Al-jubori, 2005; Othman, 2004). Variances may be due to difference in sample size, test used for diagnosis, population characteristics of each governorates and their exposure to relevant risk factors, laboratory tests, technical errors and immune state of the patients. Toxoplasma IgM antibodies rate 7.14 % also critical to women aging from 16 to 25 years in this study and if they were not aborted, it will be dangerous and highlighting post-

delivery outcomes of toxoplasmosis. This rate is agreed with 6.91 % recorded by (Sadik *et al.,* 2012) in India. Controversy to 42.15% of Toxo-IgM recorded in India by Chopra *et al.,* 2004. Interpretation of high rate of sero-positive CMV 34.92 % required understanding the fact, that CMV has the capability to persist in its human host indefinitely as latent infection in several glands and the kidneys (Collennberge et al., 2006). In addition, CMV has ability of escaping host defenses specially, when CMV establish latency in host cells allowing the virus to persist without triggering immune responses, in addition the virus has ability to encodes protein that enable it down regulate the MHC and to inhibit NK cell killing. The result of the present study is disagree with that recorded in India by (Rubina *et al*,.2004), whom they record 15.98 % of seropositive CMV, the difference may be due to very large score of sampling 1918 samples. The result of CMV IgM is not agree those recorded by (Sadik *et al.,* 2012 and Padmavathy *et al.,* 2013) whom they record the following rates (0 % and 9.2 %) respectively. Although the rate of sero-positive of RV in the present study is high 21.2% that contributing 1.58 % of rubella IgM antibodies and 19.44 % of Rubella IgG antibodies. The later may considered protection against previous infection, because it is fact that Rubella infection mostly produce lifelong immunity so as CMV doing (Salman, 2007). While 1.58 of Rubella IgM had value during gestation which may lead to abortion or post-delivery outcomes . The rate of IgM is but it is very low when it was compared to that recorded in Australia by (Nicoloas, 2005), whom they recorded the ranged rate (84.2% to 96.5 %) from testing 220 blood samples using mini-vides kit. The results obtained in the present study showed that the overall rate of 16.26% for HHSV infections (IgM-13.33% and IgG-2.38%) is critical for women in third trimester especially IgM, because it means acute infection with probability of transmitting the infection to fetus during passage through birth canal at the time of delivery (post-delivery outcomes such as pneumonia, conjunctivitis). HHSV-IgG mostly indicate protection with probability of sero-conversion from latency in some cases (Salman, 2007). In addition to high records of HHSV-2 IgM positive in sera of 17 young aged women from a total of 41 is highlighting the exposure to degree of sexually transmitted diseases (STD) in women community in this province, and the predisposing factors might be attributed to sexual activities, hormonal changes, use of contraception or bad care in ignoring contraceptive methods by men. Furthermore it might be the fact that most of HHSV-2 infections were asymptomatic. The result of HHSV-2 in present study was lower than that recorded in Tikrit-Iraq by (Aljumiali *et al.,* 2013), whom they found 24.2% of HHSV-2 among 538 sera of women with BOH. Pregnant women in the present study contributing 15.07% (38 women), all this population is small size, but finding of 36.84% of HHSV-2 and 23.68% of Toxoplasma IgM antibodies reflects the degree of injury facing pregnant women specially. Toxoplasmosis rate 27.77% among women in first trimester of gestation, while high rate of HHSV-2 among women in third trimesterof gestation 66.66% give rises idea of postnatal infections. Drug that used for treatment of women infertility prior to conceiving had role in women getting TORCH positive specially CMV and *Toxoplasma*, this might be attributing to adverse effect of some infertility drug due to bad sanitation level of some women in Kirkuk city. Regarding high efficacy of revealing TORCH in the present study than RLICA can be explained by using sandwich ELISA method which has produce high

affinity between TORCH antibodies and solid face antigen in the bottom of ELISA well than the reaction between antigen coated on immbolized antibodies in chromatochraphy device in addition the later test not require substrate that present in ELISA method which enhance and encourage binding between TORCH antibody in serum with specific antigen in solid phase. (Ali, 2008). Relationships between TORCH and number of family member, body mass index, contraception were not significant.

The present study demonstrates a strong association between the infectious agents (Toxoplasma, Rubella and CMV) and BOH in women specially among young aged women. It is therefore recommended that all antenatal cases with such history should be routinely screened for these agents. Early diagnosis will help in proper management of the cases. This study also emphasizes the need for immunization in prospective mothers and adolescent girls who have not received MMR vaccine in their childhood.

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