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REVIEW

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Viral infection and its impact on fertility, medically assisted reproduction and early pregnancy – a narrative review

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Abstract

Viral infections can significantly affect the physiopathology of reproductive organs, leading to fertility problems, reducing the success rates of assisted reproductive technologies, and negatively impacting pregnancy. This review aims to summarize the current evidence on viral pathogens that are either suspected or confirmed to play a role in reproductive medicine and their effects on early pregnancy. For instance, viral hepatitis and human immunodeficiency virus can decrease sperm quality. Human papilloma virus infection in men appears to cause infertility, while herpesviruses pose a greater risk to fetuses rather than to fertility. The Zika virus disrupts early embryo development, necessitating a delay in conception for those suspected or confirmed to be infected. The effects of SARS-CoV-2 on reproduction are still unclear. Rubella and cytomegalovirus can cause serious congenital defects, making pre-conception screening essential, and a Rubella vaccine is recommended. More rigorous studies are needed to clarify the roles of various infectious agents, enhance fertility treatments, and improve pregnancy outcomes while reducing complications.

Keywords Viral infection, Fertility, Pregnancy, Medically assisted reproduction

Background

Viruses, being among the smallest infectious particles, absolutely require a host cell to replicate and survive. By utilizing appropriate cell receptors, they attach to and penetrate cells to replicate and spread throughout the body, triggering an immune response. DNA viruses typically replicate inside the cell nucleus, while RNA viruses replicate within the cytosol. Viral infiltration may result in cell decay, but some viruses remain inside cells without destroying or replicating them (entering a latent phase), and under certain conditions, they can render the cells immortal [1].

The virome, collectively encompassing all viruses that have infected an organism, is also a component of the reproductive system's microbiome. It is noteworthy that the quantity of viruses (around 380 billion) in a single

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human body is roughly ten times greater than the total number of bacteria [2]. To date, only approximately 1% of the human virome has been identified [3].

Viral infections have the potential to damage organs within both the female and male genital tracts, ultimately leading to compromised fertility. It is worth noting that in more than half of men, the cause of infertility remains unclear with viral infections being among the potential contributing factors [4]. Certain viruses can bypass the blood-testicle barrier and enter testicular tissue, triggering an immune response and resulting in inflammation, along with its associated consequences [5].

The following publication will discuss the role of individual viruses in infertility and impact on medically assisted reproduction and early pregnancy, both at a basic level and considering diagnostics in everyday medical practice.

Impact on fertility and assisted reproduction technology

Human immunodeficiency virus (HIV)

Human immunodeficiency viruses (HIV-1 and HIV-2) are RNA viruses belonging to the retrovirus family. HIV-1 typically progresses more rapidly and is globally prevalent, while HIV-2 is more common in specific regions like West Africa, Spain, Portugal, and India [6]. There is a 60% genetic similarity between their nuclear proteins, dropping to 40% for surface proteins, which is crucial for designing tailored diagnostic tests and treatments [7]. Therefore commercial tests detect antibodies against certain capsular antigens of both HIV subtypes [8].

Transmission pathways are as follows:

- Sexual intercourse–the risk of HIV transmission to a healthy partner is about 0.08% per act, equating to 1 transmission per 1,250 exposures if the man is infected. When the woman is an HIV carrier, the risk lowers to 0.034% per intercourse, or 1 transmission per 2,500 exposures [9]. The risk of HIV transmission from an infected male to a healthy woman increases with the number of virus RNA copies present in semen and amounts to 1/100 when the number is 100,000 copies, dropping to 3/10,000 when the number of RNA copies is 1,000 [10];
- Blood transfusion and blood products administration.
- Organ transplantation.
- Vertical and perinatal–The probability of a child becoming infected from an HIV-positive mother has been estimated at 15–20% [10]. The more advanced the mother's disease, the higher the risk. Past analyses indicate that 5–10% of children infected this way died within their first year of life, while almost 30% died before their 5th birthday [11].

Patients infected with HIV may intentionally avoid intercourse to prevent virus transmission, resulting in increased use of barrier contraceptives and fewer pregnancies. Additionally, HIV infection, alongside other inflammations, has been found to reduce ovarian reserve and affect the hypothalamic-pituitary-ovary axis. These effects can further contribute to decreased fertility and reproductive health in individuals living with HIV [12].

Nearly half of HIV-positive women are observed to experience a disturbed menstrual cycle [13]. This disturbance can result from the presence of concomitant diseases such as renal failure or liver dysfunction, as well as stress factors that disrupt gonadotropin-releasing hormone (GnRH) secretion, such as significant body weight loss [13]. Additionally, this group tends to have lower testosterone concentrations [14]. Some studies suggest a correlation between amenorrhea and immunosuppression, where a lower CD4 cell count is associated with a higher percentage of menstrual disorders. Furthermore, abnormal uterine bleeding (AUB), including heavy and prolonged menstrual bleeding and irregular, frequent, or intermenstrual bleeding, is more frequently observed in HIV-positive patients, particularly those with thrombocytopenia or undergoing antiretroviral therapy [13].

The presence of HIV has been proved in the semen plasma and in spermatogonia. HIV attacks the body by entering CD4 cells and can enter the sperm by binding to galactosylalkacylglycerol receptors (GalAAG receptors) present on the sperm cell membrane [15]. HIV infection deteriorates the quality of semen, and its parameters decrease when the functioning of the immune system worsens. Likewise, antiviral treatment may negatively affect sperm parameters (sperm cell count, volume, and progressive movement) and increase the loss of germ cells in the testicle [16].

Disturbed functioning of the seminal vesicles and the prostate explains the decrease in the volume of semen and an increase in its viscosity in HIV-positive patients [17]. Orchitis, hypogonadism, oligozoospermia, and azoospermia have been observed among patients with developed AIDS. However, it should be noted that decreased fertility in patients with HIV infection may also result from coexisting infections in the genitourinary system [12]. In the semen of men undergoing fertility screening, the presence of genetic material not only of HIV but also CMV, adenovirus, HHV, and HPV was detected. What is more important, many viral diseases are asymptomatic and are not related to the presence of leukocytospermia in semen [18].

In the context of HIV infection, studies have indicated that HIV itself or its treatment can influence outcomes of ART. Observational studies report pregnancy rates per IVF cycle ranging from 9.2to 45% [19, 20]. Retrospective case-control studies comparing IVF outcomes between

HIV-infected and non-infected patients show conflicting results [21–25]. Some studies show lower rates of pregnancy and live births rates (LBR) among HIV-positive individuals (15–16), while others report no significant differences (17–18) or even better outcomes in couples where the man was HIV-positive [19]. However, recent research suggests poorer outcomes(lower cumulative pregnancy rates and LBR), particularly among women and couples where both partners are HIV-positive [26]. Further studies are needed to fully understand the impact of HIV on ART outcomes.

Hepatitis B and C viruses (HBV, HCV)

HBV belongs to Hepadnaviridae family of viruses, and its transmission pathways are as follows:

- Through blood and blood products – the most important source of the infection spread.
- Sexual intercourse.
- Organ transplantation.
- From a mother to a child, including perinatal transmission.

The presence of HBV may be associated with longer delay in conception and ovulation disorders [27].

Hepatitis C virus (HCV) belongs to the Flaviviridae family. Its primary mode of transmission is through blood exposure, but it can also be transmitted vertically, sexually, and through organ transplantation. While HCV RNA has been detected in follicular fluid, there is no evidence to suggest that it affects oocyte development, regardless of the level of viremia. Women with cirrhosis due to HCV infection often exhibit elevated estrogen levels and impaired progesterone metabolism, potentially leading to diminished response to ovulation stimulation [28, 29]. According to Karampatou et al. HCV infection, more often than HBV infection, may be connected with decreased ovarian reserve, as specified by anti-Müllerian hormone (AMH) concentration [30].

By incorporating viral DNA, sperm cells can act as vectors for HBV, even during the IVF procedure. HBV genes have been shown to be expressed in a 2-cell embryo. Despite HBV infection exacerbating semen parameters, there are reports suggesting that it does not affect the outcome ofassisted reproductive technologies (ART) procedures.

Among the potential mechanisms, it has been proven that:

- HBV surface protein interferes with the activity of the sperm cells mitochondria, thus affecting the sperm cells mobility.
- HBV infection increases oxidative stress in the sperm cells, leading to their apoptosis, which manifests itself as an increased percentage of DNA fragmentation, caspase activation and phosphatidylserine externalization [31].

Similar to type B virus, HCV reduces the number of sperm cells in the ejaculate and diminishes their mobility and morphology. However, no clinically relevant research has been conducted to investigate the implications of these changes [30].

While the impact of maternal chronic liver disease on pregnancy outcomes has been explored in multiple studies, there remains a lack of clear data regarding the success rate of ART in this population. Based on current literature, in vitro fertilization treatment (IVF) treatment was generally well tolerated [32–34], but specific management aspects require careful consideration. In addition to earlier discussed complications, patients with liver disease, including HBV or HCV, may have a higher risk of developing ovarian hyperstimulation syndrome (OHSS). In the retrospective analysis of forty-two women with chronic liver disease, the average implantation rate and live birth rate (LBR) per IVF cycle were found to be 60.8% and 39.9%, respectively [32]. These rates showed no significant variation among patients with cirrhosis, those without cirrhosis, and those who had undergone liver transplantation (LT). Implantation rates reported in different fertility centers may vary due to differences in patient selection criteria, stimulation protocols, and other factors [32]. In general, IVF shows promising outcomes, and it is advisable for women with liver disease to undergo pre-pregnancy counseling before starting IVF treatment. Additionally, close monitoring of liver enzyme levels and immunosuppression during IVF therapy is crucial for these individuals [26].

Human T-lymphotropic virus (HTLV)

Human T-lymphotropic viruses T1 and T2 are retroviruses. HTLV-1 can cause HTLV-1-related myelopathy and leukaemia in humans [35]. HTLV-2 is associated with neurological diseases occurring in tropical countries, but its morbidity has not been fully explained yet. These viruses' transmission may only occur by multiplying infected cells: through bloodborne transmission, sexual contact, vertical transmission, and during breastfeeding. The viruses occur endemically, with HTLV-1 in Japan and on Caribbean Islands, and HTLV-2 on Caribbean Islands, among Native Americans of both Americas, and within drug addict communities [4].

There is limited data available on the influence of HTLV-1 on fertility. Based on the existing evidence, HTLV-1 infection has been associated with erectile dysfunction in up to 55.2% of men [36–39]. However, no differences in HTLV-1 infection prevalence were noted based on fertility status in women [40]. Regrettably, there

is a scarcity of reliable scientific research regarding the impact of these viruses on the outcome of ART. Based on these studies, it is known that the HTLV infection does not affect the final results of IVF procedures using the ICSI method [40]. Fertilization, implantation, and pregnancy rates showed no significant differences between the groups. Additionally, there were no variations in the number of embryos transferred (on day 2 or 3) and cryopreserved embryos, multiple pregnancies, or abortion rates between the groups [34]. Further research is needed to elucidate the potential impact of HTLV infection on infertility.

Human papillomavirus (HPV)

Apart from its well-documented pathogenic effect on the cervix epithelium and its role as the cause of cervical cancer, HPV can also affect the epithelium of the ovaries [12]. Its activity and infection consequences are not only tissue-specific but also depend on the type of the virus [41].

A literature review on the clinical impact of HPV infection on female fertility presents conflicting findings [42, 43]. A large cohort study in Denmark, involving 11,088 young women, found no association between HPV infection and infertility [43], which was supported by a meta-analysis of 11 studies comprising 15,450 women. However, recent research suggests a significant association with infertility, though not as an independent cause. Additionally, a study by Isaguliants et al. noted lower pregnancy rates in HPV-infected women [44]. More studies are required to clarify the possible negative role of HPV infection on infertility.

Propensity to HPV infection may depend on the human leukocyte antigen (HLA) system as well as the organism's ability to resolve the infection. Getting pregnant is dependent on partner's HLA to a certain extent, so it can therefore be assumed that the lower fertility among patients with HPV infection can be a result of the patient's HLA allels/ haplotypes set and epitope types presented by certain types of HPV [45].

HPV vaccination in women has not been proven to increase the risk of infertility. In a group of women between 18 and 33 years old who were vaccinated against HPV, a higher risk of infertility was not documented (the reported infertility percentage was a slightly higher than 8%) [46, 47].

HPV genetic material is detected in 10% of asymptomatic men [31]. However, data on the impact of HPV infection on fertility are insufficient. The virus proliferates in squamous cells during mitosis. Released virions can attach to the sperm cell's head (capsid protein L1 and syndecan-1), potentially affecting sperm parameters. HPV infection may be responsible for some cases of idiopathic asthenozoospermia [48], adversely affecting sperm concentration and morphology [49]. For instance, in men with confirmed HPV infection, sperm concentration in semen may be lower compared to healthy men, although sperm mobility and morphology remain unaffected [50]. Furthermore, HPV infection may lead to an increase in DNA fragmentation [51]. Experimental studies suggest that HPV can penetrate into the oocyte along with the sperm cell, potentially inhibiting embryo development [52]. In men, HPV infection reduces pregnancy chances and increases miscarriage risk more than in women [31]. In general, existing literature suggests that the presence of HPV in semen can have adverse effects on sperm quality and reproductive results, leading to reduced pregnancy rates and increased risk of miscarriage, particularly compared to women [31]. These effects are observed regardless of whether conception occurs naturally or through ART treatment [53–55]. Hence, some researchers propose that routine clinical practice should include investigating seminal HPV in male partners of infertile couples undergoing ART cycles [50].

Studies indicate that therapeutic HPV vaccination in HPV-positive men may improve pregnancy rates in natural conception and reduce miscarriage rates [56]. The use of the HPV vaccine in patients with detectable semen infection reduces the viremia percentage after one year [57]. These findings suggest that patients with seminal HPV infection undergoing ART cycles could benefit from vaccination. Additional studies are needed to establish the vaccine's efficacy in removing seminal HPV infection and to determine the potential benefits of vaccination on reproductive health.

The influence of HPV infection on the success of ART remains a subject of debate. Overall, current evidence does not indicate that HPV contributes to impaired MAR (medically assisted reproduction) pregnancy outcomes, particularly when the infection affects the female partner [58]. However, as previously mentioned, male infection may heighten the risk of miscarriage and spontaneous premature delivery [59].

Zika virus

The Zika virus, a member of the Flaviviridae family, is primarily transmitted by Aedes spp. mosquitoes, resulting in mild infection in 50–80% of cases. Other modes of transmission, including blood transfusion, sexual contact, prenatal transmission, congenital infection in the fetus, laboratory exposure, and bites from infected animals, have also been identified, leading to more severe health consequences, particularly neurological issues like Guillain–Barré syndrome [60]. It is believed that Zika virus infection in women may often be temporary compared to men. The virus can be detected in cervical swabs for up to 3 days and in vaginal swabs for up to 14 days from the onset of symptoms. Animal studies have shown that the

spread of the virus depends on the route of transmission, although infected cells are not highly prevalent in the uterus or ovaries. Clearance of the virus from the female reproductive system occurs more rapidly compared to semen [60].

Women diagnosed with Zika virus infection or returning from endemic regions are advised to avoid pregnancy for 2 months [56].

In men, Zika virus infection may result in heamatospermia and prostatitis [53]. The virus has been detected in various components of semen and sperm cells, including plasma, sperm cell heads, leukocytes, and epithelial cells, particularly in individuals with initially high viremia and prolonged virus shedding in semen. Studies investigating the relationship between Zika virus infection and fertility have been conducted in animal models under induced immunosuppression conditions to facilitate proper virus replication [53]. These studies have demonstrated that the infection can induce inflammation in the testicles, epididymis, and accessory glands [60].

Men diagnosed with Zika virus infection or returning from endemic regions are advised to use barrier contraception for 3 months as a precautionary measure [56].

The influence of Zika virus on ART remains an area with limited research. Scientific literature addressing the potential effects of Zika virus on ART proceduresis is scarce. Nonetheless, anecdotal evidence suggests that active Zika infection in women might result in the presence of viral RNA in some of their oocytes [61].This highlights the significance of testing couples undergoing ART, as there is a genuine risk of embryo contamination due to the presence of Zika RNA in these oocytes [61].

Human herpes viruses (HHV)

Human herpes viruses (HHV), such as HHV2 (also known as HSV2), have been identified as risk factors for pelvic inflammatory disease (PID), contributing to a certain percentage of infertility [12]. HHV 6A and 6B have been reported to be involved in endometriosis-related infertility pathogenesis and idiopathic infertility, where HHV could modify NK cell function within the endometrium [48].

On average, HHV1/2 presence is detected in less than 4% of the male population based on semen analysis. DNA material is present in 2–50% of semen samples, and in almost 19% of the tested samples, more than one type of this virus is detected, which may indicate frequent, asymptomatic HHV 1/2 infection occurrence [62]. HHV infection can be correlated with a reduced number of sperm cells in the ejaculate and a deterioration of their mobility, affecting the function of the prostate and epididymis [10, 12]. Animal model studies have shown that HHV 1/2 infection causes degeneration of spermatogenic cells, impairs the interaction of germ cells with Sertoli cells, and induces apoptosis of germ cells. HHV 1/2 infection increases the risk of failure in fertilization in the IVF procedure, while the use of antiviral treatment has a positive effect on the chances of getting pregnant [63].

A recent review aimed to evaluate how HSV impacts semen parameters [64]. Out of articles that were examined [63, 65–69] some studies indicated a decrease in sperm motility and count due to virus infection [65, 66, 68, 69], while one study [66] showed a notable reduction in semen volume caused by HSV. These findings collectively identify HSV as a contributor to male infertility. Additionally, in two studies, acyclovir treatment improved semen parameters and resulted in successful pregnancies [65, 68]. Hence, the authors recommended screening and treating HSV before using assisted reproductive technologies in infertile men. In a systematic review [64], HSV infection did not show any association with sperm morphological defects. Based on the studies reviewed, it can be concluded that HSV could be a risk factor for male infertility, affecting both the quantity and quality of sperm.

There is a growing body of evidence suggesting that during ART, vertical transmission of HSV through sperm cells is possible, thereby increasing the risk of miscarriage [70]. Screening for viruses in seminal fluids may be crucial to prevent transmission to the partner, particularly when asymptomatic infection is suspected, as it could potentially compromise pregnancy. Therefore, further research is warranted to comprehensively assess the impact of HSV transmission during ART on pregnancy outcomes, underscoring the importance of thorough screening protocols in mitigating potential risks to both partners.

Cytomegalovirus (CMV)

Cytomegalovirus belongs to Herpesviridae family. Most infections are asymptomatic, though recurrence in patients with immunological system deficiency may affect almost all organs, including the endocrine system. This virus is resistant to freezing process, and it has been found in banked semen. CMV presence was detected in cervical mucus and patients with obstruction of the fallopian tubes were slightly more often CMV-positive [71]. However, CMV presence in semen or cervical mucus has not been proven to diminish the migration of sperm in the woman's genital tract in the normal conditions [72].

Although no direct association between CMV infection and standard semen parameters has been proven, there is evidence to suggest a positive correlation with deterioration of semen morphology and sperm cells count [62]. Histological examination of testicular explants from infected men revealed a notable decrease in germinal cells and a gradual destruction of the germinal

epithelium, indicating the potential cause of these toxic effects [73].

In another study there were no significant differences in reproductive outcomes between CMV IgG-seropositive men and seronegative individuals undergoing ART [74]. Although data is limited, these findings suggest that CMV does not play a significant role in male reproductive function or influence sperm fertility potential in the context of assisted reproductive outcomes.

SARS CoV-2

SARS-CoV-2 possesses one of the largest genomes among all known RNA viruses. Its spike protein plays a pivotal role in recognizing the angiotensin-converting enzyme 2 (ACE-2) receptor, facilitating cell adhesion and fusion—a function shared with HIV, influenza, and Ebola viruses. Infection with SARS-CoV-2 triggers an inflammatory response involving T helper cells, interferon gamma, tumor necrosis factor alpha, and interleukin 2 [75].

ACE-2 and Type 2 transmembrane serine protease type 2 (TMPRSS2) are crucial for SARS-CoV-2 to adhere to target cells. While the renin-angiotensin-aldosterone system, along with ACE-2, plays roles in processes like folliculogenesis, steroidogenesis, oocyte maturation, and ovulation in the female reproductive system [76], reproductive cells are less susceptible to SARS-CoV-2 infection compared to respiratory or cardiovascular cells. However, co-expression of ACE-2 and TMPRSS2 increases vulnerability. In the endometrium, ACE-2 expression starts low but rises during the implantation window, whereas TMPRSS2 and TMPRSS4 expression increases from early to mid-secretory phases [77]. Moreover, expression levels positively correlate with patient age, indicating increased vulnerability in women of older reproductive age [78].

Studies by Boudry et al. [79] and de Miguel-Gomez et al. [80] found no detectable SARS-CoV-2 RNA in endometrial samples. Similarly, investigations into follicular fluid and cumulus cells from 16 women with recent positive SARS-CoV-2 tests less than 48 h before oocyte retrieval showed no viral RNA presence [79]. Moreover, endometrial biopsies taken during oocyte pick-up did not exhibit any histopathologic changes. Additional research confirmed the absence of the virus in follicular fluid [81]. Furthermore, based on single-cell RNA sequencing (scRNA-seq) dataset research, the uterus is considered to be at low risk of SARS-CoV-2 infection [82].

Ovarian follicular cells express basigin/CD147 (BSG) and the endolysosomal cathepsin L mRNA, with low abundance co-expression of both proteins [83]. Additionally, ACE2 mRNA and protein expression increased in human ovulatory follicles after hCG administration [84]. Although the possibility of SARS-CoV-2 affecting ovarian follicles was suggested and demonstrated in laboratory settings [85], no viral RNA was detected in cumulus cells from 16 COVID-19-positive women [79].

Despite the theoretical premises mentioned above, studies to date have not shown any long-term complications in the functioning of the female reproductive system associated with SARS-CoV-2 infection [86].

The severity of SARS-CoV-2 infection may be more pronounced in men compared to women, possibly due to differences in ACE-2 receptor expression levels between the genders. Another potential factor is higher concentrations of androgens in men, which can lead to increased expression of TMPRSS2, thereby facilitating viral infection [87].

The impact of the virus on the male reproductive system remains unclear and necessitates further investigation. It is hypothesized that viral amino acids may disrupt the activity of the host's adrenocorticotropic hormone (ACTH), resulting in decreased glucocorticoid levels [88]. Additionally, during SARS-CoV-2 infection, decreased levels of angiotensin are observed, which may also diminish testosterone production. However, studies conducted thus far have not shown significant effects of SARS-CoV-2 on the hypothalamic-pituitary-testis axis. Typically, patients exhibit elevated levels of luteinizing hormone (LH) without signs of axis dysfunction [88].

On the other hand, post-mortem examinations of men who suffered from Covid-19 showed some cases of orchitis with exfoliation of spermatocytes, elongation of spermatids, oedema and vacuolization of Sertoli cells. At the same time, it has not been proven that the virus has a significant impact on sperm parameters, although its influence on the male reproductive system, according to the available data, is more distinct than on the female reproductive system [75]. Any negative effects on spermatogenesis seem to resolve to after a complete spermatogenic cycle [67].

In 2023, Ata et al. published a study that synthesized available data on the impact of COVID-19 on fertility and ART [89]. The majority of studies reviewed did not suggest a significant impact of COVID-19 on ovarian reserve, ovarian function, or follicular fluid parameters. Additionally, there is evidence to suggest that a history of asymptomatic or mild SARS-CoV-2 infection in females does not adversely affect laboratory and clinical outcomes in both fresh and frozen embryo transfer cycles [80]. However, there is currently a lack of data regarding the minimum required interval, if any, between COVID-19 recovery (also considering the male partner) and ART treatment.

Despite conflicting data, there is evidence suggesting that embryos, especially late blastocysts, possess the receptor and protease machinery necessary to be susceptible to SARS-CoV-2 infection. However, the presence of SARS-CoV-2 viral RNA in embryos has not been

investigated. Therefore, practice decisions should be guided by clinical and laboratory assessments.

Mumps virus

The mumps virus belongs to the single-stranded RNA viruses of the Paramyxoviridae family. It damages Leydig and Sertoli cells, triggers an inflammatory process with cytokine release (interferon alpha - IFN α, tumor necrosis factor alpha -TNF α), thus determining insufficient testosterone production and cell death. Mumps virus infection causes unilateral inflammation of the epididymis and testicle in 20–30% of man past puberty, 15% of them develops bilateral atrophy with decreased concentration and mobility of sperm cells and sometimes even azoospermia [90]. The mumps virus has been detected in semen up to 14 days after infection. However, it is important to note that sexual transmission is not considered significant in the overall transmission of the virus [91].

While mumps commonly affects the salivary glands, it can also involve the ovaries. Mumps oophoritis, an inflammation of the ovaries due to mumps virus infection, has been associated with ovarian damage and subsequent premature ovarian insufficiency (POI) [92]. Although mumps oophoritis is a relatively rare complication, documented cases have demonstrated its potential to cause premature menopause [92]. These findings underscore the importance of considering viral infections, such as mumps, in the differential diagnosis of unexplained POI.

The role of virological tests in the diagnosis of infertility

Virological tests in the initial diagnosis of infertility

In routine infertility diagnosis, virological tests are conducted to assess individuals undergoing ART. These tests are not aimed at identifying potential unknown causes of infertility per se. Furthermore, the presence of chronic viral diseases in one partner may necessitate the use of ART.

Virological screening prior to medically assisted reproductive procedures

For patients undergoing IVF treatment, screening for HIV, HBV, HCV, and determination of serological status for rubella virus are recommended [93–96]. This is essential for several reasons. Firstly, these viral infections can remain asymptomatic for many years, leading carriers to be unaware of their status. Secondly, detecting these infections prompts necessary treatment to reduce the risk of transmission to offspring and partners. Lastly, awareness of potential infections prompts the implementation of special precautions when handling tissues and cells from affected patients. Germ cells from individuals with HIV, HBV, or HCV should be stored separately in germ cell and embryo banks. Additionally, ART candidates must present their rubella virus serological status, as primary rubella infection during pregnancy poses significant risks to the fetus, making vaccination crucial for those lacking immunity.

The possibility of usingassisted reproductive technology in people with chronic viral infection

The primary objective of ART in individuals with chronic viral infections is to enable reproduction while minimizing the risk of transmitting the infection to both the partner and offspring. However, complete elimination of the transmission risk may not be feasible, necessitating individualized approaches based on the couple's preferences and available techniques. Below, we discuss the key considerations for managing the most common viral diseases in this context.

HIV

Antiretroviral therapy can effectively suppress viral replication in HIV-positive patients. Therefore, it is recommended to maintain therapy to achieve undetectable viral loads in serum. HIV infection status alone should not be a reason to deny antiretroviral therapy [56].

HIV positive man and HIV negative woman

In such cases, several options can be considered: natural conception, assisted reproduction techniques using specially prepared partner's sperm (sperm washing), or the use of donor sperm. However, some authors suggest that natural conception may be permissible only after meeting certain restrictive conditions [97]. The risk of transmission to a partner during unprotected intercourse is considered negligible if all of the following requirements are met:

- The man consistently and correctly uses highly active antiretroviral therapy (HAART).
- Serum viral load has remained consistently less than 50 copies/ml for at least 6 months.
- There are no coexisting infections.
- Unprotected intercourse occurs during ovulation to minimize the exposure of the partner, as it is procreative [93].

In addition, pre-exposure HIV prophylaxis may be used during the conception period.

However, other guidelines recommend the use of ART techniques in the case of a seropositive partner [96]. Special techniques of sperm washing can significantly reduce the amount of virus in semen, although they do not fully eliminate the risk of HIV transmission [93]. The recommended semen processing involves performing a discontinuous density gradient centrifugation followed by two semen washing steps, and then a swim-up procedure

[56]. This process helps eliminate round cells, seminal fluid, and most immobile sperm from the semen. Additionally, the prepared semen can undergo PCR testing to detect the presence of viral RNA. Only HIV-negative tested semen should be utilized for ART [56]. The safest and most effective technique appears to be the use of IVF-ICSI from washed semen [98].

HIV positive woman and HIV negative man

In such cases, intra-uterine insemination is preferred to minimize the risk of infection to the partner. The patient should be on antiretroviral therapy, preferably achieving undetectable viremia. The consideration of more advanced ART techniques depends on the presence of factors limiting natural fertility. Oocytes retrieved from female patients testing positive for HIV do not necessitate special preparation techniques for fertilization [56].

HBV

Patients with an active or chronic infection should undergo consultation with an infectious disease specialist. Given the availability of an effective vaccine, it is advised that the partner of an HBV-infected individual receive full vaccination before attempting reproduction. Barrier contraception should be utilized until vaccination is completed [56, 99]. In situations involving HCV infection, the selection of treatment approach should be guided by the underlying cause of infertility. When counseling a couple where the woman is infected with HBV or HCV, it's crucial to emphasize that the utilization of medically assisted reproduction techniques does not completely eliminate the risk of transmitting the disease to the offspring [56].

HCV

The guidelines for managing an HCV diagnosis in one of the partners mirror those outlined for HIV infection as described previously. These include the option of natural conception post-treatment and the utilization of assisted reproduction techniques with processed semen. Prior to treatment initiation, consultation with an infectious disease specialist is recommended [56]. It is crucial to highlight the optimal timing of initiating antiviral treatment before attempting reproduction, given its current effectiveness rate of 98% in achieving a cure. It's advisable to commence attempts to conceive six months following the completion of treatment to mitigate the teratogenic potential of ribavirin [99]. The selection of a technique for MAR should be guided by the underlying cause of infertility. Currently, there is insufficient evidence to favor one technique over another [56].

Human T-lymphotropic virus (HTLV)

There is a risk of sexual transmission of the virus to the unaffected partner. If infertility treatment is required, the choice of treatment technique should depend on the cause of infertility. The influence of female infection on the outcomes of ART procedures remains uncertain. Furthermore, there is a lack of studies comparing the effects of different semen preparation methods on fertility outcomes [56].

Zika virus

The initiation of infertility treatment procedures, regardless of the technique used, should be postponed for a period of 3 months if an infection is detected in one of the partners or if a partner has returned from areas endemic to the Zika virus. If an infection is diagnosed in one of the partners during treatment, the cycle should be stopped, and the couple should use barrier contraception for 3 months [56].

Donation of reproductive cells other than partner donation - the role of virological tests

In non-partner donation (egg donors or sperm donors) testing for infectious diseases is of particular importance. While there is a risk of unknowingly infecting the partner in partner donation, in non-partner donation, all responsibility for preventing the transmission of infectious diseases rests with the center that uses treatment with donor cells. Moreover, a single donor can infect multiple recipients. Recent years have brought enormous progress in molecular techniques of virological diagnostics, revolutionizing current diagnostics that are largely based on serological tests. Diagnostics using molecular biology techniques make it possible to detect viral infections without the need for a waiting period due to the "serological window".

To minimize the risk of accidental infection of the recipient of reproductive cells, it has been widely accepted that people at high risk of viral infections (injecting drug users, those engaging in frequent unprotected intercourse with numerous partners, and sex workers) should not be included in the donation process.

Blood-transmitted viral infections

For the reasons described above, all donors undergo testing for the presence of viral diseases that could potentially be transmitted to the recipient or to offspring. For diagnostics, simultaneous serological tests and molecular tests detecting viral nucleic acids testing (NAT) are preferred. In the case of serological tests only, it is necessary to apply a withdrawal period for the collected tissues and repeat the tests after the time that allows to pass the serological window, in practice it is 6 months [94].

Table 1 Virological tests in donors of reproductive cells

Virus	Type of test	Test frequency	Minimum grace period
HIV	HIV Ag/Ab i/lub HIV RNA PCR	Semen - before donation (serology) Oocytes – 2 months before donation (serology) + before stimulation (serology + PCR)	Semen: serology + NAT -> 3 months serology -> 6 months after donation or after fertilization Egg cells - Cycle with freezing: Serology + NAT -> 3 months, Serology -> 6 months from freezing Fresh cycle: withdrawal can be waived if serological + NAT tests have been performed
HBV	HBc Ab + HBs Ag i/lub HBV DNA PCR		
HCV	HCV Ab lub HCVAg/Ab i/lub HCV RNA PCR		
HTLV	HTLV-1 i 2 - Ab		

HIV Ag / Ab - qualitative test, detects the HIV p24 protein (antigen) and antibodies against the M and O proteins of the HIV-1 and HIV-2 envelope.

HBc Ab - testing of IgM and IgG antibodies against the core antigen (c) HBV.

HBs Ag - qualitative test detects HBV surface protein (s).

HCV Ab - qualitative test detects IgG against 4 different virion antigens.

HCV Ag - detects the presence of the core (c) antigen of the virus, difficult to obtain in routine diagnostics in Poland.

HTLV-1 and 2 - Ab - detects the presence of anti-HTLV antibodies.

Contemporary recommendations in this regard are summarized in the Table 1.

HPV

Semen testing for HPV is currently limited, and there are no specific recommendations for testing sperm donors in this regard. However, vaccination against HPV may be considered for women who are expected to be recipients of reproductive cells or undergoing assisted reproduction techniques.

Zika virus

Patients who have recently visited Zika virus endemic areas should undergo quarantine before being included in the donation procedure [60]. It is advised to store reproductive cells separately based on viral status, as the Zika virus can survive and transmit in liquid nitrogen (LN2). Cryo-tanks and transport shippers should be emptied, dried, and disinfected to minimize the potential for cross-contamination [56].

HHV 1 i 2

The presence of symptomatic genital herpes is a contraindication to sperm donation.

CMV

In the context of CMV infection, preference is given to seronegative donors in both IgM and IgG antibody classes [94]. Donation of reproductive cells from individuals who are IgM negative and IgG positive is acceptable, but in such cases, the risk of recent CMV infection should be assessed individually.

Impact of viruses on early pregnancy

The presence of a viral infection during embryonic development and early pregnancy can lead to an unfavorable outcome. Autopsy studies have revealed that viral infections contribute to approximately 2.5% of early pregnancy losses [100].

Certainly, the viromes and bacterial composition within the various levels of the reproductive system are interdependent and change along with the development of pregnancy.

Most research on viruses and their effects on pregnancy focuses on the later stages of pregnancy. Data on the pre- and peri-implantation period are not adequately represented in the available literature. The mechanisms by which the virus attacks the developing embryo vary depending on the type of virus, but it can generally be said to occur through ascending infection or due to the development of viremia and subsequent infection of chorionic/placental tissues [101]. In the chorion/placenta, viral infection induces necrosis of the villous epithelium and apoptosis of cells directly affected by the virus. Mitotic divisions cease, limiting the development of precursor cells, while damage to the epithelial cells of blood vessels leads to ischemia in the developing organism. Among the most common viral infections in pregnancy are those from the TORCH group, namely rubella virus, cytomegalovirus, herpes simplex virus as well as varicella-zoster virus, and parvovirus B19.

The known viruses that cause intrauterine infection through vertical transmission include the aforementioned viruses, as well as the hepatitis E virus. Conversely, HIV, HSV, HAV, HBV, and HCV are primarily transmitted through horizontal perinatal transmission.

HIV

The HIV provirus integrated into the genome of reproductive cells can be transferred to the developing embryo during the fertilization procedure [102].The risk of HIV transmission from mother to child in the absence of any intervention measures is approximately 7%, indicating the existence of protective mechanisms in the placenta against viral transmission. This risk primarily correlates with the maternal CD4 + cell count and current viremia levels [103]. However, the utilization of antiretroviral drugs during pregnancy, labor, and in the neonatal period, along with elective Caesarean section in HIV-positive pregnant women and avoidance of breastfeeding, significantly reduces the risk of vertical viral transmission from over 30% to less than 2% [104].

HBV, HCV

Studies have shown that the percentage of implantation and the number of the highest quality embryos in HBs Ag (+) patients were lower compared to the control

group, although no significant differences were observed in the percentage of pregnancies, abortions, and live births between both groups [27, 105]. Pregnancy itself does not alter the severity or course of HCV infection. Furthermore, HCV infection does not lead to congenital defects in the fetus, pregnancy loss, or an increased risk of prematurity [106]. The risk of vertical mother-to-child transmission varies widely, ranging from 0 to 80%, but typically hovers around 8%. However, this risk significantly escalates in correlation with viremia, sometimes reaching up to 60%, particularly if the mother is co-infected [106, 107].

HPV

There are assumptions suggesting that HPV might contribute to early pregnancy loss, supported by the detection of HPV genetic material in aborted tissues [108].

However, research on HPV's impact on early pregnancy outcomes yields somewhat conflicting results. Perino et al. reported that the risk of early miscarriage tends to rise when HPV infection is detected in the male partner or in both parents [109].

Zika virus

The Zika virus is known to target cells in the developing chorion and placenta, posing a threat to the developing blastocyst even during the pre-implantation period [103]. Experimental studies have demonstrated that the Zika virus can infect trophectoderm cells in human embryos, potentially leading to early pregnancy loss [101].

One of the most common symptoms of congenital Zika virus infection is fetal microcephaly, with the severity of central nervous system abnormalities often linked to infection during the first trimester to the early second trimester of pregnancy. Infections during this period tend to result in more severe outcomes. While many complications of Zika virus infection focus on later pregnancy, such as intrauterine growth restriction, reduced amniotic fluid, placental dysfunction, or fetal edema, specific features of the congenital Zika syndrome have been identified. Moreover, the Zika virus replicates in placental cells, serving as a reservoir from which the virus can be excreted even long after the initial infection [60]. Despite these risks, there is currently no evidence suggesting that pregnant women are inherently more susceptible to Zika virus infection.

HHV 1/2

HHV 1/2 (formerly HSV) infection, like other viruses, can remain latent for extended periods. Studies on a small group of women have indicated that the presence of HHV 1/2 in trophoblast tissues is more frequent in patients experiencing early pregnancy loss compared to those undergoing elective abortion [110]. Certain studies suggest that human herpesvirus 6 A/B (HHV-6 A/B) infection of natural killer (NK) cells might result in impaired implantation and subsequent placental ischemia, thereby contributing to the development of pre-eclampsia (PE) [111].

CMV

To date, the most frequently identified virus at the maternal-fetal interface is CMV, belonging to the Herpesviridae family. The incidence of CMV infection is approximately 0.5–1.0% of all live births in developed countries and 0.6–6.0% in developing countries [112].

CMV interacts with heparan sulfate, which is ubiquitously expressed on cell surfaces, and subsequently enters cells through interactions with integrin subunits [113].

CMV infection during pregnancy is a significant global concern, often remaining asymptomatic. However, it stands as the primary cause of congenital infections, as well as non-genetic sensorineural hearing loss and neurodevelopmental delays in infants. It is estimated that 0.5-2% of children are born with CMV infection. In children of mothers who had primary CMV infection in pregnancy, about 10–13% suffer from mental retardation and about 8–10% from bilateral hearing loss. On the other hand, about 90% of children remain asymptomatic after birth. Congenital CMV infection syndrome affects fetuses of mothers who became infected before 16 weeks of gestation [114] ventriculomegaly (>15 mm), microcephaly (<2 standard deviation), periventricular echogenicity, hydrocephaly, increased cisterna magna width (>8 mm), vermian hypoplasia, periventricular cysts, corpus callosum agenesis, lissencephaly, and porencephaly [115]. Ventriculomegaly and microcephaly are associated with poor fetal outcomes

[116]. CMV is never completely eradicated from the body and remains dormant in CD14+monocytes [117]. The risk to the fetus after reactivation of the infection in the mother is less than 1%. Additionally, the presence of CMV has been confirmed in samples taken from placental villi [72].

SARS-CoV-2

There is currently no evidence suggesting higher susceptibility to SARS-CoV-2 infection in pregnant women. However, the expression and co-expression of SARS-CoV-2 receptor genes in trophoblast, syncytiotrophoblast, and hypoblast raise concerns about vertical transmission of the virus. This transmission could potentially lead to reduced angiotensin concentration levels, causing constriction of small vessels and inflammation, thereby increasing the risk of thrombosis and its obstetric consequences [118].

According to the latest meta-analysis, which included 120 studies involving a total of 168,444 pregnant women

with SARS-CoV-2 infection in the first or second trimester, there is no indication that SARS-CoV-2 infection during these trimesters increases the risk of miscarriage [119].

In relation to ectopic pregnancy, the occurrence rate among women with SARS-CoV-2 infection [119] is comparable to that of the general population (1.4% vs. 1–2%, respectively) [120].

Rubella

The maternal immunity, acquired either through prior rubella infection or vaccination, provides protection against intrauterine infection. However, in susceptible pregnant women, the virus can breach the placental barrier and disseminate to the fetus via the bloodstream. Infections during the first trimester pose the greatest risk to pregnancy, with an 80% transmission rate to the child compared to 25% at the end of the second trimester. Additionally, the risk of fetal malformation is nearly 90% if the infection occurs early in pregnancy, decreasing to 0% if the mother becomes infected after week 20 of pregnancy. Furthermore, approximately 20% of rubella infection cases during the first two months of pregnancy result in miscarriage [103, 121].

Other viruses

Receptors for Coxsackie viruses and Adenoviruses have been observed within the uterus and the developing embryo, making their involvement in early pregnancy loss highly probable [122]. Additionally, the presence of type 2 adeno-associated virus (AAV-2) may contribute to early pregnancy loss independently, without requiring co-infection with another virus such as CMV, HPV, or HSV. AAV-2 attacks trophoblast cells, thus partially participating in the pathogenesis of conditions like preeclampsia, preterm labor, and natural abortion [123]. Within the herpesviridae group, alongside HSV and CMV, lies the Epstein-Barr virus, known for causing infectious mononucleosis. This virus exhibits an affinity for the oral mucosa and reproductive organs, where, following a latency period of varying lengths, it may sporadically replicate, leading to disease recurrence [62]. Although measles cases in pregnant women are rare, data from the United States indicate a rising trend in infections among older individuals due to an increasing number of unvaccinated individuals from childhood [124]. The measles virus is highly contagious and infection during pregnancy poses an increased risk of pregnancy loss, primarily affecting the mother's health. The final dose of the measles vaccine is administered at 6 years of age [125]. The risks associated with early pregnancy in influenza virus infection have not been fully estimated. Viremia during influenza is uncommon, and transplacental transmission is rare. However, studies in animal models suggest that such complications as behavioral disturbances or changes in brain tissue may arise from influenza virus infection [126].

Conclusion

Viruses can have significant impacts on human fertility and pregnancy outcomes. Certain viral infections have been linked to infertility, miscarriages, and complications during pregnancy. It is crucial for future research to delve deeper into understanding the mechanisms by which viruses affect fertility and pregnancy, as well as to identify potential preventive measures and treatment strategies. In everyday clinical practice, healthcare professionals should pay close attention to the possibility of viral infections as a potential cause of infertility and pregnancy complications, ensuring timely diagnosis, management, and support for affected individuals.

Abbreviations

AAV-2	Adeno-associated virus
ACTH	Adrenocorticotropic hormone
AMH	Anti-Müllerian hormone
ART	Assisted reproductive technologies
CMV	Cytomegalovirus
GalAAG	Galactosylalkacylglycerol
GnRH	Gonadotropin-releasing hormone GnRH
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B viruse
HCV	Hepatitis C viruse
HHV	Human herpes viruses
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPV	Human papillomavirus
HTLV	Human T-lymphotropic virus
IFNα	Interferon-α
IVF in	Vitro fertilization
LBR	Live births rate
LH	luteinizing hormone (LH)
LT	Liver transplantation (LT)
MAR	Medically assisted reproduction
NAT	Nucleic acids testing
NK	Natural killer
OHSS	Ovarian hyperstimulation syndrome
PE	Preeclampsia
PID	Pelvic inflammatory disease
scRNA-seq	Single-cell RNA sequencing
TMPRSS2	Transmembrane serine protease type 2
TNF α	Alpha tumor necrosis factor

Author contributions

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Consent for publication
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