Toxoplasma and Risk of Spontaneous Abortion: A Meta-Analysis in A Population of Iranian Women

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Abstract

Toxoplasma gondii is found as an intracellular protozoan parasite in the Apicomplexa phylum that can be transmitted to the fetus and causes miscarriage, infection, and asymptomatic neonatal disease. In the present study, we characterized the seroprevalence rate of anti-*Toxoplasma gondii* antibodies in a population of Iranian women with a recent a spontaneous abortion. We examined our national and international databases including Irandoc, Magiran, SID, Medlib, Scopus, PubMed, and the Science Direct. The search strategy was carried out by using keywords and MeSH terms. The statistical analysis was performed by STATA 14.2. By using the random effects model and the fixed effects model the statistical analysis was performed while the heterogeneity was ≥75 and ≤50%, respectively. We used the chi-squared test and I^2 index to calculate heterogeneity among studies, and for evaluating publication bias, Funnel plots and Egger tests were used. The seroprevalence positive rate of IgG among women who had experienced abortion was observed 32% [95% confidence interval (CI): 20-45%] based on the random-effects model. The seroprevalence positive rate of IgM based on the fixed-effect model and positive IgG rate based on the random-effect model was evaluated 4% (95% CI: 3-6%) and 32% (9% CI: 3-42%) among women immediately after an abortion, respectively. According to the finding of our study, toxoplasmosis can be one of the most significant causes of abortion.

Keywords: Iran, Pregnancy, Spontaneous Abortion, *Toxoplasma gondii*

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Introduction

Toxoplasma gondii is found in Apicomplexa phylum as an intracellular protozoan parasite, that is common among human and warm-blooded animals. Cats are the main hosts, and other pets and birds are the intermediate hosts of this protozoan (1). The disease can be transmitted through eating raw or undercooked meat containing Toxoplasma cysts, water or food contaminated with oocyte from cat feces, consuming raw milk (2), whole blood or leukocytes transfusion (3), organ transplants, or rarely by artificial insemination with semen from infected males (4). It is also congenitally transmitted to the fetus through the placenta (5). There are no clinical symptoms in healthy individuals (6); but it occurs in people with immature or impaired immune systems, especially those with AIDS/HIV, encephalitis, and systemic infections (7).

Primary infection during pregnancy can be transmitted to the fetus. Depending on the fetus's age, it causes miscarriage, infection, and asymptomatic neonatal disease (subclinical but progressive, especially in the central nervous system and eye) (8, 9). The estimated risk of transmitting the infection to the fetus in the 1st, 2nd, and 3rd trimesters of pregnancy is estimated to be 15, 44, and 71%, respectively (10). After transmission of *Toxoplasma gondii* through the placenta, the parasite enters to target organs such as immune-privileged sites like the brain, eyes, and liver (11, 12), leading to miscarriage, stillbirth (13), or serious consequences such as blindness, strabismus (14), epilepsy, encephalitis, intracerebral calcification, hydrocephalus, microcephaly, mental retardation and thrombocytopenia (15).

Therefore, due to the severe risks of primary toxoplasmosis infection during pregnancy for mothers and its devastating consequences for the fetus, it is clear that the problem could be tackled by screening programs and women's serological care during pregnancy to early diagnosis and timely treatment. Suppose specialists want to take appropriate action for diagnosis, timely treatment, and control of the country's disease. In that case, it is necessary to have comprehensive information about the prevalence of Toxoplasmosis miscarriage and also, reduce its economic and psychological burden. Although the results of different studies in this field are contradictory, we focused on the seroprevalence of anti-*Toxoplasma gondii* antibodies and spontaneous abortion.

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Protocol

According to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist in July 2020 (16), this study was conducted.

Eligibility criteria

The study population in the present Systematic reviews and Meta-Analysis includes a population of Iranian women with spontaneous abortion in the last pregnancy who had tested for anti-T. gondii antibodies. All cross-sectional and case-control studies in English and Persian languages were included. We did not limit our study due to patient follow-up time, the low sample size and also, and specific time duration. Moreover, we excluded all papers that checked the level of anti-*T. gondii* antibodies in women with a history of abortions (not immediately after the abortion). Duplicate studies or review studies were excluded. We considered all Pregnant women with spontaneous abortion as a case group and pregnant women with normal delivery as a control group in this study.

Information source

In this study, a manual search was performed in international databases such as EMBASE, Scopus, PubMed, Web of Science, Springer, Google Scholar, and Cochrane Library databases and also national databases including SID, Magiran, Irandoc, and HAYAT for cohort, case-control and cross-sectional that released until July 2020.

Search strategy

To develop the search and reach conclusive studies with maximum sensitivity, the search was done in vocabulary search and subjective search strategy, and subject heading. The search strategy was carried out using keywords and MeSH terms: pregnant women, pregnancy, *Toxoplasma gondii*, *T. gondii*, toxoplasmosis, Anti Toxoplasma, Anti *Toxoplasma gondii*, abortion, miscarriage, and fetal loss. Scope and advanced search were performed.

Study selection and Data extraction

The 3467 studies were found (312 Persian, 3155 English articles) and nine of them were selected. Two researchers of our team independently performed all procedures. Another two independent reviewers extracted data from these 9 articles by using a standard form containing general study information and type of study, diagnostic method, sample size, number of women with immunoglobulin (Ig) G-positive, IgM-positive, and the number of both IgG- and IgM-positive (Fig.1).

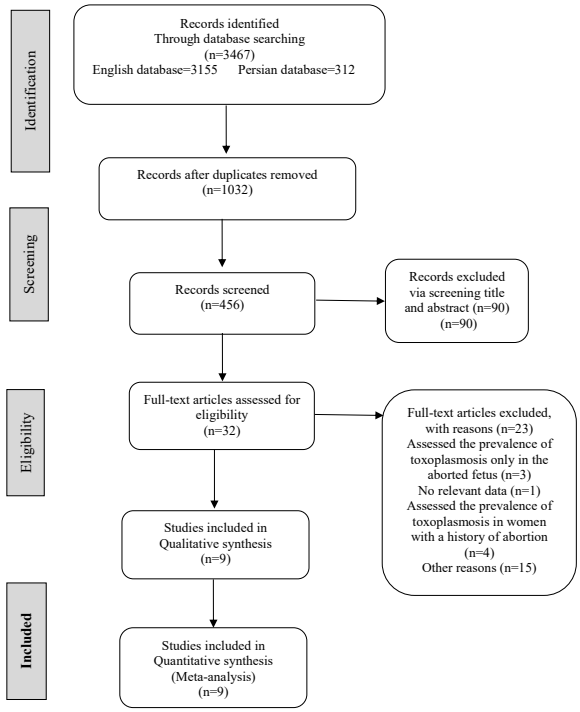

Fig.1: Flow diagram of the study design process.

Risk of bias in individual studies (Quality assessment) The Newcastle-Ottawa scale (NOS) was used to evaluate the risk of bias in individual studies (17) with 9 and 8 points for case-control and cross-sectional studies, respectively, that indicate the risk of bias. The 1-3, 4-6, and 7-9 scores of bias were categorized as, low, intermediate, and high quality, respectively for case-control studies. In the cross-sectional studies, 1-3, 4-5, and 6-8 scores were categorized as low, intermediate, and high quality, respectively (Table 1).

Table 1: The quality of reviewed articles

First author's name (Refrence)	Type of study	Selection				Comparability	Outcome			Total
		1	2	3	4	1	1	2	3	
Rasti et al. (18)	Case-control	*	*			*	*	*		5
Gharavi (19)	Cross-sectional	*			**	*	**		-	6
Aali et al. (20)	Case-control	*	*	*	*	*	*	*	*	8
Amin et al. (21)	Cross-sectional	*	*			*	**		-	5
Eslamirad et al. (22)	Cross-sectional	*	*	*		*	**		-	6
Ghasemi et al. (23)	Case-control	*	*		*	**	*	*	*	8
Matin et al. (24)	Cross-sectional	*	*	*		*	**	*	-	7
Kheirandish et al. (25)	Case-control	*	*	*	*	*	*	*		7

The numbers represent the questions in each section. The selection section has 4 question, the comparability section has 1 question and the outcome section has 3 question.

Table 2: General information of review studies

ID	First author's name (Ref.)	Geographical region	Type of study	Diagnostic method	Sample size	Number of IgG+	Number of.IgM+	Number of.IgM+and IgG+
1	Rasti et al. (18)	Tehran	CC	IFA	42	6	3	29
2	Gharavi et al. (19)	Tehran	CS	IFA	28		3	
3	Aali et al. (20)	Kerman	CC	ELISA	57	25	3	
4	Amin et al. (21)	Zanjan	CS	ELISA	264	99	21	23
5	Eslamirad et al. (22)	Arak	CS	ELISA.PCR	87	24		
6	Ghasemi et al. (23)	Tehran	CC	ELISA.PCR	82	22	3	
7	Matin et al. (24)	Ardabil	CS	ELISA.PCR	200	86	8	13
8	Kheirandish et al. (25)	Khorramabad	CC	ELISA	240	114	8	
9	Arefkhah et al. (26)	Kohgiluyeh and boyer-ahmad	CS	ELISA. real-time PCR	100	7	3	0

CC; Case-control, CS; Cross-sectional, IFA; Immunofluorescence assay, ELISA; Enzyme-linked immunosorbent assay, and PCR; Polymerase chain reaction.

Synthesis of results

The Statistical analysis was done by STATA ver 14.2. The analysis was performed using both random-effects and fixed-effects models when the heterogeneity was ≥75 and ≤50%, respectively. Using the metan command, the seroprevalence rate of IgG+, IgM+, and IgG+ IgM+ was computed. To calculate heterogeneity among studies, the chi-squared test and the I2 index were used. I2 values of ≤25, 50, and ≥75% are low medium and high heterogeneity. The related confidence interval of 95% was estimated by using forest plots as visuals.

Risk of bias across studies

For estimation of publication bias the Begg's and Egger test was used (27).

Results

This study includes 1100 pregnant women with spontaneous abortion. In 9 studies, IgG and IgM positivity were evaluated. Four diagnostic methods have been used in these studies: indirect immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR) and real-time PCR (Table 2).

The seroprevalence rate of IgG positivity in the women who had experienced abortion was determined to be 32% (95% CI: 20-45%) based on the random-effect model (Fig.2).

Also, the Seroprevalence rate of IgM positivity based on the fixed-effect model and both IgG and IgM positivity based on the random-effect model was evaluated 4% (95% CI: 3-6%) and 25% (9% CI: 3-42%) in women immediately after an abortion, respectively (Fig.3).

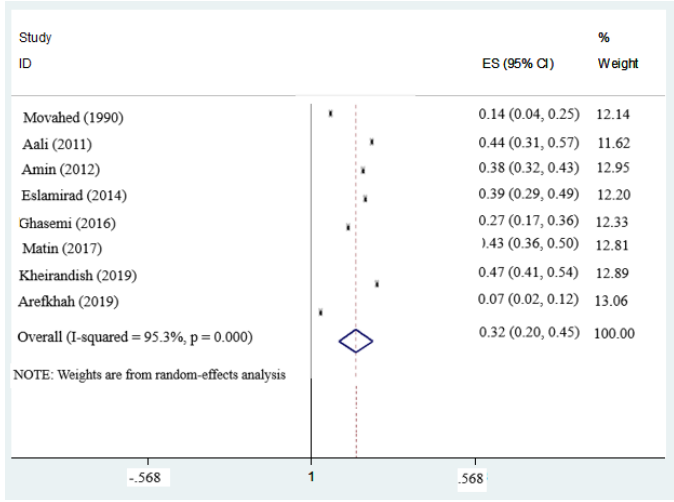

Fig.2: Seroprevalence rate of *T. gondii* IgG antibody positivity in the women with abortions in their current pregnancy based on the random-effected model. ID; Identification, ES; Effect size, and CI; Confidence interval.

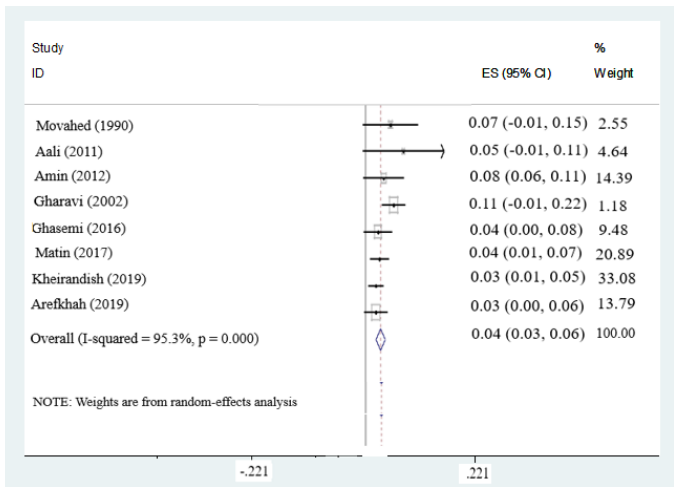

Fig.3: Seroprevalence rate of *T. gondii* IgM antibody positivity women with abortions in their current pregnancy based on the random-effected model. ID; Identification, ES; Effect size, and CI; Confidence interval.

Using the Begg's and Egger's tests, no significant publication bias was observed for either outcome (Begg's test, P=0.083; Egger's test, P=0.163, Fig.4).

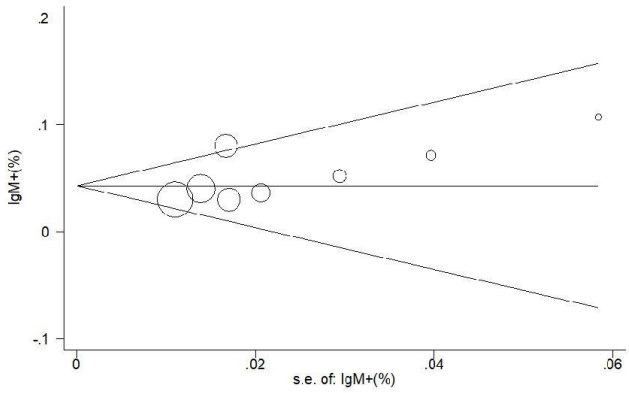

Fig.4: Begg's funnel plot and risk of studies publication bias. s.e.; Standard erro.r

Discussion

Toxoplasmosis is a parasitic disease with a wide geographical distribution. The parasite can pass through the placenta barrier and causes severe complications in the fetus (28). If a pregnant woman becomes infected in the first trimester of pregnancy, it can cause miscarriage, stillbirth, or severe fetus complications (13). In this meta-analysis, the seroprevalence of IgG anti- *T.gondii* antibody ,which indicates the mother's previous infection with this infection, was figured out 32%. The seroprevalence of IgM anti- *T.gondii* antibody ,an indicator of a recent and active infection of the mother, that alarms a risk of infection transmission from mother to fetus, was found 4%. The seroprevalence rate of both IgG and IgM positivity was assessed 25% in these women immediately after the abortion. In general, the presence of IgM or IgA-specific Toxoplasma parasite in the mother's serum indicates recent infection. Still, suppose the anti-Toxoplasma gondii IgG antibody serum level increases during pregnancy, and the IgM antibody titer is positive for the disease. In that case, the woman is more likely to develop active toxoplasmosis (29).

Previous studies have estimated the overall prevalence of latent toxoplasmosis at 33.8% in the pregnant women (30). In line with our study, the results of Nayeri et al. (31) study indicated the global prevalence of anti-T. gondii IgG antibody in women with abortions in their current pregnancy is about 33%. In addition, the incidence of abortion in Chinese IgM-positive women in 2003 was estimated at 12.6%, while in the control group it was estimated to be about 2.7% (32). Therefore, the rate of abortion was significantly higher in the toxoplasmosis affected women in their present pregnancy that is in line with our study. In Brazil and central Kenya, more than half of referred women to health centers had antibodies against Toxoplasma, 58% and 81.4% respectively (33, 34). These results are much higher than the results obtained in the present study. This difference can be due to differences in regional food culture, such as more use of raw or undercooked meat foods, the higher prevalence and density of oocyte-repellent cats in this area, and climatic conditions of different geographical areas. Among the results consistent with our study, we can mention the study of Iddawela et al. (35) of Sri Lanka in which 29.9 and 0.37% of pregnant women in the first trimester of pregnancy were positive for IgG and IgM antibodies, respectively. Elfadaly et al. (36) also showed in Egypt that 42.1% of women have antibodies against the *T.gondii*. Using ELISA on 203 blood samples of pregnant women in Saudi Arabia, Alghamdi et al. (37) found that 32.5% of their participants showed IgG positive, and 6.4% are IgM positive. Although, the prevalence of anti-Toxoplasma antibodies in women in other parts of the world is consistent with the results of our study.; for example, 27.9% in Palestine and 33% in Venezuela (38, 39).

In a study conducted by Decavalas et al. (40) in Greece, the results showed that 50.2% of women who had an abortion were infected by toxoplasmosis, and none of them had IgM antibodies in their blood serum. In a study, Sahwi et al. (41) examined the causes of abortion in a population of Egyptian pregnant women. Although 19% of women with recurrent abortion were IgM positive, they observed no statistical difference in comparison with the control group. They concluded that there was no significant association between acute toxoplasmosis and abortion. However, the findings of our showed that there is a significant relationship between chronic toxoplasmosis and recurrent abortion.

It is plausible that several limitations may have influenced the results obtained. The limitations of the present studies naturally include: i. The use of different diagnostic methods and kits with different sensitivities in the studies. Ii. Lack of a large cohort study in women with toxoplasmosis who have had an abortion in Iran to date.

Conclusion

The results show a significant proportion of Iranian pregnant women are at risk for toxoplasmosis, and the rate of anti- *T.gondii* antibodies IgG -IgM positivity in Iranian pregnant women with a spontaneous abortion was 25%, which indicates that toxoplasmosis is could be one of the causes of abortion in the Iranian pregnant women.

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Authors' Contributions

M.D., F.K., R.A.; Designed the conception of the study. M.F.K, Gh.B., M.Sh., M.D., A.M; Static analysis. All authors contributed to the drafted manuscript, revised it critically, and approved the final version.

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