Review Article

The Issue of Embryo Implantation in Women during the Coronavirus Outbreak: An Overview

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Abstract

The Coronavirus is a major health problem nowadays, which affects people's lifestyle. This pandemic virus shared a variety of phenomena in case of symptoms and side effects. One of the major issues regarding novel coronavirus is the effect of infection on pregnancy which accounts for an essential process of human life. Considering the pathogenesis of Coronavirus, overexpression of inflammatory cells and cytokines accounts a pivotal step in the development of symptoms. The over-expressed cytokines in response to covid-19 infection would render the inflammation and disruption of the immune system and tissue damage. Like coronavirus infection, implantation the main step of a successful pregnancy, activates the inflammatory cells and cytokines. The association of infection with pregnancy raises the concern about the effect of covid-19 on embryos and giving normal birth, especially in women who decide to get pregnant or are in the pregnancy period. The current review focused on immune system responses to the Coronavirus and comparison with immune system activation during implantation. It concluded that further laboratory research and studies are needed to better understand and draw general conclusions about the role of the virus in embryo implantation.

Keywords: Coronavirus, Implantation, Embryo, Immune response

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Introduction

One of the principal life issues gives birth to a child. Embryo implantation, which is an important and necessary process for reproduction, begins with the embryo's attachment to the uterine epithelium cells. The embryo, as an allogeneic, cause inflammatory responses that could threaten the embryo implantation. These inflammatory reactions are essential for successful implantation and subsequent in evolving pregnancy as well. Approximately all viruses absorb and activate inflammatory cells, especially macrophages. These inflammatory cells release molecules that cause damage or defect in the relevant

tissue[5,15]. Molecules released from injured tissues are including cationic proteins, lipid mediators, cytotoxic cytokines, respiratory bursts, and metalloproteinases. Accumulation of oxygen mediators produced by mitochondria would arrest the respiratory tract and contribute to tissue damage, while, both innate and acquired immune are involved in viral infections, which could cause tissue damage. About 70% of viruses are RNA viruses with diversity in their genome. The rate of mutation in RNA viruses is more prevalent due to an enzymatic error in RNA replication, which leads to various viral variants with various host types. The RNA virus is divided into single-stranded (ssRNA) or double-stranded (dsRNA) type, in which a single-stranded can be a plus-strand (sense strand, which acts as mRNA) or a minus strand (antisense strand), or it can be segmented or not segmented. There are 8 families of positive sense RNA (+ssRNA) viruses that infect vertebrates, including *Picornaviridae*, *Astroviridae*, *Caliciviridae*, *Hepeviridae*, Flaviviridae, *Togaviridae*, *Arteriviridae* and *Coronaviridae*[38]. Due to the importance of the immune system at the time of the Coronavirus outbreak, the researchers aimed to examine the interaction of the host's immune system with *Coronavirus* and its association with embryo implantation.

Positive- Strand RNA (+ssRNA) viruses and immune system

Innate response to RNA viruses

The innate immune response is the first and most important defensive mechanism against foreign components[20]. The signaling cascade of innate immune response starts with pattern recognition receptors (PRR) which interact with pathogen-associated molecular patterns. Toll-like receptors of 3, 7, and 8 are addressed as the important receptors[14, 60]. The NOD-like receptors (NLRs)[28] and retinoic acid-inducible gene I (RIG-I)[7] are well described in virus immune response as a PRP receptor. These mentioned receptors are sensing the double-strand RNA virus[20]. Therefore, the innate immune system would recognize the foreign materials followed by downstream signaling, which ended up with induction the transcription of interferon types I (IFNα/β)[30] and III[4], and proinflammatory cytokines (chemokines and cytokines)[20,50]. Followed by activation of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) (JAK-STAT) signaling pathways[13], which stimulate the expression of interferon-stimulated genes (ISGs)[46]. Protein kinase A (PKA) and 2, 5- oligoadenylate synthetase (OAS) are two main ISGs, which recognize the dsRNA viruses. OAS initiates the degradation of host and viral cells by activating RNase L, while PKA inhibits the translation and activation of inflammatory elements; also, both OAS and PKA are involved in RLR (RIG-I like receptors) RLRs)) mediated antiviral immune response[46, 48]. RNA virus shields itself in viral replication organelles (ROs) to escape from innate immune response, which is created by rearrangement of host membranes[31,43]. Also, the virus could mimic the eukaryotic mRNA by having 5-cap, especially in the *Coronaviridea* family. Virus protects the N and O linked methylation on CAP structure to run away from recognition by receptors.

In contrast, administering their endonuclease (EndU) that cleavage the viral RNA exposed to the cytosol to escape from recognition by PKA and OAS[47]. Concerning the recent public health, *Coronavirus*, a positive-strand dsRNA virus, promotes stimulation of numerous cytokines including, IL-2, IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL- 13, IL-17, M-CSF, G-CSF, GM-CSF, IP-10, IFN-γ, MCP-1, MIP 1-α, hepatocyte growth factor (HGF), TNF-α, and vascular endothelial growth factor (VEGF), in a different phase of infection[11, 12, 36]. Among them, the inflammatory cytokines have a major effect on the pathogenesis of the disease. IL-1 is the main inflammatory cytokine produced during viral infection; IL-1β plays a key role in activating cytokine storms followed by *Coronavirus* infection. In other words, the novel Coronavirus (COVID-19) activates and maturates the IL-1β, that the elevated level of IL-1β is observed in the severe form of the disease associated with hypercoagulation, loss of pulmonary function, and higher mortality risk[10]. During the first phase of infection, IL-6 is secreted and induces acute-phase proteins such as, C-reactive protein (CRP), fibrinogen, serum amyloid A (SAA), α1- antitrypsin, and haptoglobin from the liver. Therefore, the high level of IL-6 is related to poor prognosis of disease and risk of cardiac damage[10]. TNF-α is responsible for proinflammatory response mediated by IL-1β and IL-6 and regulation of

inflammatory signaling and contribution of malignant tumors. It is confirmed that TNF-α is a hallmark of severe infection in patients infected with Covid-19 and middle- east respiratory syndrome (MERS)[17,52]. In summary, positive-sense RNA viruses reassemble in ROs and thus would escape from the immune system. However, the delivery of the virus to its receptors induces an antiviral signaling pathway. Following the induction of IFN-I and III and ISG from various cell types and induction of INF-II production from specific immune cells, the GTPase induced by IFNs, confer the accessibility of virus to immune cells and enhance immune cells the clearance of virus from ROS[43].

Adaptive immunity to RNA viruses

The main purpose of the innate response to virus infection is to invoke and generate an acquired response. The acquired response involves humoral and cellular immunity. The main manifestation of humoral response is the production of antibodies against foreign particles as the cellular immune system identifies the infected cells through T cells and promotes killing the infected cells[26,51]. It can be said that almost all viruses replicate in cells and disseminate to other cells, but T cells play a pivotal role in defensive mechanisms than antibodies. Antibodies mostly have an immunoprotective effect for reinfection. Both B-cell and T-cells responses begin within the lymphoid tissue. The acquired immunity is followed by antigen-presenting cells (APS) cells presenting the viral particles. Different transcription factors, including nuclear factor κB (NF-κB), activator protein1 (AP-1), interferon response factor 3 (IRF3), and interferon response factor 7 (IRF7) are activated, which promotes to inflammatory response and secretion of inflammatory cytokines such as TNF and IL-1 as well as secretion of CCL2 and CXCL8 chemokines. IRF3 and IRF7 also promote the expression of type I interferon (TNF α/β), necessary for an innate immune response, especially against *Coronavirus*. The ultimate phenomenon is to prevent the dissemination of the virus at the early stage of infection[24,32,53].

Embryo implantation and inflammatory response

Embryo implantation

Embryo implantation is the main stage of pregnancy, in which the mature blastocyst is attached to the uterine endometrium. The successful implantation occurs when the uterus gains the essential capacity to become receptive[5]. During the menstrual cycle, stromal cells of the fibroblast-like endometrium, transform into large and rounded decidual cells and maturation of microvilli on luminal epithelium following the expression of different cytokines, chemokines, adhesion, and growth factors. These changes are governed by ovarian steroid hormones, like progesterone, 17-beta- estradiol, and maternal immune response[6,9,34].

Hormones and Immune system in implantation regulation

Progesterone and estrogen are two main hormones in female reproductive organs. In contrast, progesterone is essential for initiation of implantation and successful pregnancy and in proliferation, differentiation, and maintenance of glandular and endometrial cells; estrogen promotes induction of progesterone receptors, which enhance the activity of the progesterone and ultimately develop the uterine epithelium thickness[6,22]. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and thyroid-stimulating hormone (TSH) is human chorionic gonadotropin which secreted from syncytiotrophoblasts and some tumors. These glycoprotein hormones increase cell growth and promote the differentiation and immunosuppression of corpus luteum, maintaining the implantation[8,18]. Uterine endometrial cells and individual immune cells that are called to the implant site during embryo implantation would up-regulate T helper 1 (Th1) and cytokines, such as IL-6, IL-8, and TNFα, as an early implantation indicator[16,21,58]. In the human uteroplacental unit, there are many hematopoietic cells such as NK cells (65-70%) and antigen-presenting cells (APC), including dendritic cells (DC) and macrophages (10-20%)[1,25,44]. Natural killer (NK) cells in the decidua mediate in trophoblast invasion into the uterine through the production and secretion of IL-8 and interferon-inducible protein (IP)-10. The growth of vascular in the decidua for a successful implantation is one of the key factors that mediate by NK cells with the secretion of angiogenesis molecules[33]. Dendritic Cells (DCs) are a group of antigen-presenting cells that regulate the onset of adaptive immune responses.

DCs are presented in the pregnant uterus before embryo implantation and in decidua during pregnancy[23]. There is ample evidence that APCs play a vital role in producing and secretion of cytokine profiles concerning maternal-fetal junction[23,33]. In vivo study has been shown that the deficiency of DCs in the uterus contributes to impaired implantation, followed by embryo resorption[39]. Another study in the mice showed that cell therapy using DCs significantly decreases the resorption of embryo[23]. These studies confirm the role of both immune cells and APC cells in regulating and advanced pregnancy[29]. We also showed in our previous study that cell therapy using intrauterine transmission of peripheral blood mononuclear cell (PBMC) in mice can increase the rate of implantation and pregnancy through increment of cytokines and immune factors expression required for implantation[42].

One of the IL-6 cytokine members is leukemia inhibitory factor (LIF) that stimulates the proliferation, differentiation, and survival of blastocyst and uterus epithelium for implantation[49]. The LIF bind to LIFR receptor and initiate the JAK-STAT, MAPK and PI3- kinase pathways. LIF has an essential role in cytotrophoblast invasion and interaction with maternal decidual leukocyte[3,45]. The IL-6 cytokine is one the inflammatory cytokine for initiation of innate immunity. The inflammation caused by IL-6 increases the potency of the uterus for implantation and successful pregnancy[3,54]. Vascular Endothelial Growth Factor (VEGF) is expressed in endometrial stromal for proper implantation and attachment of blastocyst into uterus, as well as it is an expression in endothelial and glandular cells during the late proliferative phase of pregnancy. The receptor of VGEF is presented in microvessels, which contribute to the development of blastocyst and implantation[40,59].

Discussion

Nowadays, *Coronavirus* is the public health emergence. This positive-sense single-strand RNA virus is one of the beta-*Coronaviridea* family[26]. The disease's clinical manifestations appear after 5 to 6 days' incubation period followed by fever, fatigue, dyspnea, headache, and diarrhea. It accounts for third zoonotic disease following sever acute respiratory syndrome (SARS) and MERS viruses[2]. The clinical manifestation of disease is due to activation of immune response and secretion of various inflammatory cytokines and chemokines. Studies have shown that, serum levels of proinflammatory cytokines and chemokines such as IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL13, IL-17, M-CSF, G-CSF, GM-CSF, IP-10, IFN-γ, MCP-1, MIP 1-α, hepatocyte growth factor (HGF), TNF-α, and VEGF are increased due to the *Coronavirus* infection[11,12,36]. Several of these inflammatory cytokines activate and operate the JAK/STAT signaling pathway. IL-6 activates the JAK-STAT (IL-6/JAK/STAT) pathway, following the production of mediators and factors that play a role in regulating the body's immune system, oxidative responses, growth of lymphocytes, and differentiation[19,35,49]. The type of inflammatory cytokines produced against the implanted embryo determines the essence of the inflammatory or non-inflammatory response in successful implantation. So those Th-1 immune responses to Th-1 cause inflammation, whereas Th-2 immune responses cause non-inflammatory reactions and balanced the activation of Th-1/Th-2 leads to successful implantation[56].

One of the cellular signaling pathways that determine whether the immune response is inflammatory or non-inflammatory is the JAK/STAT pathway, and this signaling pathway plays an important role in regulating the immune response and cross-talk of cytokines[13,49]. One of the cytokines overexpressed in the *Coronavirus* is IL-6, in which all members of the IL-6 family activate the JAK/STAT3 pathway[13,52]. LIF is a member of the IL-6 family and is a determining factor for pregnancy. In humans, LIF has critical involvement in the embryo's attachment to the uterus and even stimulates embryo differentiation, proliferation, and invasion. Some studies have shown that in cases of infertility where abortion has occurred, the level of LIF expression in decreased. JAK/STAT pathway is activated through attachment of LIF to its receptor followed by phosphorylating STATs and translocation to the nucleus which promote the expression of many genes attributed in production of cytokines, signaling mediators, adhesion molecules, and angiogenesis. Therefore, it can be said that the

Coronavirus would not prevent embryo implantation at least by activating the JAK/STAT pathway. Although, in some cases, it has been suggested that activation of the JAK/STAT pathway by IL-6 may be the cause of abortion in cases of there is no reason for abortion[37,49,52]. This could be due to an over-response of the individual's immune system, followed by over-activation of this pathway, or genetic differences in individuals, that promote the different immune response against implanted embryo. Upregulation of VEGF is observed in *Coronavirus* infections and this factor is responsible for permeability and homeostasis of vascular endothelial. VEGF regulates maternal-fetal interaction and is associated with embryonic vasculogenic and embryo attachment to the uterus[40,59]. Accordingly, again, the VEGF upregulation due to *Coronavirus* could not intercept the attachment of embryo to the uterus. Although pregnant women are said to be more susceptible for *Coronavirus* infection, this is not true only for *Coronavirus* infection but also applies for other viral infections. This may be because pregnant women's immune systems are different and may develop a severe form of viral infection, which some of them may overproduce immune responses or some may overproduce repressive responses[55]. In pregnancy occurs immunological state that maternal immune is responsible for organizing and maintaining tolerance to the allogeneic embryo, on the other hand, it must also be able to protect against microbial infection. There is evidence for the role of systemic viral infections in the pregnancy process that can affect this process[27,41]. Also, it has been shown that women infected with the SARS virus during pregnancy, are associated with an increased risk of spontaneous abortion, premature birth, and intrauterine growth restriction[57]. Thus, these pregnancy problems may be created through the straight result of *Coronavirus* on mothers. A study by Hong Liu showed that, COVID-19 can modify immune responses at the maternal-fetal interface and maternal infection and inflammation created in reaction to this virus could impact on embryonic development[38]. Therefore, further studies using animal models and stem cells are needed to investigate the role of the Coronavirus in implantation and maintenance of pregnancy in pregnant mothers.

Conclusion

The main factor for a successful implantation is activation of inflammatory signaling pathway; therefore, the concern about risk of abortion in women infected with *Coronavirus* is increased nowadays. IL-6, TNF-α/β along with VGEF, LIF and other cytokines promotes the activation of JAK/STAT pathway which followed by secretion of other inflammatory cytokine and chemokines. The over expression of these cytokine and chemokines may render the probability of abortion and unsuccessful delivery. It should be considering that the manifestation of disease in pregnant women is not completely discovered and thus, further clinical trial and system biology-based studies are needed to confirm the relation between *Coronavirus* and implantation.

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Conflict of interest

The authors further declare that, they have no conflict of interest.

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