A Retrospective Analysis of the Correlation between Trichomonas Vaginalis Infection and Infertility

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Abstract

Background: *Trichomonas vaginalis* (*T. vaginalis*) is an extracellular flagellated protozoan parasitizing the human genital and urinary tracts. *T. vaginalis* infection impacts human reproductive function, but whether it causes infertility is still a matter of debate.

Methods: In this work, we consulted 237 relevant articles, which were classified into three categories: epidemiological investigations (104), review articles (40), and research articles (62). RevMan 5.4 was used to conduct a meta-analysis of the articles reporting epidemiological investigations comparing the incidence of *T. vaginalis* infection between infertile and fertile groups.

Results: The results indicated that rate of *T. vaginalis* infection in the infertile group was lower than that in the fertile group. However, an epidemiological survey showed that the infertility rate of population infected with *T. vaginalis* was significantly higher than that of population without *T. vaginalis* infection. Most review articles stated that *T. vaginalis* infection causes infertility, while a small fraction of these articles were inconclusive. The conclusion that *T. vaginalis* infection can lead to infertility is supported by the research articles, which indicated the main pathogenic mechanisms are as follows: *T. vaginalis* impairs sperm quality, resulting in infertility; the immune response triggered by *T. vaginalis* infection impacts human reproductive function; and *T. vaginalis* impairs ovum quality, resulting in infertility.

Conclusion: Our study confirmed that *T. vaginalis* infection can lead to infertility and provides a foundation for further investigations into its pathogenesis.

Background

Trichomonas vaginalis (*T. vaginalis*) infection is a ubiquitous and curable sexually transmitted disease [1]. In female patients, this infection mainly leads to trichomonas vaginitis and urethritis. In contrast, most male patients with *T. vaginalis* infection experience no obvious symptoms, although some have urethritis and prostatitis, which can cause infertility in severe cases [2, 3]. According to estimates from the WHO, at least 174 million people worldwide are infected with *T. vaginalis* annually [4], and the global infection rates for females and males are 5.3% and 0.6%, respectively. However, these rates vary according to geographic region, for example, the infection rate among women is 3.1% in the United States [5] and 4.7% in the Mediterranean [6], whereas it is as high as 41% in the Mwanza region of Tanzania and 31% in Lakai, Uganda [2]. The rate of *T. vaginalis* infection also varies significantly in different regions of China. For instance, the infection rate among women is 1.2% in Shantou, Guangdong [7], 13.9% in Zhengzhou, Henan, 1.6% in Xinxiang, Henan [8], and 7.0% in Ningbo, Zhejiang [9].

Most females with symptomatic cases of *T. vaginalis* infection experience symptoms such as increased vaginal secretions, perineal pruritus, and irritation. The infection also plays an important role in the occurrence of cervical tumors, postoperative infections, and adverse pregnancy outcomes [6] and is a significant factor for atypical pelvic inflammation and infertility [5], which impacts female reproductive function. For male patients, trichomoniasis is a cause of nongonococcal urethritis and chronic prostatitis

[10, 11], and the extracellular secretions of *T. vaginalis* can impair sperm activity, which affects male reproductive function [12]. In addition, many studies have shown that *T. vaginalis* infection is a risk factor for Acquired Immune Deficiency Syndrome (AIDS) [13] and is a synergistic factor for Mycoplasma and Chlamydia infection [6].

Despite these findings, some articles still question whether *T. vaginalis* infection can cause infertility, and some deny its influence on fertility. Therefore, by reviewing many relevant papers, we aimed to analyze the correlation between *T. vaginalis* infection and infertility to provide evidence that *T. vaginalis* infection can result in infertility and a foundation for investigations into its pathogenesis.

Methods

Literature retrieval and classification

The databases used for literature retrieval were PubMed, Ovi-Medline medical literature, China national knowledge infrastructure (CNKI), and Wanfang Data. The keywords used for literature retrieval were “Trichomonas vaginalis” and “Infertility.” The retrieved articles were reviewed, and irrelevant articles were removed. The remaining articles were categorized as epidemiological investigations, reviews, and research articles.

Literature inclusion and exclusion criteria

Inclusion criteria for epidemiological investigations

The inclusion criteria for epidemiological investigations were as follows: (1) The article contains statistics regarding the incidence of infertility among people with or without *T. vaginalis* infection; (2) the article contains statistics regarding *T. vaginalis* infection among fertile and infertile patients; and (3) the article contains data comparing the incidence of *T. vaginalis* infection between fertile and infertile groups. For articles with the same statistical items, the most current and comprehensive ones were selected.

Exclusion criteria for epidemiological investigations

The exclusion criteria for epidemiological investigations were as follows: (1) The article does not mention the impact of *T. vaginalis* on reproductive function, or the relevant data are incomplete; (2) the article is concerned with the diagnosis and treatment of *T. vaginalis*; and (3) the article only contains data on infertility caused by *T. vaginalis* infection with no corresponding data from people without *T. vaginalis* infection.

Inclusion criterion for review articles

The article concerns the correlation between *T. vaginalis* infection and infertility.

Exclusion criterion for review articles

The article does not concern the correlation between *T. vaginalis* infection and infertility.

Inclusion criterion for research articles

The article concerns the pathogenesis of infertility caused by *T. vaginalis* infection.

Exclusion criteria for research articles

The exclusion criteria for research articles were as follows: (1) The article does not concern the correlation between *T. vaginalis* infection and infertility and (2) the article does not concern the pathogenesis of infertility caused by *T. vaginalis* infection.

Quality evaluation of and statistical methods for epidemiological investigations

The Newcastle-Ottawa scale (NOS) was used to evaluate the quality of the epidemiological investigations, and articles that scored ≥6 were considered to be high-quality articles. A meta-analysis was performed on selected articles using RevMan 5.4 software, and a forest plot was drawn to calculate the p-value and conduct the heterogeneity test. If $p < 0.05$ or inconsistency (I^2) ≥ 50%, heterogeneity among the research results was confirmed, and the origin of the heterogeneity was analyzed. The results were then analyzed using a random effect model. If $p > 0.05$ or $I^2 \leq 50\%$, good consistency among the research results was confirmed, and the results were analyzed using a fixed effect model along with the calculation of the OR and 95% confidence interval.

Results

A total of 237 articles were retrieved (Figure 1). After removing 31 irrelevant articles, the remaining 206 articles were classified into three categories, epidemiological investigations (104), review articles (40), and research articles (62).

Epidemiological investigations

Literature inclusion

A total of 104 epidemiological articles were reviewed by reading through the content according to the inclusion and exclusion criteria. After reviewing, five relevant articles were selected, and four of the articles (Table 1) concerned the incidence of *T. vaginalis* infection among patients with infertility. In these articles, people with infertility were assigned to the experimental group, while healthy people (i.e., people with normal reproductive function) were assigned to the control group. There were large numbers of samples in these articles, which were deemed as high-quality articles based on the meta-analysis (NOS score ≥ 6). The fifth article (Table 1) concerned the incidence of infertility among people with *T. vaginalis*

infection, in which people with *T. vaginalis* infection were assigned to the experimental group, while people without *T. vaginalis* infection were assigned to the control group.

Table 1
The information of five relevant epidemiological articles

Number	First author	Year	Location	Total sample	Experimental group	Control group	NOS
1	Rajabpour M	2020	Tehran	277	2/97(2.1%)	24/180(13.3%)	7
2	Gimenes F	2014	Turkey	76	7/52(13.5%)	3/24(12.5%)	8
3	Casari E	2010	Milan	952	1/396(0.25%)	3/556(0.54%)	7
4	Okonofua FE	1995	Nigeria	178	4/92(4.3%)	2/86(2.3%)	7
5	Aloui D	2015	Brazil	471	3/32(9.4%)	11/439(2.5%)	7

Note: 1-4 Experimental group: the number (incidence) of *T. vaginalis* infection among patients with infertility; Control group: the number (incidence) of *T. vaginalis* infection among people with normal reproductive function.

5 Experimental group: the number (incidence) of infertility among people with *T. vaginalis* infection; Control group: the number (incidence) of infertility among people without *T. vaginalis* infection.

Analysis of the results

A forest plot was used to illustrate the correlation between infertility and *T. vaginalis* infection, and a funnel plot was used to determine publication bias. RevMan 5.4 was employed to summarize the data from the four articles on the incidence of *T. vaginalis* infection among patients with infertility and to generate the forest plot (Figure 2) and funnel plot for publication bias estimation (Figure 3) based on the summarized data. These four articles included a total of 1,483 research subjects, with 637 cases in the experimental (infertile) groups and 846 cases in the control (fertile) groups [6, 14–16]. As shown in Figure 2, the heterogeneity test yielded $Chi^2 = 6.66$, $p = 0.08$, and $I^2 = 55\%$, indicating heterogeneity among the results from the respective studies ($p < 0.05$, $I^2 \geq 50\%$). Therefore, the random effect model was employed to perform the analysis. Using the combined data from the four articles, the OR and 95% confidence interval were calculated as 0.45 and 0.22–0.92, respectively, and z and p values of the combined effect size were as 2.19 and 0.03, respectively. Based on these results, the incidence of *T. vaginalis* infection between the infertile experimental group and fertile control group was significantly different ($p < 0.05$). As shown in Figure 3, each point in the funnel plot represents a study that was included in the analysis. The horizontal axis is the OR of the effect size, and the vertical axis is the standard error. The accuracy of the study increased with increasing sample size, and all four included epidemiological investigations are based on large samples, which are concentrated in the middle and top

part of Figure 2. However, the poor distribution symmetry of the individual sample points indicates publication bias. Since only a small number of studies were included in this work, errors may occur when determining the distribution symmetry of each point. Therefore, continuous collection of relevant articles is required for follow-up study.

Epidemiological investigations of infertility among patients with *T. vaginalis* infection are rather scarce, and we only retrieved one article (Table 1) [17]. This study included 471 research subjects, with 32 cases in the experimental group (with *T. vaginalis* infection) and 439 cases in the control group (without *T. vaginalis* infection). Three cases in the experimental group had infertility, for an incidence of 9.4%, while 11 cases in the control group had infertility, for an incidence of 2.5%. Based on these results, patients with *T. vaginalis* infection are at increased risk of infertility.

Review articles

In this work, 40 review articles were retrieved, and 11 of them met the inclusion and exclusion criteria. The conclusions of each article are summarized in Table 2. Ten of these eleven articles [12, 18–26] concluded that *T. vaginalis* infection can result in infertility, mainly caused by impaired sperm function or induction of inflammation. The remaining article [27] did not clearly state whether *T. vaginalis* infection can lead to infertility.

Table 2
The information of review articles

Title	First author	Year	Conclusion	*T. vaginalis* causes infertility
Sexually transmitted diseases and infertility	Tsevat DG	2017	*T. vaginalis* can cause inflammation of the female upper reproductive tract and lead to tubal injury and infertility.	Yes
Human parasitic protozoan infection to infertility: a systematic review	Shiadeh MN	2016	*T. vaginalis* can affect sperm activity and function in men, and can cause complications such as pelvic inflammation in women, leading to infertility.	Yes
Sexually Transmitted Disease and Male Infertility: A Systematic Review	Fode M	2016	*T. vaginalis* may have an adverse effect on sperm motility.	Yes
Trichomoniasis - are we giving the deserved attention to the most common non-viral sexually transmitted disease worldwide?	Menezes CB	2016	*T. vaginalis* can increase the pH of vaginal, which is conducive to the occurrence of bacterial vaginosis and then damage the reproductive system.	Yes
Trichomonas vaginalis:pathogenicity and potential role in human reproductive failure	Mielczarek E	2016	There is a correlation between *T. vaginalis* infection and serious adverse health consequences experienced by women, including infertility. In men, trichomoniasis has been also associated with infertility through inflammatory damage to the genitourinary tract or interference with sperm function.	Yes
The secretory products of Trichomonas vaginalis decrease fertilizing capacity of mice sperm in vitro	Roh J	2015	The extracellular polymer of *T. vaginalis* can reduce sperm activity.	Yes
Male infertility: a public health issue caused by sexually transmitted pathogens	Gimenes F	2014	*T. vaginalis* produces several cytotoxic molecules and lytic factors, mediates cytotoxicity by damaging the target cell plasma membrane, which could be a mechanism involved in male infertility, with toxicity to the sperm as well as to epithelial cells from the infected male genital tract.	Yes
Male accessory gland infection and sperm parameters (review)	La Vignera S	2011	*T. vaginalis* affects reproductive function by reducing sperm motility and the number of normal sperm.	Yes

Title	First author	Year	Conclusion	*T. vaginalis* causes infertility
Impact of T. vaginalis infection on innate immune responses and reproductive outcome	Fichorova RN	2009	*T. vaginalis* affect the reproductive system in women by causing inflammation and complications, and increasing the risk of bacterial and viral infections.	Yes
Protozoan infections in the male genital tract	Martínez-García F	1996	The secreted protein of *T. vaginalis* can kill sperm cells.	Yes
Sexually transmitted diseases and their relation to male infertility	Moskowitz MO	1992	The role of sexually transmitted diseases caused by *T. vaginalis* is controversial in male infertility.	Not applicable

Table 3
The information of research articles

Title	First author	Year	Conclusion	*T. vaginalis* causes infertility
Vaginal neutrophils eliminate sperm by trogocytosis	Olivera-Valle I	2020	*T. vaginalis* infection induces the vaginal polymorphonuclear which are highly efficient at killing sperm by way of a neutrophil extracellular traps-independent, contact-dependent and serine proteases-dependent engulfment mechanism.	Yes
The secretory products of Trichomonas vaginalis decrease fertilizing capacity of mice sperm in vitro	Roh J	2015	The extracellular polymeric substances of *T. vaginalis* can significantly decrease sperm motility, viability, and functional integrity, which result in a decreased fertilization rate in vitro.	Yes
Trichomonas adhere and phagocytose sperm cells: adhesion seems to be a prominent stage during interaction	Benchimol M	2008	The adhesion between trichomonads to the sperm cell occurr either by the flagella or sperm head, which result the decrease in the spermatozoa motility and intense semen agglutination. *T. vaginalis* interact with sperm cells provoking damage and death of these reproductive cells.	Yes
Influence of the metabolite produced by Trichomonas vaginalis on human sperm motility in vitro	Han Q	2004	The metabolite of *T. vaginalis* can reduce human sperm motility in vitro, and may be one of the causes of infertility.	Yes
The role of parasites and fungi in secondary infertility	Kranjcić-Zec I	2004	*T. vaginalis* is a common cause of tubal inflammation, which affects semen quality and leads to secondary infertility. Soluble parasite extract of *T. vaginalis* can lead to impaired motility of 50% spermatozoa in vitro and affects semen quality by increased viscosity and amount of debris, or damage spermatozoid membrane.	Yes
Correlation between trichomoniasis vaginalis and female infertility	el-Sharkawy IM	2000	Infertile women with *T. vaginalis* decrease C3 and C4, increase IgA level in vaginal discharge and increase serum prolactin. *T. vaginalis* is incriminated as one of the causes of their infertility.	Yes

Title	First author	Year	Conclusion	*T. vaginalis* causes infertility
Trichomonas vaginalis: preliminary characterization of a sperm motility inhibiting factor	Jarecki-Black JC	1988	*T. vaginalis* byproduct rapidly killed sperm in vitro, and this effects in humans may contribute to infertility in infected couples.	Yes

Research articles

We retrieved 62 research articles, and seven of them were selected [12, 28–33] based on the inclusion and exclusion criteria. Table 4 shows the information in the articles and a summary of the investigations into the pathogenesis of infertility caused by *T. vaginalis* infection. The results in this table indicate that *T. vaginalis* infection can promote infertility, and the main pathogenic mechanisms by which *T. vaginalis* infection causes infertility are as follows: (1) *T. vaginalis* impairs sperm quality, resulting in infertility; (2) the immune response triggered by *T. vaginalis* infection has negative impacts on human reproductive function; and (3) *T. vaginalis* impairs ovum quality, resulting in infertility.

Discussion

In recent years, there have been an increasing number of studies on *T. vaginalis* infection, and accumulating studies have reported a correlation between *T. vaginalis* infection and infertility. In this work, we first selected four articles on the incidence of *T. vaginalis* infection among patients with infertility [6, 14–16]. Data regarding the incidence of *T. vaginalis* infection in the infertile and healthy (people with normal reproductive function) groups were extracted for a meta-analysis, and a forest plot and funnel plot were generated. The combined effect size of the forest group was determined to be $z = 2.19$ and $p = 0.03$, which indicates that the data on the incidence of *T. vaginalis* infection in those two groups are statistically significant. The incidence of *T. vaginalis* infection in the infertile group was lower than that in the healthy group, indicating that infertility has negative effects on *T. vaginalis* infection. The distribution symmetry of the funnel plot of studies was poor, indicating publication bias. In addition, only a small number of articles were included in this study, which may also result in bias and is a limitation of the results. In the meta-analysis, some interfering factors may have also led to a higher incidence of *T. vaginalis* infection in the control group, resulting in deviation in the conclusion of the analysis. These interfering factors mainly include (1) discrepancies in education level and living conditions; (2) subjects with infertility in the experimental group may also have other infections, including Mycoplasma, Chlamydia, and other pathogens, that could cause infertility, leading to a lower incidence of *T. vaginalis* infection in the experimental group, which would affect the final results; (3) the composition of the control group is complex, as it includes both healthy people and patients with urinary tract infections and other

diseases, and patients with these disease may be more vulnerable to *T. vaginalis* infection. Therefore, the conclusions in this section cannot confirm the correlation between *T. vaginalis* infection and infertility, and qualified epidemiological data are required to reveal this correlation.

In addition, one article on the incidence of infertility among patients with *T. vaginalis* infection was included [17]. In this study, people with *T. vaginalis* infection were assigned to the experimental group, and people without *T. vaginalis* infection were assigned as the control group. Comparing the incidence of infertility between the two groups showed that the incidence of infertility in the experimental group was higher, indicating *T. vaginalis* infection has a promoting effect on the incidence of infertility. However, such articles are scarce, which may have caused deviations in our conclusions. Therefore, further studies are needed including epidemiological investigations of the incidence of infertility among people with *T. vaginalis* infection.

Several review articles on the correlation between *T. vaginalis* and infertility were selected. Consulting these articles revealed the significant impacts of *T. vaginalis* infection on the function of the human reproductive system. Many of the review articles stated that *T. vaginalis* infection can result in infertility, while one article did not clarify the correlation between *T. vaginalis* infection and infertility [27]. Upon reading and summarizing these articles, we discovered that *T. vaginalis* infection in female patients mainly causes inflammation of the reproductive tract [18, 19] and changes in the vaginal environment [20]; these disturbances can injure the reproductive tract mucosa, fallopian tubes, or pelvic cavity [18, 21, 22], which may result in a decrease or loss of reproductive function, leading to infertility. The major reason that *T. vaginalis* infection leads to infertility in male patients is that *T. vaginalis* itself or the induced inflammatory response can impair sperm cells, causing a decrease in cell viability or death of sperm cells [12, 21–26], which may result in a decrease or loss of reproductive function, leading to infertility.

We also collected and analyzed research articles on the pathogenesis of *T. vaginalis*-induced infertility. The collective results indicate that there are three main pathogenic mechanisms underlying infertility caused by *T. vaginalis* infection. First, *T. vaginalis* impairs sperm quality, resulting in male infertility. *T. vaginalis* trophozoites can adhere to sperm cells through glycoproteins, thereby enclosing and phagocytizing sperm cells [28]. Rotation of the attached *T. vaginalis* trophozoites can also interfere with the horizontal movement of sperm [29], affecting their ability to combine with an egg cell. In addition, the proteins or metabolites secreted by *T. vaginalis* may kill sperm cells or significantly diminish their viability and affect semen quality by increasing sperm viscosity and the quantity of fragments or by destroying the sperm membrane [31, 32]. Proteins secreted by *T. vaginalis* can also damage the integrity of the sperm membrane and acrosome [12], thereby impacting male reproductive function.

Second, the immune response triggered by *T. vaginalis* infection has negative impacts on female reproductive function. *T. vaginalis* infection is the most common cause of fallopian tube inflammation among female patients [31]. The inflammation initiated by the adhesion of *T. vaginalis* to the vagina can injury uterine epithelial cells [28], which can trigger inflammation of fallopian tubes. *T. vaginalis*-induced

genital tract inflammation also increase the risk of infection by other pathogens. For instance, *T. vaginalis* infection increases susceptibility to Mycoplasma and Chlamydia [13], thereby impairing reproductive function. Infection with *T. vaginalis* may also lead to pelvic inflammation [21], which affects female reproductive function. The inflammatory response induced by *T. vaginalis* can cause neutrophilia through serine protease-dependent pathogenesis. Therefore, contact between neutrophils and sperm cells leads to sperm phagocytosis and death [33]. In infertile females with *T. vaginalis* infection, the levels of C3 and C4 were decreased, while the levels of IgA and serum prolactin in vaginal secretions were increased [34], which may also be important in the pathogenesis of female infertility caused by *T. vaginalis* infection.

Third, *T. vaginalis* impairs ovum quality, resulting in infertility. Metabolites of *T. vaginalis*, such as enzymes [28, 35], may damage oocytes and consequently reduce the probability of conception, which can lead to infertility in severe cases. High quantities of *T. vaginalis* trophozoites may also block the fallopian tubes [31], causing problems with ovulation, thereby impacting female reproductive function and leading to infertility. As the molecular mechanisms of infertility caused by *T. vaginalis* remains are not yet clear, further investigations are required.

Conclusions

Epidemiological investigations, review articles, and research articles on the correlations between *T. vaginalis* infection and infertility were consulted. The results of this retrospective study indicate that *T. vaginalis* infection may lead to both male and female infertility, and the main pathogenic mechanisms involve damage to male and female germ cells and injury to the reproductive tract via induction of inflammation. Our work has further clarified the correlation between *T. vaginalis* infection and infertility and provides a foundation for further investigation into the pathogenesis of infertility caused by *T. vaginalis* infection.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Ethics Review Committee of Xinxiang Medical University (Reference No. 2015016).

Consent for publication

Not applicable.

Availability of data and materials

All of the data in the present research are contained in the article.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

ZhenChao Zhang and Xuefang Mei conceived and designed the study. Yuhua Li and Haoran Lu collected the relevant literatures. Dongxian Li and Rui Zhang classified the articles. Xianghuan Xie and Lihua Guo arranged epidemiological investigations Haoran Lu performed the meta-analysis. Xiaowei Tian, Zhenke Yang and Shuai Wang arranged review articles and research articles. Lixia Hao and Yuhua Li prepared the figures and Tables. ZhenChao Zhang and Xuefang Mei analysed the data and wrote the paper. All authors read and approved the final manuscript.

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Figures

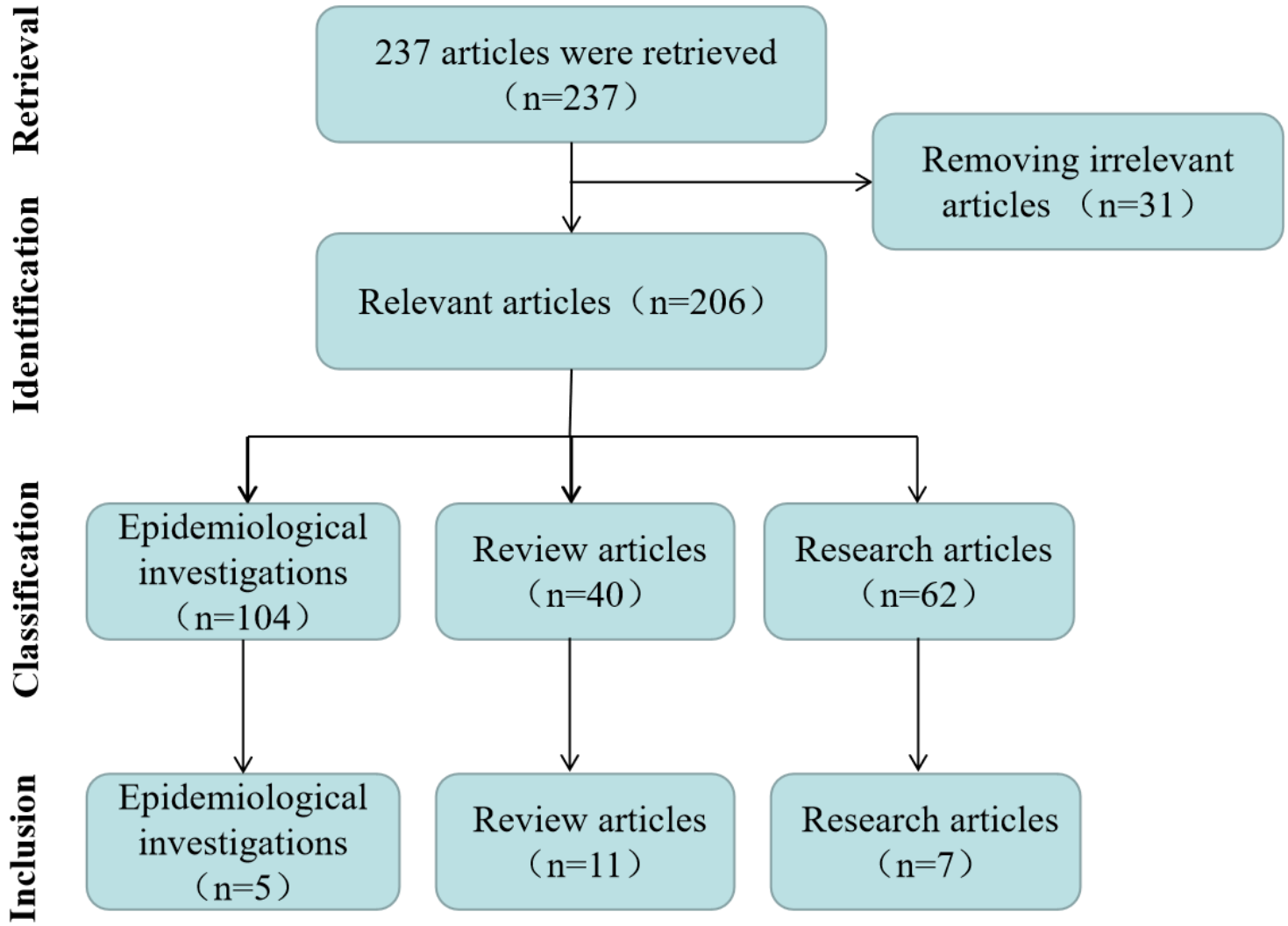

Figure 1

Flow diagram of articles retrieval, identification, classification and inclusion.

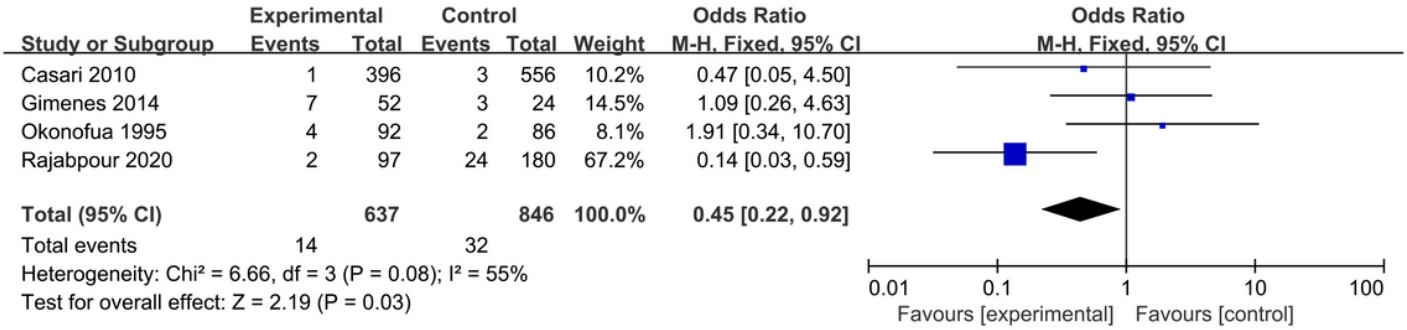

Figure 2

Forest map of Trichomonas vaginalis infection.

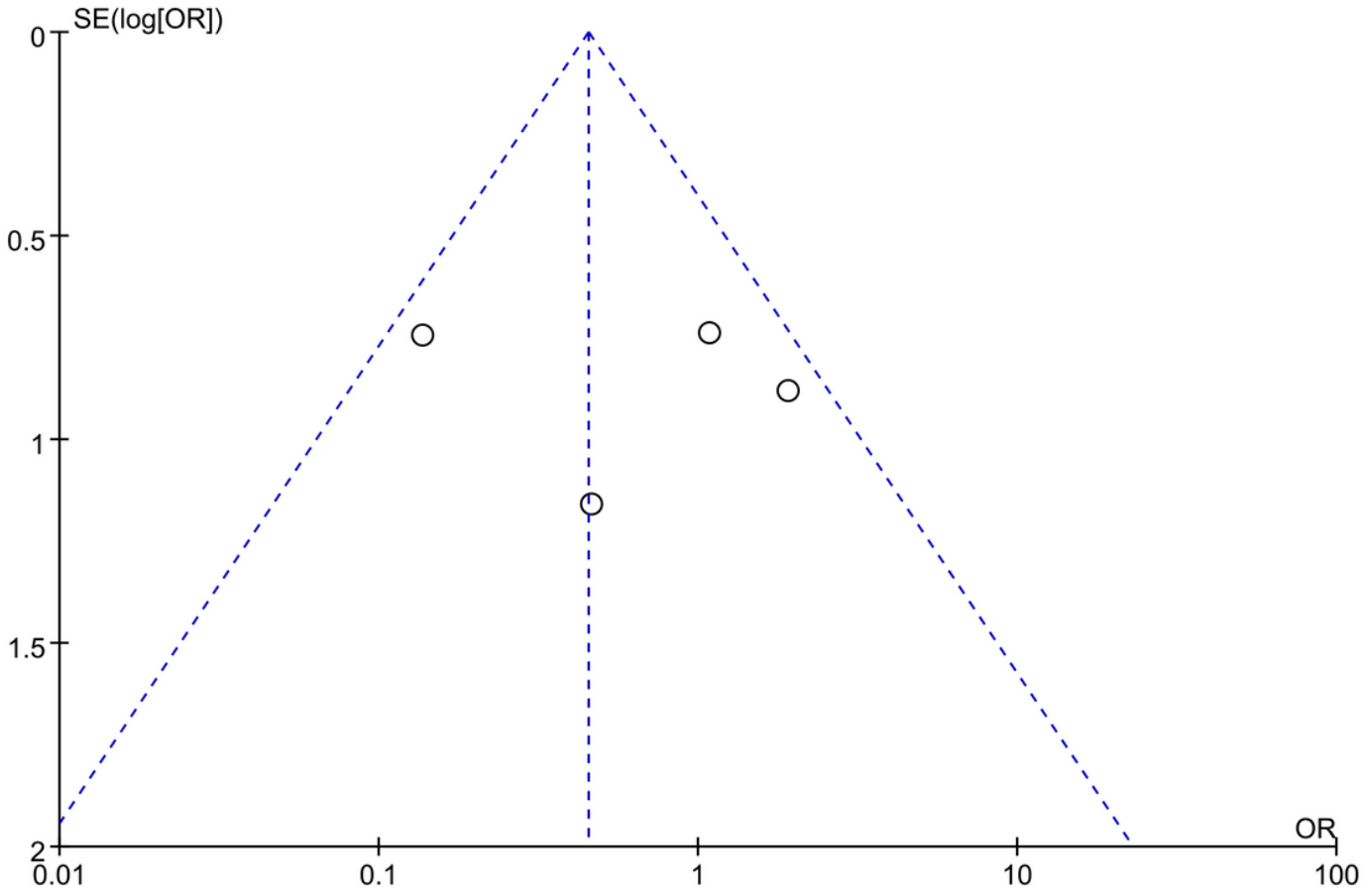

Figure 3

Funnel diagram of Trichomonas vaginalis infection.

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