Journal of Clinical and Nursing Research, 2023, Volume 7, Issue 1
http://ojs.bbwpublisher.com/index.php/JCNR
ISSN Online: 2208-3693
ISSN Print: 2208-3685

A Meta-Analysis on the Correlation Between Herpes Simplex Virus Type II Infection and Adverse Pregnancy Outcomes in China

Li Wang, Yurong Zhang, Xin Wang*

Department of Scientific Research, The First Affiliated Hospital of Xi'an Medical University, Xi'an 710077, China

***Corresponding author:** Xin Wang, 490784106@qq.com

Abstract: *Objective*: To systematically evaluate the relationship between herpes simplex virus type II (HSV-2) infection in pregnant women and the adverse pregnancy outcomes (preterm delivery, spontaneous abortion, stillbirth, monstrum, low birth weight, intrauterine growth retardation, premature rupture of membranes), so as to provide clinical guidance for the prevention and treatment of adverse pregnancy outcomes caused by HSV-2 infection in pregnant women. *Methods:* 2140 articles were collected from PubMed, China National Knowledge Infrastructure (CNKI), and other databases for the past 20 years. According to the inclusion criteria, the literatures about the relationship between HSV-2 infection of pregnant women and adverse pregnancy outcomes were screened. The effect model was determined by heterogeneity test results, and the meta-analysis was carried out by RevMan 5.3 software. *Results:* The results of meta-analysis showed that the positive rate of HSV-2 was higher in the adverse pregnancy group than in the control group (odds ratio [OR]: 7.92, 95% confidence interval [Cl]: 3.91–16.01), and the difference was statistically significant. *Conclusion:* HSV-2 infection will increase the risk of adverse pregnancy outcomes. Prevention and effective control of HSV-2 infection in early pregnancy can reduce the rate of adverse pregnancy outcome, which is of great significance to the promotion of eugenics.

Keywords: Herpes simplex virus type II; Adverse pregnancy outcomes; Meta-analysis

Online publication: January 16, 2023

1. Introduction

Herpes simplex virus (HSV) is a common pathogenic skin disease which infects human skin and mucous membrane. HSV is a DNA double stranded linear virus, which can be divided into HSV-1 and HSV-2. HSV-1 mainly infects the skin and mucosa outside the human genitalia, causing oral mucositis, herpetic keratitis, herpetic encephalitis, and many more [1]. HSV-2 is highly prevalent, it usually infects the mucous membrane and skin of the genital area, leading to genital herpes [2]. It is the most common sexually transmitted disease and the primary cause of genital ulcer. It is even distributed in the Sahara Desert of Africa [3,4]. Some studies have shown that HSV-2 can lead to adverse pregnancy outcomes (teratogenesis, spontaneous abortion, stillbirth, premature delivery, neonatal infection, etc.) in some pregnant women during the delivery period [5-10]. Therefore, the correlation between HSV-2 infection and adverse pregnancy outcomes is one of hot topics of research.

2. Materials and methods

2.1. Data sources and search strategy

Through the computer search of Wanfang Database, China National Knowledge Infrastructure (CNKI), Embase, Pubmed, VIP, and other database published since 1999 to 2019, the related studies on HSV-2 infection and adverse pregnancy outcomes were searched for the full text of the selected literature. The search terms include "Herpes simplex virus 2," "HSV-2 infection" and pregnancy," "pregnant women," "adverse pregnancy outcomes," "premature delivery," "spontaneous abortion," "intrauterine growth retardation," "stillborn fetus," "abnormal fetus," "low birth weight infants," and so on. A manual search was also performed on the reference lists of eligible studies identified from the databases. During extraction of publications, we avoided subjective bias by omitting the name of the authors, publications, year, and country.

2.2. Inclusion and exclusion criteria

A study was considered eligible if it met the following criteria: (1) research on the relationship between HSV-2 infection (IgM antibody positive) and adverse pregnancy outcomes published in China and contains original data; (2) the subjects of the study were pregnant women who were definitely diagnosed with HSV-2 infection, and patients with adverse pregnancy outcomes (premature delivery, spontaneous abortion, intrauterine growth retardation, stillborn fetus, abnormal fetus, low birth weight infants), pregnant women with serious diseases (such as hypertension, psychosis, diabetes, etc.) that may lead to adverse pregnancy outcomes; (3) cohort study or control study, excluding review, case report, animal experiment and data which are not related to this study; (4) The document language is limited to Chinese or English. Literature without a control group and studies that obviously did not meet the inclusion criteria were excluded.

2.3. Outcome

Adverse pregnancy outcomes include one or more of the following [11]: (1) premature delivery, which is less than 37 weeks of gestation at the time of delivery; (2) spontaneous abortion, which is abortions that occurred within 12 weeks of pregnancy without taking any artificial measures; (3) intrauterine growth retardation, which means the birth weight of the newborn is lower than the 10th percentile of the average weight of the newborn at the same gestational age; (4) premature rupture of membranes, in which natural rupture of membranes occurs in pregnant women before delivery; (5) low birth weight infants, which is a fetal birth weight of < 2.5kg; (6) teratogenesis, which means that there is an abnormal morphological structure and function of the newborn at birth; (7) dead fetus, which means the fetus dies in the mother's womb after 20 weeks of gestation.

The study was divided into the adverse pregnancy group and the control group. The adverse pregnancy group refers to the pregnant women infected with HSV-2, causing adverse pregnancy outcomes; while the control group refers to the pregnant women infected with HSV-2 without adverse pregnancy outcomes.

2.4. Quality assessment

Two evaluators independently screened the literature, excluded the research that did not meet the inclusion criteria, carefully read the full text of the literature, judged whether it met the inclusion criteria, and checked them. In case of disagreement, they discussed it or relied on a third party to assist in judgment.

2.5. Data extraction

The data of 17 included studies were extracted, including publication time, author, research location, sample size, and outcomes. The literature data and information were processed and summarized using Microsoft Excel.

2.6. Statistical analysis

RevMan 5.3 software provided by Cochrane collaboration network was used for analysis, and binary variables were used. Odds ratios (OR) and 95% confidence interval (CI) were used as effect analysis statistics. The heterogeneity across studies was assessed using the Cochrane I^2 statistics. $I^2 < 50\%$ was considered indicative of a lack of significant heterogeneity among the included studies and a fixed-effects model was used for analysis. $I^2 > 50\%$ was considered indicative of substantial heterogeneity and a random-effects model was used for analysis. In order to assess the influence of individual studies on the pooled analysis, a sensitivity analysis was performed by exclusion of individual studies, one at a time, to determine the stability of the meta-analysis. The analytic results were further shown using a forest plot, while a funnel plot was used to evaluate possible publication bias.

2.7. Ethics statement

The Ethics Committee of the First Affiliated Hospital of Xi'an Medical University approved the study.

3. Results

3.1. Data retrieval

2140 articles were found by computer retrieval of Wanfang, CNKI, Embase, Pubmed, VIP and other databases. 354 articles were obtained by reading the title and abstract in Chinese and English, excluding duplicates and irrelevant articles. The full text was obtained and read, and 213 articles with incomplete data, unclear diagnostic criteria and unclear outcome indicators were excluded. After careful comparison, 17 articles were included according to the inclusion and exclusion criteria [12-28] for meta-analysis. All of these 17 studies were all conducted in China and published in Chinese. The document screening process is shown in **Figure 1**.

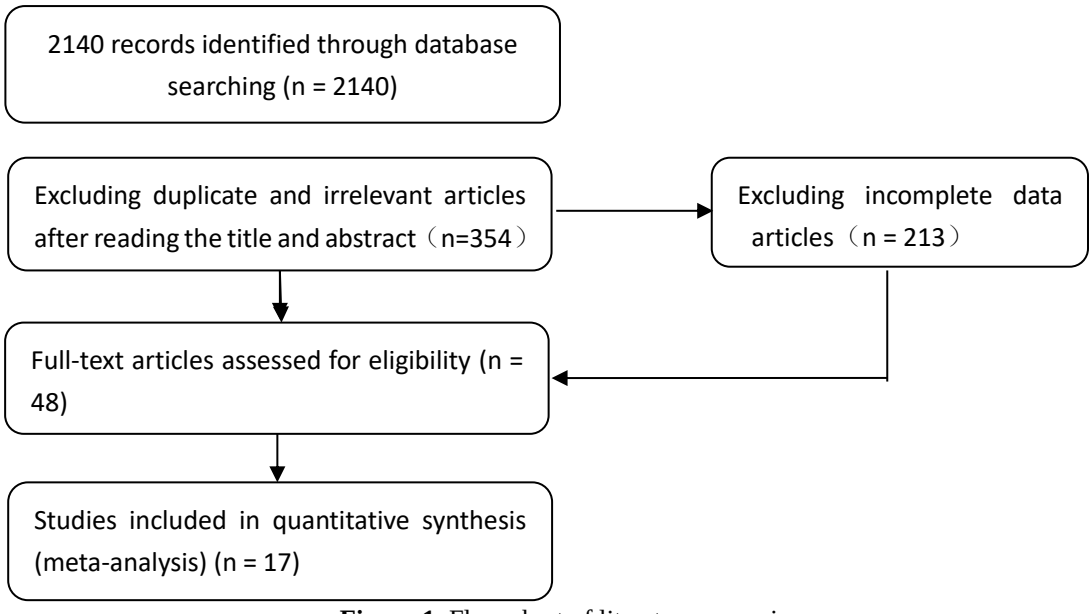

Figure 1. Flow chart of literature screening

3.2. Quality assessment

The 17 included studies all distinguished between the adverse pregnancy group and the healthy pregnancy group. RevMan 5.3 Bias Risk Assessment Scale was used to assess the bias risk of 17 studies. The bias risk assessment results are shown in **Figure 2**.

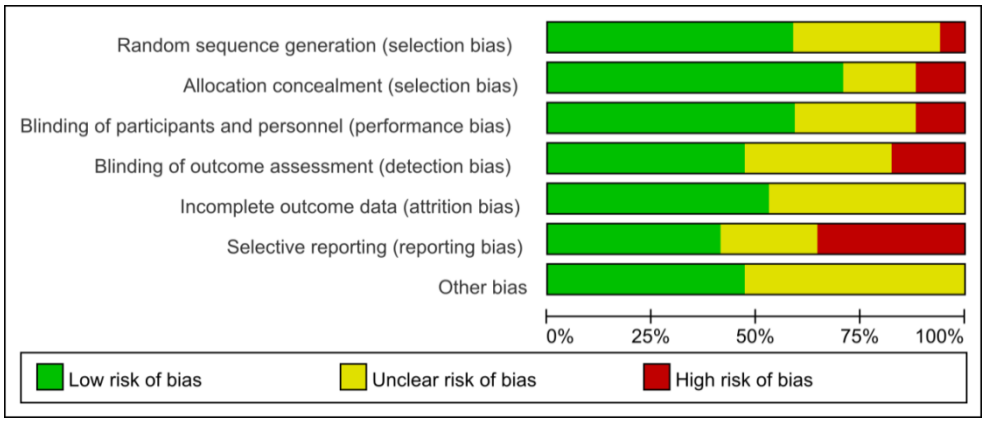

Figure 2. Statistical chart of bias risk assessment

3.3. Basic information of included literature

17 articles studied the relationship between HSV-2 infection in pregnant women and adverse pregnancy outcomes. From 2000 to 2020, the study involved 15369 pregnant women from 16 provinces in China, including Hainan, Jiangxi, Sichuan, Heilongjiang, Guangdong, Anhui, Liaoning, Ningxia, Zhejiang, Yunnan, Beijing, Guangxi, Shaanxi, Nanjing, Liaoning, and Jiangsu; with 2358 in the observation group and 13011 in the control group. In all studies, HSV-2 infection of pregnant women was detected by enzyme-linked immunosorbent assay (ELISA). The basic information of the included studies is shown in **Table 1**.

Table 1. Basic information of included studies

Included studies	Research area	Detection method	Adverse pregnancy group	Control group	Outcomes
			Number of HSV-2 infections / Total patients	Number of HSV-2 infections / Total patients	
Wu Cuiyun 2015[12]	Hainan	ELISA	3/34	0/60	①
Luo Hongquan 2005[13]	Sichuan	ELISA	14/60	6/60	②③④⑥
Shen Shubo 2004[14]	Heilongjiang	ELISA	13/116	2/88	②
Chen Yan 2014[15]	Sichuan	ELISA	95/401	83/1021	①
Li Ke 2018[16]	Anhui	ELISA	9/203	30/2414	②③④⑤⑥
Han Qian 2008[17]	Heilongjiang	ELISA	12/167	6/131	④
Xu Shu 2016[18]	Liaoning	ELISA	19/59	3/61	②
Ling Weibing 2016[19]	Guangdong	ELISA	14/120	0/120	④
Yang Yaohua 2000[20]	Ningxia	ELISA	16/54	4/54	②③④⑤⑥⑦
Yao Jintong 2019[21]	Zhejiang	ELISA	31/252	20/3590	②③④⑥⑧
Luo Lan 2006[22]	Nanjing	ELISA	2/120	8/2147	②③⑥
Hu Jinghui 2013[23]	Zhejiang	ELISA	7/100	0/94	②
Song Zhiqin 2002[24]	Beijing	ELISA	9/50	4/50	②③⑥
Wang Rong 2013[25]	Guangdong	ELISA	7/52	0/52	④
Li Shengchu 2007[26]	Guangxi	ELISA	45/115	7/100	②④
Liu Lina 2018[27]	Shaanxi	ELISA	135/375	10/2880	②③⑥
Lv Bin 2016[28]	Liaoning	ELISA	40/80	9/80	②

Adverse pregnancy outcomes: ① Adverse pregnancy; ② Spontaneous abortion; ③ Dead fetus;④ Premature delivery; ⑤ Intrauterine growth retardation; ⑥ Teratogenesis; ⑦ Premature rupture of membranes; ⑧ Low birth weight

3.4. Data analysis

3.4.1. Relationship between HSV-2 infection and adverse pregnancy outcomes

According to the type of adverse pregnancy outcomes, 17 studies were statistically analyzed with RevMan5.3 software, I^2 = 89%, and the meta-analysis was conducted by using the random effects model

method. The total HSV-2 positive rate of the adverse pregnancy group with 19.97% (OR=7.83, 95%CI: 3.86-15.87) was much higher than that (1.48%) of the control group. The difference was statistically significant ($P < 0.01$) as shown in **Figure 3**.

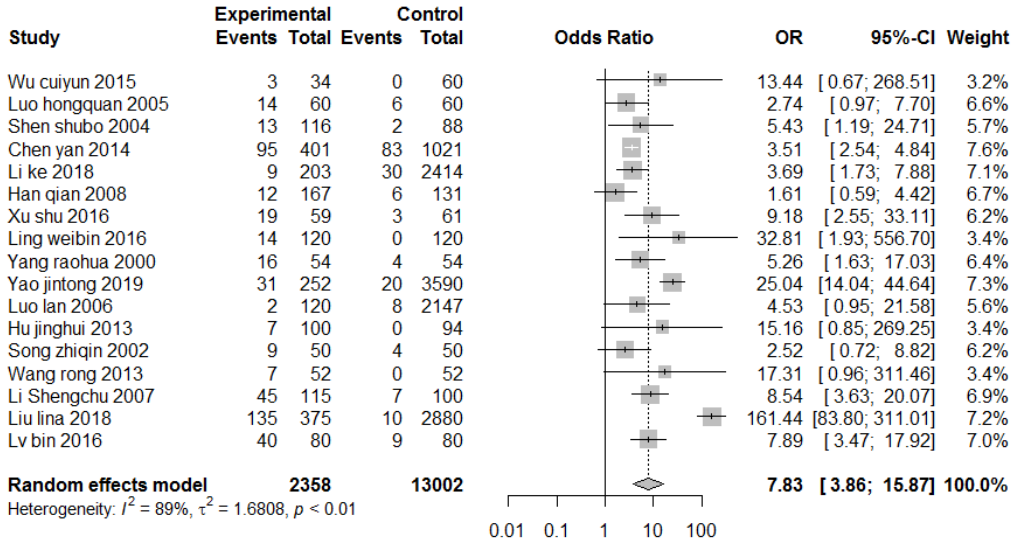

Figure 3. Forest plot of HSV-2 positive rate in the adverse pregnancy group and control group

3.5. Subgroup analysis

3.5.1. Relationship between HSV-2 infection and premature delivery

There were 3 articles that studied the premature delivery, of which 33 out of 339 premature delivery women were infected with HSV-2, while 6 out of 303 pregnant women were infected with HSV-2 in control group. I^2 = 70%, Meta-analysis using random effects model showed that the women with premature delivery had higher HSV-2 positive rate than normal pregnant women (OR = 7.27, 95% CI: 0.70–74.80), and the difference was statistically significant ($P < 0.05$) in **Figure 4**.

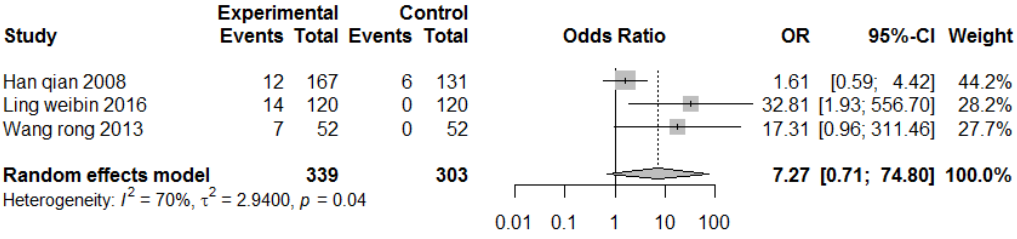

Figure 4. Forest plot of HSV-2 positive rate in the premature delivery women and normal pregnant women

3.5.2. Relationship between HSV-2 infection and spontaneous abortion

There were 4 articles that studied spontaneous abortion, which 79 of 355 spontaneous abortion women were infected with HSV-2, while 14 of 323 pregnant women were infected with HSV-2 in control group. I^2=0, Meta-analysis using fixed effect model showed that the spontaneous abortion women had higher HSV-2 positive rate than normal pregnant women (OR = 8.01, 95% CI: 4.31–14.88), and the difference was statistically significant ($P < 0.01$) in **Figure 5.**

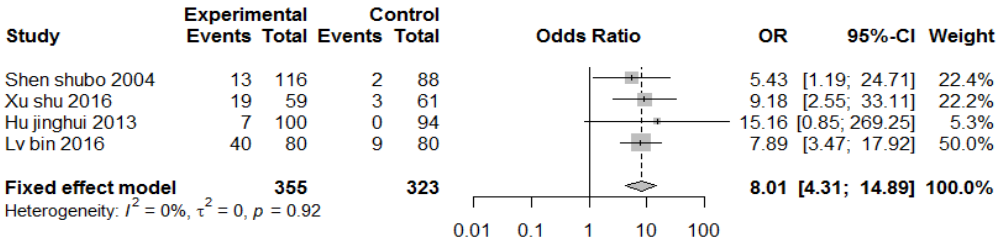

Figure 5. Forest plot of HSV-2 infection and spontaneous abortion

3.5.3. Subgroup analysis according to the living areas of the included pregnant women

3.5.3.1. The pregnant women in the north of the Yangtze River

8 studies were conducted on pregnant women in the north of the Yangtze River, such as Anhui, Qinghai, Hubei, Gansu, Ningxia, Shaanxi, Shanxi, Henan, Hebei, Shandong, Liaoning, Jilin, Heilongjiang, Neimeng, Xinjiang, Tianjin, and Beijing. 253 out of 1104 adverse pregnancy women were infected with HSV-2, while 68 of 5758 normal pregnancy women were infected with HSV-2. I^2 = 93%, the random effect model was used for meta-analysis. The results showed that the HSV-2 positive rate of the adverse pregnancy group was higher than that of the control group (OR = 7.04, 95% CI = 1.96–25.26) in the north of the Yangtze River. The difference was statistically significant (P < 0.01) as shown in **Figure 6**.

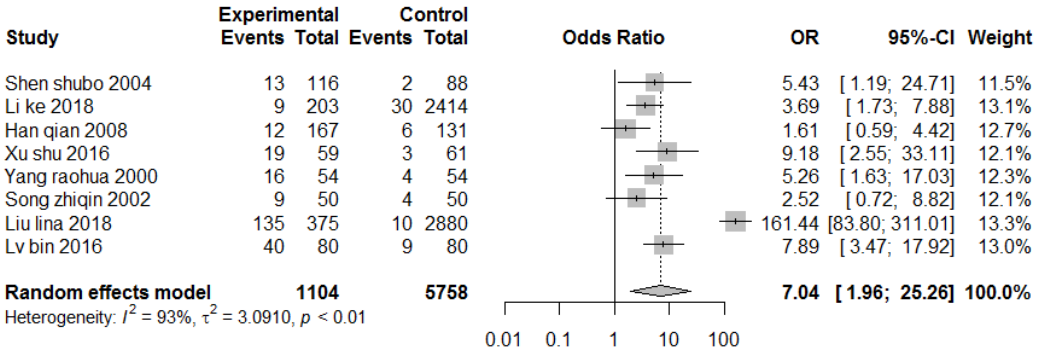

Figure 6. Forest plot of HSV-2 infection and adverse pregnancy outcome

3.5.3.2. The pregnant women in the south of the Yangtze River

There were 9 studies on pregnant women in the south of the Yangtze River, such as Jiangsu, Anhui, Zhejiang, Shanghai, Hunan, Jiangxi, Fujian, Yunnan, Guizhou, Sichuan, Chongqing, Guangxi, Guangdong, Hong Kong (China), Macao, Hainan, and Taiwan (China). 218 of 1254 adverse pregnancy women were infected with HSV-2, while 124 of 7244 women with normal pregnancy were infected with HSV-2. I^2 = 80%, the random effects model was used for meta-analysis. The results showed that the HSV-2 positive rate of the adverse pregnancy group was higher than that of the control group (OR = 8.19, 95% CI = 3.64–18.46) in the south of the Yangtze River, with a statistically significant difference, (P < 0.01) as shown in **Figure 7**.

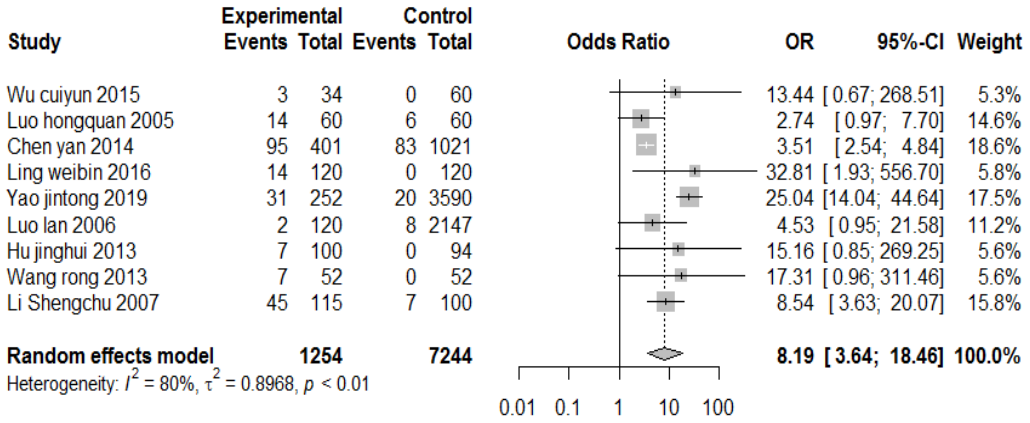

Figure 7. Forest plot of HSV-2 infection and adverse pregnancy outcome

3.6. Sensitivity analysis

The positive rate of HSV-2-IgM antibody was tested by Egger's test, which showed that there was no significant publication bias (P = 0.6956). The metaninf function was used to examine the impact of each study on the total amount of combined effects. The results showed that when a random study was excluded, the number of combined effects and the total amount of combined effects were both in 95% CI, and indicated that the results of meta-analysis were stable as shown in **Figure 8**.

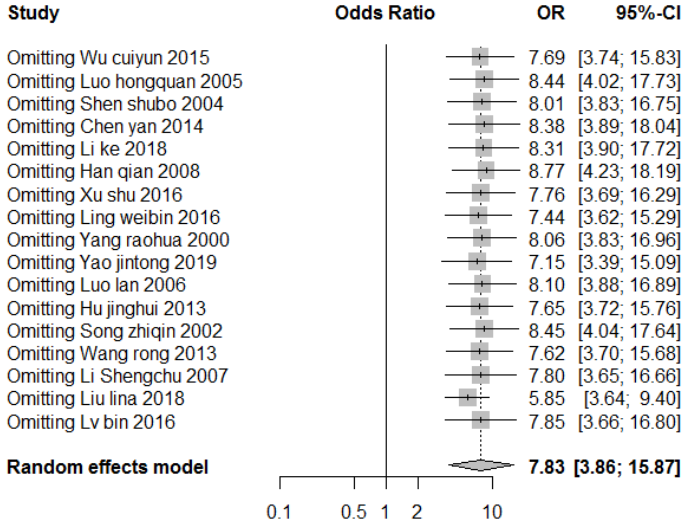

Figure 8. Sensitivity analysis of HSV-2-IGM positive rate

3.7. Publication bias analysis

The ordinate is set to SE (log [OR]) and the abscissa is set to OR. A funnel plot is drawn in RevMan 5.3. It is clear that studies with more sample data are densely distributed at the tip of the funnel plot, while studies with less sample size are mostly distributed on both sides in a funnel shape (**Figure 9**). Egger's test was used to detect the symmetry of funnel graph, and the results showed that there was no large publication bias in all studies.

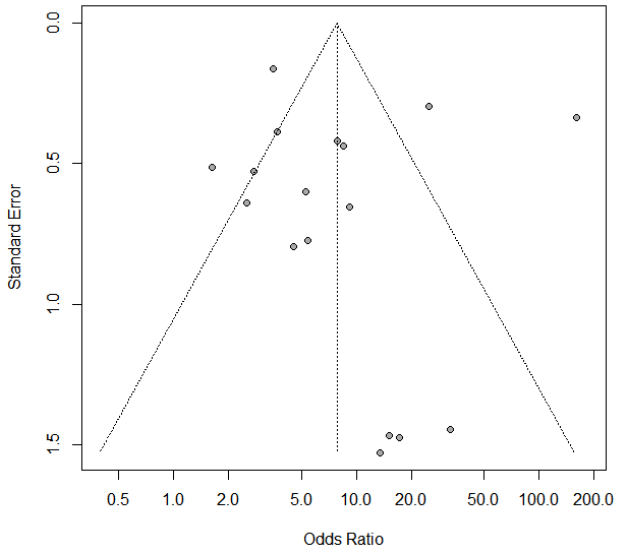

Figure 9. Funnel plot

4. Discussion

HSV-2 is a common pathogen which infects pregnant women and has a serious adverse effect on the growth and development of the early fetus, especially in the early pregnancy. Early pregnancy is a critical period for the formation of fetal organs and systems. Therefore, pregnant women infected with HSV-2 in early pregnancy are more likely to have adverse pregnancy outcomes. For women who have been infected with HSV-2, HSV-2 will reproduce in the body, and then infect the nerve endings. It will hide in the dorsal ganglion through the axon. At the right time (pregnancy, immune system defects, violent emotional fluctuations, etc.), the virus can be reactivated, causing pregnant women to be infected with HSV-2 again [29]. It is worth noting that when pregnant women are infected with HSV-2 during pregnancy, the virus can be transmitted to the embryo through the mother infant route (cervix, placenta), leading to natural abortion, neonatal growth retardation and other adverse pregnancy outcomes. During the delivery of pregnant women, newborns can also be infected through the birth canal, which is often difficult to diagnose. Therefore, it is extremely important to do a good job in screening infectious diseases before pregnancy and protecting pregnant women and fetuses infected with HSV-2, which is of great significance in guiding clinical monitoring and preventing adverse pregnancy outcomes of pregnant women caused by HSV-2 infection.

In the 20 years from 1999 to 2019, the genital herpes caused by HSV-2 infection in the Chinese population has increased year by year, which has become an important reason for adverse pregnancy outcomes among pregnant women in China. Most HSV-2 infections are latent infections with mild symptoms. Epidemiological statistics from around the world show that HSV-2 is far less prevalent in developed countries than that in developing countries. In some countries, the overall probability of HSV-2 infection in adult women is about 20%–30% higher than that in men [30]. In this paper, meta-analysis of the HSV-2 infection of pregnant women with adverse pregnancy outcomes in different regions of the country is carried out. It is found that the HSV-2 positive rate of pregnant women with adverse pregnancy outcomes (stillbirth, teratogenesis, spontaneous abortion, premature delivery, intrauterine growth retardation) is much higher than that of normal pregnant women. The subgroup analysis shows that there is a higher percentage of premature delivery and abortion among pregnant women infected with HSV-2 compared to normal pregnant women, and the differences are statistically significant, Therefore, HSV-2 infection can cause adverse pregnancy outcomes in pregnant women. The subgroup analysis of the relationship between pregnant women from different regions infected with HSV-2 and their adverse pregnancy outcomes showed that the positive rate of HSV-2 in the adverse pregnancy group in the southern and northern populations

was higher than that in the control group. The results were similar, which means that regional factors had no significant impact on the relationship between HSV-2 infection and adverse pregnancy outcomes.

A sensitivity analysis was carried out on the research results. When one study was randomly removed, the amount of combined effects and the total amount of combined effects were both in 95% CI, indicating that the meta-analysis results were stable and reliable. However, there are still some limitations of the data analysis of this paper. When analyzing the correlation between HSV-2 infection and spontaneous abortion in pregnant women, the included research data is heterogeneous, which means that the adverse pregnancy outcome might be affected by multiple factors, and the influencing factors involved in each study are inconsistent. Besides, the number of studies included is small, and the number of HSV-2 infection in spontaneous abortion group was also small, so the small sample size will affect the analysis results. There are few articles included in the study, which are Chinese articles, which means that there is some degree of publication bias.

HSV-2 infection will increase the risk of adverse pregnancy outcomes of pregnant women. Prevention and effective control of HSV-2 infection in early pregnancy can reduce the risk of adverse pregnancy outcomes of pregnant women, which is of great significance to the country's promotion of smooth delivery and childcare.

Author contributions

Li Wang was responsible for designing and conceptualizing, writing, and revising this paper. Yurong Zhang was responsible for extracting data from the literature, and Xin Wang was responsible for statistical analysis and mapping.

Funding

This study was supported in part by grants from Science and Technology Innovation Team Project of Xi'an Medical University, China (2021TD14), Industrialization Project of Shaanxi Provincial Department of Education, China (20JC031) and the First Affiliated Hospital of Xi'an Medical University, China (XYFYPT-2021-02).

Disclosure statement

The authors declare no conflict of interest.

References

[1] Ryan KJ, Ray CG, 2004, Sherris Medical Microbiology, 4th Edition, McGraw Hill.

[2] HSV-1 and 2 Assay for the Detection of HSV in Cutaneous and Mucocutaneous Lesion Specimens. J Clin Virol, 99–100:1–4.

[3] Sonia B, David B, Diane R, et al., 2017, Ancient Recombination Events Between Human Herpes Simplex Viruses. Mol Biol Evol, 34(7): 1713–1721.

[4] Petro C, Gonzalez P A, Cheshenko N, et al., 2015, Herpes Simplex Type 2 Virus Deleted in Glycoprotein D Protects Against Vaginal, Skin and Neural Disease. eLife, 4(4): 1-18.

[5] Chen P, Ma L, Liu E, et al., 2015, Epidemiological Characteristics of Herpes Simplex Virus Type 2 Infection in Different Populations. International Journal of Biological Products, 38(4): 189–192.

[6] Looker KJ, Magaret AS, Turner KM, et al., 2015, Global Estimates of Prevalent and Incident Herpes Simplex Virus Type 2 Infections in 2012. PLoS One, 10(1): e114989.

[7] Bradley H, Markowitz LE, Gibson T, et al., 2014, Seroprevalence of Herpes Simplex Virus Types 1 and 2 United States, 1999-2010. J Infect Dis, 209(3): 325–333.

[8] Looker KJ, Garnett GP, Schmid GP, 2008, An Estimate of the Global Prevalence and Incidence of Herpes Simplex Virus Type 2 Infection. Bull World Health Organ, 2008, 86(10): 805–812.

[9] Smith JS, Robinson NJ, 2002, Age-Specific Prevalence of Infection with Herpes Sim-Plex Virus Types 2 and 1: A Global Review. J Infect Dis, 186, Suppl 1: S3–S28.

[10] World Health Organization, 2007, Global Strategy for the Prevention and Control of Sexually Transmitted Infections: 2006-2015: Breaking the Chain of Trans-Mission, World Health Organization, Geneva.

[11] Yue X, Fu Q, Fu Y, 2017, Meta-Analysis of the Relationship Between Simple Hypothyroidism and Adverse Pregnancy Outcomes. Journal of Preventive Medicine of the PLA, 9: 1098–1102.

[12] Wu C, Qiu M, 2015, Analysis of Adverse Pregnancy and HSV-2 IgM IgG Antibody Detection Results. Hainan Medical Journal, 1: 133–134.

[13] Luo H, Du X, Liu C, et al., 2005, Effect of Herpes Simplex Virus Infection on Pregnant Women and Fetuses. Sichuan Medical Journal, 3: 302–303.

[14] Shen S, Liu F, Liu M, 2004, Analysis of Cytomegalovirus Antibody, Herpes Simplex Virus Antibody and Toxoplasma Antibody in pregnant women with Spontaneous Abortion. Heilongjiang Medical Journal, 10: 775–776.

[15] Chen Y, 2014, Analysis of 1876 TORCH Test Results. Chinese Journal of Laboratory Diagnostics, 12: 2052–2054.

[16] Li K, Zhou H, 2018, Study on the Correlation Between TORCH Infection and Pregnancy Outcome of Pregnant Women. Chinese Journal of Eugenics and Genetics, 5: 65–66.

[17] Han Q, Zhou W, Duan L, et al. 2008, Study on the Relationship Between TORCH Infection and Premature Delivery of Pregnant Women. Chinese Journal of Eugenics and Genetics, 8: 84

[18] Xu N, 2016, Analysis of Related Factors Between TORCH Infection and Spontaneous Abortion. Chinese Medical Guide, 35: 169–170.

[19] Ling W, Xie S, Pan G, et al., 2016, Study on the Correlation Between TORCH Series Pathogenic Microorganism Infection and Premature Delivery. China Contemporary Medicine, 8: 95–97.

[20] Yang Y, Yu L, Zhang L, et al., 2000, Study on the Relationship Between Adverse Pregnancy and TORCH Infection. Journal of Ningxia Medical College, 22(06): 407–408.

[21] Yao J, 2019, Clinical Observation on TORCH Serological Detection and Pregnancy Outcome in Pregnant Women. Modern Practical Medicine, 8: 1086–1087.

[22] Luo L, Feng Y, Guo Z, et al., 2006, Pregnancy and TORCH Infection. Journal of Kunming Medical College, 2: 78–81.

[23] Hu J, 2013, Study on the Correlation Between Habitual Abortion and TORCH Infection. Chinese Journal of Hospital Infection, 1: 106–107.

[24] Song Z, Lv B, Zhang A, 2002, Effect of TORCH Infection in Pregnant Women on Fetus. Chinese Journal of Eugenics and Genetics, 3: 72–73.

[25] Wang R, Fan W, Liu Z, 2013, Study on the Correlation Between Premature Delivery and TORCH Infection in Pregnant Women. Journal of Practical Medicine, 14: 2413-2414.

[26] Li S, 2007, Pathogen Detection of Early Abortion and Premature Pregnancy. Guangxi Medical Journal, 4: 496–497.

[27] Liu L, 2018, TORCH Examination Results of Women Before Pregnancy and Early Pregnancy in Chang'an District and its Relationship with Adverse Pregnancy Outcomes. Clinical Medical Research and Practice, 28: 138–139.

[28] Lu B, 2016, Analysis of TORCH Test Results in Patients with Spontaneous Abortion. Journal of Community Medicine, 19: 75–76.

[29] Yan H, Su D, Zhao Y, et al., 2007, Research Status of Genital Herpes and Ethical Issues in Diagnosis and Treatment. Medicine and Philosophy (Clinical Decision Forum), 5: 68–70.

[30] Lai W, Shao C, 1996, Epidemiology and Risk Factors of Genital Herpes. Journal of Dermatology and Venereology of Foreign Medicine, 22(5): 261–265.