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The association of ToRCH infection and congenital malformations: A prospective study in China

Yuanyuan Wang[a], Shaoping Li[a], Nana Ma[a], Quanhua Zhang[a], Haiyan Wang[b], Jingjing Cui[a], Shijin Wang[a,*]

[a] Department of Gynaecology and Obstetrics, The First Affiliated Hospital of Xinxiang Medical University, Xinxiang, 453000, China
[b] Department of Ultrasound, The First Affiliated Hospital of Xinxiang Medical University, Xinxiang, 453000, China

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ABSTRACT

Objective: ToRCH infections (toxoplasmosis, rubella, cytomegalovirus and Herpes simplex virus) have long been known to be associated with bad obstetric outcomes. Little information is available about the impact of ToRCH infection on reproduction in china nearly for ten years. We designed a prospective study among 1863 pregnant women to investigate the association of ToRCH infection and congenital malformations.

Study design: All participants had set up a maternal health Handbook and were managed through the maternal and child health care system. They underwent regular pregnancy check-up, including physical measurements (weight, abdominal circumference and blood pressure), laboratory examinations (blood, urine) and ultrasound scan. ToRCH IgM antibodies were tested by chemiluminescence immunoassay.

Results: 102 participants were infected with ToRCH and the total infection rate was 6.06% (102/1683). CMV infection rate (3.15%, 53/1683) was the highest. The positive rate of ToRCH IgM antibodies increased significantly in participant with upper respiratory tract infection (14.6%, 32/219) or with adverse pregnancy history (4.8%, 70/1464). Among 85 ToRCH infected participants, adverse pregnancy outcome were observed in 57 cases which included abortions (31.8%, 27/85), premature births (8.2%, 7/85), congenital malformations (12.9%, 11/85), and stillbirths (9.4%, 8/85). Furthermore, congenital malformations was much higher than that in those without ToRCH infection (1.1%, 17/1598) ($P < 0.001$).

Conclusion: ToRCH infection was a significant risk factor of severe damage to the fetus, especially congenital malformations. ToRCH screening for pregnant women can reduce the incidence of adverse pregnancy and prevent birth defects in china.

Introduction

Toxoplasma gondii, Rubella virus, Cytomegalovirus and Herpes simplex viruses (type 1 and 2) were classified as ToRCH pathogens by Nalimias in 1971 [1]. They are some of the most common infectious agents associated with adverse pregnancy outcomes. Toxoplasma gondii is usually an asymptomatic and benign infection in immunocompetent individuals, but during pregnancy, the infected women may undergo miscarriage, stillbirth, and intrauterine malformations in the fetus [2–4]. Like Toxoplasma gondii, Rubella virus can cause a series of severe damage to the fetus, including hearing impairment, cataracts, and cardiac defects, collectively known as congenital rubella syndrome (CRS) [5,6]. Cytomegalovirus is a kind of common virus with species-specific. Humans are the hosts of this virus, which can infect the same type of virus again, as well as its variant type. The virus transmits through direct contact with saliva, urine and genital secretions. It is considered to be the most common cause of viral intrauterine infections, accounting for 0.3–2.4 per cent of all live births. Primary CMV infection during pregnancy has the highest intrauterine transmission risk, which can lead to severe fetal damage, such as growth retardation, microcephaly, and intracerebral calcifications [7–9]. HSV is the most common sexually transmitted viral disease (STD) worldwide. HSV-1 is transmitted during childhood by non-sexual contacts, while HSV-2 is always transmitted sexually and is the major cause of genital herpes [10–12]. About 70% of neonatal HSV infections are caused by HSV-2. The most common route of infection is by contact with herpetic lesions in the birth canal during delivery [13]. Transplacental infection of the fetus with HSV may rarely cause spontaneous abortion, intrauterine growth retardation, or congenital malformations [14].

* Corresponding author.
E-mail address: 13569858153@163.com (S. Wang).

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Now many developed countries have listed ToRCH testing as a routine screening program for pregnant women. Furthermore, the outbreak of intrauterine infection with Zika virus in Brazil, which has led to microcephaly in newborns, has again aroused global concern about ToRCH infection [15]. However, little information is available about the impact of ToRCH infection on the outcome of pregnancy in china over the last decades. In this study, we designed a prospective study among 1863 pregnant women to investigate the correlation between ToRCH infections and abnormal pregnant outcomes (Fig. 1). The results showed that ToRCH infection was a significant risk factor of severe damage to the fetus, especially congenital malformations. The present study provides information that ToRCH screening and appropriate intervention for pregnant women can reduce the incidence of adverse pregnancy and prevent birth defects in china.

Material and methods

Study population

A prospective study was designed that included 1863 pregnant women, belonging to all classes of society, in the age group of 19–43 years (average 29.7) and the gestational age is 6–20 weeks, attending the antenatal clinic in the First Affiliated Hospital of Xinxiang Medical University, from January 2017 to August 2018. Detailed information was showed in Table 1.

Pregnancy check-up

All pregnant women had set up a maternal health handbook and were managed by maternal and child health care system. They underwent regular pregnancy check-up, including physical measurements(weight, abdominal circumference and blood pressure), laboratory examinations (blood, urine) and ultrasound scan.

Serological detection

The elbow vein blood of participants was collected (3 mL) for ToRCH IgM antibodies test. ToRCH IgM antibodies were measured with an automated chemiluminescence immunoassay (LIAISON XL; DiaSorin, Italy). Samples with concentrations of anti-TOX IgM ≥8 AU/mL, anti-RV IgM ≥25 AU/mL, anti-CMV IgM ≥22 U/ mL and anti-HSV (types 1 and 2) IgM ≥1.1 Index were considered as positive. The local ethics committee approved the study.

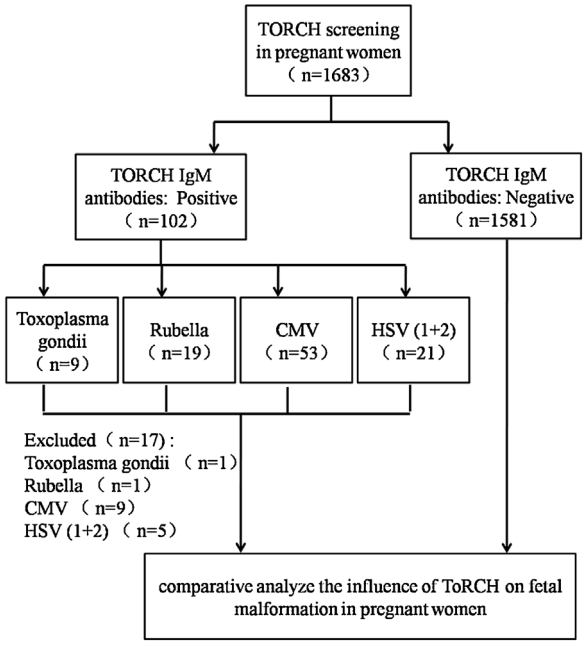

Fig. 1. Flow of participants.

Table 1
Demographic profile of the pregnant women.

Risk factors	Variables	No. (*Total* = 1683)	Percentage (%)
Age	<20	52	3.1
	20–39	1468	87.2
	>40	163	9.7
Education level	Less than diploma	996	59.2
	Diploma and above	687	40.8
Job	House holder	146	8.7
	Practitioner	1537	91.3
Region	City	1123	66.7
	Rural area	560	33.3
Family income	< 5,000	189	11.2
	5000–10,000	1267	75.3
	> 1,0000	186	14.5
Dietary habits[a]	Yes	1045	62.1
	No	638	37.9
No. of children	None	878	52.2
	1	719	42.7
	2	86	5.1
Trimester	1st	1331	79.1
	2nd	352	20.9
upper respiratory tract infection	Yes	219	13.0
	No	1464	87.0
History of adverse pregnancy	Yes	162	9.6
	No	1521	90.4

[a] Uncooked vegetables.

Statistical analysis

Data was analyzed using the Fisher's exact test. A P-value of <0.05 was regarded as statistically significant.

Results

ToRCH infection in pregnant women

The present study was designed to prospectively investigate the association between ToRCH infection and adverse events in pregnancy. To understand the prevalence of ToRCH in pregnant women, 1683 pregnant women were screened for ToRCH IgM antibodies by chemiluminescence immunoassay. The data showed that 102 of the 1683 Participants were infected with ToRCH and the total infection rate was 6.06% (102/1683). Table 2 displayed the proportions of ToRCH IgM positive individuals. The positive rate of Toxoplasma gondii IgM antibody was 0.54% (9/1683), rubella IgM antibody was 1.13% (19/1683), CMV IgM antibody was 3.15% (53/1683) and HSV (1 + 2) IgM antibody was 1.24% (21/1683). The infection rate of CMV was significantly higher than that of other three pathogens ($P < 0.001$). This suggests that CMV is the most prevalent ToRCH pathogen in Chinese pregnant women at present.

Table 2
Seroprevalence of ToRCH infections in pregnant women.

Pathogen	IgM antibodies number of positive	Positive rate (%)
Toxoplasma gondii	9/1683	0.54
Rubella	19/1683	1.13
CMV[a]	53/1683	3.15
HSV (1 + 2)	21/1683	1.24
Total	102/1683	6.06

CMV = cytomegalovirus; HSV(1 + 2) = herpes simplex virus (types 1 and 2).
[a] Compared with the other three pathogens, p = 1.125e-08.

Table 3
Influence of upper respiratory tract infection on the positive rate of ToRCH IgM antibody in pregnant women.

TORCH IgM antibodies	Upper respiratory tract infection	
	Yes (n = 219)	No (n = 1464)
Positive No. (%)	32 (14.6)[a]	70 (4.8)
Negative No. (%)	187 (85.4)	1394 (95.2)

[a] Compared with the pregnant women without upper respiratory tract infection, p = 4.388e-07.

Relationship between ToRCH infection and upper respiratory tract

Table 4
Influence of adverse pregnancy history on the positive rate of ToRCH IgM antibody in pregnant women.

TORCH IgM antibodies	History of *adverse pregnancy*	
	Yes (n = 162)	No (n = 1521)
Positive No. (%)	39 (24.1)[a]	63 (4.1)
Negative No. (%)	123 (75.9)	1458 (95.9)

[a] Compared with the pregnant women without adverse pregnancy history, p = 4.443e-16.

infection

Among 1683 Participants, 219 suffered from upper respiratory tract infection during pregnancy. Fever was their common clinical symptoms. There is an increasing tendency for this group to infect ToRCH. Their total positive rate of ToRCH IgM antibodies was 14.6% (32/219), which was significantly higher than that in other else pregnant women (4.8%, 70/1464) without upper respiratory tract infection (P < 0.001, Table 3). This suggests that the key populations of ToRCH screening should include the pregnant women with upper respiratory tract infection during pregnancy.

Relationship between adverse pregnancy history and ToRCH infection

As shown in Table 1, 162 participants had adverse pregnancy and delivery history (e.g. abortions, stillbirth, etc.). Infection with any one of the ToRCH agents was detected in 39 of the 162 (24.1%). However, the total positive rate of ToRCH IgM antibodies was only 4.1% (63/1521) in other normal pregnancy women. The difference between them was statistically significant (P 0.01, Table 4), which indicate women with a bad history of pregnancy are the susceptible to ToRCH.

Relationship between adverse pregnancy outcomes and ToRCH infection

We divided 1683 participants into 2 groups, namely the ToRCH IgM positive group (n = 102) and the ToRCH IgM negative group (n = 1598), as displayed in Fig. 1. In the ToRCH IgM positive group, 17 of them eventually chose to terminate the pregnancy and 85 continued. Post-delivery adverse outcomes were observed in 57 of the 85 (67.1%) cases which included abortions (31.8%, 27/85), premature births (8.2%, 7/85), congenital malformations (12.9%, 11/85), and stillbirths (9.4%, 8/85). The association of IgM antibodies to various ToRCH infections in this group was displayed in Table 5. Antibody positivity was highest for CMV (72.7%) followed by rubella virus (72.2%), Toxoplasma gondii (57.1%) and herpes simplex virus (types 1 and 2) (50%).

In the ToRCH IgM positive group, 11 cases of congenital malformations were further classified to 7 cases of hydrocephalus, 2 cases of small head deformity, 1 case of congenital heart enlargement, 1 case of myocardial hypertrophy, and 2 cases of cheilopalatognathus. These data are presented in Table 6, together with the associated torch pathogens. To comparative analyze the influence of ToRCH on fetal malformation in pregnant women, we followed up all pregnant women in the ToRCH IgM negative group and found that the fetal malformation rate in this group was 1.1% (17/1598), which was much lower than that in the ToRCH IgM positive group (P < 0.001, Table 7). This indicates that ToRCH infection in pregnant women is an important factor leading to fetal malformation.

Discussion

TORCH is the most widely recognized pathogen of eugenics in the world [16]. During pregnancy, the immunity of pregnant women decreases due to the changes of endocrine system, especially the weakening of T lymphocyte immune function, which is prone to the primary infection of TORCH or the potential recurrence of virus activation. Most of them cause mild maternal morbidity, but have serious fetal consequences, such as abortion, malformation and stillbirth [17,18]. In the present study, the total infection rate of ToRCH was 6.06%, and the positive rate of CMV IgM antibody (3.15%) was significantly higher than that of other three pathogens (P < 0.01), which was different from that reported by Li ten years ago [19]. This may be related to regional differences, economic and cultural conditions, health conditions, population composition, dietary habits and lifestyles.

In most cases, pregnant women with normal immune function often have no symptoms or mild symptoms after infection with

Table 5
Clinical outcomes of pregnant women (n = 85) with TORCH infection.

Pathogen	IgM antibodies number of positive	Adverse reproductive outcome				
		Total No. (%)	Abortions No. (%)	Premature birth No. (%)	Congenital malformations No. (%)	Stillbirth No. (%)
Toxoplasma gondii	7	4(57.1)	3(42.9)	—	—	1(14.3)
Rubella	18	13(72.2)	7(38.9)	1(5.6)	3(16.7)	2(11.2)
CMV	44	32(72.7)	15(34.1)	4(9.1)	6(13.6)	4(9.1)
HSV (1 + 2)	16	8(50.0)	2(12.5)	3(18.6)	2(12.5)	1(6.3)
Total	85	57(67.1)	27(31.8)	7(8.2)	11(12.9)	8(9.4)

CMV = cytomegalovirus; HSV(1 + 2) = herpes simplex virus (types 1 and 2).

Table 6
Cases of congenital malformations positive for TORCH.

Congenital anomaly	Number of newborns	Type of infection
Hydrocephalus	7	Rubella, CMV and HSV (1 + 2)
microcephaly	2	Rubella and CMV
Cardiomegaly	1	HSV (1 + 2)
cheilopalatognathus	1	CMV

CMV = cytomegalovirus; HSV(1 + 2) = herpes simplex virus (types 1 and 2).

Table 7
Relationship between congenital malformations and TORCH infection.

Congenital anomaly	TORCH IgM antibodies	
	Positive (n = 85)	Negative (n = 1581)
Yes No. (%)	11 (12.9)[a]	17(1.1)
No No. (%)	74 (87.1)	1564 (98.9)

[a] Compared with the pregnant women without ToRCH infection, p = 7.82e-08.

ToRCH. Most of them are symptoms of upper respiratory tract infections including fever, sore throat, headache, and systemic fatigue. In our study, the total positive rate of ToRCH IgM antibody in pregnant women with symptoms of upper respiratory tract infection was significantly higher than that of other pregnant women with no symptoms of upper respiratory tract infection ($P < 0.001$). These findings suggest that the symptoms of upper respiratory tract infection may be a manifestation of ToRCH active infection in pregnant women. In such cases, therefore, the ToRCH infection of pregnant women and fetuses should be monitored in time in order to provide appropriate interventions. In addition, our data showed that the positive rate of ToRCH IgM antibody in pregnant women with the history of malformation and abnormal pregnancy was significantly higher than that in normal pregnant women ($P < 0.001$). These results suggest that the history of malformation and abnormal pregnancy have a close relationship with ToRCH infection. Pregnant women with a history of adverse pregnancy should be listed as the focus of ToRCH screening.

ToRCH is one of the most harmful pathogens to the fetus. The degree of its harmfulness to the fetus is closely related to maternal infection and autoimmune status. When pregnant women are infected for the first time, because the body has not corresponding antibodies and can not resist the invasion of pathogens, pathogenic microorganisms are easy to spread to the fetus, resulting in abortion, intrauterine growth retardation, congenital malformation, premature birth and so on. Moreover, the teratogenic effects of infection ToRCH on embryos were more obvious in pregnant women during the early stages of pregnancy. In this study, we found that among 85 pregnant women infected with ToRCH, 57 had adverse pregnancy outcomes, and the rate of adverse pregnancy was 67.1%, similar to that reported by Kishore [17]. Moreover, the incidence of spontaneous abortion (31.8%) was significantly higher than that of the general population (15%), which further confirmed ToRCH infection is closely related to spontaneous abortion.

In some cases, ToRCH pathogens cause defects in embryonic development. Zhang [20] detected the gene of ToRCH pathogen in 79 congenital heart disease and 46 non-congenital heart disease myocardium. They found that positive rate of RV, TOX and HSV genes in congenital heart disease group was significantly higher than that in control group, suggesting ToRCH was an important risk factor for congenital heart disease. We also found ToRCH is an important risk factor for fetal malformation. There were 11 cases of congenital malformations in the ToRCH IgM positive group (12.9%, 11/85), which was far more than that in the ToRCH IgM negative group (1.1%, 17/1598). Furthermore, CMV is the most common TORCH pathogen causing congenital malformation (54.5%, 6/11). This may be related to the fact that CMV is the most prevalent pathogen in pregnant women.

In summary, ToRCH infection was currently an important risk factor for adverse pregnancy outcomes in china, particularly congenital malformations. Thus, it is advocated to give priority to prevention and widely publicize the harm of ToRCH infection in women of childbearing age. First, avoid contact with cats before pregnancy, do not eat immature meat, pay attention to personal hygiene, and reduce the exposure of susceptible factors; second, rubella vaccination is the most effective measure to prevent and control the rubella epidemic and the occurrence of congenital rubella syndrome; third, to avoid birth defects and improve the quality of the birth population, women should be give torch screening before and during pregnancy. It also provides effective intervention and treatment for infected women, and terminates the pregnancy if necessary.

Conclusion

In this study, we investigated prospectively the correlation between ToRCH infections and abnormal pregnant outcomes among 1863 pregnant women. We found that ToRCH infection was a significant risk factor of severe damage to the fetus in china, especially congenital malformations. Thus, it is necessary to increase the propaganda and education on prevention of ToRCH infection in the early pregnancy, and carry out the general survey of ToRCH infection in the early pregnant women to prevent congenital ToRCH infection, which can contribute to reduce the incidence of adverse pregnancy and prevent birth defects in china.

Authors contributions

Y. Wang. and S. Wang. conceived the project; Y. Wang., S. Li., N. Ma., Q. Zhang. performed all the works. S. Wang. supervised the project. Y. Wang., S. Li., N. Ma. analyzed the data. H. Wang., J. Cui. provided samples and gave suggestions on data analysis. All authors discussed the data and contributed to the content of the manuscript. Y. Wang. and S. Wang. wrote the paper.

Declaration of Competing Interest

The authors declare no conflict of Interest.

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