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The role of viral infection in implantation failure: direct and indirect effects

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Abstract
Implantation is the key initial complex stage of pregnancy. Several factors are involved in implantation, but acute and controlled inflammation has been shown to play as a key role. On the other hand, the role of viral infections in directly infecting blastocyst and trophoblast and inducing chronic and uncontrolled inflammation and disrupting microRNAs expression can make this review strongly attractive and practical. We aim to provide an overview of viral infections as the potential etiology of unsuccessful implantation pathophysiology through alteration of the cellular and molecular endometrial microenvironment. Based on our search, this is the first review to discuss the role of inflammation associated with viral infection in implantation failure.

Keywords Implantation, Virus, Inflammation, Infection

Introduction

Implantation or nidation is an initial complex stage in which the blastocyst burrows into the endometrium of the female's uterine wall and, if successful, the female is considered pregnant [1, 2]. Apposition, adhesion and penetration are the three main stages of implantation. Apposition occurs when the blastocyst is unstably attached to the endometrial surface. The next stage is adhesion as the association of the luminal epithelium with the trophoblast and the resistance of the blastocyst to displacement by lavage of the uterine lumen [3, 4]. Stromal vascular permeability is increased (localized) at the blastocyst attachment site and is considered the first sign of attachment [3].

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The last stage is penetration, so that the stroma is invaded by the embryo through the epithelium to access the maternal vasculature. Trophoblasts and the decidua control and limit the extent of invasion [3, 4]. Because the embryo is different from the mother's cells, it may be considered a pathogen by the mother's immune system if it does not secrete immunosuppressive agents [5, 6]. Many factors are involved in proper embryo implantation and uterine receptivity to modulate endometrial functions. These include cytokines, chemokines, and growth factors [7]. The uterus-embryo cross talk triggers changes in the endometrium, which is critical to the receptivity of the uterus [8]. There is a negative human chorionic gonadotropin (hCG) test in urine or blood during implantation [9]. Failure of the implantation process is one of the most common causes of female infertility. Recurrent Implant Failure (RIF) is a clinical condition in which good quality embryos fail to implant in the uterus after multiple in vitro fertilization (IVF) attempts [9, 10]. Several mechanisms are involved in implantation failure, including leiomyoma, endometriosis, polycystic ovarian syndrome (PCOS), hydrosalpinx, and exposure to toxic substances and infections [4, 11, 12]. Microorganisms

(viruses and bacteria) repeatedly invade the endometrial cavity/tissue. Implantation failure can be due to subclinical endometrial infection and/or chronic inflammation [13]. Although much research has evaluated and confirmed the involvement of bacterial infection agents in implantation failure [12], viral involvement is still questionable and needs more detailed studies. Viral infection of the trophoblast can impair its function, resulting in abnormal implantation. Possible causes of implantation failure include viruses that have little or no pathogenicity [14].

The current study set out to discuss the role of viral infection in implantation failure.

Inflammation and immune cells in implantation

There is a complex microenvironment in the placenta between the mother and the embryo that contains immune substances [15]. The mother's immune system has a crucial role in the embryo implantation, as the embryo is semi-allogeneic and different from the mother's cells [16]. Recent research has shown that implantation is a pro-inflammatory condition [17]. Besides, inflammation is proven to play a key role in maintaining and regenerating the uterus [18]. Pro-inflammatory cytokines produced by endometrial stromal cells that inflame the endometrium prior to the blastocyst invading [19, 20].

There are two types of the immune response, including T helper cell 1 (Th1) and Th2 [21, 22]. In Th1 response tends to produce the proinflammatory cytokines including interferon-γ (IFN γ), interleukins (IL1, IL2, IL6, IL12, IL15, and IL18), and TNFα. This response is involved in defense against intracellular parasites, and autoimmune responses [23, 24]. From the other point of view, in Th2 response IL4, IL5, IL-6, IL-9, IL10, IL13 (regulatory cytokines), and granulocyte macrophage colony stimulating factor (GM-CSF) are involved. This response is known as anti-inflammatory [25]. One of the immune system's primary responses is inflammation, which consists of molecular mediators, cytokines, chemokines, and immune cells [26]. Different factors are involved in provoking of the inflammatory process, including infection, viral and bacterial, and tissue injury [18].

This is an incredibly important point to remember, as a distinction must be made between acute and chronic inflammation, with acute inflammation being indispensable for implantation success, whereas chronic inflammation is destructive and causes RIF [27]. The inflammatory process causes local endometrial injury, which prolongs endometrial receptivity [18]. Furthermore, the positive effect of local endometrial injury on the success rate of IVF has been supported by a recent meta-analysis [28]. One study showed a decrease in the expression of programmed death 1 (PD-1) (an immune checkpoint) and T cell immunoglobulin and mucin domain-3 (TIM-3) in the peripheral lymphocytes after the successful implantation of the blastocyst (on days 3 and 6). Since both of them are essential factors in anti-inflammatory process, this indicates that inflammation is involved in implantation [29]. On the contrary, at the end of menstruation, the decline in progesterone leads to the activation of the pro-inflammatory NF-kB pathway, and indeed causes the up-regulation of pro-inflammatory cytokines, matrix metalloproteinases and prostaglandins [18, 30]. Cytokines involved in the implantation process were described in details by Sieg et al. [27]. The essential function of antigen-presenting cells (APCs) in the cytokine profiles between maternal and fetal tissues has been confirmed by several studies [31, 32]. Another important factor is reactive oxygen and nitrogen species (RONS). Level of RONS may be involved in the implantation process so that overproduction of RONS can cause cell and tissue damage, as well as interfere with signaling pathways [33]. Nitric oxide (NO) plays a critical role in both endometrial tissue preparation for successful implantation and endometrial decidualization [34].

Immune cells have a critical function in inflammation, leading to tissue remodeling through the secretion of various cytokines and chemokines [18, 24, 31, 35]. Uterus infiltrated cells are uterine-specific natural killer (uNK) cells (65–70%), regulatory T Cells, Uterine Mast Cells (uMCs), macrophages, dendritic cells (DCs), and APCs (10–20%) [36–40]. These cells secrete cytokines and chemokines that are pro-inflammatory [24]. "Decidual natural killer (dNK) cells are differentiated from peripheral blood NK cells". These dNK cells have some characteristics, including poor cytolytic activity, secreting IFN-gamma-inducible protein 10 (IP-10; CXCL10), IL-8 and some other cytokines that are involved in trophoblast invasion and embryonic development [31, 41]. DCs, which act as initiators and coordinators of the innate adaptive immune response [42]. Prior to implantation, uterine DCs (uDCs) accumulate in the pregnant uterus. They remain in the decidua for the entire duration of pregnancy [32, 43]. One of the most important effects of uDC depletion is severe impairment of implantation [44]. Another important cell is the macrophage, which is involved in the decidualization and implantation [45, 46]. DCs and macrophages are involved in angiogenesis and remodeling of tissue by secreting chemokines, cytokines, and enzymes [46]. The first immune cells to be involved at the site of infection are neutrophils, which cause the amplification of inflammatory signals and attract immune cells. But the infiltration of neutrophils into the endometrial tissue is prevented, perhaps by suppressing the cytokine signaling involved in their recruitment [47, 48]. Although T cells are crucial in the implantation, they constitute a smaller proportion of the immune cells

of decidual compared to dNK and macrophages [16, 49, 50]. Th and T regulatory (Treg) cells have the key roles during implantation and pregnancy [16, 50]. All in all, immune cell infiltration is crucial in cell differentiation, tissue renewal and the development of a receptive endometrium.

In fact, there is a reciprocal relationship between sex steroids (progesterone, and estrogen) and inflammation. In addition, inflammation is related to successful implantation [18, 24, 51–53]. A challenging question is whether the maternal immune system is a friend or foe of pregnancy.

Impact of virus-induced heat shock proteins on embryo implantation

Heat shock proteins (HSPs), also known as chaperones are highly conserved protective protein substrates that are produced in all cells [54]. There are several processes involved. These include proper protein folding, protein trafficking, and assembly and/or disassembly of complex proteins [55]. Environmental stressors such as free oxygen radicals, hyperthermia, inflammation and infection lead to the expression of HSPs [56]. The role of HSPs in immunomodulation is that it causes the up-regulation of some factors such as some chemokines, interleukins (IL-1, IL-6, and IL-12), nitric oxide (NO), tumor necrosis factor (TNF-α), and even the maturation of DCs [55].

HSPs play a critical role in pregnancy, especially in the implantation process, where they are tasked with maintaining the proper microenvironment in the endometrial cells [56, 57]. HSPs can affect all stages of reproduction because they are the first proteins synthesized during embryonic development [58]. In mouse and rabbit models, HSPs have been shown to be produced during embryo preimplantation [59]. In addition, HSC70 is constitutively expressed during mouse embryo implantation [60].

Viral infection results in the cellular heat shock response and modulation of the expression of HSPs involved in implantation [61]. It has been demonstrated that some HSPs such as hsp60, hsc70, and hsp90 are up-regulated, while hsp28 is down-regulated [62, 63]. Previous researches have shown alteration of the HSPs during viral infection. Viruses such as Herpes simplex virus type 1 and 2 (HSV-1 and HSV-2), Varicella Zoster virus (VZV), Cytomegalovirus (CMV), Hepatitis C virus (HCV), Polioviruses (PV), and Epstein-Barr virus (EBV) [61, 64–68]. Viral infection of chick embryo cells has been shown to induce the expression of HSPs [69].

In general, it can be concluded that changes in the expression of HSPs by viruses can lead to disruption of the embryo implantation process.

Viral-induced immune responses

Viruses are necessary but not enough to cause disease, as are other pathogens, which are infection enigma [70]. Viral infection during pregnancy has several consequences, including premature birth, miscarriage and intrauterine growth restriction [71]. Viruses involved in implantation failure through two ways include: (i) direct way: infect endometrial and blastocyst cells, which leads to apoptosis, alteration of gene expression and decreasing trophoblast invasive activity; (ii) indirect way: disrupting the immune response (Fig. 1). The immune system has one primary strategy against viral infection. It is to eliminate the infected cells by type I IFNs (IFN-α and IFN-β), pro-inflammatory cytokines, and cytotoxic lymphocytes [72, 73]. The role of inflammatory cytokines in viral infection is mediated through several pathways including: (a) producing antiviral effector molecules directly, (b) indirect provocation of recruiting immune cells and the phagocytosis of infected cells, and (c) activation of acquired immune responses includes cytotoxic T lymphocytes (CTLs) and neutralizing antibodies [73–75]. Infected macrophages and DCs produce interleukins (IL-1β, IL-6, IL-15, IL-18), and TNF as the major inflammatory cytokines [72, 73].

Human decidua contain a variety of immunocompetent cells including T cells, NK cells and macrophages [13]. Conversely, different cell types are involved in antiviral responses such as NK, DCs, monocyte, macrophages, and T cells [72, 76, 77]. NK cells have an important role in the elimination of virus-infected cells through the production of IFN-γ, which induces other antiviral mechanisms. Another cell is monocyte, which gives rise to DCs and macrophages when inside the tissue [72, 73]. Macrophages play a number of critical roles, including tissue homeostasis, wound healing and inflammation. Some macrophages prevent other cells from being infected by producing the highest levels of type I IFNs locally [73, 78, 79]. During viral infection, DCs have some functions such as antigen presentation, and cytokine production [72, 80]. Excessive leukocyte infiltration and activation of tissue-resident leukocytes are responsible for tissue inflammation during viral infection [81].

One of the critical factors for successful implantation is the local microenvironment at the cellular and molecular level at the fetal-maternal interface [13]. Many studies have shown that viral infection leads to changes in the cellular and molecular microenvironment of the target tissue. There are various imbalances such as inflammation, misplaced immune cell infiltration, production of RONS and alteration of normal cell signaling [82–86].

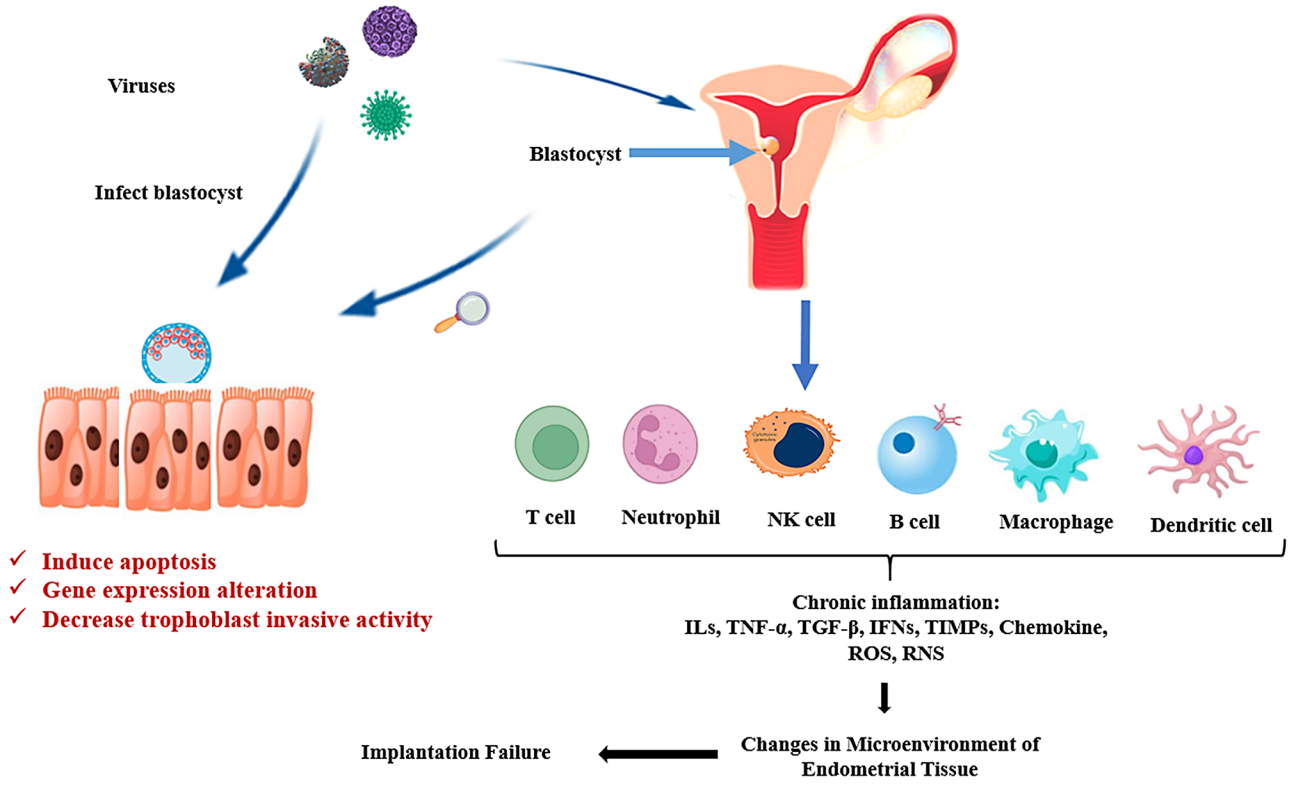

Fig. 1 Viruses lead to implantation failure by direct infection and disrupting the immune response

Virus infection and implantation failure

Viruses can infect the reproductive tract and affect the cells of these areas by modulating metabolism, biochemistry and the immune system. Therefore, there is an urgent need to assess the involvement of viruses in the embryo implantation and pregnancy outcomes. In support of this notion, some of the following evidence has been presented:

i. Viruses can infect trophoblast cells,
ii. Viruses have crucial roles in apoptosis of trophoblast cells, trophoblast gene expression alteration, decreases trophoblast invasive activity,
iii. The viral genome was detected in placental tissue of implantation failure cases,
iv. Detection of IgM antibodies against viruses [14] (Fig. 1).

In addition, implantation can be affected by viral infection by disrupting the normal function and secretory activity of endometrial cells in several ways, including:

- Immune modulation and cytokine production: As previously written, viral infections can modulate immune response and alter cytokine secretion by embryonic cells, resulting in an unfavorable microenvironment for implantation [5, 14, 87].
- Hormonal alterations: disruption of the hormonal balance occurs by some viral infections. Viruses cause damage to specific endocrine cells through replication in infected cells, cell lysis, and as a result of the immune response against viruses. Changing the production of progesterone and/or estrogen causes the implantation process to be impaired [88]. In SARS CoV-2 infection, alterations in hormonal levels have been seen, including increased level of luteinizing hormone (LH), prolactin, and follicle-stimulating hormone (FSH) [89]. HIV infection leads to increased activity of the pituitary gland, as evidenced by increased levels of TSH, prolactin, and ACTH [90]. Interestingly, some viruses encode some peptides called viral hormones with homology to human hormones (structural and/or functional) [91]. Inhibin β A chain, TGF-β1, TGF-β2, fibroblast growth factor, and IGF-2 are viral hormones that play a role in different stages of pregnancy [91].
- Apoptosis: some viruses cause implantation failure by inducing apoptosis in embryonic cells [92].
- Alteration of cell adhesion molecules: viruses can interfere with the normal expression of cell adhesion molecules on the surface of various cells such as immune cells and epithelial cells like those found in embryos [93–95].

Viral infection can change the gene expression patterns of endometrial and embryonic cells. For example, CMV causes disruption of the development of extracellular matrix (ECM), integrins and ultimately results in decreased cell adhesion and tissue invasion ability (implantation) [96–98]. Also, some viruses such as HHV-6 A interfere with trophoblast invasion by integrating their DNA into the host cell [99].

Overall, the success of implantation may be significantly influenced by the interaction between embryonic cell secretions and viral infections. However, specific details on the range of effects on secretions may require further study. There is lots of research that has been done on the influence of bacterial infection on embryo implantation [56, 100, 101], but the role of viral infection has not been reviewed much. We have set out to discuss the effects of some viruses on the implantation process as follows.

Human papillomavirus (HPV)

HPV is an oncogenic virus belonging to the Papillomaviridae family, which can infect the skin and mucous membranes [72]. HPV has multiple effects on reproductive function [102]. HPV infection in different tissues such as breast, prostate and lung results in increased expression of RONS, ILs (IL-1α and β IL-6, IL-8), NF-κB, MIP-1α, and TNF-α [84, 85, 103, 104]. This viral infection is correlated with inflammation in mucous membranes, and skin [105]. HPV can cause chronic inflammation, change cell signaling, physiological cell death and cell transcriptome [85, 103, 106–108]. On the other hand, the negative immune-mediated effects of HPV on the implantation have been demonstrated in several studies [109]. Changes in cellular gene expression occur during persistent HPV infection, resulting in the expression of proinflammatory cytokine genes and abnormal immune cell infiltration [72, 84, 85, 103]. Another critical effect of HPV on cells (by E5 and E7 proteins (early proteins)) is to lead to down-regulation of some cell surface molecules such as human leukocyte antigen-G (HLA-G) and major histocompatibility complex class I (MHC I) that cause these cells to be lysed by NK cells, which are normally insensitive to NK cell lysis [110–112].

The trophoblast expresses the HLA-G as a requisite agent in the implantation process [112, 113]. In addition to the inverse effects of HPV on implantation, it causes activation of the immune response against the developing embryo by down-regulating the MCH I molecule [114]. HPV can lead to reduced implantation of trophoblastic cells through increased trophoblastic apoptosis, which was demonstrated by Zuo et al. [115, 116]. Also, Gomez et al. showed a greater rate of apoptosis (3- to 6-fold) in trophoblastic cells with HPV infection [117]. It has also been found that HPV can be transmitted during fertilization and subsequently to the embryo [118–120]. The genome of HPV types 16 and 18 were detected in 108 patients with miscarriages [121]. The higher rate of HPV DNA detection in early miscarriage cases compared to voluntary terminations of pregnancy can demonstrate that HPV is involved in the pathophysiology of early pregnancy loss [122]. The effects of HPV on early development in the embryonic stage was demonstrated by Henneberg and colleagues. They showed the HPV type-specific effects on the blastocyst, as if HPV-16 led to a decrease in blastocyst formation, whereas HPV-18 was involved in inhibiting the blastocyst hatching process [123]. In another study, embryos exposed to HPV-16 were also shown a reduced implantation rate (less than 37.2%) by Hong et al. [121].

There is several research confirming the HPV effect on alterations in the immune response and cellular physiology that are involved in implantation. HPV as a frequent member of sexually transmitted infections (STI) may be an important hallmark in implantation failure. Most studies have reported the role of HPV types 16 and 18, but other HPV types may also be involved. Therefore, further studies are needed to clarify the involvement of all HPV types in implantation.

Herpes simplex virus (HSV) type 1 and 2

HSV types 1 and 2 (HSV-1 and HSV-2) are common members of the Herpesviridae family [72]. Both of them are in charge of cellular physiology alterations and necrosis, which leads to the inflammatory response [72, 124]. It has been shown that HSV-infected patients have concentrated inflammatory cytokines and high expression levels of apoptosis-related genes. This situation is also associated with HSV load [125]. Some pro-inflammatory cytokines such as IFN-α and -β, IL-6, IL-12, and TNF-α are involved in HSV immune mediated pathogenesis [126]. In a mouse model study, Felker and colleagues demonstrated that HSV-2 infection results in up-regulation of inflammatory cytokines and chemokines at the implantation site. They demonstrated the ability of HSV-2 to infect implantation sites such as the maternal decidua. Their results suggest that trophoblast cells can be infected by HSV-2 t within implantation sites and induce abnormal trophoblast invasion [127]. The involvement of HSV in reproductive disease and pregnancy loss has been documented previously [128, 129]. Tsibizov et al. evaluated the impact of HSV-infected sperm on the fertilization efficiency and the frequency of embryo implantation. Their results indicated that the frequency of implantation was five times lower and the negative influence of HSV on the implantation [130]. In an interesting study, Yueh and colleagues have shown that up-regulation of VP16 (α-trans-inducing factor (α-TIF)) as a multifunctional protein of HSV is detrimental to preimplantation

development. They indicated that VP16 exerts its effects at the transition from the 2-cell to the 4-cell stage and leads to a reduction in blastocyst survival [72, 131].

Although the effect of HSV on implantation has been discussed, further researches is needed to determine its exact role in implantation failure.

Epstein - Barr virus (EBV)

Epstein-Barr virus (EBV) or Human herpesvirus type 4 (HHV4) is one of the most common viruses in humans (90% of the adult humans are seropositive) and belongs to the *Herpesviridae* family [72, 132]. EBV has been implicated in chronic inflammation in prostate, thyroid and breast tissue [83, 86, 133]. One study demonstrated that EBV infection was associated with the high levels of expression of inflammatory agents, which are involved in various pregnancy complications such as implantation failure [82]. There has been evidence that inflammation is increased in both latent and lytic EBV infection, and that inflammasome is triggered during EBV reactivation [134]. In research, Moghoofei et al. demonstrated a positive correlation between EBV gene products (EBER, LMP-1, and LMP-2 A) and inflammatory agents including NF-κB, IL-1, -6 and −10, IFN- α and -β, TNF-α, and ROS [86]. Implantation failure may be caused by this inflammatory state.

One of the most important effects of EBV on implantation is its influence on HLA-G, a cell surface molecule on placental tissue. HLA-G expression is up-regulated by IL-10, which has been demonstrated to be involved in the tumor cells' immune evasion [135, 136]. HLA-G, an antigen presenting protein, inhibits some immune cells such as NK cells, CD8 T and CD4 T cells, which is the most important factor in the immunosuppressive state responsible for immune tolerance during pregnancy [137]. The up-regulation of HLA-G is derived from the uterus environment, which is a fascinating concerted biological process and is involved in the immunological protection of the developing embryo [6]. Inflammation-related side effects may occur if immune tolerance mechanisms are disrupted. On the other hand, EBV can alter the expression of programmed cell deathligand 1 (PD-L1) [138]. This molecule is an immune checkpoint inhibitor and produced in placental trophoblasts and amniotic epithelial cells, which causes reduced lymphocyte proliferation through the secretion of immunosuppressive agents [139, 140]. Further research is needed to elucidate the involvement of EBV in the implantation failure.

Cytomegalovirus (CMV)

Human CMV or human herpesvirus type 5 (HHV-5) is another member of the Herpesviridae family with a seroprevalence of 60–90% worldwide [72, 141]. During CMV infection, there is a high number of differentiated T cells (CD4+and CD8+) producing IL-1, IFN, TNF-α, granzyme B and perforin that may be involved in the implantation failure [142, 143]. Dons'koi et al. demonstrated that CMV infection gives rise to pro-inflammatory response in implantation failure cases. Also, they reported a dramatic up-regulation of HLA-DR on NK, T and NKT cells and a decrease in the number of CD8+NK lymphocytes in CMV-positive cases compared to negative ones. This research team claimed that the imbalance of CD8, CD69 and CD158 expression in NK subsets predicts implantation failure [144]. It has been shown that there is a significant association between anti-CMV IgG (previous exposure) and Recurrent Pregnancy Loss (RPL) [145]. Several research have reported the high rate of anti-CMV IgG in recurrent miscarriage cases, including Augustine et al. (85.7%), Sherkat et al. (90.6%), Kafi et al. (97.8%), and Hammed et al. (92.9%) [145–147].

Fisher et al. could not detect the CMV genome but they indicated that this virus has a role in implantation failure through diminishing normal functions of the placental trophoblasts [148]. CMV gene expression is affected by acidic environment and estrogen in such a way that CMV replication is inhibited by acidic environment and only the immediate early (IE) and early (E) genes are expressed [149–151]. There are fundamental effects exerted by CMV gene expression patterns on host cells and the immune system. Some proteins are translated by the IE and E genes, which are involved in causing chronic inflammation [152]. As most of the data on the involvement of CMV in embryo implantation and female reproduction is somewhat inconclusive, further studies with more detail are needed to clarify new aspects.

Human herpesvirus 6, 7 and 8

Human herpesvirus 6 (HHV-6), HHV-7 and HHV-8 (KSHV) are other members of the Herpesviridae family [72]. HHV-6 is divided into two variants, including HHV-6 A and HHV-6B, which primarily infects T cells [153]. However, it has broad tropism for a variety of cells [154]. Some researchers have indicated shedding of HHV-6 from the genital tract (25%) [155–157]. HHV-6 and HHV-7 have critical roles in implantation failure by altering the uterine microenvironment and by disrupting endothelial cell function [154, 158, 159]. One study investigated the prevalence of HHV-6 in the endometrial tissue of RIF cases (37% compared to 0% in controls). There was also no any difference in expressing the following NK cell-related markers such as CD16a, CD56, and CD57 and T cell markers such as CD3e in HHV-6 positive cases than normal controls [160]. Marci et al. found HHV-6 A genome in 43% of endometrial biopsies from women with primary unexplained infertility and 0% in controls. Interestingly, genome of HHV-6B was not detected in endometrial biopsies while it was detected in PBMCs of both

groups (25% and 28% of infertility and control women, respectively). Since the role of NK cells in implantation is one of the most controversial issues, this research group demonstrated that endometrial HHV-6 A-specific NK cells were induced. Besides, they showed an up-regulation and down-regulation of IL-10 and IFN-γ in infertile women with HHV6-A infection, respectively [154]. The high load of HHV6-A genome was reported in a previous study as 670.000–250.000 copies/ug [154].

According to previous studies, the endometrial tissue of infertile women is a suitable site for HHV-6 A infection, and unidentified microenvironmental factors are the determinants of HHV-6 A replication/infection. For example, high levels of estradiol may act as a positive cofactor in the induction of HHV-6 infection in the endometrium [154, 161]. HHV-6 A may contribute to altering the immune phenotype of eNK cells and cytokine levels such that Th2 IL-10 cytokine increases while Th1 IFN-γ cytokine decreases, which correlates with condition of female infertility [154, 162]. Moreover, HHV-6 infection up-regulates IL-10 by monocytes while decreasing the production of IFN-γ by T cells [163, 164]. Also, a positive correlation between HHV-6 antibody levels and implantation failure was found in two studies by Ando et al. and Drago et al. [165, 166].

Infection of cells by HHV-7 make cellular changes and alterations in the gene expression, though the full impact on cell function is still being researched and there is no research on the role of this virus in implantation failure. More studies are needed to clarify the role of HHV-7 in infertility and implantation problems, as well as to determine if screening for and treating HHV-7 infections could improve outcomes for women undergoing fertility treatments.

HHV-8 can induce a change in the cellular physiology and disrupt the immune system. B-lymphocyte is the main target cells of HHV-8. This virus causes chronic inflammation (cytokine and ROS production) by producing vIL-6 (viral interleukin 6) [167]. This situation leads to implantation failure. Trophoblast and endothelial cells are permissive host cells for HHV-8, which negatively affects them by increasing apoptosis rates [168].

The ability of the Herpesviridae family to modulate immune responses is the most critical point about the ability of these viruses to cause fertility disorders such as implantation failure.

Hepatitis B virus (HBV)

HBV is a double-stranded DNA virus (partially) belongs to the Hepadnaviridae family, which causes hepatitis B [72, 132]. Although HBV can cause potentially serious conditions in endometrial tissue, its presence is rare and occurs in women with chronic HBV infection [169]. Immune system responses resulting in changes in the female genital tract microbiome, which are implicated in implantation failure are some consequences of chronic HBV infection [170]. HBV triggers the inflammatory response through the NF-κB pathway via TLR2 and MyD88 leading to the production of IL-1, -2, -4, -6, -12, -17, IFNs, and TNF-α [171, 172]. Mucin 1 (MUC1) and osteopontin (SPP1) are crucial in endometrial receptivity [173]. Złotkowska and colleagues evaluated the expression of several chemokines including CCL2, CCL4, CCL5, CCL8, CXCL2, CXCL8, CXCL10, and CXCL12 in endometrial epithelial cells. They demonstrated that the provision of a suitable microenvironment for successful implantation is mediated by CCL8, while CXCL12 plays a critical role in enhancing endometrial receptivity and promoting embryo attachment [173]. Previous research indicated that the up-regulation of some chemokines, such as CXCL9-11, 10, 11, and 13 in endometrial tissue from HBV-positive patients compared to healthy individuals [171]. HBV proteins such as HBx promote up-regulation and/or down-regulation of some of the chemokines listed above [174].

All these alterations can result in implantation failure by modulating endometrium gene expressions. Li et al. showed some changes including reduced toxicity and cell functional activities of NK cells and a decrease in the number of CD3+CD4+helper T cells in HBV infected women, which contribute to adverse pregnancy outcomes such as implantation failure [175]. By inducing widespread chronic inflammation, HBV infection also causes implantation failure [176, 177]. In a study, 190 women who were undergoing their first IVF and embryo transfer cycles, the implantation rate (as one of the most important factors) was dramatically higher in HBV-positive women in comparison to controlled ones [178].

Further studies are needed regarding HBV infection due to the severe effects this virus causes.

SARSCoV-2

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) belongs to the Coronaviridae family with a positive single-stranded RNA [179]. The main consequence of SARS-CoV-2 infection is cytokine storm or hypercytokinemia, in which pro-inflammatory cytokines are released in an uncontrolled and excessive manner [180, 181]. An important effect of this virus is the up-regulation of angiotensin converting enzyme 2 (ACE2) and serine 2 (TMPRSS2), which ACE2 is highly expressed in many tissues and serves as a receptor for SARS-CoV-2 [182, 183]. Endometrial tissue is affected by SARS-CoV-2 through TMPRSS4 and, it is confirmed by microarray data [182, 184].

In an interesting study, a single-cell RNA-sequencing dataset and two microarray datasets were applied to determine SARS-CoV-2-related gene expression profiles.

Qi and colleagues demonstrated the up-regulation of Basigin (BSG) in the endometrial tissue of women with RPL. Their results indicated the endometrial tissue is highly susceptible to SARS-CoV-2 infection, leading to implantation failure [185]. In contrast, a meta-analysis study reported that no significant differences were found in implantation rates between the infected group and controls (OR 0.99, 95% CI 0.67–1.46; $P=0.96$). The results of this study suggest that, infection with COVID-19 does not affect the rate of implantation in IVF treatment [186]. In addition, during COVID-19 VEGF is up-regulated, but cannot result in the attachment of embryo and implantation failure [187, 188]. A research group evaluated whether COVID-19 infection is related to implantation failure. The results demonstrated that no significant differences were found in the implantation rates in three groups, including infected patients before and after frozen embryo transfer (FET) (29.14% and 30.38%), and patients without infection (31.03%) [189].

In the case of SARS-CoV-2 further research is crucial to investigate the role of the Coronavirus in implantation.

Zika virus (ZIKV)

ZIKV is a member of the Flaviviridae family, which are enveloped viruses with positive-strand RNA [190]. This virus impair neuronal development and its pathogenesis is by suppressing the Akt-mTOR pathway and leading to cellular dysregulation [191].

Previous studies have demonstrated that ZIKV can affect the blastocyst and endometrial tissue to cause secretion of IL-6, VEGF-A, and Chemoattractant Protein-1 (MCP1) by the embryo, confirming a possible role of ZIKV in the blastocyst implantation [192]. VEGF-A, and MCP1 are crucial for implantation [193, 194]. Some members of the Flaviviridae family cause some changes during pregnancy, such as inflammation in the placenta, and up-regulation of VEGF and MCP1 [195]. Tan et al. demonstrated the effect of ZIKV on implantation failure and miscarriage. Also, 50–70% reduction in pregnancy rates was reported in a mouse model following subcutaneous ZIKV inoculation. They showed that ZIKV infection targets trophectoderm cells and leads to apoptosis [196]. Another study has shown that ZIKV replication can occur in the trophectoderm and during implantation, altering trophoblast function [197].

Although there are few previous investigations on ZIKV involvement in implantation, further in vivo research is necessary for the determination of the role of ZIKV in embryo implantation.

Microbial-host interaction is the strongest shaping force in how the immune system evolves and develops. Infections of the genital tract and the pathological inflammation associated with them are vital to the successful process of reproduction.

MicroRNAs

However, several previous reviews have discussed the role of microRNAs (miR or miRNAs) in embryo implantation. In this study, we will discuss some miRNAs that have deregulated expression levels are involved in implantation failure and are also affected by viral infections. One of the main ways that viruses can affect the implantation failure is that viruses lead to altering the expression miRNAs in endometrial tissue. MiRNAs are a class of non-coding regulatory RNAs, which have about 19–25 nucleotides (nt) in length [198, 199]. Totally, more than 300 human miRNAs have been identified that affect various biological functions by the regulation of the expression of about 60% of human protein-coding genes [198, 200–202]. Because viruses as intracellular parasites can modify how targeted cells behave. Viruses can alter the expression of cellular miRNA and, in fact, they disrupt cellular processes [203, 204]. Viruses can be affected by miRNAs in two ways as follow; direct way as targeting viral mRNAs in the 3′UTR (untranslated region) and indirectly, by modulating the expression of host factors that are essential for the replication of the virus [204, 205].

The differential expression of miRNAs have been demonstrated in different stages and/or pathological conditions of endometrial tissue [206, 207]. Furthermore, the different miRNAs profiling has been seen in endometrium from failed and recurrent failed implantation [208]. There are two main types of miRNAs in implantation, including pro-implantation miRNAs and anti-implantation miRNAs. Pro-implantation miRNAs are up-regulated prior to implantation, while anti-implantation miRNAs are up-regulated in the event of implantation failure [209]. The differential expression of 13 miRNAs (10 miRNAs were up-regulated and 3 were down-regulated) in RIF patients was first reported by Revel et al. in 2011 [210].

The first one was miR-145, which is expressed in a number of tissues such as the prostate, the ovary, the heart and the uterus [211]. MiR-145 has also contributed to the regulation of decidua cell proliferation and in the differentiation of endometrial tissue [211, 212]. Several targets were introduced for this miR such as octamer-binding transcription factor 4 (OCT4), mucin 1 (Muc1), homeobox A10 and A11 (HOXA10, HOXA11), estrogen receptor alpha (Era), and insulin-like growth factor 1 receptor (IGF1R) [207]. A previous study has shown an up-regulation of miR-145 in patients with RIF compared to controls (a 3-fold increase) [213]. Up-regulation of miR-145 has been shown to be involved in the inhibition of mouse embryo attachment to the endometrium [214]. Another critical effect of miR-145 in the genital tract is on implantation by down-regulating of Phenylalanine ammonia-lyase 1 (PAL-1) [210, 213]. Furthermore, this

miR leads to infertility through inhibiting the expression of HOXA10 and HOXA11 [215]. HPV causes a significant decrease in miR-145 expression in penile cancer [216]. Yu et al. showed the significant down-regulation of miR-145 in HPV-positive cervical cancer cases compared to HPV-negative ones [217]. There is a reciprocal relationship between miR-145 expression and HPV replication, so that HPV causes significant down-regulation of miR-145 and up-regulation of it can inhibit HPV replication [216, 218]. MiR-145 inhibits the expression of certain HPV mRNAs such as E1 and E2 (early protein), which are involved in viral replication [219]. A significant association has been indicated between EBV infection and lower levels of miR-145 expression in some tumor tissues compared to normal ones [220]. Okoye and colleagues have shown that an up-regulation of miR-145 status in HSV-2 infection of cervical lesions compared to HSV-2 negative tissue. They also showed that miR-145 was up-regulated in cases of viral mono-infection and down-regulated in cases of viral co-infection compared to participants without viral infections [221]. It has also been shown that CMV inhibits miR-145 expression. This leads to the up-regulation of Sox2 and subsequently to the proliferation of some cells [222].

Mir-22 was first identified in HeLa cells. Then was identified in a some tissues [223]. This miR is involved in various biological pathways such as apoptosis, cell proliferation and cell migration and it is a tumor suppressor [224, 225]. On the basis of the role played by immune cells and their secretions in the process of implantation, recent research demonstrated that the expression level of PD-L1 is decreased by miR-22, which causes T cell-mediated immune responses [226]. Moreover, this miR leads to activate myeloid DCs to indirectly regulate the T helper 17 (Th17) in the mouse model [227]. Interestingly, miR-22 is considered as an anti-implantation miRNA that is up-regulated during normal implantation in RIF patients. This miR through targeting T-Lymphoma Invasion and Metastasis-Inducing Protein 1 (Tiam1) results in the dysregulation of decidualization in endometrial stromal cells. Tiam1 and Race1 are involved in implantation [228]. One study showed that up-regulation of miR-22 caused down-regulation of Tiam1, resulting in embryo implantation in mice. It has also been shown that estrogen (E2) and progesterone (P) interact to regulate miR-22, Tiam1, and Rac1 [229]. In addition, the dysregulated expression of miR-22, Race1 and Tiam1 are associated with a decreased progesterone to estradiol (P/E2) ratio in RIF patients [207]. HPV E6 protein (early protein) leads to down-regulation of miR-22 through suppression of p53 in cervical cancer cell lines [224]. In contrast, a significant correlation between HPV-16 infection and up-regulation of miR-22-3p was demonstrated by Kwon et al. [230]. Several studies showed a significant correlation between HBV infection and down-regulation of miR-22 [231, 232]. The effect of HHV-6 A on miR-22 is in such a way that this virus significantly increases the expression of miR-22 in the cells of the endometrium [99].

MiR-181 plays an important role in the cellular processes such as angiogenesis, apoptosis, autophagy, and the pro-differentiation of some cell lineages including immune cells (NK/NKT cells, B cells, and T cells), megakaryocytes and myoblasts [233, 234]. In patients with RIF, miR-181 is down-regulated [235]. Some sex hormones such as estrogen cause down-regulation of miR-181 by regulating the expression level of empty spiracles homeobox 2 (EMX2) [207, 236]. Down-regulation of miR-181 results in up-regulation of Leukemia inhibitory factor (LIF) and subsequent implantation success. LIF belongs to the IL-6 family, which leads to the uterus for embryos to be implanted [207, 237]. Another important effect of miR-181 is the downregulation of KLF transcription factor 12 (KLF12), which is involved in endometrial receptivity. The expression level of KLF12 is found to be high in endometriosis and RIF patients [238]. Some viral infections such as HPV and SARS-CoV-2 cause down-regulation of miR-181 while other viruses like EBV, HBV, and HHV-6 A lead to up-regulation [239–241].

The expression of miR-661 was evaluated in a study that showed significant up-regulation of this miR in blastocysts from women with failed implantation [242]. MiR-661 causes down-regulation of Mdm2 and Mdm4 that leads to p53 activation [243]. On the other hand, in addition to causing the proteolytic degradation of p53, HPV causes down-regulation of miR-661 to prevent the activity of p53 [85, 244, 245]. Also, HBV leads to down-regulation of miR-661 [246].

One of the HBV proteins (HBx) down-regulates miR-661 that suppresses Metastasis-associated protein 1 (MTA1) with some important cellular functions in endometrial tissue [247, 248].

Previous data suggests that miR-30 is involved in both the physiological (tissue development) and pathogenic disease processes [249]. This miR is up-regulated in the endometrium and has a negative correlation with forkhead box P3 (FOXP3), which regulates CXCL12 expression [250]. On the other side, the immune-tolerant environment in the endometrium is associated with uNK cells attracted by CXCL12 [208]. One study profiled miRNA expression in uterine aspirates collected overnight before frozen embryo transfer. Park and colleagues reported that three miR, miR-891a, miR-198, and miR-522, were down-regulated in the implantation failure cases [251].

All in all, virus alters some cellular and molecular processes in the endometrial cells. Viruses by deregulation of cellular miRNAs lead to disruption of the cell

microenvironment and many cellular functions such as the implantation process.

Conclusion

In this review, we reviewed studies analyzing the role of viral infections and miRNAs expression changes in the endometrium, which are crucial in the likelihood of successful implantation. Although several studies have been conducted on factors involved in embryo implantation, based on our search the role of viruses and the role of interaction of viruses and cellular miRNAs has not been investigated in previous studies. All these results suggest that viruses play a crucial role in the implantation failure process as a confounding factor. However, further studies are needed to confirm the role of viral infection and viral-induced miRNAs in implantation failure.

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MR and MM provided outlines for the manuscript. MR and MM drafted the manuscript. MM provided critical revision to the abstract and manuscript. MR and MM approved the final version.

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Data availability
All included articles during the current study could be made available through the corresponding author upon reasonable request.

Declarations

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This study did not require ethical approval or patient consent. All analyses were performed according to previously published studies.

Consent for publication
Not applicable.

Competing interests
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