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REVIEW ARTICLE

The effects of human immunodeficiency virus, human papillomavirus, herpes simplex virus-1 and -2, human herpesvirus-6 and -8, cytomegalovirus, and hepatitis B and C virus on female fertility and pregnancy

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ABSTRACT

Female infertility may be defined as a woman of reproductive age being unable to become pregnant after a year of regular unprotected sexual intercourse. Social, genetic, endocrine, physiological, and psychological factors as well as lifestyle habits (i.e., smoking and alcohol consumption), either alone or in combination with male factors, are major causes. However, approximately 15–30% of cases of female infertility remain unexplained. Numerous investigations have also indicated that microbiomes play an important role in human reproduction. All parts of the female reproductive system may be influenced by infectious and pathological agents, especially viruses, and these may interfere with reproductive function and so are risk factors for infertility, although in many cases an exact role is unclear.

We present an overview of the impact of common viral infections on female reproduction, searching Medline, PubMed, Scopus, and Google scholar databases for potentially relevant studies of viruses known to have a potential effect. Human immunodeficiency virus (HIV), herpes simplex virus (HSV) and human herpesvirus (HHV) increase infertility rates whilst human papillomavirus (HPV), cytomegalovirus (CMV), and hepatitis B and C virus (HBV, HCV) infections mostly lead to higher abortion and miscarriage rates. Moreover, HPV infection is linked to increased tubal infertility, endometriosis, and pelvic inflammatory disease. HPV was the most frequently observed infection and with lower pregnancy rate and foetal death in women undergoing IVF treatments. Assisted reproductive treatment could be a safe and effective approach for HIV and HBV infected women.

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Introduction

Infertility is a critical component of reproductive health and affects about 15% of couples throughout the world [1]. In primary infertility, couples have never been able to conceive; while in secondary infertility there is difficulty in a subsequent conception after having conceived (either carried the pregnancy to term or had a miscarriage) [2,3]. Female infertility constitutes 37% of all infertility cases [4], and may be defined as a woman of reproductive age being unable to become pregnant after having regular, unprotected intercourse for at least a year. Social, genetic, endocrine, physiological, and psychological factors and lifestyle habits (i.e., smoking and alcohol), either alone or in combination with male factors, are major causes of female infertility. However, approximately 15–30% of cases remain unexplained [5].

Numerous investigations have indicated that microbiomes play an important role in human reproduction. Pathological agents, especially viruses, have been considered as major causes of idiopathic infertility in different studies. These microorganisms have a negative affect on human reproductive function, whilst women are more likely to be influenced by viral infections than are men. Secondary infertility is the most prevalent form of female infertility worldwide, often due to reproductive tract infections [6]. Sexually transmitted infections (STIs) causing infertility could potentially be a simple by-product of infection-related damage in the affected tissues. Different infertility factors including vaginal, cervical, uterine, tubal, and pelvic peritoneal factors have been frequently associated with the presence of these microorganisms within the vaginal microbiome. Many tubal infertility factors including pelvic inflammatory diseases (PID), endometriosis, pelvic adhesions, tubal occlusion, and tubal dysfunction are related to untreated sexually transmitted diseases (STDs) including bacterial (e.g. *Chlamydia trachomatis, Neisseria gonorrhoea*), parasitic (e.g. *Toxoplasma gondii, Entamoeba histolytica*), fungal (e.g. Trichomoniasis, Candida species) and viral infections (e.g. human papilloma virus, herpes simplex virus) that can ascend the reproductive tract and lead to tubal inflammation, scarring, blockage, and damage [7–10].

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Viral infections may facilitate the spread of vaginal flora to the upper genital tract by disrupting the endocervical canal barrier and lead to upper tract disorders such as PID and endometriosis. PID is a leading cause of tubal infertility and is an inflammatory disorder of upper genital tracts in women that includes various combinations of endometritis, salpingitis, pelvic peritonitis, and tubo-ovarian abscess. Although *Neisseria gonorrhoeae* and Chlamydia infection are two of the recognized microbial causes of PID, a variety of viral infections have also been related to PID, and significantly reduce fertility. Chronic endometritis is linked with salpingitis and is frequently identified in apparently uncomplicated infections of the vagina or cervix. However, vaginal infections are less frequent causes of endometritis, leading to uterine synechiae, and are less common than tubal occlusions resulting from salpingitis. Endometriosis may cause uterus, ovary, and fallopian tubes adhesions, thereby preventing the transfer of the egg to the tube. The presence of different viral infections in the female genital tract has also been associated with an increased incidence of endometriosis [9,11,12]. Impaired follicular growth, aberrant circulating hormone concentrations, and reduction of oocyte fertilization and implantation rates are the most common causes of infertility in women with endometriosis [13]. Furthermore, cervical infertility involves the inability of spermatozoa to enter the uterus due to damage to the cervix or cervical factors such as cervical stenosis, anti-sperm antibodies, and cervical infections from different STDs [14–16]. However, several have failed to link viral infections and infertility [17–20].

High prevalence of viral infections may significantly increase the prevalence of STDs in the female reproductive tract, resulting in an increased rate of tubal diseases and infertility. The most likely mechanism is the ability of these pathological agents to induce upper-tract disease from lower-tract flora generally considered non-pathogenic in immunocompetent women. Viruses can also gain access to the placenta and lead to foetal infection and result in abnormalities or death. There are four different routes by which viral pathogens can infiltrate into foetal–placenta tissues and affect pregnancy and foetal development: (a) through ascendant infection of the urogenital tract infection; (b) through the maternal vascular endothelium to the trophoblasts, (c) through infected macrophages in maternal blood acting on placental trophoblasts, and (d) through paracellular routes from the maternal blood to foetal capillaries [21,22]. Finally, an important viral defence mechanism is natural killer (NK) cells known to be present in the uterine myo- and endometrium. Malfunction in NK responses may inappropriately activate immune system cells and interfere with embryo implantation and development.

The true impact of viral infections and their importance for female reproduction is not well established. We seek to highlight their importance in female reproductive health and evaluate their influence on reproductive function and pregnancy outcomes. The most common viruses linked to female fertility and increasing pregnancy complications are the human immunodeficiency virus (HIV), herpes simplex virus (HSV), human herpesvirus (HHV) human papillomavirus (HPV), cytomegalovirus (CMV), and hepatitis B and C viruses (HBV, HCV).

Method

We searched Medline, PubMed, Scopus, and Google Scholar databases to find potentially relevant papers concerning the effect of different viral infections (HIV, HPV, HHV, HSV, CMV, HBV, and HCV) in female infertility published from 2000 until February 2020. We searched these databases using keywords that were a combination of virus names and words associated with female reproductive problems such as female infertility, primary infertility, secondary infertility, pregnancy complications, fertilization, PID, tubal infertility, endometriosis, abortion, miscarriage, failed pregnancy, reproductive disorder, reproductive failure, foetal death, pregnancy outcome, premature rupture of membranes, ectopic pregnancy, stillbirth, reduced pregnancy rates, recurrent spontaneous abortion, recurrent miscarriage, implantation, in vitro fertilization (IVF), and assisted reproductive technology. This procedure was carried out for every virus.

Full articles relevant to the topic were considered. Population-based studies investigating the link between different viruses and female reproductive problems were included. Retrospective as well as cross-sectional and controlled design studies were taken into consideration. In vitro based experimentations that explained the effect of different viral infections on the female reproductive system were also considered. Animal model studies and studies related to the effect of vaccination or preventive drugs on female fertility were excluded. Studies with a limited number of women that may give false negatives and false positives were excluded. We also excluded reports of minimal importance on the topics. This strategy identified 1147 studies related to the area of this study.

Predesigned forms were used to extract data, these being first author, year of publication, country of origin, viral infection, the total number of patients, the total number of controls, the effect on infertility, the effect on pregnancy outcomes, and the detection methods. We included the most important and updated studies to record the detrimental effects that were caused by different viruses on female reproductive system, implicating in infertility and adverse pregnancy outcomes. Of the 1147 articles, 124 articles met our inclusion criteria (Figure 1). These were collected

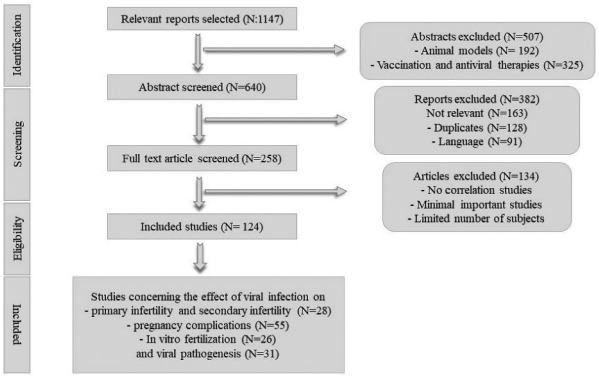

Figure 1. Flow chart for the search methodology.

into four groups according to the reproductive health aspect focused upon: those concerning the effect of viruses on primary infertility, on secondary infertility, on pregnancy outcomes in natural and in vitro fertilization among different populations and concerning the pathological mechanisms by which different viruses exerted their detrimental effects.

The result of these searches are as follows.

Human immunodeficiency virus

HIV is well-recognized as a life-threatening virus all over the world. With 25 million deaths and an additional 33.2 million infections (of which 50% are women) it will soon be the world's worst pandemic [23]. The virus infects several cell types of the host immune system: CD4 + T lymphocytes, macrophages, and dendritic cells. Studies showed that HIV+ve women are more likely to be infertile than their HIV-ve counterparts. However, the exact underlying mechanism by which HIV affects female reproductive function is unknown, but reduced CD44 levels following HIV infection are related to the sustained immunological effects that eventually decreased fertilization rates [24]. Conflicting results were provided by the investigation of 566 HIV+ve women, where although the initial CD4 counts was low, levels stayed the same during pregnancy and the final results showed no association between HIV infection, pregnancy rate and increased rates of adverse maternal or neonatal outcomes [25]. This may be explained in that a good immunovirological response in HIV+ve women could develop during pregnancy and so prevent adverse outcomes [26].

An additional underlying mechanism for infertility may be mitochondrial function. This hypothesis suggests that sufficient energy production from mitochondria was relevant to the oocyte viability and foetal development in HIV+ve patients [27,28]; therefore, any mitochondrial defect in the oocytes could lead to cell dysfunction and infertility. This suggestion was supported by the results of a study that showed mitochondrial DNA depletion in the oocytes of HIV+ve infertile females was the major cause of their infertility. The oocytes from these women had lower mtDNA content that could probably justify their poor reproductive outcome [27,29].

Higher incidence of PID and tubo-ovarian abscesses among HIV+ve is another risk factor for infertility that significantly increased the risk of tubal diseases and infertility [30,31]. Several studies have shown how certain endocrinological effects of HIV status can influence the ovarian function. HIV+ve women are more likely to have changes in the menstrual cycle function, protracted anovulation, and prolonged amenorrhoea, which implies impaired ovarian function, and could be considered as potential causes of pregnancy failure [32,33]. A direct effect of HIV leading to pituitary-gonadal failure has also been proposed [34]. The strong association between HIV acquisition and vaginal flora abnormalities is another risk factor [35]. Several studies have demonstrated the high prevalence of STDs in HIV+ve women [36], so this group could be at risk for tubal disease and infertility

Many studies have reported reduced fertility potential among HIV+ve women in different populations [37–41] (Table 1). There was a significant increase in foetal loss rates among pregnant women at the early stages of HIV infection in a study in Uganda and very few pregnancies were recognized in advanced stages [42]. The association between infertility and HIV was further confirmed in different studies. HIV+ve women appeared to have more fertility problems, decreased live births, and lower pregnancy rates [38,41,43]. Dhont et al. also found a strong association between HIV infection and tubal infertility [44]. On the contrary, no association between pregnancy rate and HIV infection was observed in a study from France [45]. Miscarriage, spontaneous abortion, and stillbirths are common among HIV+ve women [46,47], although Coley et al. showed no significant difference between HIV+ve women and the risks of foetal loss or low birth weight [48].

Very few studies have investigated the effects of HIV infection on IVF outcomes. A recent study showed that the pregnancy rates per transfer was significantly lower for HIV+ve cases compared with controls, as were the implantation and the live birth rates [49]. Other investigations on the effectiveness and safety of assisted reproduction techniques (ART) declared it a safe and effective technique for HIV+ve couples, with acceptable IVF outcomes and pregnancy rates [50–53]. Sahadat et al. showed that in females with well-controlled HIV infection, the fertility rate was not different; however, the live birth rate per embryo transfer was significantly lower for HIV+ve women compared with controls, although this may have been due to their age [54]. Thus although HIV infection has detrimental effects on pregnancy outcomes, and increases the miscarriage rates among them, it does not have the same adverse impacts on IVF outcomes, especially in cases when the woman is the solo infected partner. For

Table 1. Characteristic of population-based studies related to HIV infection.

Study	Year	Region	Cohort/ Controls/Cases	Outcome
[31]	2007	Spain	130 HIV+ve	Increased tubal occlusions[a]
[38]	2003	USA	4139 HIV+ve	Increased infertility[a]
[33]	2016	France	201 HIV+ve/ 603 HIV-ve	Increased tubal disease[a]
[37]	2017	UK	$8 \times 10^5/1 \times 10^6$	Decreased fertility[b]
[43]	2010	UK	2926/5307	Decreased fertility[b]
[25]	2011	Italy	566 HIV+ve	No effect on PR[b]
[8]	2006	UK	65 HIV+ve	Increased tubal infertility[b]
[44]	2010	Rwanda	283/312	Increased tubal infertility[c]
[49]	2016	France	82/82	Lower PR and FR[c]
[45]	2000	France	124/241	No effect on PR[c]
[51]	2017	Belgium	312/104	No effect on IVF outcome[c]
[54]	2013	USA	60/60	No effect on pregnancy rate, increased stillbirth[c]
[24]	2005	France	473 HIV+ve	Decreased PR and live births
[41]	2005	USA	1702 HIV+ve	Decreased PR and live births
[34]	2016	India	50 HIV+ve	Increased gonadal abnormalities
[53]	2005	France	50 HIV+ve undergoing IVF	No effect on ART outcome
[42]	2004	Kenya	99/92	Reduced PR, Increased foetal loss
[46]	2013	France	788/148	Increased miscarriage and stillbirth
[47]	2013	Nigeria	1368/1702	Adverse pregnancy outcome and abortion
[48]	2001	USA	502/107	Adverse pregnancy outcomes

a: primary infertility, b: secondary infertility, c: primary and secondary infertility. PR = pregnancy rate, FR = fertility rate, ART = assisted reproduction technique, IVF = in vitro fertilisation

HIV infected women who desire to become pregnant, ART would probably be a safe and effective procedure.

Human papillomavirus

HPV infections are often asymptomatic and many are often unaware of their infection until being tested. HPV can exert a negative effect and lead to fertility alteration via two different pathways: (i) an infectious virion-producing pathway, and (ii) non-infectious cancer-producing pathway [55]. Several in vitro studies have suggested that HPV could negatively affect embryo development, mostly during very early stages, possibly by effects on the endometrial implantation of trophoblastic cells that lead to abnormal placentation and early pregnancy loss [56]. The ability of HPV to complete its life cycle in trophoblastic cells was suggested by Liu et al [57]., whilst You et al. showed that due to some similarities between HPV and trophoblastic cells in the gene expression repertoire, these cells are considerably permissive to this virus. They reported that trophoblastic cells previously cultured with HPV 16,18,11, and 31 had an active viral genome expression (both early and late genes). You et al. showed, in an in vitro study, a significant reduction in both trophoblastic cell counts and trophoblast-endometrial cell adhesion a week after the exposure to HPV-31, HPV-16 E6 and E7 oncogenes [58,59]. Boulenouar et al. explained by in vitro findings a down-regulation of E-cadherin, an essential protein for cell-to-cell adhesion, in trophoblastic cells expressing the HPV-16 viral genome [60]. These effects were confirmed by Gomez et al, who showed a 3- to 6- fold higher rate of apoptosis when using a plasmid containing the HPV-16 genome for trophoblasts transfection, compared to use of an empty plasmid [61]. Indeed, HPV trophoblasts infection not only corrupts the embryo's health but also its ability to invade the uterine wall.

Studies in different populations have demonstrated the negative influences of HPV on female reproductive function (Table 2). One found a significant association between HPV prevalence in the cervix and placenta with spontaneous abortion and spontaneous delivery [62]. The fact that HPV-16 can induce apoptosis in a first-trimester trophoblast cell line could be an explanation for this result. Different studies found HPV infection in pregnant women to be significantly associated with premature rupture of membranes and placental abnormalities [63], which could be the major risk factors for abortion [64,65]. In contrast, others found no significant association between HPV prevalence and spontaneous abortion or miscarriage rates [66,67], even though HPV prevalence was higher in women experiencing spontaneous abortion [68], hypothesizing that immune reactivity that happens during miscarriage could be a mechanism to prevent HPV infection [67]. However, several studies showed no effects of HPV infection on IVF outcomes [69–71], although a clear relationship between HPV infection and IVF failure was reported by Zhang et al. who indicated that the rates of IVF failure and miscarriage were significantly higher among HPV+ve women [72]. Yang and colleagues also indicated no significant association between HPV infection and the rates of pregnancy outcome, livebirth, preterm birth, and early and

Table 2. Characteristic of population-based studies related to HPV infection.

Study	Year	Region	Controls/ Cases	Outcome
[15]	2013	Sudan	30/70	Increased infertility[c]
[73]	2013	China	69/80	No effect on PR[c]
[70]	2008	China	629/415	No effect on IVF outcome[c]
[11]	2017	Iran	49/50	Increased endometriosis
[13]	2010	Germany	30/66	Increased endometriosis
[19]	2019	Denmark	8734/1861	No effect on infertility
[56]	2000	Austria	44/135	Increased abortion
[63]	2011	USA	227/160	Increased preterm birth and placental abnormalities
[64]	2012	N. Africa	432/319	Increased abortion
[65]	2013	Korea	267/54	Increased PROM
[66]	2011	Poland	78/51	No effect on SA
[67]	2013	Italy	49/475	No effect on RM
[68]	2013	Mexico	138/139	No effect on SA
[72]	2019	China	285/54	Decreased PR and livebirth
[69]	2002	Sweden	197./214	No effect on fertility
[71]	2016	Czech	51/362	No effect on IVF outcome

See Table 1 for abbreviations and notes. PROM = premature rupture of membranes, SA = spontaneous abortion, RM = recurrent miscarriage.

late abortion [73]. Thus, there is ample evidence suggesting that HPV in responsible for higher miscarriage rates among infected females and poor ART outcomes. However, most HPV infections in ART studies are restricted to the effects of the virus during the early stages of embryo development. Future studies are needed to elucidate the consequences of HPV infection in the late embryos' development and ART outcomes (Table 2).

Herpes simplex virus

Herpesviruses are ubiquitous pathogens: most infections are asymptomatic or unrecognized. They include HSV-1 and HSV-2 (also known as HHV1 and HHV2), HHV-6, HHV-7 (that causes mild infections) and HHV-8 (a marker for AIDS).

HSV can infect both oro-facial areas and genital tracts. Primary genital HSV-1 or HSV-2 infection can lead to abortion, premature labour, and congenital and neonatal herpes. HSV-2 infection enhances HIV acquisition and transmission and may play a role in infertility [74]. The two suggested mechanisms by which it leads to infertility are lower-genital tract ulcerations that develop the spread of lower genital tract pathogens to upper genital tracts and enhances PID, and increasing the host inflammatory responses in upper genital tracts that may cause tubal damages and increase infertility.

Several studies have linked infertility with HSV-2 infection [44,75,76], although others failed to show any significant association between HSV-2 infection and decreased fertility [77–79](Table3). In contrast to several studies which did not confirm the negative effects of HSV-2 infection on foetal loss [77,78], the important role of HSV infection in pregnancy loss was frequently demonstrated in others studies [80–82]. Ashshi and colleagues collected tubal samples from 135 women, of whom 84 suffered an ectopic pregnancy, reporting that, with a 21.4% prevalence, HSV 1/2 is a major risk factor for this complication with an odds ratio of 1.7 [83]. Taken together, HSV, especially in combination with HIV infection, can negatively influence pregnancy rates and lead to increased miscarriage, abortion, and infertility rates. However different studies have investigated the adverse impacts of HSV infection on female reproductive function, only a few were focused on the impact of HSV infection on IVF and the underlying mechanisms, which warrants more attention.

HHV-6 was first discovered and isolated from the peripheral blood lymphocytes of patients with AIDS and those with lymphoproliferative disorders. By disrupting endothelial cell functioning, HHV-6 can interrupt the appropriate formation of the uterine environment for implantation and foetal development and lead to infertility and increased pregnancy loss, among other complications [84]. A small study of 30 infertile women and 36 control women, [85] found HHV-6A in peripheral blood mononuclear cells in 25% and 28% of women respectively, but in endometrial biopsies its presence was 43% and 0% respectively. Dividing the infertile women by the presence or absence of HHV-6A, both $CD56^{bright}$ and $CD56^{dim}$ forms of endometrial NK cells were lower in those with the virus, but there was no difference in CD14 + ve mononuclear cells. Furthermore, levels of IL-10 were higher and IFN- γ lower in the HHV-6A positive women, but there was no difference in TNF-α, IL-22 or IL-12. Further studies by the same group showed that NKG2D activating receptor and FasL were two of fundamental components in acquiring the cytotoxic function of eNK cells during HHV-6A infection in endometrial epithelial cells, and increased levels of CCR2, CXCR3, and CX3CR1 chemokine receptors in eNK cells during HHV-6 infection. Additionally, endometrial epithelial cells up-modulated the corresponding ligands, including MCP1 (Monocyte chemotactic protein 1, CCL2), IP-10 (Interferon gamma-induced protein 10, CXCL10), and Eotaxin-3 (CCL26) which significantly led to infertility [86].

A further underlying mechanism described by Bortolotti and colleagues is the ability of HHV-6A infection to negatively affect the maternal immune system and lead to defective trophoblast invasion due to modifications in the expression of essential attractant signalling molecules such as HLA-G and MUC1. Their observations suggest that HHV-6A infection attenuates decidualization and lead to a reduction in the protein levels of HLA-G and MUC1. The immune dysregulation in HHV+ infertile women due to high levels of IL-15/Fn-14 and IL-18/TWEK mRNA expression and a decrease in $CD4+ CD25+ CD127^{dim/-}$ regulatory T cells, could lead to defective trophoblast invasion and result in a miscarriage [87]. Di Stefano et al. examined the in vitro and in vivo susceptibility of placental cells to

Table 3. Characteristic of population-based studies related to HSV infection.

Study	Year	Region	Cohort/ Controls/ Cases	Outcome
[18]	2000	Germany	1262 infertile women	No effect on infertility[a]
[75]	2008	Hungary	512/539	Increased infertility[a]
[76]	2011	India	784/113	Increased infertility[a]
[78]	2017	South Africa	564/51	No effect on IVF outcome[b]
[15]	2013	Sudan	30/70	Increased infertility[c]
[44]	2010	Rwanda	283/312	Increased tubal infertility[c]
[9]	2006	USA	736 women with STD	Increased endometriosis
[79]	2018	China	100 women with abortion	No effect on abortion
[77]	2002	Norway	281/961	No effect on pregnancy rate and foetal death
[82]	2011	India	374/76	Increased abortion
[83]	2015	Saudi Arabia	51/84	Increased risk of ectopic pregnancy

See Table 1 for notes. STD = sexually transmitted disease

HHV-8 infection, finding it may infect placental cells and impact pregnancy outcome [88]. They also indicated that the endothelial and trophoblast cells are both permissive to HHV-8 infection and showed that HHV-8 infection can negatively influence trophoblast cells by increasing the apoptosis rates [88]. It has also been reported that high levels of oestradiol in infertile women could act as a co-factor facilitating HHV-6 endometrium infection [89]. This may cause disproportionate replication of HHV-6 in endometrial epithelial cells and lead to detrimental effects on reproductive functions consequently [85]. HHV-6 DNA has also been found in the blood and tissue samples from women with several types of gestational problems, including spontaneous abortions and preterm birth [90]. Although more studies focused on HHV-6 infection (Table 4), some findings investigated the effects of HHV-8 infection on female infertility and increased rates of abortion [91].

All these observations suggest that HHV could be a major risk factor for female infertility by causing specific gene expression changes in NK cells and immune dysfunctionality that may lead to foetal death and pregnancy loss. Few studies have focused on the impacts of HHV on pregnancy outcomes and IVF which demands more attention.

Cytomegaloviruses

CMVs are important opportunistic pathogens that share structural similarities and biological properties of latency and reactivation. CMV infection is common during pregnancy and is considered a risk factor for miscarriage. It can impair foetal development through placental infection and in very severe cases may lead to stillbirth. A possible mechanism is that the virus negatively affects the invasive capability of extravillous trophoblasts by causing a significant decrease in c-erbB-2, MMP-2 and MMP-9 expression [92]. A recent study has suggested another mechanism by which CMV interferes with female reproduction. Dons'koi et al reported that CMV seropositivity is associated with a specific proinflammatory immune phenotype in women with implantation failure, citing significantly increased levels of HLA-DR expression on T-lymphocytes, NK-lymphocytes, and NKT-like cells, as well as decreased levels of CD8 + NK lymphocytes in CMV+ infertile women who underwent IVF treatment [93].

There is relatively little information concerning the prevalence of CMV infection and its influence on fertility potential and pregnancy outcome (Table 5). Some studies on placenta tissue and among pregnant women indicate that CMV is a major pathogen associated with foetal death, miscarriage, and preterm delivery [81,94–97], suggesting that CMV infection might be playing an important role in adverse pregnancy outcomes. In women undergoing IVF, CMV-ve women had higher numbers of inseminated and good quality oocytes in comparison to seropositive cases, suggesting the possible detrimental effects of this virus on IVF outcomes [98].

All of the above studies make it difficult to draw any firm conclusion regarding the influence of CMV on female reproduction. However, CMV infection in studies with larger sample sizes report increased pregnancy loss among patients. Further studies, especially in IVF treatment, are needed to elucidate out more about it.

Hepatitis B virus

Chronic HBV infection is associated with significant impairment of immune response and may serve as a surrogate for other infections and altered microbiome in the female genital tracts, hence contributing to infertility [99]. Li et al recently was suggested that the decreased frequencies of $CD3^{+}CD4^{+}$ helper T cells and decreased rates of peripheral NK function and toxicity lead to higher early miscarriage rates and adverse pregnancy outcomes in HBV+ve females [100]. Also, tubal damage resulting from HBV infection in either partner may be due to an increased risk of pelvic infection in the woman, and so to infertility [10]. In addition, decreased fertility rates among patients with advanced chronic liver disease, regardless of the cause, was shown to be mainly due to the frequent occurrence of anovulatory cycles and amenorrhoea [101]. Miscarriage rates, preterm birth, and low birth weight are all significantly higher among HBV+ve women [101–105]. Surprisingly therefore, of 190

Table 4. Characteristic of population-based studies related to HHV infection.

Study	Year	Region	Cohort/ Controls/Cases	Outcome
[88]	2008	Italy	60 HHV-8 seronegative women	Decreased PR
[90]	2014	Italy	61 pregnant women with miscarriage history	Decreased PR[a]
[87]	2019	Italy	100/67	Decreased PR
[91]	2001	Senegal	379/58	Increased abortion

[a]: secondary infertility. PR = pregnancy rate.

Table 5. Characteristic of population-based studies related to CMV infection.

Study	Year	Region	Cohort/ Controls/Cases	Outcome
[79]	2018	China	100 women with abortion	No effect on abortion
[94]	2006	Australia	105 women with abortion	Increased foetal death
[95]	2015	China	624/440	Increased miscarriage
[96]	2006	Japan	993/844	Increased adverse pregnancy outcome
[97]	2018	Japan	906/1287	Increased preterm birth

Table 6. Characteristic of population-based studies related to HBV infection.

Study	Year	Region	Controls/Cases	Outcome
[10]	2017	China	779/52	Increased tubal damage and infertility[a]
[107]	2019	China	7656/894	Reduced implantation and pregnancy outcome[b]
[109]	2010	China	1545/131	No effect on IVF outcome[b]
[108]	2014	China	448/224	Increased infertility[c]
[106]	2010	China	287/287	Increased live birth, PR, and implantation rate[c]
[110]	2014	China	246/123	No effect on IVF outcome[c]
[111]	2018	Iran	27,602/71	No effect on IVF outcome[c]
[102]	2016	China	20,491/513	Higher miscarriage rate
[103]	2005	China	253/253	Increased preterm birth
[104]	2011	USA	1.6×10^6/1458	Increased preterm birth
[105]	2017	Sweden	1×10^6/2990	Increased preterm birth

See Table 1 for notes and abbreviations

women undergoing their first IVF and embryo transfer cycles, the ongoing pregnancy and implantation rates and live birth rates in the HBV+ve group were significantly higher compared to controls [106].

HBV infection increases the risk of pelvic infection, causing tubal damage and infertility [10], whilst a high frequency of infertility and reduced implantation rates [107] and fertilization rates [108] were also reported among HBV+ve women undergoing IVF treatment. However, other studies showed that HBV infection did not impact the IVF pregnancy outcomes, nor considered to be a cause of infertility [109–111]. A part-explanation for these discrepancies is the possibility that infected ovaries or oocytes exhibit a different response to ovarian stimulation during IVF/ICSI treatment. Women often had different rates of fertilization, embryogenesis, and implantation, implying that HBV infection in those undergoing ART treatment may not have detrimental effects on embryo development and it might be a safe and an effective method for HBV+ve women want to become pregnant. A summary of the studies focused on HBV infection and its association with female infertility is shown in Table 6.

Hepatitis C virus

HCV infection has been reported to be significantly related to failing ovarian function and subsequent follicular depletion occurring in the context of a more generalized dysregulation of other fertility-related factors [112], whilst HCV can modify the cellular ultrastructure of trophoblasts *in vitro*, suggesting a possible link with miscarriage [113]. Further insights into uterine defence from HCV are provided by Giugliano et al [114]. Using a trophoblast cell line and primary trophoblast cells, they showed robust up-regulation of interferons and chemokines that elicit the recruitment and activation of decidual NK cells. However, they also speculate that HCV sensing up-regulates HLA-E expression and so triggers an apoptotic response in extravillous trophoblasts that may contribute to complications in the pregnancy.

Several published data, especially from IVF studies, supported a key role for anti-Mullerian hormone (AMH), as an accurate marker of ovarian reserve and a predictor of female fertility in HCV infected patients. Ovarian follicle cells are responsible for producing AMH, so its expression represents an early and sensitive marker of a woman's reproductive potential, with declining levels being a reliable indicator of ovarian senescence. HCV+ve females in different studies showed menopausal levels of AMH, which could reflect failure of reproductive function [115,116]. In addition, very low AMH levels in HCV+ve women correlated with poor responses to stimulation by exogenous gonadotropins, which in turn lead to a higher incidence of apoptosis, reduced rates of ovarian follicle development, lower implant success rates [117–119], higher miscarriage rates [120, and reduced pregnancy rates [118,121].

Ovarian senescence in HCV+ve women in different is linked to a higher risk of miscarriage, stillbirth, pre-eclampsia [120,122]], preterm birth [104,105], prematurity, and foetal death [123] (Table 7).

Conflicting results are present in IVF studies of the effects of HCV infection on pregnancy. Hanafi et al. reported no morphology changes in the embryo of controls and cases, but the number of oocytes and pregnancy rate was significantly lower among the HCV+ve group [118]. Similarly, Englert and colleagues showed that the number of embryos and ovarian responses were significantly lower among HCV+ve women [120]. Contrary to these findings, in a study on 1424 couples undergoing IVF, no effect of HCV infection on IVF outcomes was found [124]. This evidence points to HCV having a negative effect on the female reproductive system and pregnancy outcome, but observations in IVF studies are inconclusive. Further investigations are required to confirm HCV negative impacts on IVF treatment.

Conclusions

Viruses can interfere with the female reproductive function and may be considered as potential risk factors for infertility. The viruses we have focused upon have potentially negative effects on the female reproductive system and can be transmitted both vertically and horizontally and threaten partners, the foetus, and the neonate. Although current investigations have provided valuable information on different genital or non-genital viral infections that may influence fertility and pregnancy outcomes, lack of scientific information on the role of some viruses leaves considerable scope for additional studies. We conclude that, at a minimum:

- HIV, HSV, and HHV infections play a major role in female infertility

Table 7. Characteristic of population-based studies related to HCV infection.

Study	Year	Region	Controls/ Cases	Outcome
[105]	2011	USA	999/1.6 × 10^6	Increased preterm birth
[106]	2017	Sweden	1 × 10^6/2056	Increased preterm birth
[119]	2011	Egypt	40/40	Reduced pregnancy rate
[120]	2007	Belgium	84/42	Decreased ovarian response
[121]	2018	Italy	20,415/6085	Increased miscarriage rate
[123]	2002	Iraq	94/3491	Increased miscarriage rate
[124]	2017	Egypt	170/158	Increased prematurity and foetal death
(124)	2015	China	1256/90	No effect on IVF outcome

- HPV, HCV, HBV, and CMV infections lead to higher rates of abortion and miscarriage.
- HPV infection is strongly linked to increased tubal infertility, endometriosis, and PID.
- HPV is also the most frequently observed infection associated with lower pregnancy rate and foetal death in patients undergoing IVF.
- HBV infection brings an higher rate of pre-term delivery
- ART is a safe and effective method for HIV and HBV infected females who wish to have children.

Many aspects of viral infections on female reproduction remain unclear, requiring further investigation. These will provide a better understanding of epidemiology and pathogenesis and may lead to targeted treatments. Finally, asymptomatic infections, coupled with recurrent and latent infections, are the major challenges. The best approach to overcome this problem is to increase awareness and encourage women to check their sexual health status and, if necessary, pursue appropriate treatment.

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