

Toxoplasma Infection and Its Association with Spontaneous Abortion: A Comprehensive Meta-Analysis in Iranian Women

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Abstract– The Apicomplexa phylum contains the intracellular protozoan parasite *Toxoplasma gondii*, which can infect humans and cause miscarriage, spread of infection, and asymptomatic newborn illness. In the current study, we assessed the incidence of anti-*Toxoplasma gondii* antibody in Iranian women who had recently experienced an unplanned abortion. We looked through domestic and foreign data sources, such as Irandoc, Magiran, SID, Medlib, Scopus, PubMed, and Science Direct. MeSH phrases and keywords were used in the search method. Using STATA 14.2, the statistical examination was completed. The statistical evaluation was carried out with a heterogeneity of 75% and 50%, respectively, using the random effects and fixed effects model. To determine study heterogeneity, we employed the chi-square test and I² index. Funnel charts and Egger testing were used to assess publication bias. According to the random-effects model, the seroprevalence positivity percentage of IgG among women who experienced abortions was detected at 32% [confidence interval, 94% (CI): 20-45%]. In women who had recently had an abortion, the seroprevalence affirmative rate of IgM according to the fixed-effect model was estimated to be 4% (94% CI: 3-6%) and the positive IgG rate depending on the random-effect theory to be 34% (9% CI: 3-42%), respectively. Our study's findings suggest that toxoplasmosis may be one of the major factors contributing to abortion.

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

1. Introduction

The Apicomplexa phylum contains *Toxoplasma gondii*, an intracellular protozoan pathogen that affects humans and other warm-blooded animals often. This protozoan's primary hosts are cats, although intermediate hosts include various animals and birds [1]. The disease can be spread by ingesting undercooked or raw meat contaminated with *Toxoplasma* cysts, drinking raw milk, receiving an organ transplant, receiving a transfusion of whole blood or leukocytes, and in rare cases, artificial insemination using the semen of infected males. Additionally, the placenta allows it to congenitally pass from mother to fetus [5]. Healthy persons don't experience any clinical signs [6]; however, those with immature or compromised immune systems, particularly those with AIDS/HIV, encephalitis, and systemic infections [7].

The fetus may get a primary infection while the mother is pregnant. It can result in miscarriage, infection, and silent newborn illness (subclinical but progressing, particularly in the brain, spinal cord, and eye), depending on the age of the fetus [8, 9]. In the first, second, and third trimesters of pregnancy, the risks of infection transmission to the baby have been calculated to be 15, 45, and 71%, correspondingly [10]. *Toxoplasma gondii* enters the body after being transmitted through the placenta and targets immune-privileged areas like the brain, eyes, and liver [11, 12]. This can result in miscarriage, stillbirth, or more severe consequences like blindness, strabismus, epilepsy, an encephalitis intracerebral calcifying, hydrocephalus, microcephaly, mental retardation, and thrombocytopenia [15].

Therefore, it is obvious that the issue could be solved by testing initiatives and women's serological care while pregnant to ensure early diagnosis and prompt treatment due to the serious risks associated with primary toxoplasmosis infection throughout the pregnancy for women and its devastating effects on the fetus. Let's say experts want to take the proper steps to diagnose, treat, and manage the sickness throughout the nation. In that scenario, it is essential to lessen the financial and psychological cost of toxoplasmosis miscarriages and to have thorough knowledge of its prevalence. We concentrated on the prevalence of infection of anti-Toxoplasma gondii antibody and spontaneous abortion despite the conflicting findings of several studies in this field.

2. Related works

This study was carried out in accordance with the Preferred Items for Reporting for Systematic Assessments and Meta-Analysis (PRISMA) checklist as of July 2020 [16].

2.1 Eligibility criteria

Iranian women who experienced a spontaneous abortion during their most recent pregnancy and who had tested positive for anti-T. gondii antibodies make up the research population in the current Systematic Reviews and Meta-Analysis. All case-control and cross-sectional studies conducted in both English and Persian were considered. Due to the short sample size, patient follow-up length, and specific time period, we did not restrict our study. Additionally, we disregarded any studies that examined the quantity of anti-T. gondii antibody in women who had previously had abortions but not just after the procedure. Studies that were duplicates or reviews were not included. In this study, we used pregnant women with regular deliveries as the control group and all pregnant women with spontaneous abortions as the case group.

2.2 Information source

In this study, a manual search was conducted in national databases like SID, Magiran, Irandoc, and HAYAT as well as international databases like EMBASE, Scopus, PubMed, Web of Science, Springer, Google Scholar, and the Cochrane Library for cohort, case-control, and cross-sectional that published until July 2018.

2.3 Search strategy

The search was done in subject heading, subjective search method, and vocabulary search to develop a search and reach decisive research with maximum sensitivity. Pregnant women, pregnancy, Toxoplasma gondii, T. gondii, the infection known as Anti Toxoplasma, Anti Toxoplasma gondii, abortion, premature delivery, and foetal loss were the keywords and MeSH terms used in the search strategy. Advanced search and scope were used.

2.4 Study selection and Data extraction

Ten out of the 3460 studies (311 Persian and 3145 English papers) were chosen. All procedures were carried out independently by our team's two researchers. A standard form with general study information, the type of study, the diagnostic method, the sample size, and the percentage of women with immunoglobulin, or Ig, G-positive, IgM-positive, as well as the amount of both IgG- and IgM-positive antibodies was used by two additional independent reviewers to extract data from these nine articles (Fig. 1).

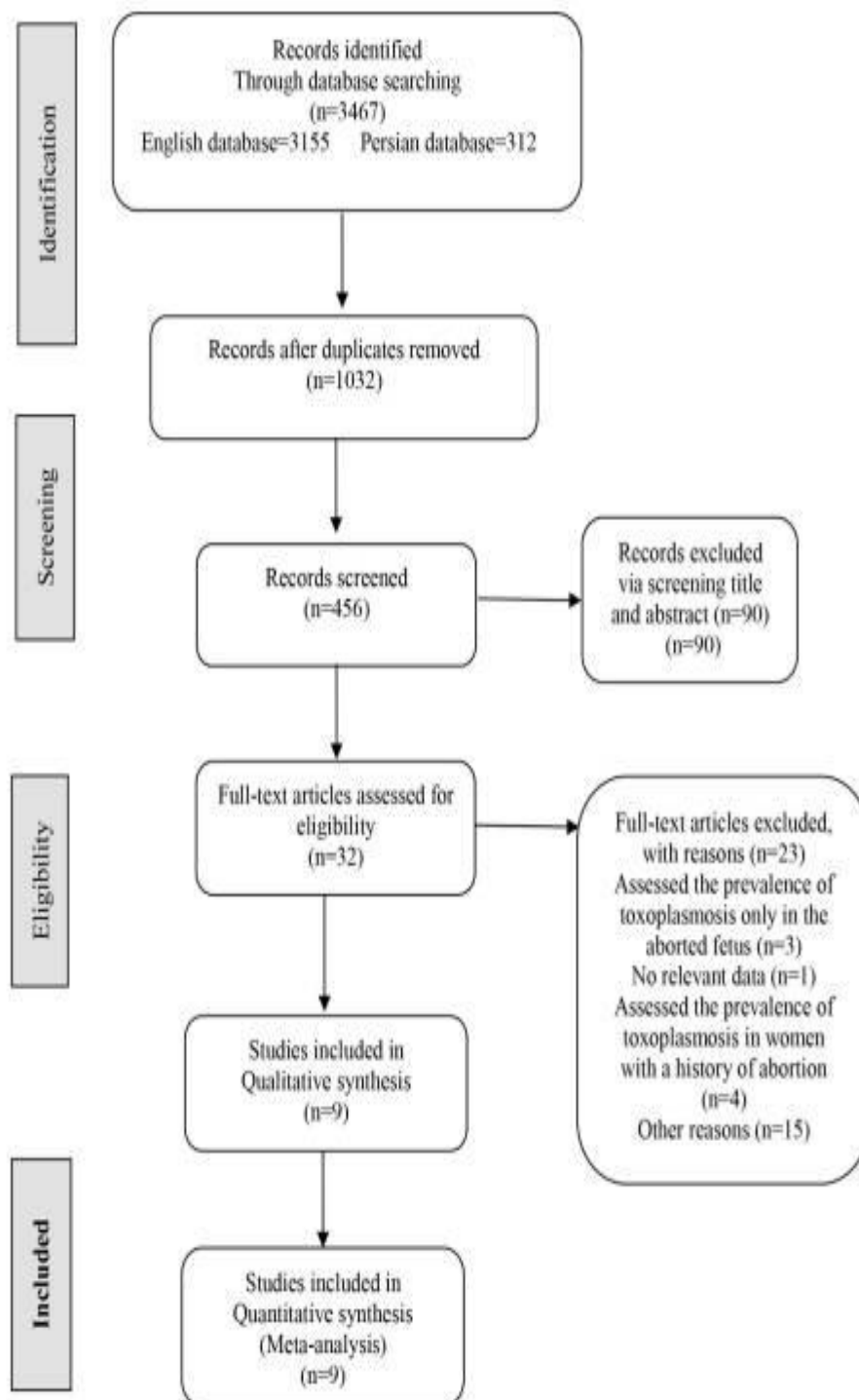


Fig 1. Flow diagram of the study design process.

Individual study bias risk (quality evaluation) The Newcastle-Ottawa scale (NOS), with scores of 9 for case-control studies and 8 for cross-sectional studies, was used to assess the likelihood of bias in individual research [17]. For case-control studies, the bias ratings of 1-3, 4-6, and 7-9 were classified

as low, middle, and high quality, respectively. Scores of 1-3, 4-5, and 6-8 were classified as poor, intermediate, and excellent quality, respectively, in the cross-sectional investigations (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	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

3. Synthesis of results

STATA version 14.2 was used to conduct the statistical analysis. When the heterogeneity was between 75% and 50%, respectively, the analysis was run using both random-effects and fixed-effects models. Employing the metan control, the seroprevalence percentages of IgG+, IgM+, and IgG+ IgM+ had been computed. The chi-square test and the significance score were used to determine how heterogeneous the studies were. I2 values of 25, 50, and 75% indicate minimal, moderate, and great heterogeneity, respectively. Forest plots were used as a visual aid to estimate the 95% confidence interval related to the data.

3.1 Risk of bias across studies

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

4. Results

1100 pregnant women who spontaneously aborted are included in this study. IgG and IgM positivity was assessed in 9 investigations. These research have utilised ELISA, PCR, PCR real-time, PCR indirect immunofluorescence assay, and indirect fluorescence assay (IFA) as four diagnostic techniques (Table 2).

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.P CR	87	24		
6	Ghasemi et al. [23]	Tehran	CC	ELISA.P CR	82	22	3	
7	Matin et al. [24]	Ardabil	CS	ELISA.P CR	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.

Based on the random impact model, it was found that the seroprevalence percentage of IgG positive in the women whose had undergone abortions were 32% (95% confidence interval [CI]: 20-45%) (Fig.2).

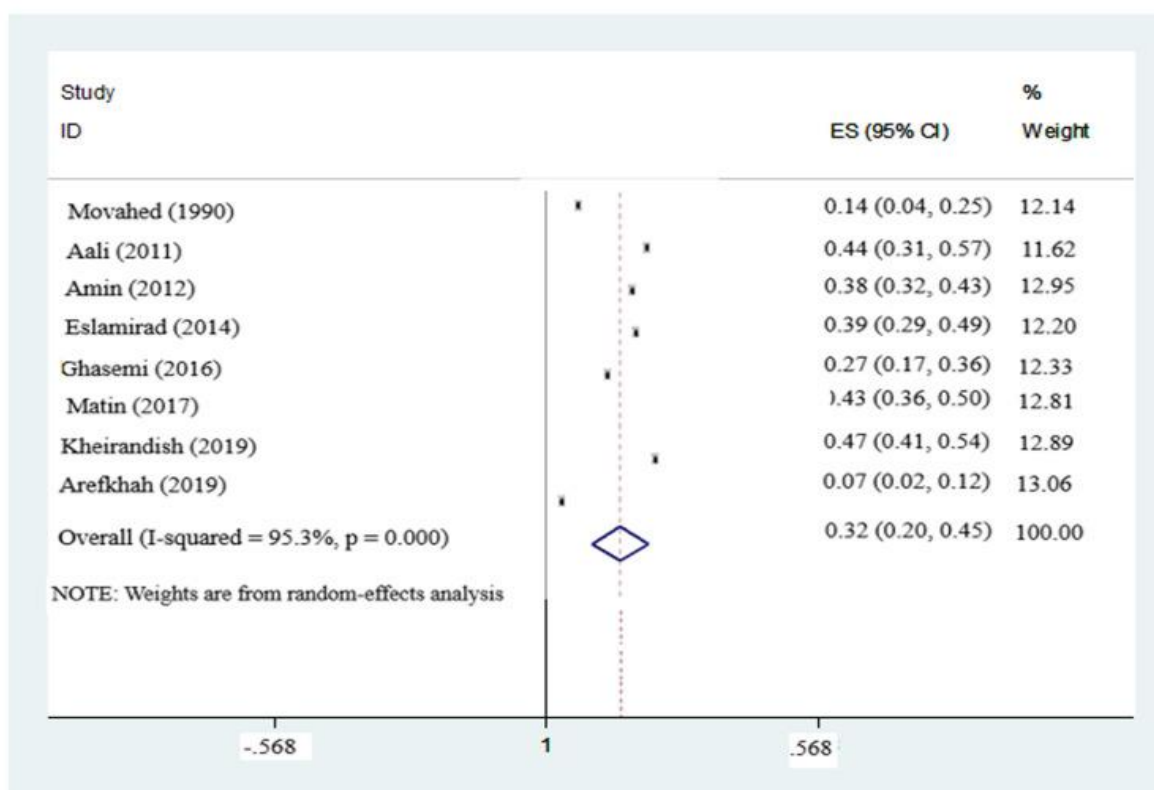


Fig 2. Seroprevalence rate of T. gondii IgG antibody positivity in the women with abortions in their current pregnancy based on the random-effected model.

ID; Identification, ES; Effect size, and CI; Confidence interval.

Additionally, the fixed-effect model's evaluation of the prevalence percentage for IgM positivity was 4% (95% CI: 3-6%), and the random-effect model's evaluation of combined IgG and IgM positive was 25% (9% CI: 3-42%), respectively, in women who had had abortions recently (Fig. 3).

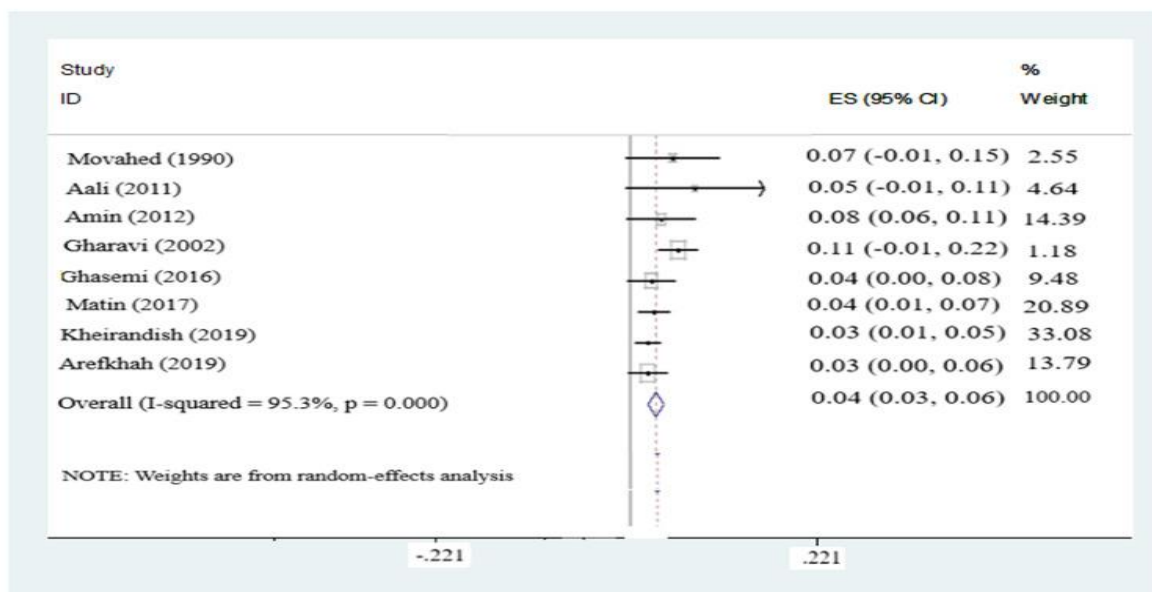


Fig3. Seroprevalence rate of *T. gondii* IgM antibody positivity women with abortions in their current pregnancy based on the random-effected model.

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).

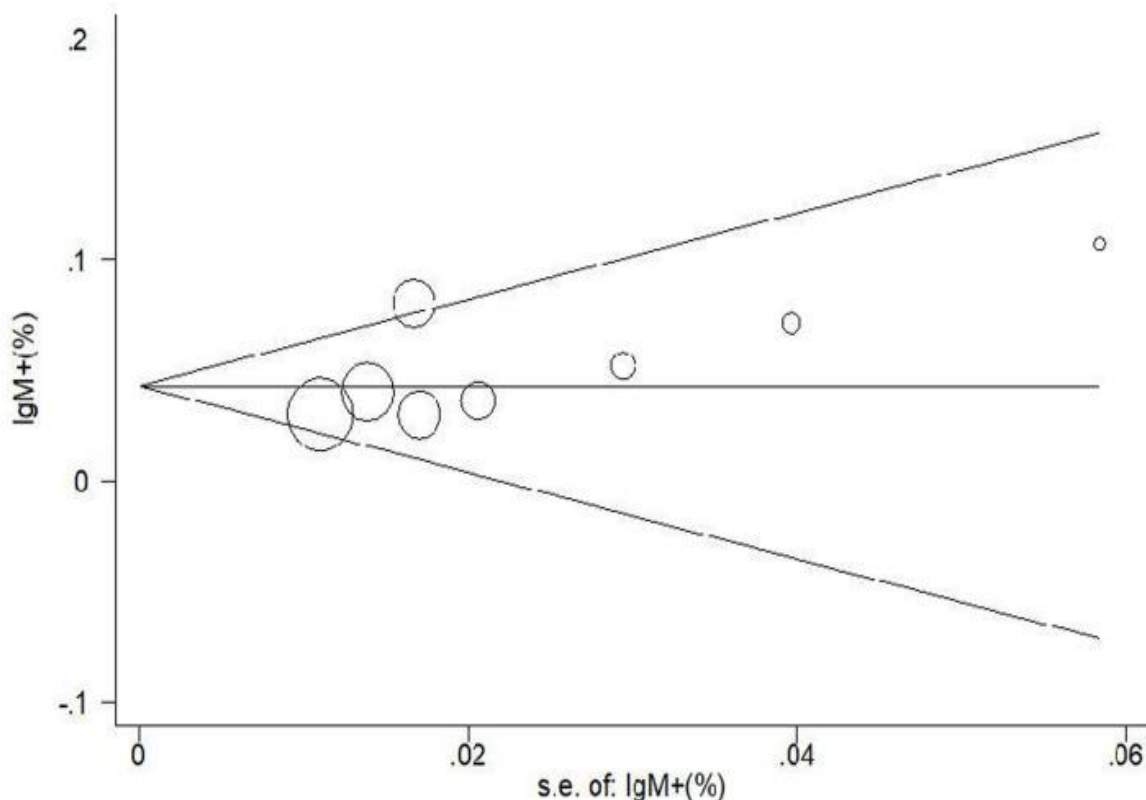


Fig 4. Begg's funnel plot and risk of studies publication bias.

s.e.; Standard error

5. Discussion

A parasite illness with a broad geographic distribution is toxoplasmosis. The parasite can cross the placenta membrane and seriously harm the developing foetus [28]. A first-trimester infection in a pregnant woman can result in miscarriage, stillbirth, or serious foetus issues [13]. The prevalence of IgG anti-T.gondii antibody, which suggests the mother's prior infection with this illness, was calculated to be 32% in this meta-analysis. The prevalence of IgM anti-T.gondii antibody, which alerts to the possibility of transmission of infection from mother to foetus and is a sign of recent and ongoing infection in the mother, was found to be 4%. In these women right after the abortion, the seroprevalence rate for both IgG and IgM positive was estimated to be 25%. In general, a recent infection is indicated by the detection of IgM or IgA-specific the pathogen infection in the mother's serum. However, assume the IgM antibody level is diagnostic for the condition and the anti-Toxoplasma gondii IgG blood level rises throughout pregnancy. The likelihood of the woman developing active toxoplasmosis increases in those situations [29].

According to earlier research, pregnant women often have a 33.8% incidence of latent toxoplasmosis [30]. In agreement with our investigation, Nayeri et al.'s [31] findings showed that 33% of women who had abortions during their current pregnancies worldwide had anti-T. gondii IgG antibodies. Additionally, in 2003, it was reported that 12.6% of Chinese IgM-positive women had abortions, compared to 2.7% of the control group [32]. Among line with our study, the frequency of abortion was considerably greater among toxoplasmosis-affected women throughout their current pregnancies. In Brazil and central Kenya, 58% and 81.4%, respectively, of women sent to health centres exhibited

antibodies against *Toxoplasma*. These results are significantly better than the ones found in the current study. The greater usage of raw or undercooked animal items, the higher incidence and density of oocyte-repellent cats in this region, and the climatic circumstances of various geographic locations can all contribute to this variance in regional food culture. The study by Iddawela et al. [35] of Sri Lanka, in which 29.9 and 0.37% of pregnant women during the first trimester of maternity were positive for IgG and IgM the antibodies, respectively, is one of the outcomes that is consistent with our data. Elfadaly et al. [36] also discovered that 42.1% of Egyptian women have *T.gondii* antibody levels. Alghamdi et al. [37] discovered that 6.4% of their participants are IgM positive and 32.5% of their participants exhibited IgG positive using ELISA on 203 specimens of pregnant women in Saudi Arabia. Although the results of our study are consistent with the prevalence of anti-*Toxoplasma* antibodies in women in various regions of the world, for instance, 27.9% in Palestine and 33% in Venezuela [38, 39].

50.2% of women who had abortions tested positive for toxoplasmosis in a research by Decavalas et al. [40] in Greece; none of these women exhibited IgM antibodies in the results of their serum. In a study, Sahwi et al. [41] looked at the reasons why pregnant Egyptian women had abortions. Despite the fact that 19% of women who had recurring abortions tested IgM positive, there was no statistically significant difference between this group and the control group. They came to the conclusion that there was no conclusive link between abortion and acute toxoplasmosis. The results of our study, however, revealed a substantial link between repeated abortion and chronic toxoplasmosis. It is conceivable that a number of restrictions may have affected the outcomes. The use of various diagnostic tools and kits with various sensitivities in the investigations is unavoidably one of the studies' shortcomings. ii. There hasn't yet been a sizable cohort research in Iran looking at toxoplasmosis-positive women who have undergone abortions.

6. Conclusion

According to the findings, a sizable portion of pregnant Iranian women are at greater risk for toxoplasmosis, and 25% of Iranian pregnant women who had spontaneous abortions tested positive for anti-*T.gondii* IgG-IgM antibodies. This suggests that toxoplasmosis may be one of the reasons why Iranian pregnant women have abortions.

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