

Seroprevalence of *Toxoplasma gondii* infection among Iranian pregnant women: a systematic review and meta-analysis

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Abstract

Background: Toxoplasmosis is a great public health concern due to its capacity for prenatal transmission. Serologic studies have reported various estimates for seroprevalence of toxoplasmosis among Iranian pregnant women. Estimation of the pooled prevalence of this infection is necessary for policy-making.

Aims: The aim of this study was to estimate the prevalence of *Toxoplasma gondii* infection in Iranian pregnant women using systematic review and meta-analysis.

Methods: We searched national and international databases to identify relevant studies. To enhance the search sensitivity, we evaluated all references and interviewed relevant researchers and research centres. The final studies for meta-analysis were selected according to the quality assessment as well as inclusion/exclusion criteria. Because of the heterogeneity of the primary results, random effects models were used to estimate the pooled prevalence of *T. gondii*. We included 43 studies with a total sample size of 22 644 in the meta-analysis.

Results: The pooled seroprevalence of overall toxoplasma infection, IgG antibody and IgM antibody was estimated at 41.3% (95% CI: 35.8–46.8), 39.2% (95% CI: 33.3–45.1) and 4.0% (95% CI: 3.1–4.9) respectively.

Conclusions: Our study showed that a considerable proportion of Iranian pregnant women are at high risk for toxoplasmosis.

Keywords: Toxoplasmosis, *Toxoplasma gondii*, infection, pregnancy, Iran

Citation: Malary M; Hamzehgardeshi Z; Moosazadeh M; Afshari M; Ahmadi I; Moghaddasifar I; et al. Seroprevalence of *Toxoplasma gondii* infection among Iranian pregnant women: a systematic review and meta-analysis. East Mediterr Health J. 2018;24(5):488-496. <https://doi.org/10.26719/2018.24.5.488>

Received: 09/09/15; accepted: 23/04/17

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Introduction

Toxoplasma gondii is an obligate intracellular protozoa with a complicated life cycle. This agent causes toxoplasmosis among humans and animals and is one of the most prevalent chronic infections, infecting one-third of the world population (1–5). Three main modes are responsible for fetal: consumption of including raw or semi-cooked meat, eating the oocytes defecated by cats and vertical transmission from an infected pregnant mother to her fetus (6–7). Consideration of toxoplasmosis among pregnant women (owing to the risk of maternal transmission) and immunocompromised patients is of great importance for control programmes because infection can lead to serious pathologic outcomes among neonates with congenital toxoplasmosis and patients with immunodeficiency status (8–9). Knowing the burden of this infection will help health systems focus on prevention of risk factors.

A number of serological tests, such as the latex agglutination test, enzyme-linked immunosorbent assay (ELISA) and indirect fluorescence antibody test, have been used in the detection of antibodies against *T.*

gondii in pregnant women. However, ELISA is the most commonly used diagnostic technique (7,9).

Previous research has shown that toxoplasmosis infection was more common among those with history of close contact with cats, raw meat and vegetable consumption, and low education level (3). The most important benefit in the serology of toxoplasma is to detect whether the pregnant woman has acute infection or not, and if so, whether it occurred before pregnancy (10). The main problem in diagnosis among pregnant women is long-term antibody IgM, but *T. gondii*-specific antibody (IgM) does not necessarily indicate acute infection (11). In many cases, laboratory diagnosis of latent and acute *T. gondii* is based on detecting *T. gondii*-specific IgM and IgG antibodies (7). There are several serologic tests for anti-toxoplasma IgM and IgG, among which ELISA has maximum sensitivity and specificity (2). Chronic infection before pregnancy cannot be transmitted to the fetus, but acute untreated infection during pregnancy may lead to congenital toxoplasmosis with neonatal complications (6). The risk of transmission and the severity of fetal disease is based on gestational age and progressive antibody titration (8), so this risk

varies between 0–9% (congenital infection during the first trimester) and 35–59% (congenital infection during the third trimester) (12). Although the infection is usually asymptomatic or mild and self-limiting (fever, agitation, lymphadenopathy), infection occurring during pregnancy causes vertical transmission to the fetus (3) leading to pathologic complications such as hydrocephaly (2,3), microcephaly, chorioretinitis (12), blindness (2,3), mental retardation (2,12), epilepsy (12), jaundice (12), abortion (2,3,12) and fetal death (2,3,12). These complications can be accompanied by disabilities, reduced quality of life and a high socioeconomic burden (8).

Prevention of toxoplasmosis by screening is mandatory in some countries and is recommended in some others such as the United States of America and Canada (12). There is no routine screening programme for toxoplasmosis in the Islamic Republic of Iran (8) and there is no agreement on the best strategy for control of congenital toxoplasmosis (11) although treatment is very important, especially among immunocompromised patients and pregnant women (1).

Seroprevalence of toxoplasmosis has been reported as 30–60% in developed and developing countries (3). In an Iranian study, the incidence of congenital infection during pregnancy was reported to vary from 1 to 8 per 1000 pregnancies (8). According to a systematic review, the global annual incidence of congenital toxoplasmosis was estimated at 190 100, equivalent to a burden of 1.20 million disability-adjusted life years. This burden was greater in South America, some Eastern Mediterranean countries and other low-income countries (13).

Various primary studies have been published estimating the prevalence of toxoplasmosis among pregnant women in the Islamic Republic of Iran. Combining the results of these studies using systematic and meta-analytic methods will be of great importance. Therefore, in this study, we used the methods outlined above to estimate the pooled seroprevalence of toxoplasma antibodies among Iranian pregnant women.

Methods

Data sources and search strategy

The current study is a systematic review and meta-analysis of estimation of the seroprevalence of toxoplasmosis among Iranian pregnant women.

All electronic papers published in national and international databases including SID, Iranmedex, Magiran, Irandoc, Pubmed, Google Scholar, Scopus and Science Direct from 1990 until 10 March 2015 were enrolled in this study. The search strategy was performed using the following keywords as well as their Farsi equivalents: “toxoplasmosis”, “*Toxoplasma gondii*”, “toxoplasma infection”, “*T. gondii*”, “Iran”, “pregnant”, “seroepidemiology”, “seroprevalence”, “IgG antibody”, “IgM antibody”, “prevalence”.

Searching was done from 11 to 20 March 2015. We used “OR” to identify studies with any of the keywords in their titles, abstracts and full texts. Limiting the

search strategy was carried out applying “AND” to select studies with all of the required keywords. To provide more relevant keywords and studies leading to increased search sensitivity, we investigated all references used in these papers. One of the researchers randomly evaluated the search action and found that all required studies had been entered in the systematic review. Moreover, to find unpublished studies, we asked some well-known Iranian parasitologists working in the medical universities and infectious diseases research centres to introduce any relevant manuscripts which had not been published. However, we did not find any evidence during this phase of the search. All stages of the search as well as the follow-up actions were performed by 2 independent researchers. Any disagreement was settled by a third researcher.

Selection of studies

We extracted the full texts or abstracts of all documents collected during our search. During primary screening, repeated studies were excluded by investigation of the title and abstract. Secondary screening was conducted among studies selected during the primary phase to select more relevant studies with evaluation of the full text. In this stage, abstracts and full texts of the papers were investigated to exclude irrelevant and duplicated studies.

Inclusion criteria

All studies published in Farsi or English that achieved an adequate quality score (> 8 of 12) during the assessment process and also those estimating seroprevalence of toxoplasmosis, IgG and IgM titration among Iranian pregnant women were selected. These titrations were categorized according to the standards defined by the companies manufacturing the relevant substances (in most studies, antibody titration > 1.1 IU/mL for indirect fluorescence antibody test and ELISA was considered positive).

Exclusion criteria

Studies without estimations of IgG or IgM seroprevalence, studies without sample size reporting, abstracts submitted in congresses whose full texts were not available and case-control studies which could not report prevalence estimations were excluded from the study.

Quality assessment

After selecting relevant studies based on titles and contents, to select the documents of satisfactory quality, we applied the STROBE checklist (14). This checklist includes 22 items covering various components of the methodology such as sample size estimation and selection, study population, data collection methods, instrument for data collection, statistical analysis, geographical distribution of the study, aims of the study and appropriate illustration of the results based on the study objectives. Scores were determined from 0 to 44. Based on the STROBE checklist assessment, documents were divided into 3 groups: low quality, score < 15.5; moderate quality, score 15.5– 29.5; and high quality, score

30.0– 44.0. Studies with score < 15.5 were excluded from the meta-analysis.

Data extraction

Title of the study, first author's name, date and area of the study, total sample size, type of study, serologic method used, mean age of participants, seroprevalence of toxoplasmosis, prevalence of positive IgG and IgM (according to the cut-off points defined by the companies who manufactured the kits) were extracted from each of the selected studies. Extracted data were entered into *Microsoft Excel* for descriptive data analysis.

Analysis

All extracted data were entered into *Stata*, version 11 software. The standard error of toxoplasma seroprevalence for each study was calculated based on binomial distribution. The heterogeneity of the study results was determined using the Cochrane (Q) test and I-squared (15). The random effects model was used to estimate the combined seroprevalence of toxoplasmosis as well as IgG/IgM seropositivity rates. The effects of potential factors in heterogeneity were assessed using

the meta-regression method. We illustrated the point prevalence in forest plots, including the study weights (size of each box) and 95% confidence interval (CI) (lines crossing the boxes).

Results

We found 12 545 documents from national and international databanks using relevant keywords (12 541) and reviewing the references (4 papers). After limiting the search strategy and excluding duplicated papers, the number of relevant articles decreased to 1885. Reviewing the titles and abstracts, 1696 irrelevant records were removed. Out of the remaining papers, 146 were excluded after full text review and according to other exclusion and inclusion criteria. Finally, 43 papers (6,7,9,12,16–54) were considered eligible for inclusion in the systematic review and meta-analysis (Table 1; Figure 1).

The final selection of papers was published from 1990 to 2015 (Table 1), 15 articles in English and 28 in Farsi. Type of study was explained in 34 papers, including 1 cohort and 33 descriptive and cross-sectional studies. The age of

Table 1 Baseline characteristics of included studies in meta-analysis of seroprevalence of *Toxoplasma gondii* in Iranian pregnant women of

Reference	Publication year	Publication language	Type of study	Quality score	Sample size	Serological method	Prevalence of women with positive antibody (%)		
							IgG	IgM	IgM + IgG
Abdi (34)	2008	English	Cross-sectional	26	553	IFA	44.8	–	44.8
Akhlaghi (48)	2014	English	–	32	400	ELISA	29.0	1.0	30.0
Akhlaghi (13)	2013	English	Cross-sectional	27	200	IFA & ELISA	39.6	5.7	45.3
Alleyassin (51)	1990	English	–	29	320	IFA	77.2	–	77.2
Anvaritafti (39)	2012	Farsi	Cross-sectional	28	181	ELISA	32.0	–	32.0
Arbabi (54)	2001	Farsi	descriptive	27	340	IFA % ELISA	–	–	66.7
Athari (45)	1994	English	–	26	495	IFA	–	–	32.7
Cheragipour (44)	2010	Farsi	Cross-sectional	30	390	ELISA	23.6	7.4	31.0
Cheragipour (43)	2009	Farsi	Cross-sectional	31	331	ELISA	28.7	10.5	39.2
Dalimiasl (40)	2011	Farsi	Cross-sectional	31	300	ELISA	26.3	0.3	26.6
Ebrahimzadeh (52)	2013	Farsi	–	30	221	ELISA	30.8	1.4	30.8
Eskandareian (37)	2009	Farsi	–	29	255	IFA	62.7	–	62.7
Fallah (9)	2008	English	Cross-sectional	32	576	IFA	–	–	33.5
Firozivand (41)	2014	English	Cross-sectional	30	200	ELISA	39.5	2.5	41.0
Gasemi (35)	2011	Farsi	–	27	127	IFA	47.2	–	47.2
Ghorvi (42)	2002	Farsi	–	34	4120	IFA	67.6	0.4	68.0
Ghasemloo (47)	2014	English	Cross-sectional	31	785	ELISA	31.1	0.0	31.1
Javadi (49)	2014	English	Cross-sectional	29	195	ELISA	58.9	5.1	60.5
Hajsoleimani (7)	2012	English	–	28	500	ELISA	37.2	1.4	38.6
Hamidi (50)	2015	English	Descriptive	33	2523	ELISA	27.0	2.0	29.0
Sotudehjahromi (30)	2002	Farsi	Cross-sectional	31	418	ELISA	34.2	7.9	39.7
Tabatabaei (31)	2015	English	Cross-sectional	27	200	ELISA	29.0	2.0	31.0
Talari (32)	2003	Farsi	Descriptive	28	270	IFA	26.7	5.5	32.2
Talari (33)	2001	Farsi	Descriptive	31	562	IFA	33.8	7.8	41.6
Fooladvand (46)	1998	Farsi	Cross-sectional	29	365	ELISA	37.8	5.7	43.6
Yad (6)	2014	English	Cross-sectional	33	501	ELISA	27.8	1.3	29.1

Table 1 Baseline characteristics of included studies in meta-analysis of seroprevalence of *Toxoplasma gondii* in Iranian pregnant women of (concluded)

Reference	Publication year	Publication language	Type of study	Quality score	Sample size	Serological method	Prevalence of women with positive antibody (%)		
							IgG	IgM	IgM + IgG
Jalai (16)	2013	Farsi	Cross-sectional	34	211	ELISA	30.8	1.4	30.8
Babaie (36)	2013	English	-	35	419	ELISA	34.4	18.8	34.4
Jamshidi (12)	2012	English	Cross-sectional	35	600	ELISA	41.9	0.0	41.9
Kalantari (17)	2013	Farsi	Cross-sectional	29	175	ELISA	60.6	0.0	60.6
Magsood (18)	2013	Farsi	Cross-sectional	33	350	ELISA	30.0	2.9	32.9
Manoochehrinaeini (19)	2004	Farsi	Cross-sectional	32	394	IFA	27.4	0.0	27.4
Manoochehrinaeini (20)	2006	Farsi	Cross-sectional	30	384	IFA	-	-	27.6
Mardani (21)	2004	Farsi	Cross-sectional	31	600	ELISA	41.0	-	41.0
Moosavi (22)	2014	Farsi	Cross-sectional	28	185	ELISA	10.3	0.6	10.3
Parvizpoor (23)	2010	Farsi	Cross-sectional	27	201	ELISA	43.2	28.3	55.0
Rasti (24)	2014	English	Cohort	34	798	ELISA	42.7	0.6	43.3
Rostaminejad (53)	2012	Farsi	Descriptive	32	496	ELISA	31.0	7.0	38.0
Saffar (25)	1997	Farsi	Descriptive	33	612	ELISA	71.0	-	71.0
Sharbatkhori (26)	2014	English	Cross-sectional	33	555	ELISA	39.8	3.4	40.4
Sharifi-mood (27)	1998	Farsi	Cross-sectional	32	200	IFA	27.0	1.3	27.0
Siyadat Panah (28)	2013	English	Cross-sectional	36	1057	ELISA	69.9	5.3	75.0
Sohrabi (29)	2007	Farsi	Cross-sectional	31	79	ELISA	35.4	-	35.4

IFA = indirect fluorescence antibody test.

ELISA = enzyme-linked immunosorbent assay.

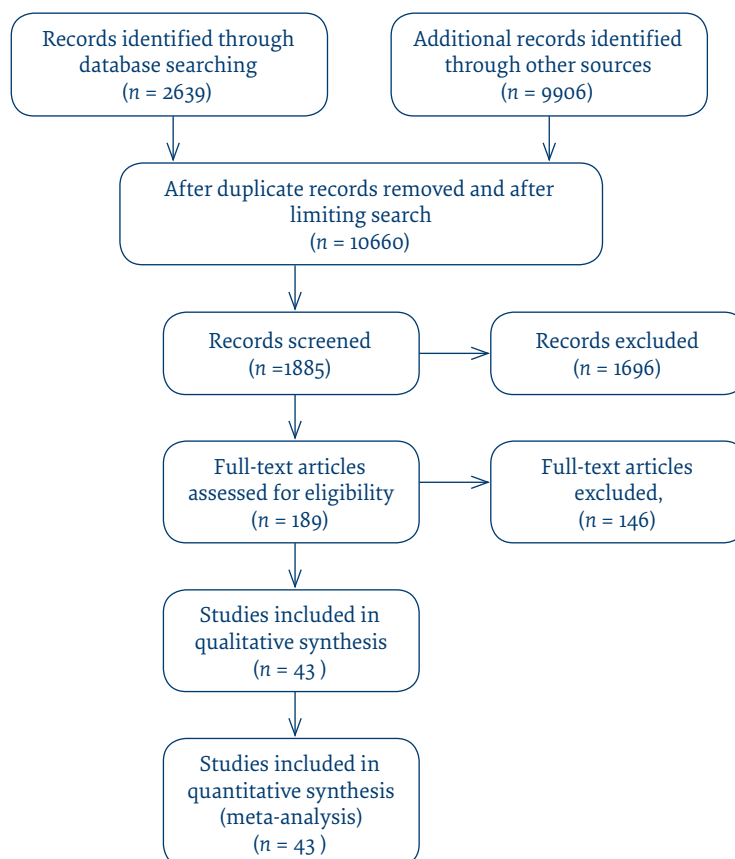


Figure 1 Selection process of studies

the participants was stated in 14 records, varying between 21.0 and 29.9 years. Serologic methods used for diagnosis of toxoplasma infection were indirect fluorescence antibody test (12 studies), ELISA (29 studies) and both (2 studies).

This meta-analysis involved 22 644 pregnant women from different areas in the Islamic Republic of Iran. Minimum and maximum sample sizes were 72 and 4120 respectively. Raised IgG titration ranged between 10.3% (23) and 77.2% (51) (10.8% and 76.6% respectively adjusting by Bayesian analysis). In addition, the prevalence of raised IgM varied from 0.0% (12,17,19,47) to 28.3% (23) (Bayesian adjusted values 0.4% and 11.9%).

The pooled prevalence of toxoplasmosis among Iranian pregnant women was estimated at 41.3% using the random effects model (I-squared: 98.7%, $Q = 3279.2$; $P < 0.0001$) and 45.4% using the fixed model. According to the heterogeneity between the included studies, the results provided by the first model are acceptable. Values for the seroprevalence of raised IgG and IgM using the random effects model were 39.2% (I-squared: 98.7%, $Q = 3178$; $P < 0.0001$) and 4.0% (I-squared: 94.3%, $Q = 453.8$; $P < 0.0001$) respectively. These high I-squares indicate considerable heterogeneity between the results.

Excluding the extreme results of some studies (23,28,51,53), the total prevalence of toxoplasmosis, raised IgG prevalence and raised IgM prevalence were estimated at 40.3% (I-squared: 98.3%, $Q = 2322$; $P < 0.0001$), 38.9% (I-squared: 98.7%, $Q = 2751.3$; $P < 0.0001$) and 3.1% (I-squared: 91.8%, $Q = 293$; $P < 0.0001$) respectively. Also, according to the meta-regression analysis, publication year had no significant effect in heterogeneity among primary studies.

Discussion

Our systematic review and meta-analysis showed that more than 41% of Iranian pregnant women are seropositive for *T. gondii* antibodies.

According to the results of the other systematic reviews and meta-analyses, Seroprevalence of toxoplasmosis among Iranian pregnant women is similar to that in the general population in the Islamic Republic of Iran, but is lower than the prevalence of toxoplasmosis in other high risk groups, e.g. immunocompromised groups such as patients with HIV/AIDS, or cancer and kidney transplant patients (3,8,55) (Table 2). These differences are related to the different characteristics of the studies (general populations, immunocompromised groups, different nutritional behaviours, geographical conditions and various diagnostic serologic methods).

Some research has shown that prevalence of toxoplasmosis is higher in temperate climate regions and lower in cold and hot and dry areas. Inappropriate conditions for growth and development of oocytes in the areas with hot and dry climates may be an explanation for low prevalence of toxoplasmosis in such areas (9,22).

Prevalence of toxoplasmosis among pregnant women in a Chinese study was less than 10% (56), which was

Table 2 Seroprevalence of *Toxoplasma gondii* in the Iranian population group based on other meta-analyses

Reference	Population group	Sample size (No.)	Pooled estimate based on random effect (%)
Daryani (3)	General population	52 294	39.3
Borna (8)	Women of childbearing age	13 480	39.9
Ahmadpour (55)	HIV/AIDS patients	1 032	50.1
Ahmadpour (55)	Cancer patients	1 071	45.1
Ahmadpour (55)	Transplant patients	702	55.1

lower than the rates estimated in our meta-analysis. That was also the case for a study carried out in Norway which estimated the IgG seroprevalence as 9.3% (57). Out of 760 pregnant women investigated in a study in Thailand, 25% were seropositive for toxoplasmosis (22% IgG positive and 3% IgG+IgM positive) (58). Two different studies, reported the seroprevalence of Korean pregnant women as 3.7% (59) and 0.8% (60).

Seroprevalence of IgG and IgM among Indian pregnant women was 45% and 3.3% respectively (61) corresponding values for 1149 Turkish pregnant women were 60.4% and 3.0% respectively (62). A systematic review conducted in Brazil indicated that more than 50% of primary school children as well as 50–80% of women during the reproductive period were seropositive for toxoplasmosis (63). The variability was due to multiple factors such as contact with faeces of infected cats, adult oocyte consumption, nutritional behaviours and climate.

Congenital toxoplasmosis is one of the most important fetal diseases and is also a major factor for developing mental retardation. Infection during pregnancy can facilitate the development of such pathologies. During the first months of pregnancy particularly, *T. gondii* infection can cause abortion and even stillbirth (64). Incidence of the congenital infection during pregnancy was estimated as 1–8 per 1000 pregnancies in a 2013 Iranian review (8). Therefore, in IgM-seropositive pregnant women, a treatment regimen for acute infection is necessary to prevent the development of congenital toxoplasmosis and its complications. Diagnosis of *T. gondii* infection among pregnant women in populations with low prevalence is critical, however, it is not possible for all pregnant women and is restricted to suspected cases. Therefore, routine screening among low-risk pregnant women is not recommended; it is only suggested for those with a higher risk of infection (65).

Unfortunately, we could not perform a meta-analysis based on the different climatic areas of the Islamic Republic of Iran because of the low number of studies

conducted in temperate and cold regions. Variations in the primary studies due to factors such as different cut-off points for positive IgG, sampling methods, questionnaires used, situations for data collection, sample sizes and date of studies are other limitations of our study.

This systematic review and meta-analysis provides a comprehensive understanding of the seroepidemiology of *T. gondii* among Iranian pregnant women. Such background evidence can provide important guidelines for policy-makers to implement screening and educational programmes for high-risk populations in the Islamic Republic of Iran.

Acknowledgments

The authors thank the Student Research Committee and Deputy for Research of Mazandaran University of Medical Sciences for their kind cooperation.

Funding: This study was financially supported by Mazandaran University of Medical Sciences.

Competing interests: None declared.

Séroprévalence de l'infection à *Toxoplasma gondii* chez les femmes enceintes iraniennes : examen systématique et méta-analyse

Résumé

Contexte : La toxoplasmose est une importante préoccupation de santé publique du fait de sa capacité de transmission prénatale. Différentes études sérologiques ont fait état de séroprévalences de la toxoplasmose variées chez les femmes enceintes iraniennes. L'estimation de la prévalence globale de cette infection est nécessaire en vue de l'élaboration de politiques.

Objectif : Le but de la présente étude est d'estimer la prévalence de l'infection à *Toxoplasma gondii* en République islamique d'Iran au moyen de l'examen systématique et des méthodes de méta-analyse.

Méthodes : Nous avons effectué des recherches dans différentes bases de données nationales et internationales pour identifier les études pertinentes. Afin de renforcer la sensibilité de la recherche, nous avons évalué toutes les références et interrogé les chercheurs et centres de recherche concernés. Les études finales requises pour la méta-analyse ont été sélectionnées en fonction des résultats de l'évaluation de la qualité ainsi que des critères d'inclusion/exclusion. En raison de l'hétérogénéité des résultats primaires, des modèles à effets aléatoires ont été utilisés pour estimer la prévalence globale de *Toxoplasma gondii*. Nous avons recruté 43 études, la taille totale de l'échantillon étant de 22 644 dans la méta-analyse.

Résultats : Les séroprévalences globales de l'infection à *Toxoplasma gondii*, des anticorps IgG et des anticorps IgM ont été estimées à 41,3 % (IC à 95 % : 35,8-46,8), 39,2 % (IC à 95 % : 33,3-45,1) et 4,0 % (IC à 95 % : 3,1-4,9) respectivement.

Conclusion : Notre étude a montré qu'une proportion considérable de femmes enceintes iraniennes courent un risque élevé de toxoplasmose.

مستوى الانتشار المصلي لعدوى المقوسة العوندية بين النساء الحوامل الإيرانيات: استعراض منهجي وتحليل وصفي

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الخلاصة

الخلفية: يمثل داء المقوسات شائعاً خطيراً للصحة العامة بسبب إمكانية انتقاله للجنين أثناء الحمل. وأفادت دراسات مصلية مختلفة وجود مستويات انتشار مصلي مختلفة لداء المقوسات في صفوف النساء الحوامل الإيرانيات.

الهدف: يعد تقدير مستوى الانتشار المجمع لهذه العدوى أمراً ضرورياً لرسم السياسات. ومن ثم، فقد تمثل الهدف من هذه الدراسة في تقدير مستوى انتشار عدوى المقوسة العوندية في إيران باستخدام استعراض منهجي وأساليب التحليل الوصفي.

طرق البحث: عمدنا إلى البحث في قواعد بيانات وطنية ودولية مختلفة لتحديد الدراسات ذات الصلة. ولتحسين الحساسية البحثية، قمنا بتحليل جميع المراجع، كما أجرينا مقابلات مع الباحثين والمراكز البحثية المعنية. واختيرت الدراسات النهائية المطلوبة لأغراض التحليل الوصفي وفقاً لنتائج تقييم الجودة إلى جانب معايير الشمول/الاستبعاد. ونظراً لتناثر النتائج الأولية، استخدمت نماذج الآثار العشوائية لتقدير مستوى الانتشار المجمع لعدوى المقوسة العوندية. وأجريت تحاليل إحصائية باستخدام برمجية STATA SE V.11. ولقد ضم التحليل الوصفي 43 دراسة منشورة، بعينة إجمالية بلغت 22,644.

النتائج: قُدرت مستويات الانتشار المصلي المجمع لعدوى المقوسة العوندية وأضداد الجلوبيولين المناعي G وأضداد الجلوبيولين المناعي M بمقدار 41,3% [95% CI: 35,8-46,8]، و39,2% [95% CI: 33,3-45,1]، و4,0% [95% CI: 3,1-4,9] على الترتيب.

الاستنتاج: أظهرت دراستنا أن نسبة كبيرة من النساء الحوامل الإيرانيات تواجهن مخاطر مرتفعة للإصابة بعدوى المقوسة العوندية.

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