Int J Fertil Steril
International Journal of Fertility & Sterility
Homepage: https://www.ijfs.ir/
Systematic Review
Vol 17, No 3, July-September 2023, Pages: 152-159

The Impact of Herpes Simplex Virus on Semen Parameters in Men with Idiopathic Infertility: A Systematic Review

Atefeh Yas, M.Sc.[1], Elahe Mansouri Ghezelhesari, M.Sc.[1], Elnaz Iranifard, M.Sc.[1], Ali Taghipour, Ph.D.[2, 3], Malihe Mahmoudinia, M.D.[4], Robab Latifnejad Roudsari, Ph.D.[5, 6*]

1. Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran
2. Social Determinants of Health Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
3. Department of Epidemiology, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran
4. Maternal and Neonatal Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
5. Nursing and Midwifery Care Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
6. Department of Midwifery, School of Nursing and Midwifery, Mashhad University of Medical Science, Mashhad, Iran

Abstract

Infertility due to the male factor is one of the major problems of infertile couples. One of the factors contributing to male infertility could be the herpes simplex virus (HSV). The aim of this systematic review was to evaluate the impact of HSV on semen parameters. This systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). Different English and Persian databases including Web of Science, PubMed, Scopus, Cochrane Library, EMBASE, ProQuest as well as SID, Magiran and Iranmedex were searched by two researchers, independently, without time limit until April 15, 2022. Observational studies that reported the relationship between HSV and semen parameters in men with idiopathic infertility were included in this review. The Newcastle-Ottawa Quality Assessment Scale was used for quality assessment of the included studies. Out of 356 retrieved articles, 12 observational studies comprising a total of 1460 patients were reviewed. Four studies examined the effect of HSV1 virus, two studies examined the effect of HSV2 virus and five studies examined the effect of both viruses on semen parameters. Seven studies reported at least one significant association between HSV infection and semen parameters. Sperm count and sperm motility were semen parameters further affected by the virus. In conclusion, HSV can be one of the risk factors for male infertility and it can affect semen parameters. However, due to the dearth of studies, further research with more robust designs are recommended.

Keywords: Herpes Simplex Virus, Infertility, Men, Semen, Sperm

Citation: **Yas A, Mansouri Ghezelhesari E, Iranifard E, Taghipour A, Mahmoudinia M, Latifnejad Roudsari R. The impact of herpes simplex virus on semen parameters in men with idiopathic infertility: a systematic review. Int J Fertil Steril. 2023; 17(3): 152-159. doi: 10.22074/IJFS.2022.552037.1289.**

Introduction

Infertility is one of the problems of couples, and it is called, the lack of ability for couples to have children during one year of unprotected intercourse, affecting 10-15 percent of couples, and it causes a lot of problems for them (1-3). In keeping with the newest World Health Organization (WHO) statistics, 50-80 million people universally suffer from infertility (4, 5). A large number of research has found that about half of all instances of infertility occur due to female factors, 20-30 percent due to male factors, and 20-30 percent is unknown (5, 6). Recent meta-analyses by researchers showed that male factors are responsible for 20-70 percent of infertility instances (5, 7). Those findings are notably broader than outcomes previously observed. In various studies, several factors have been cited for male infertility (8-10). One of these factors is the herpes simplex virus (HSV), the effect of which some studies have shown on semen parameters (11-13).

HSV is a usual human pathogen, inflicting infections of orofacial membrane (HSV-1) and reproductive organ mucosal surfaces (HSV-2). Productive infection leads to the formation of vesicular lesions within the membrane epithelia, followed by unfolding of the virus to sensory neurons and institution of a latent infection, which will stay in the body throughout the lifetime of the host.

Received: 19/April/2022, Revised: 05/November/2022, Accepted: 26/December/2022
***Corresponding Address: P.O.Box: 913791319, Department of Midwifery, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran**
Email: latifnejadr@mums.ac.ir

Royan Institute
International Journal of Fertility & Sterility

Reactivation of the dormant virus results in recurrent disease at or contiguous to the location of the primary infection. During active infection, HSV takes over the host cell and a new code replication manages the viral gene (14, 15).

The HSV virus can stay for a long time with low copy numbers in the seminal fluid without presenting any symptoms (6, 11, 12). Recent studies have shown that HSV semen contamination is a possible risk factor for male infertility by affecting semen parameters such as sperm count, vitality, motility, and morphology by changing the pH of semen, changing the concentration or number of leukocytes, or increasing DNA fragmentation (11, 12, 16-18). Other later studies have not confirmed these findings (19-21), and extra analysis and synthesis of data is required to work out whether or not HSV infection contributes to male infertility.

Based on an extensive search among studies published in Persian and English on the reviewed topic, to the best of our knowledge, no systematic review has been published to evaluate the effect of HSV on semen parameters in male infertility. Previous reviews either were not systematic or have not specifically evaluated the effect of HSV on semen parameters to produce strong evidence; although there are some reviews on the impact of viral agents, as a whole, on the semen of infertile men such as, hepatitis B virus, human papilloma virus and epstein-barr virus (22-26). It should be noted that in the meta-analysis conducted by Malary et al. (27) in Iran, the prevalence of HSV virus in infertile men was reported, but the effect of the virus on semen parameters was not investigated. Also, since systematic reviews provide the highest level of evidence for evidence-based medicine (28), this systematic review was conducted to produce higher level of evidence with respect to the effects of HSV on semen parameters.Thus, due to the contradictory results that has been published about the effect of HSV on the quantity and quality of semen parameters, and considering that no systematic review has been conducted in this regard, the present systematic review was performed to identify the impact of HSV on semen parameters.

Materials and Methods

Data sources and search strategy

The present systematic review is based on the PRISMA 2020 guideline. Two researchers (AY, RLR), independently, searched English databases including Web of Science, PubMed, Scopus, Cochrane Library, EMBASE, ProQuest as well as SID, Magiran and Iranmedex databases to find Persian language articles without time limit until April 15, 2022. The search strategy was based on PICO: (P: men with idiopathic infertility and herpes simplex virus, I: none, C: fertile men, O: semen parameters including sperm count, sperm vitality, sperm motility, sperm volume and sperm morphology). The keywords used for searching included a combination of words: herpes simplex virus, HSV, men, infertility, sperm, semen, semen parameters with their equivalents in Mesh, and a combination of words with AND, OR functions. The type of study included cross-sectional and case-control studies. All the mentioned databases were searched to look for articles using the relevant keywords, in addition, the reference list of relevant articles, were manually searched to identify further studies missed by electronic search. The research question was as follows: What effect does the HSV has on semen parameters?

The PRISMA 2020 flowchart for systematic reviews was used to present the selection process of the studies (Fig.1).

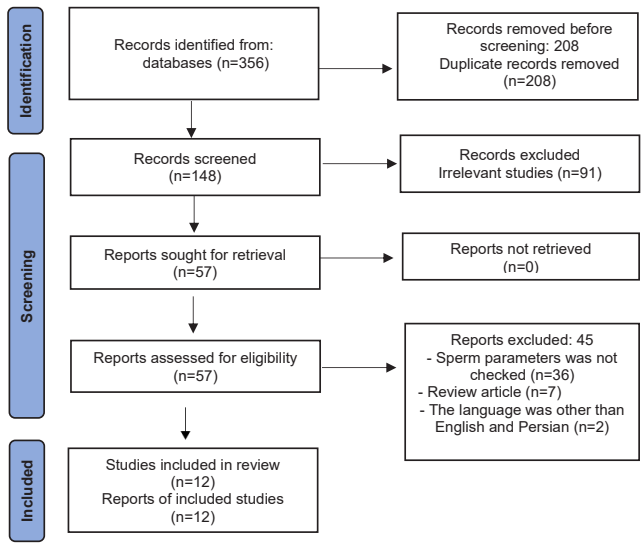

Fig.1: PRISMA 2020 Flow diagram of the study selection for systematic review.

Inclusion and exclusion criteria

Observational studies including cross-sectional and case-control studies that reported the relationship between HSV and semen parameters in men with idiopathic infertility were selected for review. Case reports, review articles, letters to the editor, and animal studies were excluded from the review. Also, the presence of anti-sperm antibodies, azoospermia, undescended testis, chromosomal abnormalities and a history of orchitis, epididymitis, varicocele and/or sexually transmitted infections in men were among the exclusion criteria.

Outcome measures

Outcome measures in this review included sperm motility, sperm vitality, sperm count, sperm morphology and semen volume.

Data extraction

Abstracts of articles were selected for screening using the search strategies described already. The title and

abstract of the articles were reviewed by two researchers, independently (AY, EI). If the article was related to the research topic, the full text of the article was reviewed. Articles with abstracts and texts other than English and Persian were excluded from the review. Also, articles with no published full text were removed from the review. Preliminary data were extracted by two researchers (AY, EMG) including the first author name, year of publication, country of publication, sample size, type of semen parameters studied and conclusion of the study. If two researchers disagreed in submitting an article to the study for review, they reviewed the inclusion and exclusion criteria and the research question and based on them, decided whether to include the article in the review process. The third researcher (AT) reviewed the article if the previous two researchers did not agree. However, disagreements between the two researchers were resolved through discussion with the third senior researcher (AT).

Quality assessment of studies

The type of articles extracted, included cross-sectional and case-control studies. Methodological quality assessment of studies was conducted by two researchers, independently (AY, EI) using the Newcastle Ottawa Quality Assessment Scale (29). Any disagreements between the two researchers were resolved through discussion with the third senior researcher (RLR).

Newcastle Ottawa Quality Assessment Scale has three sections for evaluating case-control studies: Selection (4 questions), Comparability (1 question) and Exposure (3 questions). The selection section receives a maximum of 4 points, the Exposure section receives a maximum of 3 points and the Comparability section receives a maximum of 2 points. Following assessment, a total of 9 points are awarded to the whole tool and the articles are rated as high, medium or poor quality (low quality ≤5 points, Medium=6-7 points, High=8-9 points).

To evaluate cross-sectional studies, this tool has three parts: Selection (4 questions), Comparability (1 question) and Outcome (2 questions). Selection gets a maximum of 5 points, Comparability gets a maximum of 2 points and Outcome gets a maximum of 3 points, and in total, the whole tool gets 10 points. Finally, the quality of the articles is rated as high, medium or poor (Low quality ≤5 points, Medium=6-7 points, High ≥ 8 points).

Results

In the first stage of searching the studies, 365 articles were retrieved. After removing 208 duplicate articles, 148 articles were assessed for title and abstract. Following removal of irrelevant articles, 57 articles were reviewed for the full text. Finally, 12 studies that examined the impact of HSV on semen parameters in men with idiopathic infertility were included in the systematic review (11-13, 16-21, 30-32). The characteristics of the comprised articles in this systematic review are summarized in Table 1.

Table 1: Basic characteristics of the included studies in the systematic review

ID	First author/ year of publication	Country	Study design	Age (Y)/sample size (n)	Cause of infertility	HSV type (HSV-1/ HSV-2)	Outcome measures	Main findings	Quality assessment score
1	Kapranos et al. (16), 2003	Greece	Cross-sectional	Not reported, (n=113 infertile men)	Idiopathic male infertility	HSV1	Sperm motility, Sperm count	HSV, by affecting the most important factors of semen quality, plays an important role in male infertility.	High
2	Bezold et al. (17), 2007	Germany	Cross-sectional	22-55 years, (n=241 infertile men)	Idiopathic male infertility	HSV-1, HSV-2	Sperm motility, Sperm count	HSV was associated with poor semen quality.	High
3	Kurscheidt et al. (12), 2018	Brazil	Cross-sectional	18 years or older, (n=279 infertile men)	Idiopathic male infertility (Semen analysis for fertility evaluation)	HSV-1, HSV-2	Sperm count, Vitality, Sperm motility, Sperm volume (mL)	HSV infections may have changes on the 2 equally important components of semen, spermatozoa, and seminal fluid, which may influence fertility.	High
4	Kotronias and Kapranos (11), 1998	Greece	Cross-sectional	Not reported, (n= 80 infertile men)	Idiopathic male infertility	HSV-1, HSV-2	Sperm count, Sperm motility	HSV seems to play an important role in male infertility.	Low
5	Pallier et al. (30), 2002	Praise	Case-control	-	HSV2	HSV2	Sperm motility	Slight difference was reported in the percentage of motile forms when seminal fluid –free sperm were incubated with HSV.	Medium

Table 1: Continued

ID	First author/ year of publication	Country	Study design	Age (Y)/sample size (n)	Cause of infertility	HSV type (HSV-1/ HSV-2)	Outcome measures	Main findings	Quality assessment score
6	Mergani et al. (19), 2019	Sudan	Case-control	Not reported, (n=90 infertile men, 45 control group, 45 case group)	HSV2	HSV2	Sperm count, Sperm motility	HSV type 2 antibodies had no objective impacts on sperm concentration or sperm motility among Sudanese infertile males.	High
7	Bocharova et al. (18), 2008	Russia	Cross-sectional	Not reported, (n=23 infertile men)	HSV	HSV	Spermatocytes I in pachytene and diplotene stage of meiosis	A partial spermatogenic arrest at the early stages of meiotic prophase I in HSV patients	Medium
8	el Borai et al. (31), 1997	Tokai	Case-control	Not reported, (n=169 Case=153 infertile men, control=16 fertile men)	HSV1	HSV1	-	No difference in the distribution of sperm quality within the 2 groups, herpes positive and negative	Low
9	Monavari et al. (13), 2013	Iran	Cross-sectional	Not reported, (n= 70 infertile men)	HSV1, HSV2	HSV1, HSV2	Sperm Count, Sperm motility, Sperm morphology	Asymptomatic seminal infection of HSV plays an important role in male infertility by adversely affecting sperm count	High
10	Neofytou and Sourvino (20), 2009	Greece	Case -control	Not reported, (n=172 infertile man, control=80 whit normal semen parameters, case=92 with abnormal semen parameters)	HSV1	HSV1	Sperm motility, Sperm count	The DNA of herpes viruses is frequently detected in the semen of asymptomatic fertile and infertile male patients. Further studies are required to investigate the role of herpes viruses in male factor infertility.	High
11	Moretti et al. (21), 2017	Italy	Cross-sectional	Not reported, (n=73 men)	HSV1	HSV1	Sperm count, Sperm motility, Sperm volume	The DNA of herpes viruses is frequently detected in the semen of asymptomatic fertile and infertile male patients. Further studies are required to investigate the role of herpes viruses in male factor infertility.	Medium
12	Tajedini et al. (32), 2017	Iran	Cross-sectional	34.1 ± 5.7 year (n=150 infertile men)	HSV1, HSV2	HSV1, HSV2	Sperm count, Sperm motility	HSV was associated with a decrease in the number of sperm in the semen.	Medium

HSV; Herpes symplex virus.

The design of the eight studies (11-13, 16-18, 21, 32) that were systematically reviewed in the present study was cross-sectional, four studies were case-control (19, 20, 30, 31), and their publication year was from 1997-2019. Half of these articles received a "High" score in quality assessment (12, 13, 16, 17, 19, 20), two of the articles received a "Low" score (11, 31) and the rest of articles received a "Medium" score (18, 21, 30, 32).

The total sample size was 1,460 infertile men with no obvious clinical signs of the virus. Also, the cause of infertility in these men was unknown. The sample size in the articles ranged from 23 (18) to 279 (12) people. WHO criteria was adopted for collecting, preparing, and analyzing semen sample according to the literature (33). In all studies, male infertility was referred to as the incapacity of couples to have children after twelve months of intercourse without the use of contraceptives. In all studies, semen sample was taken for sperm analysis after three days of sexual inactivity.

Four studies only measured the effect of HSV1 in

semen on semen parameters (16, 20, 21, 31). Two studies examined only the effect of HSV2 on semen parameters (19, 30). Five studies measured the effect of both HSV1 and HSV2 viruses on semen parameters (11-13, 17, 32). One study did not identify the type of HSV virus and HSV was generally mentioned in the article (18).

Out of the 12 studies included in the present review, in seven studies (11-13, 16-18, 32) at least one significant association was observed between semen contamination with HSV1 or HSV2 and a decrease in the quantity or quality of semen parameters. In these studies, sperm count and sperm motility were more affected by HSV and the virus had a small effect on the volume of semen, so that, in one study (12) it caused a significant reduction in the volume of semen.

Detection of HSV in semen: In the studies included in this review article, fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) methods were used to identify the HSV virus in semen.

Studies reporting no association: In five (19-21, 30, 31) out of 12 studies, HSV virus had no impact on the quantity and quality of semen parameters. In one of these five studies, HSV was found in the semen of 24% of infertile men, but the virus was not detected in the semen of any of the fertile men (31).

In another study, HSV2 was injected into the semen of a number of infertile men and sperm motility was compared between the two groups. In the HSV2 positive group, sperm motility was lower than the other group, but this difference was not statistically significant (30).

Studies reporting association: Seven studies (11-13, 16-18, 32) in this review reported at least one significant association between semen contamination with HSV1or HSV2 virus and the quantity or quality of semen parameters. HSV1 in three studies (11, 13, 16) and HSV2 in two studies (11, 13) were associated with a significant reduction in sperm count and motility. Out of the five studies that measured the effect of HSV1 and HSV2 on semen parameters, three studies (12, 17, 32) just reported HSV in the results and did not examine semen parameters separately for each type of herpes simplex virus. In one of these studies (32), the HSV virus was related with a considerable reduction in sperm count. In two other studies (12, 17), the presence of HSV virus in semen was associated with decreased sperm count, sperm motility and sperm volume.

In the study by Kotronias and Kapranos (11), in HSV-positive men, sperm motility and sperm count were significantly lower than in HSV-negative men. Also, in the subsequent study of these authors, with a higher sample size, the presence of HSV in the semen of infertile men was associated with a significant reduction in sperm count and sperm motility (16). Bezold et al. (17), reported similar results. In their study, the presence of HSV virus in the semen of infertile men was associated with a significant reduction in sperm count, sperm motility and sperm concentration. In two other studies conducted in Iran by Tajedini et al. (32) and Monavari et al. (13), contamination of semen with HSV, significantly, reduced sperm count in infertile men. In the study of Bocharova et al. (18), HSV positive patients illustrated a significant reduction within the range of spermatocytes I, in the pachytene and diplotene stages of meiosis, reduction in the proportion of spermatocytes II and spermatids, and a two-fold increase in the number of unrecognizable premature germ cells. The data obtained demonstrate a partial spermatogenic detention at the early stages of meiotic prophase I in HSV patients. Sperm vitality and morphology were each examined in one study and HSV infection was not related with sperm morphological defects (13) and sperm vitality (12).

Semen parameters

Sperm mortality

The effect of semen contamination with HSV type one or two was investigated on sperm motility in ten studies (11-13, 16, 17, 19-21, 30, 32). In one study, HSV1 infection caused a significant decrease in sperm motility (16). But in three studies there was no significant relationship between HSV1 infection and decreased sperm motility (13, 19, 21). Also, in one study, a significant correlation was observed between HSV2 infection and decreased sperm motility (13), whereas no significant correlation was observed in the two other studies (19, 30).

In the articles by Bezold et al. (17) and Kotronias and Kapranos (11), which had not specified the type of virus in the results, a significant relationship was generally observed between HSV infection and decreased sperm motility and in the Kurscheidt et al. (12) and Tajedini et al. (32) articles, in general, no significant relationship was observed between HSV infection and decreased sperm motility.

Sperm count

In six studies, the relationship between sperm count and semen contamination with HSV type one or two was investigated (11, 13, 16, 19, 20, 32). In two studies, a significant correlation was observed between HSV1 infection and sperm count reduction (13, 16). However, in one study, no significant relationship was observed (20).

In one study, there was a significant relationship between HSV2 and decreased sperm count (13), and in another study, no significant relationship was observed (19). Kotronias and Kapranos (11) and Tajedini et al. (32) found a significant relationship between semen contamination with HSV1 and HSV2 with decrease in sperm count.

Sperm volume

In one study, a significant correlation was observed between semen infection with HSV1 and HSV2 with a decrease in the volume of the semen sample (12). In

another study, no significant relationship was observed between HSV1 and reduction of semen volume (21).

Sperm concentration

In the study by Moretti et al. (21), no significant difference was observed between HSV1 infection and changes in sperm concentration. But in the study by Bezold et al. (17) and Kotronias and Kapranos (11) a significant correlation was observed between HSV1 and HSV2 infection with changes in sperm concentration.

Sperm morphology

A significant relationship was observed between HSV2 infection and the reduction of normal sperm morphology, but no significant relationship was observed between HSV1 and sperm morphology (13).

Discussion

The present review was conducted to identify the impact of HSV on semen parameters. Twelve articles were included in the study, and in seven studies (11-13, 16-18, 32) at least one significant association was observed between semen contamination with HSV1 or HSV2 and a decrease in the quantity or quality of semen parameters. Sperm motility and sperm count were reduced in six studies due to virus infection (11-13, 16, 17, 32) and in one study (12) HSV caused a significant reduction in the volume of semen. In these studies, HSV was identified as the cause of male infertility, so that, acyclovir treatment in two studies improved semen parameters and led to a successful pregnancy (11, 16). Therefore, these authors recommended screening and treatment for HSV before assisted reproductive technologies in infertile men.

Akhigbe et al. (34), reported that HSV can infect almost all organs of the male reproductive system and it can cause direct damage to sperm and change sperm quality such as decreased sperm count, motility and morphology. Nawaz et al. (35), also mentioned that HSV DNA is mostly discovered in semen with low sperm count, indicating the connection of sperm HSV DNA and possible fertile problems. HSV infection affects the functions of the male genital glands and is related with male infertility and malformed semen parameters. Ochsendorf (36), inferred that infection of semen with the HSV may destroy sperm count and motility, but this has not yet been proven. It has been highlighted in two other studies that HSV infection may influence male infertility via harmful effects on semen parameters including sperm count, sperm motility and apoptotic loss of germ cells (37, 38). But the results of the study by Afrakhteh et al. (39), showed that semen samples of both fertile and infertile participants were negative for HSV1 and HSV2; therefore, infection of semen with HSV is not associated with impaired semen parameters. The results of the study by Elhadi et al. (40), in infertile men also showed no association between HSV2 DNA and low sperm count, which is inconsistent with the results of the mentioned studies and may be due to differences in sample size and virus detection methods.

In our systematic review, HSV infection was not related with sperm morphological defects (13) but in a study by Komijani, et al. (41), it was found that HSV infection resulted in abnormalities in the sperm head and neck, which could finally lead to infertility. Animal studies have also shown that infection of the testes of mice with HSV and retrograde ascent of the virus into the seminiferous tubules leads to irreversible atrophy of the germinal epithelium, sperm damage and infertility and the reduction of HSV thymidine kinase levels, which resulted in marked reduction of spermatozoa abnormalities and amendment of fertility (42, 43). A nearby ligand/receptor connection may exist between the virus and seminal cells, which cause the effect of the virus on the quantity and quality of sperm. These receptors mainly include: i. Glycosaminoglycans (GAGs), particularly heparan sulfate which is situated at the cell surface and can intervene with passage of numerous infections including HSV-1 and HSV-2 and ii. Nectin-1 and nectin-2, individuals from the immunoglobulin superfamily, are expressed in numerous organs, tissues, and cell lines, which are regularly contaminated by HSV. Nectin-1 articulation on murine spermatids, which would advance connection with the infection, has likewise been seen (38).

To the best of our knowledge, the present study is the first systematic review on the effect of HSV on semen parameters, in which articles both in Persian and English languages related to the purpose of the study were included in the review and this is considered as the strengths of the present study. One of the limitations of this study was that it was not possible to do meta-analysis. The reason for not conducting a meta-analysis and just carrying out a systematic review was that in the included articles in this review, the data were presented in some articles as continuous data and in others as percentage or median. Therefore, it was not possible to combine them and conduct a meta-analysis. Further studies are needed to make conduction of future meta-analysis possible. Also, since no meta-analysis was found regarding the effect of HSV on semen parameters, discussing the findings and comparing the results with other meta- analyses was limited.

Conclusion

According to the studies reviewed in this article, it can be concluded that HSV can be one of the risk factors for male infertility and affect the quantity and quality of sperm. Infection of semen with HSV reduces the parameters of sperm count, motility and volume and does not affect morphology and sperm vitality. In order to better assess the range of effects, future studies should include consideration of other semen parameters, including semen volume, sperm viability, as well as investigating how the HSV virus could damage the sperm production process.

Acknowledgements

The authors whose articles were reviewed are sincerely appreciated for their assistance in providing informational support for this systematic review. There is no financial support and conflict of interest in this study.

Authors' Contributions

A.Y., R.L.R., M.M.; Study design. A.Y., E.I.; Screening and quality assessment of the articles. A.Y., E.M.G.; Extraction of the preliminary data. A.Y., R.L.R., A.T.; Interpretation of data. A.Y., R.L.R., E.I., E.M.G., A.T., M.M.; Drafting and critical revision of the manuscript and final approval of the manuscript. All authors agreed to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved. All authors read and approved the final manuscript.

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