TITLE: CONGENITAL TOXOPLASMOSIS AMONG INDIAN NEONATES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

This review aims to give an overview of toxoplasmosis, a zoonotic illness widely present worldwide. The research delves into the occurrence of toxoplasmosis in new borns in India, with the aim of offering a thorough insight into the disease's status. The primary objective is to guide the creation of interventions to tackle this critical health concern, particularly its implications for abortion and congenital disorders. Systematic searches were conducted across various databases, including PubMed, ScienceDirect, Google Scholar, and Springer, to identify original studies examining the prevalence of Toxoplasma gondii infections in new borns in India. The search process resulted in the inclusion of a total of 7 studies in the systematic review, 7 of which were entered into the meta-analysis. Estimate value 0.298 indicates overall effect size. The p value is < 0.01 shows highly significance. I2 value is 98.65% which shows heterogenicity.

INTRODUCTION

Toxoplasmosis is a disease caused by infection with obligate intracellular parasite toxoplasma gondi. It is problematic when acquired during pregnancy, due to the risk of vertical transmission. The infection is usually asymptomatic, including during pregnancy, so serological screening in routine prenatal care is essential for early diagnosis and identification of susceptible pregnant women. Cases of congenital toxoplasmosis can evolve with miscarriage, neurological and visual abnormalities, or be asymptomatic at birth developing late clinical manifestations. Congenital infection is confirmed by serology with identification of IgG and IgM antibodies against T. gondii and the avidity test, based on detection of toxoplasma DNA in the amniotic fluid by polymerase chain reaction (PCR). The latter test has high sensitivity (87%) and specificity (99%), contributes to diagnosis of fetal infection, and reduces unnecessary treatment with sulfadiazine, pyrimethamine, and folinic acid. Early diagnosis and prompt and adequate treatment reduce future damage to the fetus. Social factors have also been related to the risk of developing congenital toxoplasmosis, since some factors interfere directly in the quality of prenatal care, with late collection of serological samples, delay in starting treatment, and delay in referral to follow-up at treatment centers. Despite the importance of this disease, there is still no international consensus on its surveillance in pregnant women. Acute toxoplasma infection acquired after birth is usually asymptomatic. This condition should be distinguished from chronic toxoplasma infection which describes the '*persistence of tissue cysts'* containing parasites in clinically asymptomatic patients. The seroprevalence of toxoplasmosis is dependent on locale and age of the population studied. The clinical

implications of toxoplasma infection in pregnant women are manifold. Such patients may have spontaneous abortions, stillbirths, or premature delivery in addition to various foetal anomalies.

METHODS AND MATERIALS

Search strategy

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were used to conduct this study. Our search was limited to articles, publications investigating the prevalence of *T. gondii* infections among neonates in indians, databases, including PubMed, ScienceDirect, Springer, and Google Scholar, The search process was carried out using the following keywords: "toxoplasmosis," "*Toxoplasma gondii*," "*T. gondii*," "congenital toxoplasmosis," "newborn," "neonate," "infant," "fetus," "meta-analysis," "systematic review," "Indian."

Inclusion and exclusion criteria

Following the removal of duplicate entries, original studies and brief reports were evaluated according to the following inclusion criteria: (1) investigation of the incidence of *T. gondii* in Indian neonates; (2) assessment of only mothers and their infants; (3) diagnosis of toxoplasmosis by performing PCR on amniotic fluid or detecting IgG and/or IgM antibodies against *T. gondii* in the serum, and cord blood; and (4) adoption of a cross-sectional design. The exclusion criteria were: (1) irrelevancy; (2) publication in languages other than English or Persian; (3) inclusion of aborted fetuses; (4) lack of suitable data; and (5) review articles.

Study selection and data extraction were After the decision was made to include a paper, information was extracted on the first author, year of publication, research location, sample size, language, type of study, number and age of positive cases, diagnostic tests, and type of antibody using a data extraction form. The data generated are given below.

STUDY	R	N
A A Adesiyun	43.7%	504
H V Manjunathachar	61.1%	144
A H Zargar	53.14%	2371
Sarman Singh	22.4%	1464
Sarman Singh	3.3%	1080
Bharat	48%	1141
Abhishek	21%	8397

META-ANALYSIS

In this study, forest plots were used to estimate the pooled effect size and effect of each study with confidence intervals (CIs) to provide a visual summary of the data. In addition, common approaches, including the Cochran Q test and I^2 statistic, were used to evaluate heterogeneity among the studies, with I^2 values of <25%, 25-50%, and >50% considered to indicate low,

moderate, and high heterogeneity, respectively. The assessment of heterogeneity and a fixed-effects model (Mantel-Haenszel) were used to compute the overall effect.

RESULTS AND INTREPRETATION

Correlation Coefficients

Fixed-Effects Model (k = 7)

	Estimate	se	Z	p	CI Bound Lower	CI Bound Upper
Intercept	0.298	0.00814	36.6	< .001	0.282	0.314
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Heterogeneity Statistics

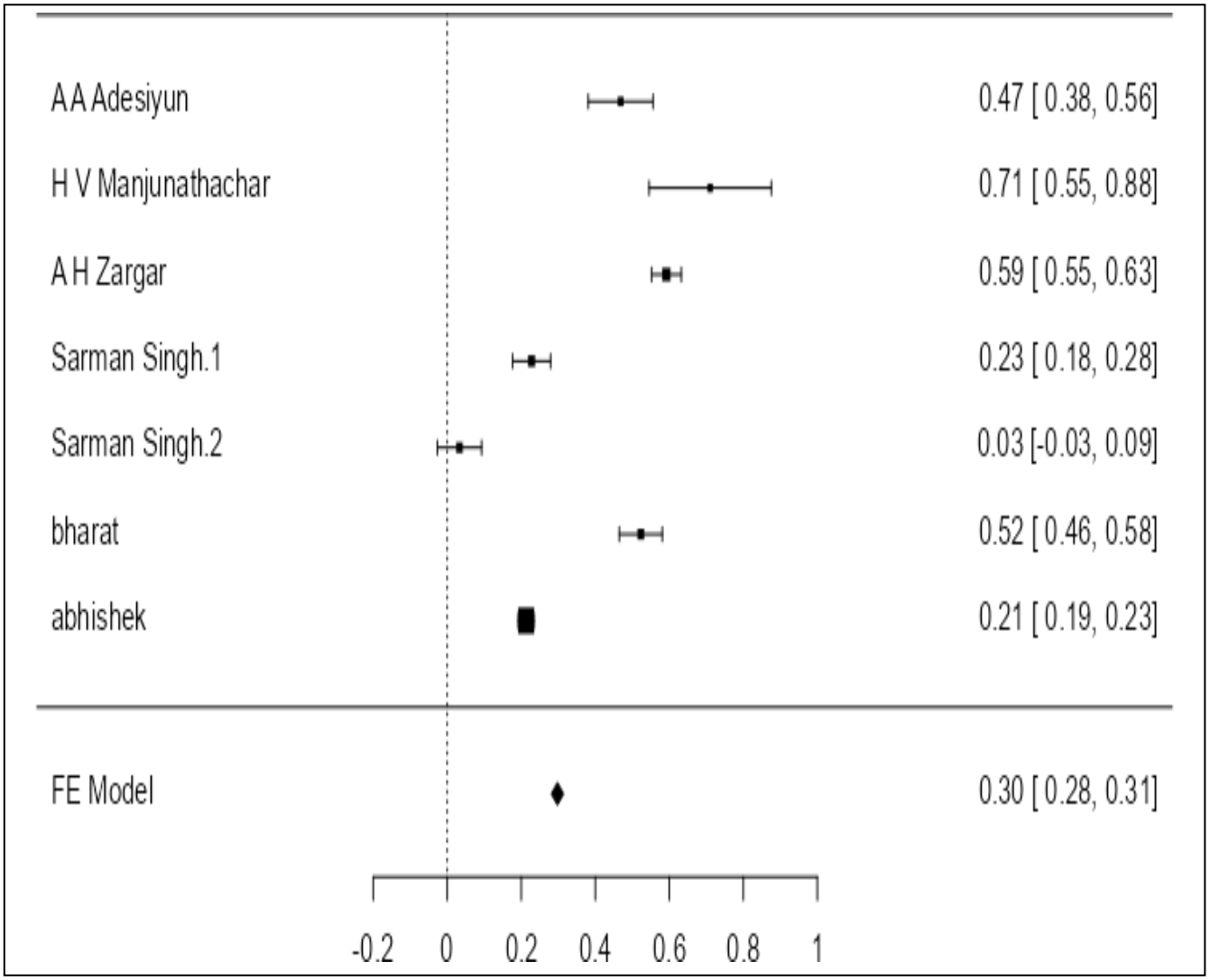
Tau	Tau²	I²	H²	R²	df	Q	p
0.000	0 (SE= NA)	98.65%	74.031	.	6.000	444.189	< .001

The analysis was carried out using the Fisher r-to-z transformed correlation coefficient as the outcome measure. A fixed-effects model was fitted to the data. The Q-test for heterogeneity (Cochran 1954) and the I² statistic are reported. Studentized residuals and Cook's distances are used to examine whether studies may be outliers and/or influential in the context of the model. Studies with a studentized residual larger than the 100 x (1 - 0.05/(2 X k))th percentile of a standard normal distribution are considered potential outliers (i.e., using a Bonferroni correction with two-sided alpha = 0.05 for k studies included in the meta-analysis). Studies with a Cook's distance larger than the median plus six times the interquartile range of the Cook's distances are influential. The rank correlation test and the regression test, using the standard error of the observed outcomes as predictor, are used to check for funnel plot asymmetry.

A total of k=7 studies were included in the analysis. The observed Fisher r-to-z transformed correlation coefficients ranged from 0.0330 to 0.7105, with the majority of estimates being positive (100%). The estimated average Fisher r-to-z transformed correlation coefficient based on the fixed-effects model was \hat{\theta} = 0.2977 (95% CI: 0.2818 to 0.3137). Therefore, the average outcome differed significantly from zero (z = 36.5631, p < 0.0001). According to the Q-test, the true outcomes appear to be heterogeneous (Q(6) = 444.1892, p < 0.0001, I² = 98.6492%). One study (abhishek) had a relatively large weight compared to the rest of the studies (i.e., \mbox{weight} \ge 3/k, so a weight at least 3 times as large as having equal weights across studies). An examination of the studentized residuals revealed that several studies (A A Adesiyun; H V Manjunathachar; A H Zargar; Sarman Singh.1; Sarman Singh.2; bharat; abhishek) had values larger than ± 2.6901 and may be potential outliers in the context of this model. According to the Cook's distances, one study (abhishek) could be considered to

be overly influential. The regression test indicated funnel plot asymmetry ($p < 0.0001$) but not the rank correlation test ($p = 0.7726$).

FOREST PLOT

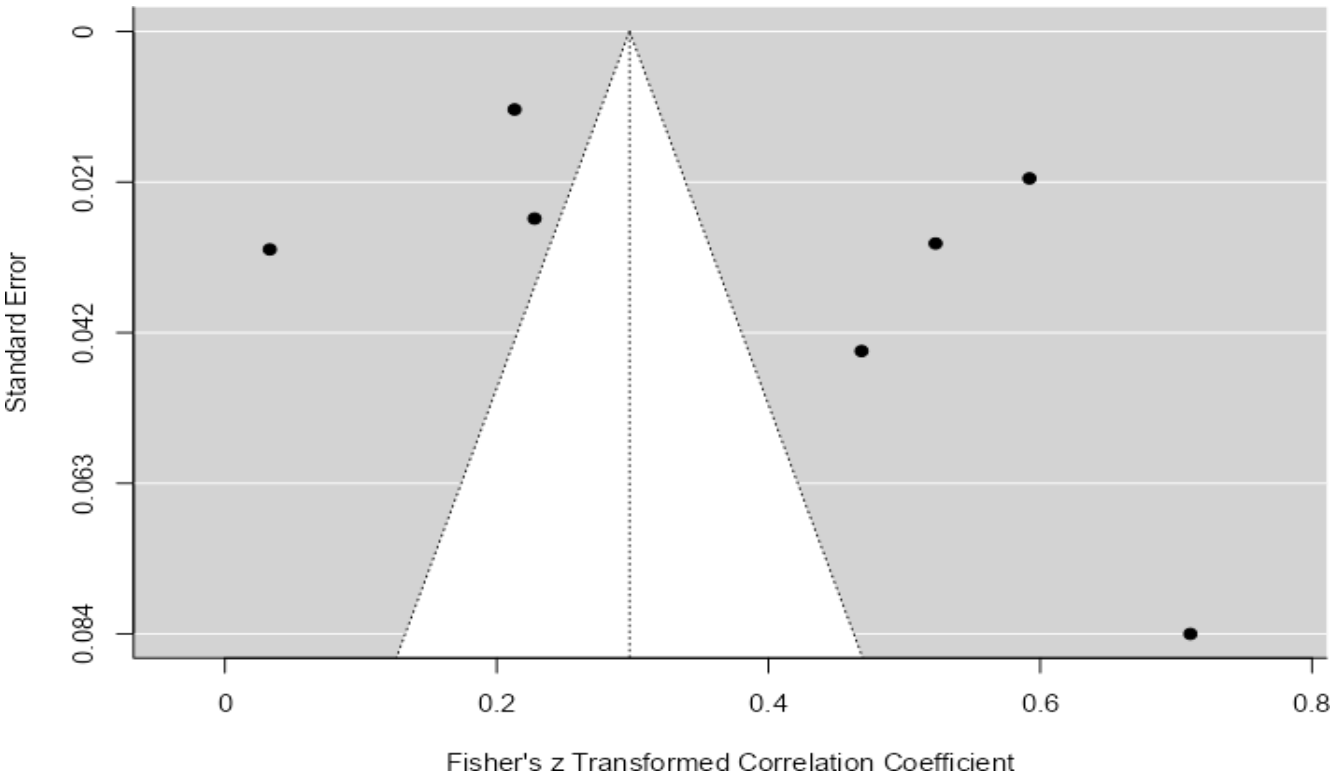


PUBLICATION BIAS ASSESSMENT

Test Name	value	p
Fail-Safe N	3308.000	< .001
Begg and Mazumdar Rank Correlation	0.143	0.773
Egger's Regression	8.538	< .001
Trim and Fill Number of Studies	2.000	.

Note. Fail-safe N Calculation Using the Rosenthal Approach

FUNNEL PLOT



CONCLUSION:

In conducting the meta-analysis utilizing Fisher r-to-z transformed correlation coefficients and employing a fixed-effects model, the study encompassed a total of seven contributing research endeavors. The calculated Fisher r-to-z transformed correlation coefficients varied from 0.0330 to 0.7105, with an overarching positive trend evident in the majority of estimates (100%). The application of a fixed-effects model resulted in an estimated average Fisher r-to-z transformed correlation coefficient of ɵˆ = 0.2977 θ =0.2977 (95% CI: 0.2818 to 0.3137), signifying a statistically significant departure from zero (θ = 36.5631 , θ < 0.0001 z=36.5631,p<0.0001). However, the analysis brings attention to pronounced heterogeneity among the true outcomes, as indicated by the Q-test (θ (6) = 444.1892 , θ < 0.0001 , θ 2 = 98.6492 Q(6)=444.1892,p<0.0001,I 2 =98.6492). The influence of individual studies was assessed, revealing that the study labeled "abhishek" wielded a substantial weight, potentially exerting a disproportionate impact on the overall findings.

Further scrutiny using studentized residuals identified several studies as potential outliers, with "abhishek" notably standing out. Cook's distances singled out "abhishek" as an overly influential study. The funnel plot asymmetry test signaled potential publication bias, as reflected in the regression test (θ < 0.0001 p<0.0001), while the rank correlation test did not show significant asymmetry (θ = 0.7726 p=0.7726). In summary, while the meta-analysis points to a significant average correlation, the high heterogeneity, potential outliers, and the influence of certain studies, especially "abhishek," underscore the need for cautious interpretation. The detected funnel plot asymmetry suggests the possibility of publication bias, urging further investigation before drawing definitive conclusions from these findings.

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