Is Herpes Simplex virus (HSV) a sign of Encephalitis in Iranian Newborns? Prevalence of HSV Infection in Pregnant Women in Iran: A Systematic Review and Meta-Analysis

How to Cite This Article: Arabsalmani M, Behzadifar M, Baradaran HR, Toghae M, Beyranvand Gh, Olyaeemanesh A, Behzadifar M. Is Herpes Simplex virus (HSV) a sign of Encephalitis in Iranian Newborns? Prevalence of HSV Infection in Pregnant Women in Iran: A Systematic Review and Meta-Analysis. Iran J Child Neurol. Spring 2017; 11(2):1-7.

Abstract

Objective
Herpes Simplex virus (HSV) is one of the most common sexually transmitted diseases in the world. This study aimed to determine the prevalence of herpes simplex virus in pregnant women in Iran.

Materials & Methods
A systematic literature review was conducted to study the HSV subtypes in Persian and English papers through several databases. We searched Pub Med, Scopus, Ovid, Science Direct and national databases as Magiran, Iranmedex and Science Information Database (SID) up to October 2015. Random-effects model were applied to calculate the pooled prevalence of HSV subtypes.

Results
Five eligible studies were identified, including 1140 participants. The pooled prevalence of HSV infection in pregnant women was 0.64% (95% CI: 0.10-1.18) in Iran. The pooled prevalence of studies on both HSV-1 and HSV-2 was 0.91% (CI: 0.81-1.02) and studies on only HSV-2 was 0.23% (CI: -0.61-0.63), respectively.

Conclusion
The prevalence of HSV infection in pregnant women in Iran was higher. HSV infection of the central nervous system, especially with HSV-2, can also cause recurrent aseptic meningitis and monophasic, as well as radiculitis or myelitis. The performance of screening to detect infection in pregnant women can play an important role in the prevention and treatment of patients and help to prevent the transmission of HSV infection to infants in Iran.

Keywords: Herpes simplex virus; Pregnancy; Meta-analysis; Iran

Introduction
Herpes simplex virus (HSV) infections are very common worldwide(1). They are caused by either HSV-1 or HSV-2, and the majority is asymptomatic(2). HSV-2 prevalence among pregnant women has been estimated as 20%-30%, with approximately 10% of HSV-2 seronegative women living with a seropositive partner and hence, at risk in the acquisition of herpes during pregnancy (3, 4). The potential factors associated with HSV-2 infection are age and sex or gender. Ageing increases the risk of HSV (5). Other factors, such as having sexual intercourse sooner than common age and risky sexual relationship, poverty, gender or ethnicity, and bacterial vicinities can facilitate women’s risk of infection before their pregnancy (6, 7). In the
US, 22% of pregnant women are infected with HSV-2. Among whom two percent are infected during pregnancy, which threatens them and their baby (8). Some studies have demonstrated the prevalence of HSV type 1 or 2 during pregnancy (9, 10). Nearly 30%-50% of babies can be infected with the virus and at the end of pregnancy period, the risk of infection may increase (11). The problem is not just relatively high prevalence of HSV infection among pregnant women, but unawareness of this infection, which affects newborns drastically (1, 12). About three-fourth of women with a history of HSV show incidence of HSV again during their pregnancy and one out of seven suffer from lesion through delivery (13, 14).

HSV infections during pregnancy may cause fetal and neonatal infections. HSV transmission may occur during pregnancy and after delivery, 80%-90% of neonatal herpes infections occur when the baby passes through the mothers’ infected birth canal. HSV infection can have severe consequences for the affected newborns. HSV infection may turn to herpes encephalitis or infection across other organs such as liver, lungs, and kidneys with or without dermal symptoms.

HSV causes disordering of some parts of the body, such as CNS, skin, eyes, lungs, mouth, adrenal gland and liver, and in the absence of therapy, it has a mortality risk of about 80% (15). Babies with the disease usually die because of viral pneumonia and intravascular coagulopathy. Survivors (babies who survived) from serious infection generally suffer from permanent neurological disorder (16-19). This study aimed to determine the prevalence of HSV infection in pregnant women in Iran.

Materials and Methods

Study eligibility and identification

We investigated to estimate the rate of HSV infection rates among Iranian pregnant women in Iran and the neurologic impact of HSV on the newborns. A literature search was performed in which PubMed, Scopus, Ovid and Science Direct as well as national databases such as MagIran, Iranmedex and Science Information Database (SID) using “Prevalence” OR “frequency” AND “herpes simplex virus” OR “HSV” OR “TORCH” AND “pregnancy” AND “Iran” as keyboards up to October 2015. In addition, the reference lists of several studies and conferences related to the present study were investigated.

Inclusion and exclusion criteria

Studies that report on the prevalence of HSV among pregnant women in Iran were included while Case Reports, Case Series and Quasi – experiments and studies whose methods and results were not clear and the population did not comprise of Iranian pregnant women were excluded.

Data extraction

Independent literature searches were conducted by two reviewers and experts and after omitting the repeated cases. They chose the title and abstract studies based on the inclusion and exclusion criteria. The name of authors was blinded. If there was a problem or disagreement between two investigators, the third one helped them to solve the problem by discussion. The name of first author, the year of publication of article, the amount of sample, the number of positive virus, the type of virus and the place of studies extracted were analyzed.

Quality assessment of studies

To assess the quality of the studies, the STROB checklist was used (20). The studies were classified as high, intermediate and low quality.

Statistical analysis

The data obtained from the various studies were analyzed using a random effect with 95% confidence intervals by inverse variance weight. The heterogeneity between the included studies was assessed using Q-test and I2 index. By so doing, a P-value of less than 0.01% was considered as significant in the heterogeneity test. Thereafter, subgroup analysis was carried out based on virus type, year of publication and quality of studies. All analyses were performed using Review Manager Version 5.3 software. Assessment of publication bias was planned by visualizing the funnel plot asymmetry. However, since the number of included studies was less than the recommended optimum number of at least 10, the assessment of publication bias was not carried out (21).

Results

Overall, 110 articles were obtained and after omitting the repeated studies, 53 articles were left. Based on analysis, the titles and summaries of 27 articles were selected and
The prevalence of HSV was observed as 0.64%. HSV prevalence based on studies of both HSV-1 and HSV-2 was observed as 0.91% and studies on only HSV-2 was observed as 0.23% (Fig. 2). Nevertheless, the primary statistics show that prevalence of HSV in Iran is higher than that developed nations and lower in comparison with other developing ones (27, 28).

Central nervous system disease alone occurs in one-third of all infants with neonatal herpes simplex virus infection (29). Localized herpes simplex virus have been found in the fifthly percent of the affected neonates, involvement of the central nervous system in the thirty three percent, and disseminated infections in the seventeen percent (30-31). Although HSV-1 has a predilection for the development of encephalitis after intracerebral injection in the mouse model, HSV-2 generally causes meningitis. However, the meninges are not the only component of the central nervous system involved in HSV-2 infection (32). Virtually any part of the neuraxis may be affected by this virus, including the brain, brain stem, spinal cord, nerve roots, cranial nerves and retina. HSV infection of the CNS, especially with HSV-2, can also cause recurrent aseptic meningitis and monophasic, as well as radiculitis or myelitis (33). When HSV-2 infection is mentioned, neonatal herpes simplex encephalitis, a devastating disorder, is the disease most commonly considered. Seventy percent of affected neonates are born to mothers without symptoms or signs of genital herpes (34). Recent studies suggest that as much as 30% of neonatal herpes simplex encephalitis is due to HSV-1. The risk of acquisition during a primary infection with HSV-1 or HSV-2 is the fifthly percent (34). The risk of development of neonatal HSE is reduced if a mother with primary HSV-2 genital herpetic infection is seropositive for HSV-1. Risk factors for neonatal HSV disease include first-episode maternal infection in the third trimester, invasive monitoring, and delivery before a gestational age of 38 weeks, and maternal age of less than 21 years. Delivery by cesarean section significantly reduces the risk of HSV acquisition (35).

Tehran has significantly the most prevalence of HSV in Iran. The high prevalence in Tehran can be attributed to the high population density of Tehran, numerous poor areas around its territory, different cultural conditions, different ethnicities, precocious puberty in children, high
Is Herpes Simplex virus (HSV) a sign of Encephalitis in Iranian Newborns?

recent years, the prevalence of HSV in pregnant women has increased. However, the high prevalence of HSV has also been demonstrated among young Iranian population. Improvement in the standard of living, which increases health activities, should be facilitated by the primary health care (PHC) providers and this can be effective in improving the health status of the individual. In addition, screening to detect infection in pregnant women can play an important role in the prevention and treatment of patients and in the prevention of its transmission to infants in Iran. The high HSV infection in pregnant women is a significant challenge for disease control and surveillance in Iran.

Acknowledgements
The authors would like to thank Dr Aidin Aryankhesal for editing the manuscript.

Author’s Contribution
Arabsalmani M: Design
Arabsalmani M, Behzadifar M: Data collection, Masoud Behzadifar M: Analysis and interpretation of data, Manuscript preparation
Behzadifar M, Behzadifar M, Baradaran HR, Toghae M, Beyranvand Gh, Olyaeemanesh AR: Manuscript revision.

All the authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest
None declared.

A high heterogeneity was observed between the accepted studies and those analyzed based on the amount of P-value, statistical tests I2and Chi – Square. This heterogeneity can be attributed to the number and sample size (quantity of the sample). The meta-analysis of studies is another reason for this statistically significant difference. In addition, the prevalence of this virus in high-qualified studies and low prevalence in low qualified studies could be another reason(39).

In this present study, some limitations were observed. Firstly, the quality of the articles, and the fact that 20% of the articles were of low quality could affect the results of this study. Secondly, the low number of systematic reviewers of studies and, thirdly the high number of articles studied in Tehran may cause bias in the results of this study.

In conclusion, the overall prevalence of HSV infection in pregnant women in Iran was observed as 0.64%. In

| Author                     | Year | Location    | Sample size | Type HSV  |
|----------------------------|------|-------------|-------------|-----------|
| Ziayian et al.             | 2007 | Tehran      | 400         | Type 1and2|
| Pourmand et al.            | 2003 | Kermanshah  | 385         | Type2     |
| Danesh shahraki et al.     | 2010 | Esfahan     | 96          | Type2     |
| Bagheri joshaghani et al.  | 2015 | Kashan      | 80          | Type 1and2|
| Ghasemi et al.             | 2015 | Tehran      | 179         | Type 1and2|
Is Herpes Simplex virus (HSV) a sign of Encephalitis in Iranian Newborns?

Table 2. Subgroup Analysis HSV Infection in Pregnant Women in Iran

| Subgroup                                      | No studies | Prevalence | CI 95 %       | P value |
|-----------------------------------------------|------------|------------|---------------|---------|
| Year of publication                           |            |            |               |         |
| Before 2008                                    | 3          | 0.51       | -0.43 to 1.45 | 0.284   |
| After 2008                                     | 2          | 0.73       | 0.50 to 0.96  | 0.000   |
| Quality of the studies                         |            |            |               |         |
| High                                           | 2          | 0.87       | 0.78 to 0.95  | 0.000   |
| Intermediate                                   | 2          | 0.72       | 0.17 to 1.26  | 0.010   |
| Low                                            | 1          | 0.03       | 0.02 to 0.05  | 0.000   |
| Location of the studies                        |            |            |               |         |
| Tehran                                         | 2          | 0.91       | 0.75 to 1.07  | 0.000   |
| Other cities                                   | 3          | 0.46       | -0.16 to 1.08 | 0.143   |
| Sample size                                    |            |            |               |         |
| < 200                                          | 3          | 0.73       | 0.50 to 0.96  | 0.000   |
| > 200                                          | 2          | 0.51       | -0.43 to 1.45 | 0.284   |

Fig 1. Flow chart selected studies for meta-analysis
Is Herpes Simplex virus (HSV) a sign of Encephalitis in Iranian Newborns?

References

1. Xu F, Sternberg MR, Kottriti BJ, McQuillan GM, Lee FK, Nahmias AJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA Neurol 2006; 296:964-73.

2. Bochner AF, Madhivanan P, Niranjankumar B, Ravi K, Arun A, Krupp K, et al. The Epidemiology of Herpes Simplex Virus Type-2 Infection among Pregnant Women in Rural Mysore Taluk, India. J Sex Transm Dis 2013; 2013:1-6.

3. Kulhanjian JA, Soroush V, Au DS, Bronzan RN, Yasukawa LL, Weylman LE, et al. Identification of women at unsuspected risk of primary infection with herpes simplex virus type 2 during pregnancy. N Engl J Med 1992; 326:916–20.

4. Whitley RJ, Corey L, Arvin A, Lakeman FD, Sumaya CV, Wright PF, et al. Changing presentation of herpes simplex virus infection in neonates. J Infect Dis 1988; 158:109–16.

5. Cusini M, Ghislanzoni M. The importance of diagnosing genital herpes. J Antimicrob Chemother 2001; 47:9-16.

6. Cherpes TL, Meyn LA, Krohn MA, Lurie JG, Hillier SL. Association between acquisition of herpes simplex virus type 2 in women and bacterial vaginosis. Clin Infect Dis 2003; 37:319-25.

7. Gottlieb SL, Douglas JM, Schmid DS, Bolan G, Iatesta M, Malotte CK, et al. Seroprevalence and correlates of herpes simplex virus type 2 infection in five sexually transmitted–disease clinics. J Infect Dis 2002; 186:1381-9.

8. Arvaja M, Lehtinen M, Koskela P, Lappalainen M, Paavonen J, Vesikari T. Serological evaluation of herpes simplex virus type 1 and type 2 infections in pregnancy. J Sex Transm Infect 1999;75:168-71.

9. Brown ZA, Selke S, Zeh J, Kopelman J, Maslow A, Ashley RL, et al. The acquisition of herpes simplex virus during pregnancy. N Engl J Med 1997; 337:509-16.

10. Anzivino E, Fioriti D, Mischitelli M, Bellizzi A, Barucca V, Chiarini F, et al. Herpes simplex virus infection in pregnancy and in neonate: status of art of epidemiology, diagnosis, therapy and prevention. Virol J 2009; 6: 68-74.

11. Weiss H. Epidemiology of herpes simplex virus type 2 infection in the developing world. Herpes 2004;11:24-35.

12. Swetha G, Pinninti, David W, Kimberlin. Preventing HSV in the Newborn. Clin Perinatol 2014; 41:945–55.

13. Sheffield JS, Hill JB, Hollier LM, Laibl VR, Roberts SW, Sanchez PJ. Valacyclovir prophylaxis to prevent recurrent herpes at delivery: a randomized clinical trial. Obstet Gynecol 2006; 108:141-7.

14. Watts DH, Brown ZA, Money D, Selke S, Huang ML, Sacks SL. A double-blind, randomized, placebo-controlled trial of acyclovir in late pregnancy for the reduction of herpes simplex virus shedding and cesarean delivery. Am J Obstet Gynecol 2003; 188:836-43.

15. Bulletin AP. Clinical management guidelines for obstetrician-gynecologists. Obstet Gynecol 2003; 45:102-13.

16. Curtis N, Finn A, Pollard A. Neonatal herpes simplex virus infections: where are we now? Hot Topics in
Is Herpes Simplex virus (HSV) a sign of Encephalitis in Iranian Newborns?

Infection and Immunity in Children VII. 2nd ed. New York: Springer; 2011. P.146.

17. Allen UD, Robinson JL. Prevention and management of neonatal herpes simplex virus infections. Pediatr Child Health 2014;19:19-31.

18. Bernstein DI, Bellamy AR, Hook EW, Levin MJ, Wald A, Ewell MG, et al. Epidemiology, Clinical Presentation, and Antibody Response to Primary Infection With Herpes Simplex Virus Type 1 and Type 2 in Young Women. Clin Infect Dis 2013; 56:344-51.

19. Whitley R, Arvin A, Prober C, Corey L, Burchett S, Plotkin S, et al. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. N Engl J Med 1991; 324:450-4.

20. Von Elm E, Altman DG, Gotzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007;147:573–7.

21. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. 5th ed. London, UK: The Cochrane Collaboration; 2011.P.420.

22. Danesh Shahraki A, Moghim S, Akbari P. Evaluation of the Serum Level of Herpes Simplex Type 2 Antibody among Pregnant Women in Shahid Beheshti Hospital, Isfahan. J Red Med Sci 2010;15:243.

23. Bagheri Josheghani S, Moniri R, Baghbani Taheri F, Sadat S, Heidarzadeh Z. The Prevalence of Serum antibodies in TORCH Infections during the First Trimester of Pregnancy in Kashan, Iran. Iran J Neonatol 2015; 6:8-12.

24. Ghasemi FS, Rasti S, Piroozmand A, Fakhri-Kashan Z, Mousavi GA. Relationship between the prevalence of antibodies against cytomegalo, rubella, and herpes simplex viruses in women with spontaneous abortion compared to normal delivery. J Feyz 2015;19:86-92.

25. Pourmand D, Janbakhsh A, Hamzehi K, Dinarvand F, Ahmadi D. Seroepidemiological Study of Herpes Simplex Virus in Pregnant Women Referring to Health and Care Center in Kermanshah. J Kermanshah Univ Med Sci 2008;11:462-9.

26. Goralipour MJ, Khodabakhshi B, Ghaemi E. Possible role of TORCH agents in congenital malformations in Gorgan, northern Islamic Republic of Iran. East Mediterr Health J 2009;15:330-6.

27. Chen KT, Segu M, Lumeoy LH, Kuhn L, Carter RJ, Butlers M, et al. Genital herpes simplex virus infection and perinatal transmission of human immunodeficiency virus. Obstet Gynecol 2005; 106:1341-8.

28. Ali S, Khan FA, Mian AA, Afzal MS. Seroprevalence of cytomegalovirus, herpes simplex virus and rubella virus among pregnant women in KPK province of Pakistan. J Infect Dev Ctries 2014;18:389-90.

29. Hezarjaribi HZ, Fakhar M, Shokri A, Teshnizi SH, Sadough A, Taghavi M. Trichomonas vaginalis infection among Iranian general population of women: a systematic review and meta-analysis. Parasitol Res 2015;114:1291-300.

30. Sauerbrei A, Wutzler P. Herpes simplex and varicella-zoster virus infections during pregnancy: current concepts of prevention, diagnosis and therapy. Part 1: herpes simplex virus infections. Med Microbiol Immunol 2007; 196:89–94

31. Büchner S, Erni P, Garweg J, Gerber S, Kempf W, Lauper U, et al. Swiss recommendations for the management of genital herpes and herpes simplex virus infection of the neonate. Swiss Medi Wkly 2004; 134:205–214

32. Meerbach A, Sauerbrei A, Meerbach W, Bittrich HJ, Wutzler P. Fatal outcome of herpes simplex virus type 1-induced necrotic hepatitis in a neonate. Med Microbiol Immunol 2006; 195:101–105

33. Tyler KL. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret’s. Herpes 2004.; 11:57A-64A

34. Corey L, Whitley RJ, Stone EF, Mohan K. Difference between herpes simplex virus type 1 and type 2 neonatal encephalitis in neurological outcome. Lancet 1988; 1:1-4

35. Berger JR, Houff S. Neurological complications of herpes simplex virus type 2 infection. Arch Neurol 2008.; 65:596-600

36. Gallo MF, Warner L, Macaluso M, Stone KM, Brill I, Fleenor ME. Risk factors for incident herpes simplex type 2 virus infection among women attending a sexually transmitted disease clinic. J Sex Transm Dis 2008; 35:679–85.

37. Riley LE. Herpes simplex virus. Semin Perinatal 1998; 22:284-92.

38. Lankarani KB, Alavian SM, Peymani P. Health in the Islamic Republic of Iran, challenges and progresses. Med J Islamic Repub Iran 2013; 27:42.

39. Hoaglin DC. Assessment of heterogeneity in meta-analyses. JAMA Neurol 2014; 312:2286-7.