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Allogenic Stem Cell Transplantation and COVID-19 Antibodies: Mechanistic Insights and Recipient Concerns

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Abstract

Collecting umbilical cord stem cells is widely practiced due to its numerous benefits. Over the past decade, umbilical cord stem cells (UCSCs) have shown effectiveness in treating various conditions, such as bone pathologies, neuropsychiatry disorders, hereditary diseases, and metabolic disorders. However, factors like immunization affect the quantity and quality of cord harvesting. Studies suggest that antibodies from the mother pass through the umbilical cord to protect the infant against infections. Cleaning the umbilical cord before stem cell extraction is crucial to maintain sterility and cell integrity. Vaccinating a female donor, including for COVID-19, typically does not directly affect the stem cells. Although vaccines aim to trigger an immunological response, they generally do not affect the donor's stem cells.

Keywords

Vaccination, Stem Cell, Allogeneic, COVID, Antibodies

1. Introduction

In contemporary medicine, stem cell therapy has become a ground-breaking area that holds the promise of novel cures for a wide range of crippling illnesses. The umbilical cord Wharton's jelly has attracted a lot of attention among stem cell sources due to its potential to produce allogenic stem cells for application in

regenerative medicine. Because of their low immunogenicity and diverse differentiation potential, these special stem cells present a viable path for therapeutic uses, setting them apart from the more extensively researched hematopoietic stem cells found in cord blood [1]. In order to restore and mend damaged tissues or cells, stem cells have the capacity to differentiate and self-renew [2] [3]. Undifferentiated, unspecialized cells called stem cells can be found in the adult, fetal, and embryonic phases of development. The human body has stem cells in many different places, including the skin, adipose tissue, the placenta, the umbilical cord, bone and amniotic fluid [4]. Stem cell-based therapy has made use of several main stem cell types, including induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), embryonic stem cells (ESCs) and spermatogonial stem cells (SSCs) [5].

Vaccination, which offers vital defense against infectious diseases, has been one of public health's most outstanding successes. Vaccines have dramatically decreased mortality and morbidity linked to numerous illnesses by stimulating the immune system and equipping it to fight infectious agents [6]. Vaccination also plays a crucial role in safeguarding the health and well-being of pregnant individuals and their infants, offering protection against infectious diseases and reducing the risk of complications during pregnancy and childbirth. Some vaccines, such as those for influenza and pertussis, provide passive immunity to the newborn by transferring maternal antibodies across the placenta. This helps protect the newborn during the early months of life when they are too young to receive vaccines themselves [7]. As we all know one excellent source of stem cells is the human umbilical cord donated by the pregnant females, the importance of stem cells derived from umbilical cord tissue lies in their abundance, multipotency, immunomodulatory properties, low immunogenicity meaning they are less likely to provoke an immune response when transplanted into a recipient, and paracrine effects, all of which contribute to their therapeutic potential in stem cell therapy for various medical conditions and diseases [7].

Given that the human umbilical cord donated by pregnant individuals is an excellent source of stem cells, the importance of stem cells derived from umbilical cord tissue lies in their abundance, multipotency, immunomodulatory properties, low immunogenicity, and paracrine effects, all of which contribute to their therapeutic potential in treating various medical conditions and diseases. This raises an important query: what effects can vaccinations given to expectant mothers or those donating umbilical cord Wharton's jellies have on the characteristics and prospective uses of these remarkable allogenic stem cells?

In this study, we explore the critical issue of donor sample COVID-19 antibody status, focusing on donors who provide Wharton's jelly-derived umbilical cord stem cells. Understanding the presence and potency of antibodies in donor samples has become essential to ensuring the safety and effectiveness of stem cell therapies, especially in the context of the ongoing pandemic. Our objective is to offer a comprehensive understanding of the complex relationship among antibodies, donors, and future recipients, thereby adding significant value to the rapidly

evolving field of regenerative medicine during these extraordinary times.

2. The Human Umbilical Cord: A Potential Source of Human Umbilical Cord Mesenchymal Stem

Human umbilical cord mesenchymal stem cells (hUC-MSCs) are a valuable source of stem cells that can be obtained from umbilical cord tissue. Originating from the Wharton's jelly found in the umbilical cord, these cells have special abilities to both regenerate and modulate the immune system [1]. Because of their potential to cure a wide range of medical diseases, they have attracted a lot of attention in the field of regenerative medicine. In the field of stem cell treatment, we examine the hUC-MSCs' potential uses and capacities in this paper as a source of healing and hope. Multipotent mesenchymal stromal cells that are isolated from stromal tissues, mesenchymal stem cells have the capacity for multi-lineage differentiation, plastic adhesion, and self-renewal [8]. Mesenchymal stem cell (MSC) transplantation is often regarded as the most successful and efficient kind of cell treatment. Through the simultaneous stimulation of many pathways (trophic, paracrine, immunological regulation, and differentiation), these cells influence and improve all stages of wounded tissue regeneration [9] [10]. Human tissues such as amniotic fluid, bone marrow, amniotic membrane, dental tissues, endometrium, limb buds, peripheral blood, menstrual blood, fetal membrane and placenta, salivary gland, Wharton's jelly, sub-amniotic umbilical cord lining membrane, synovial fluid and skin and foreskin are among the many places in the body where MSCs are born [11]. Through paracrine actions which are currently thought to be the most important therapeutic mechanism and direct differentiation, MSCs offer therapeutic advantages [12]. Research suggests that MSCs' impact on cell signaling is greater than that of their inherent capacity for regeneration.

Additionally, the regeneration and repair of malfunctioning cells have been associated with cell signaling [13]. One excellent source of MSCs is the human umbilical cord. MSCs from the human umbilical cord can be extracted more swiftly and painlessly than bone marrow stem cells. MSCs have also been discovered in the umbilical cord's vascular tissue and Wharton jelly [1]. These cells have the same triple activity tissue healing, immune response control, and anti-cancer properties as bone marrow cells. hUC-MSCs can serve as a source of nourishment for other pluripotent or embryonic stem cells [14]. It is possible to get UC-MSCs in a non-invasive, morally acceptable manner, and after expansion, UC-MSCs can be produced in enormous quantities. Two umbilical arteries (UCAs) and one umbilical vein (UCV) make up the umbilical cord (UC), which is coated in amniotic epithelium and contains a particular mucous connective tissue called Wharton's jelly (WJ) [1] [15] [16].

Umbilical cord blood (UC-MSCs), Wharton's jelly (WJ-MSCs), or human umbilical cord perivascular stem cells (HUCPVCs) can all be used to generate hUC-MSCs. Despite being frequently disposed of as medical trash upon delivery, umbilical cords and UC blood (UCB/UC) are significant sources of stem cells

[17]. From UCB, at least three different types of stem cells have been identified: mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and endothelial progenitor cells. Multiple umbilical cord compartments have been found to contain MSCs. The perivascular zone, subamnion, and intervascular location of the umbilical vein subendothelium are where MSCs have been isolated from umbilical cord blood UC-MSCs provide several advantages over other MSC sources, including high abundance, off-the-shelf use, and minimally invasive retrieval [18]. Considering there are benefits to storing stem cells in human umbilical cord/blood, this treatment is still widely used. In the past ten years, studies have shown that the umbilical cord has therapeutic promise for treating genetic disorders involving metabolism and deficiencies related to bone. Umbilical cord stem cells have a larger donor pool and allow for the use of partially HLA-matched UCB units since they do not require perfect HLA matching like stem cells obtained through other methods. Compared to recipients of unrelated matched donor marrow or family member marrow allograft, the risk of developing an acute and severe graft-versus-host disease is significantly reduced in the event of cell donation in unrelated recipients. Furthermore, UCB is extensively evaluated before being stored, and it has the benefit of being immediately usable without requiring direct donor involvement [19].

3. COVID-19 Antibodies and hUC-MSCs Receipts

Following the worldwide COVID-19 epidemic, there have been unparalleled transformations in the field of medical study and therapy. Since vaccinations have been widely available, individuals and healthcare providers alike are more conscious of the value of immunity. In the field of stem cell therapy, this knowledge is especially important. As we learn more about the potential of stem cells produced from umbilical cord Wharton's jelly, recipients are becoming increasingly concerned. Amidst the pandemic, those who may benefit from stem cell therapies are intrigued by the cells' capacity for regeneration and are also highly apprehensive about the presence of COVID-19 antibodies in the donor samples [20]. The important relationship between immunity, stem cell therapy, and vaccination has been highlighted by this worry. To fully utilize these exceptional stem cells' therapeutic potential, it is imperative to comprehend the unique characteristics of donors' immunological responses, particularly considering continuing health crises. The intersection of stem cell research and vaccine initiatives becomes increasingly important in this dynamic medical landscape, highlighting the necessity for integrated approaches that take both regenerative medicine and immunization strategies into account. One common concern among patients receiving hUC-MSC therapy is the presence of COVID-19 antibodies in the given sample. This issue highlights the critical relationship between immunological markers and therapeutic use, hence highlighting the urgent necessity for thorough scientific clarification about the human umbilical cord mesenchymal stem cell therapies. It is important to address the recipient's concerns, particularly if they

have preferences or views about the use of these antibodies. Examining the complex processes behind the impact of COVID-19 antibodies in patients receiving human umbilical cord mesenchymal stem cell (hUC-MSC) therapy is essential to fully addressing the relevant concern regarding antibody status. This thorough examination provides the necessary groundwork for a sophisticated comprehension of the immune environment and how it directly affects hUC-MSC therapeutic approaches.

4. Vaccination Status in Donors of Umbilical Cord Wharton's Jelly-Derived Stem Cells: A Critical Examination

The most efficient and economical method of illness prevention is vaccination. In many nations, it has resulted in the control of illnesses like whooping cough and polio as well as the elimination of diseases like smallpox. Vaccines can be divided into numerous categories like live, attenuated vaccines, Inactivated vaccines, Subunit vaccines, Recombinant vector vaccines, Conjugate vaccines, and mRNA vaccines, which are either being developed or are now being used to prevent infectious diseases. In the ideal situation, vaccinations would activate both the innate and adaptive immune systems [21]. The initial line of defense against pathogenic agents is the innate immune system, also known as general resistance, which consists of several defensive mechanisms that are always in place. Unlike the innate immune system, the adaptive immune system targets a specific pathogenic agent specifically. Compared to the natural response, this one will take longer to manifest. The innate and acquired immune systems work together to produce antibodies (categorized into five isotypes: IgM, IgD, IgG (The only type of antibodies that crosses the human placenta significantly), IgA, and IgE), which are unique proteins that shield your body from certain invaders [22]. The function of immunization in donors of umbilical cord blood-derived stem cells is slightly different from that of Wharton's jelly-derived stem cells. Unlike the hematopoietic stem cells HSCs present in cord blood, Wharton's jelly-derived stem cells are derived from a particular area of the umbilical cord known as Wharton's jelly. Compared to stem cells generated from cord blood, these stem cells are less associated with the immune system. Stem cells derived from Wharton's jelly generally exhibit low immunogenicity. This means that they are less likely to trigger an immune response when transplanted into a recipient. Wharton's jelly-derived mesenchymal stem cells (MSCs) express low levels of major histocompatibility complex (MHC) class I molecules and lack expression of MHC class II molecules, which are involved in immune recognition and rejection. Additionally, they possess immunomodulatory properties that help suppress immune responses and promote immune tolerance. However, like all allogeneic cell therapies, there is still a possibility of immune rejection, particularly in individuals with pre-existing sensitivities or incompatibilities. Overall, Wharton's jelly-derived stem cells are considered promising candidates for allogeneic transplantation due to their favorable immunological profile.

The type of stem cell transplantation determines how much the immune system is weakened. Immune system compromise is an essential step in the HSCT (hematopoietic stem cell transplant) process since rejection and Graft-versus-host disease (GVHD-disease that arises from the graft's immune cells attacking the recipient's body cells because they believe the host to be foreign) must be avoided [23].

In Wharton's jelly stem cell transplantation, the immune system is not significantly compromised, as the primary objective is to utilize the unique properties of the mesenchymal stem cells without triggering significant immune responses [24] [25].

5. The Mechanism of Action of the COVID-19 Vaccine in the Body of UC-MSCs Donor

There are 26 - 28 proteins in the SARS-CoV-2, but only one mRNA is generated. The researchers separated the mRNA from the spike protein, which has three copies of the same protein [26]. In addition, the mRNA is contained in a lipid particle, which protects it from damage and prevents it from being mistaken for other RNA molecules. Adjuvants or preservatives are not used in COVID-19 vaccines because the vaccine stimulates itself. This nanoparticle enters the body through the injection of intramuscular injections. After attaching itself to the host cells, it inserts its mRNA into the cytoplasm, not the nucleus, so that the ribosomes can use it to synthesize the viral spike proteins [27]. The first stage that follows is the professional antigen-presenting cells' (APCs) uptake. The vaccine's components can be transported by APCs to secondary lymphoid organs, where they are presented to T- and B-lymphocytes. In the correct circumstances, this causes these lymphocytes to become activated (**Figure 1**). This protein stimulates local innate immunological responses, including the release of proinflammatory cytokines by macrophages, such as IL-2, IL-4, and IL5 [28]. This gives rise to a warning signal that facilitates dendritic cell development. Dendritic cells or macrophages absorb the antigen. Following their activation, dendritic cells go to local lymph nodes and deliver the processed antigen and major histocompatibility complex (MHC) molecules there. CD4+ T cells are exposed to inactivated vaccines in the presence of MHC class II molecules. By using their unique T cell receptors, T cells can identify the MHC/antigen complex. As a result, T cells get activated, effector T cell clones proliferate, and long-lived memory T cells the epitome of adaptive immunity form. Naive, antigen-inexperienced T cells are activated upon primary exposure to an antigen. After receiving a booster shot, preexisting memory T cells identify dendritic cells loaded with antigen, grow quickly, and develop into effector T cells, resulting in a more powerful and quick memory response. After coming into touch with their antigens, CD4+ T helper cells drive B cells to become memory B cells and antibody-secreting B cells, which then go to the periphery. These B cells have experienced "heavy-chain isotype switching", or recombination events that enable the generation of IgG rather

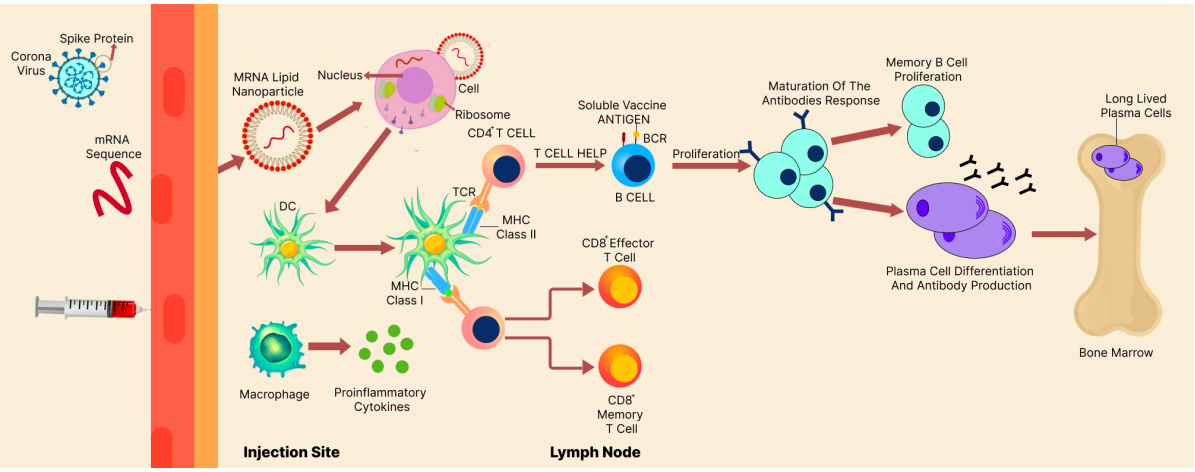

Figure 1. The immunological reaction that occurs after being immunized against the vaccine is injected into the muscle. The mRNA from the SARS-CoV-2 virus that can translate and codify for the virus's surface spike proteins is extracted and added to a lipid nanoparticle, The human body is administered this vaccination (nanoparticle) intramuscularly. It attaches itself to the host cell and then travels to the cytoplasm to insert its mRNA in order to reach the ribosomes and produce the viral spike proteins, the protein antigen is picked up by dendritic cells. These cells are then trafficked to the draining lymph node by pattern recognition receptors (PRRs), which are triggered by danger signals in the adjuvant. Here, T cells are activated via their T cell receptor (TCR) by the presentation of vaccine protein antigen peptides by MHC molecules on the dendritic cell. The T cells stimulate B cell growth in the lymph node in conjunction with signaling (by soluble antigen) via the B cell receptor (BCR). Here, the growth of B cells that are dependent on T cells causes the antibody response to mature, resulting in an increase in antibody affinity and the induction of various isotypes of antibodies. Over the following two weeks, there is a sharp increase in serum antibody levels due to the generation of short-lived plasma cells, which actively manufacture antibodies specific for the vaccination protein. Additionally, memory B cells—which facilitate immunological memory—are generated. Long-lived plasma cells settle in bone marrow niches where they can make antibodies for decades on end. When faced with a pathogen, CD8+ memory T cells can multiply quickly, and CD8+ effector T cells are crucial for getting rid of infected cells.

than IgM antibodies. A portion of these B cells go on to become bone marrow-resident, long-lived plasma cells. Antibodies travel via the bloodstream and settle on the mucosa, where they attach themselves to pathogens to stop them from invading host cells and to help phagocytes recognize them. Memory B cells have the same ability to mount quick and potent responses to subsequent immunization as memory T cells do.

6. Antibody Transfer Mechanism: Placental vs Umbilical Cord Routes

The transplacental pathway is the main way that antibodies (Abs) are passed from human mothers to their offspring. There is minimal transfer of IgM, IgA, or IgE and preferential transmission of the Abs subtype, IgG1. The placenta is a complicated structure made up of several cell types and layers that use regulated transport systems; it is not just a basic permeable membrane. Abs is not just transferred across the placental barrier by passive diffusion or leaking. Fc receptors (FcRs) are involved in active transport, which facilitates transfer. In addition to other proteins that bind Abs, the placenta contains several known FcRs. The human homologue of neonatal rat FcR (FcRn), a heterodimer with pH-dependent

IgG affinity and structural similarity to major histocompatibility complex (MHC) class I molecules, is likely the most significant factor in Ab transfer. Human FcRn heterodimer in the placenta distributes IgG to the developing foetus, most likely by means of a pH gradient that carries maternal IgG from acidic endosomes to the pH-neutral basolateral surface of the syncytiotrophoblast, and potentially even across the endothelium of the foetal blood vessel. Through its regulation of IgG transport and catabolism, the FcRn most likely plays a broad role in the regulation of IgG concentrations in tissue and serum [29]. Maternal Abs against fetal Ags that are eliminated as immune complexes may also be cleared by other IgG-binding FcRs, such as FcηRI, FcηRII, and FcηRIII on Hofbauer cells in the stroma and FcηRII on endothelial cells [30] (**Figure 2(a)**). Human breast milk is another source of Abs transfer. The polymeric immunoglobulin receptor trancytoses a significant amount of Abs, particularly secretory IgA molecules, into breast milk [31].

7. Does COVID-19 Vaccine-Induced Immunity Differ from Its Infection-Induced Immunity in UC-MSCs Donors?

Natural immunity and vaccination immunity have many similarities, yet they can sometimes occasionally differ. For instance, IgM antibodies are typically produced initially in response to an infection or vaccination with a live virus, followed by IgG and certain other types of antibodies. Furthermore, vaccination does not immediately confer protective immunity, unlike an infection acquired naturally. Your immune system forms the necessary B cell populations and antibodies over the course of a few weeks. That's why immunizations don't immediately provide complete protection. The majority of the time vaccinations produce antibodies that are identical to those that would result from a spontaneous illness. One distinction is that certain vaccines only present the portion of the relevant virus that the immune system can recognize. As a result, the immune system doesn't produce as many distinct kinds of antibodies as it would during an infection that occurs naturally. This does not imply, however, that the antibodies produced are any less potent than those produced during a spontaneous infection. Simply put, a naturally occurring infection may also result in extra antibodies, many of which may be useless. To create a vaccine, scientists meticulously choose a certain portion of the virus that has been demonstrated in laboratory experiments to elicit an antibody response that successfully neutralizes the virus [32].

8. Does Vaccination Impact the Collection of MSCs from Wharton's Jelly?

Vaccination is essential for lowering morbidity and death in patients with immunocompromised stem cell transplants. Studies have demonstrated encouraging outcomes when immunizations are given prior to transplantation to both donors and recipients. Infections are responsible for 13% to 21% of mortality following allogeneic HSCT and 7% after autologous HSCT. This means that

prophylaxis must be used, vigilance must be maintained, and evidence-based immunization guidelines must be upheld [33]. While posttransplant immunizations have received more attention in the past ten years, studies regarding the effectiveness of pretransplant vaccinations also exist. There is currently proof that immunizing donors and recipients prior to hematopoietic stem cell transplantation (HSCT) can greatly increase immunogenic T and B cell responses when patients are revaccinated following the procedure. Early post-transplant responses are caused by improved immunogenic protein vaccines and protein-polysaccharide conjugate vaccines. Avoiding polysaccharides and antigens of low immunogenicity proteins is advised [34]. The current reason why HSCT donors are not immunized is because donor immunization is sometimes impractical, there are few long-term safety data on vaccination in donors, and there are no obvious advantages for HSCT recipients of immunized donors [35] [36].

A 2022 study assessed the safety and efficacy of the mRNA SARS-CoV-2 immunization during pregnancy, as well as the degree of protection that the placental transfer of antibodies offered to the fetus. A group of twenty people who had late-pregnancy vaccinations were examined for the transplacental transfer of functional anti-SARS-CoV-2 antibodies and mRNA vaccine products during pregnancy and the early stages of infancy. Placenta tissue, cord blood, and maternal blood that were available at delivery were all analyzed for this reason. When the mother delivers, there is no sign of mRNA vaccination products in her blood, placenta tissue, or cord blood. On the other hand, we discover that early infancy is characterized by a time-dependent, effective transmission of neutralizing antibodies and IgG to the newborn. Furthermore, it was discovered that a vaccine-specific signature of SARS-CoV-2 Spike protein epitope binding in phage immunoprecipitation sequencing, which is transplacentally conveyed during pregnancy. To guarantee the transplacental transmission of protective antibodies throughout the early stages of infancy, immunization timing during pregnancy is essential [6] [37]. In conclusion, this research shows that mRNA vaccination is safe to receive during pregnancy and that it produces functional, time-dependent protective antibody responses in both women and their unborn children that last into the early stages of infancy. Such proof, however, will require in-depth research on the transplacental transfer of vaccine components as well as vaccine-related antibody dynamics, functional characteristics, and durability during infancy of transferred SARS-CoV-2 antibodies. To fully comprehend the variations in antibody production and function following vaccination and infection during pregnancy, more research is required.

9. Discussion

The global medical system has been greatly impacted by vaccination in pandemic situations, and several nations have put in place specialized emergency response plans. The process of obtaining umbilical cord and cord blood for the purpose of storing stem cells is still widely accepted because of its benefits. The effectiveness of using stem cells produced from the umbilical cord as a therapeu-

tic agent has been demonstrated, especially when treating bone-related deficiencies and metabolic genetic diseases. Simultaneously, recipients' worries have increased due to the growing use of human umbilical cord mesenchymal stem cells (hUCMSCs) in stem cell therapy, specifically with reference to the samples' COVID-19 antibody status. These concerns are frequently the result of personal opinions about the COVID-19 vaccination. In light of the lack of information on the aforementioned topic, our goal is to perform a comprehensive and critical analysis of this problem.

According to the Leclerc 2022 study, immunosuppressive medication use and a delay in B-cell recovery may modify the humoral response following HSCT vaccination. About 40% of allogeneic HSCT recipients have been found to have a limited immune response following two doses of the mRNA vaccine against SARS-CoV-2. However, a third early vaccination dosage has been demonstrated to positively affect humoral response in this subgroup of recipients who are not responding well [38] [39]. It was addressed whether pre-HSCT vaccination of donors has an impact on humoral response to early post-HSCT vaccination of recipients, at a time when they were still receiving immunosuppressive drugs. The cytomegalovirus (CMV) is a good example of how donor-natural immunization against pathogens can have an impact. Recipients who receive their hematopoietic stem cell transplant (HSCT) from a seropositive donor—provided they are seropositive themselves—benefit overall from protection against CMV re-activation when compared to recipients who receive their HSCT from a naive donor [40]. Therefore, a crucial component of the donor selection process is the donor's CMV serological status. In addition to natural immunity, also known as post-infectious immunity, the transfer of donor vaccine-induced immunity has been proposed in the past for a number of bacterial and viral diseases, including hepatitis B virus, Haemophilusinfluenzae type B, tetanus, diphtheria, and seven other viruses [41]. For Streptococcus pneumoniae or influenza, this was not the case. Given that polysaccharide antigens conjugated with proteins have been shown to be more immunogenic than polysaccharide antigens alone in hematopoietic stem cell recipients, these disparities may, at least in part, be explained by the structure and makeup of the relevant vaccination [42]. To our knowledge, no research has been done on the effect of mRNA vaccines on the immunological response during post-HSCT, despite their recent introduction.

Therefore, the post-SCT humoral response to early SARS-CoV-2 mRNA vaccination following SCT is influenced by pre-SCT donor vaccination. While additional validation is necessary, the findings justify the inclusion of a donor's serological status against SARS-CoV-2 in the donor selection algorithm and, if possible, the induction of donor immunization prior to donation. Every recipient of a stem cell transplant should, in our opinion, receive prompt and effective vaccinations. After looking through the literature, it was discovered that neutralizing antibody titers in the umbilical cord were determined to be lower than those in the mother's serum. Two papers about the placental transfer of vaccine-induced antibodies were found in the literature [43]. Nonetheless, following vaccination

against tetanus, pertussis, diphtheria, and the flu, it is typical to detect vaccine-induced IgG in the fetal serum due to a transfer across the placenta [41]. It is concerning that the mRNA vaccine against SARS-CoV-2 causes antibodies to build in mother serum, although it is still unknown if these antibodies are transferred from the mother to the fetus. Spike protein-specific antibodies and neutralizing anti-S IgG antibodies are produced by the mRNA COVID-19 vaccination, which also produces protective immunity [40]. Ten pregnant women who received vaccinations had all of their umbilical cord blood tested positive for vaccine-generated antibodies, according to a prospective cohort research that was published in March 2021 [44]. Another similar study, concerning that maternal IgG can pass across the placenta and provide the baby immunity. To determine the best timing for immunization to have the placental immunological transfer, there is not enough information available [27]. Thus, if a female donor donates her umbilical cord after receiving a COVID-19 immunization or any other vaccination, it shouldn't have an immediate impact on the cord, or the stem cells derived from it. Although the goal of the COVID-19 vaccination is to elicit an immunological response in the recipient, the vaccine's constituents normally do not enter the umbilical cord or impact its stem cells (**Figure 2**). Given that Wharton's jelly stem cell transplantation focuses on the stem cells' regenerative qualities and their low immunogenicity, the information presented above indicates that immunization is unlikely to have an impact on the procedure.

On the other hand, immunization is more likely to influence hematopoietic

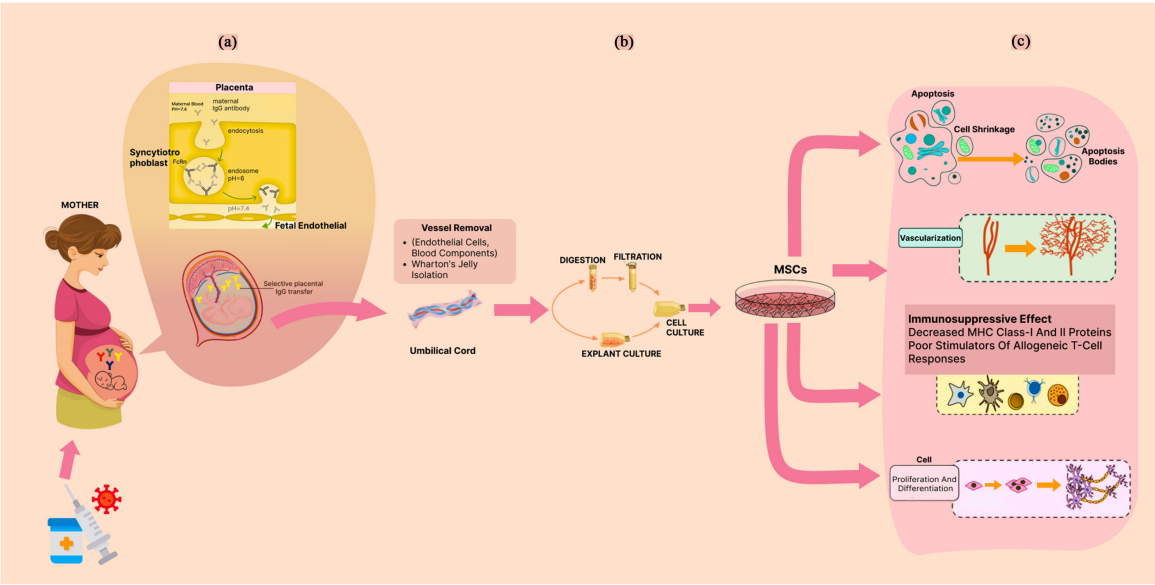

Figure 2. Illustration of how an umbilical cord is taken from a vaccinated mother and processed to derive stem cells from it. (a) How antibodies are transferred through the placenta and breast tissue. Top: The syncytiotrophoblast cell absorbs circulating IgG antibody, and two IgG molecules per FcRn bind to the acidic endosome's inner membrane. Because of the elevated pH, FcRn releases the IgG molecules upon the opening of the endosome at the basolateral side of the cell facing the fetal circulation and can then be recycled to carry out another transport cycle. (b) The procedures for processing umbilical cord tissue. (c) Properties of Mesenchymal stem cells.

stem cell transplantation (HSCT), particularly in cases where immunosuppression is used to treat GVHD. The type of stem cells used, and the unique immunological factors associated with each type of transplantation are crucial. Therefore, antibodies from the mother do pass from the mother to the infant through a variety of pathways, including the umbilical cord and blood flowing through it, protecting the newborn from infections. However, cleaning an umbilical cord before processing it for stem cell extraction is a delicate process that needs strict adherence to standards to maintain the sterility and integrity of the stem cells. A female's immune system produces antibodies and immunological responses to the viral components in the COVID-19 vaccine when she gets it. Usually confined to the immune system, these reactions have no direct effect on other body parts, such as the umbilical cord. An umbilical cord must be thoroughly cleaned and purified before stem cells can be extracted and processed to get rid of any potentially dangerous materials, such as proteins and antibodies. The goal of this purification procedure is to produce the purest, most uncontaminated stem cells possible. It is noteworthy that the advantages of using umbilical cord stem cells, particularly in the context of regenerative medicine or transplantation, include their relative naivete and absence of prior exposure to environmental variables and disease. Because of this quality, they may be useful in therapeutic settings.

To address recipients' concerns about the impact of donor vaccination on the compatibility and effectiveness of umbilical cord stem cells, several measures can be implemented.

In conclusion, to address the concern of recipients about the immune response elicited by vaccination in the donor affecting the compatibility and effectiveness of the stem cells, several measures can be taken: *Thorough Purification Processes:* Ensure that the umbilical cord stem cells undergo rigorous purification processes to remove any potential contaminants, including vaccine-related antibodies or immune cells. This can reassure recipients that the stem cells are pure and free from unwanted immune components. *Detailed Information and Transparency:* Provide recipients with comprehensive information about the purification and quality control measures in place. Transparency about the steps taken to ensure the safety and purity of the stem cells can help alleviate concerns. *Scientific Evidence and Research:* Present recipients with scientific evidence and research findings that demonstrate the safety and efficacy of umbilical cord stem cells from vaccinated donors. Highlight studies showing that vaccination does not adversely affect the stem cells' therapeutic potential or compatibility. *Quality Assurance and Regulatory Standards:* Emphasize adherence to stringent quality assurance and regulatory standards that govern the collection, processing, and transplantation of umbilical cord stem cells. Assurance from regulatory bodies can provide additional confidence to recipients. *Clinical Monitoring and Follow-Up*: Implement robust clinical monitoring and follow-up protocols for recipients of umbilical cord stem cells. By closely monitoring recipients for any adverse reactions or complications, healthcare providers can quickly address any concerns and en-

sure the treatment's safety. *Education and Counseling:* Offer educational sessions and counseling to recipients to address their concerns and provide them with a better understanding of the science behind stem cell therapy and vaccination. Educating recipients about the body's immune response and the thorough processes in place can help mitigate fears. *Individualized Risk Assessment:* Conduct individualized risk assessments for recipients to evaluate any potential risks based on their specific medical history and condition. Personalized assessments can help tailor the information and reassurance provided to each recipient. By implementing these measures, healthcare providers can effectively address the concerns of recipients and enhance their confidence in the safety and efficacy of umbilical cord stem cell therapy.

Hence, vaccination against several illnesses prior to umbilical cord blood donation is typically seen as a favorable aspect. It can give useful stem cells for transplantation without significantly raising the recipient's chance of developing immune-related problems. The quality of the cord blood unit, which is carefully examined prior to transplantation, and the recipient's compatibility are two important elements that determine whether a cord blood donation is appropriate.

10. Concluding Remarks

Vaccination is crucial for females donating umbilical cord blood for stem cells as it reduces the risk of transmitting infectious diseases to the newborn and subsequently to the collected cord blood. By minimizing the presence of infectious agents and antibodies, vaccination helps preserve the quality and purity of the cord blood, ensuring its suitability for therapeutic transplantation. Additionally, vaccinated donors protect recipients from vaccine-preventable diseases, enhancing the safety and efficacy of stem cell transplantation procedures. Overall, vaccination plays a vital role in safeguarding the health of both donors and recipients involved in stem cell therapy. Prior to the extraction and processing of stem cells from the umbilical cord, thorough cleaning and purification procedures are essential to eliminate any potential contaminants, such as proteins and antibodies. This purification process aims to yield the purest and most uncontaminated stem cells possible. In the future, ensuring the availability of high-quality umbilical cord blood for stem cell transplantation can be achieved through strategic vaccination programs. By educating pregnant individuals, integrating vaccination into prenatal care, ensuring access to vaccines, collaborating with public health initiatives, and advancing research, we can maximize vaccination coverage rates and optimize the safety and efficacy of stem cell therapies. This approach aims to promote widespread acceptance of vaccination during pregnancy, ultimately benefiting patients in need of life-saving stem cell treatments.

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Authors' Contributions

AUK wrote and conceptually designed the manuscript. AUK revised and edited the manuscript. NK revised the draft and supervised the team. DLG reviewed and revised the draft. SS and UEH assisted in the material collection of the draft.

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Availability of Data and Materials

All the data and material of this manuscript will be accessible to the readers.

Conflicts of Interest

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