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REVIEW
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Progression Course in the Birth Parturition Waste Materials Toward Application in Tissue Engineering-Based Approaches

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ABSTRACT

Today, the biological waste products produced during gestation and after childbirth, referred to as postpartum waste materials attracted the attention of scientists in different subjects of tissue engineering. As the goal of tissue engineering is to develop biological substitutes that can repair or replace damaged tissues and organs in the human body, the application of these waste materials after childbirth has become popular to achieve these goals, resulting from their positive aspects, such as having a valuable source of cells. In this review, we attempted to introduce the structural aspects and application of these waste materials in this emerging science.

Keywords: Postpartum Umbilical Cord • Amniotic Membrane • Placental • Tissue Engineering

INTRODUCTION

Researchers have looked into the potential use of postpartum waste materials as valuable sources of cells and natural-based biomaterials for tissue engineering applications [1]. These tissues are just there to sustain the fetus until it is born. Thus, they are temporary [2]. Because fetal tissues have unique qualities and are readily available as raw materials, they are of tremendous interest in medicine, particularly as a biomaterial in the field of tissue engineering and regenerative medicine.

Over the years, repairing or reconstructing damaged tissues or organs and restoring their function has been unattainable hopes that have led researchers to find a solution, and in this effort, the concept of tissue engineering has blossomed the promise to achieve this goal [3]. Tissue engineering, which is a multidisciplinary field that combines biology, engineering, and medicine to create functional tissues and organs in the laboratory, aims to develop biological substitutes that can repair or replace damaged tissues and organs in the human

body Figure 1 [1,4]. For example, tissue engineering-based scaffolds are a viable alternative for treating bone injuries. By combining a scaffold, cells, and growth factors, tissue-engineered implants would reduce the need for multiple surgeries associated with the removal of metallic stabilizers and graft harvesting used for treating bone [5]. The concept of regenerative medicine combining tissue engineering with other strategies, including cell-based therapy, gene therapy, and immunomodulation, to yield *in vivo* tissue regeneration/organ is a testament to its association with tissue engineering that subsequently the integration of two concepts created the term tissue engineering and regenerative medicine (TERM) [6].

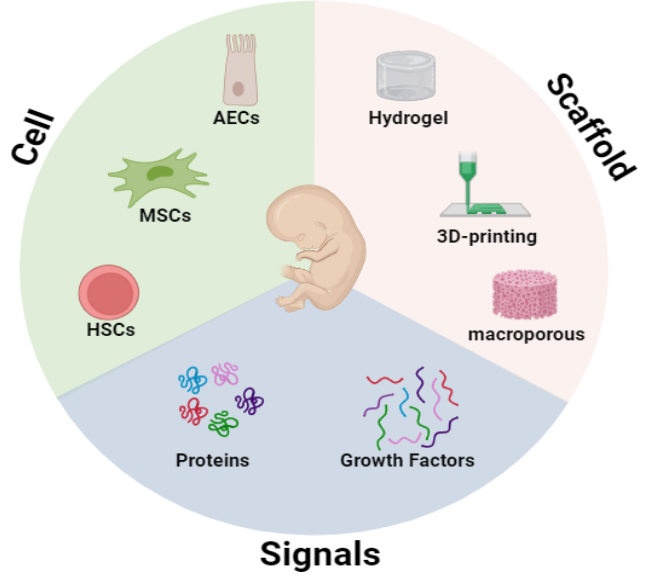

Figure 1: *The triad of tissue engineering.*

During the progressive course of tissue engineering, biomaterials play a critical role [1]. Additionally, the cell as another element of the triad of tissue engineering is appealing. Among different kinds of cells, stem cell-based tissue engineering has attracted a great deal of attention due to its potential to transform medicine and its ability to restore injured and diseased tissues [7,8]. Many synthetic materials are used in this field, but the interest of scientists in natural-based materials is noteworthy. In this way, the biological waste products, which are produced during gestation and after childbirth under the term of postpartum waste materials (the amniotic membrane, placental disk, umbilical cord, and chorion membrane (Figure 2), which are utilized in tissue engineering provides a valuable source of cells and biomaterials. The significant importance of these waste materials is related to the fact that these waste materials after childbirth provide a novel avenue to achieve the goals of TERM, resulting from their positive aspects in different aspects of this emerging science. In addition, they offer a sustainable and ethical approach by repurposing materials that would otherwise be discarded. For example, the placenta has a variety of cells with the ability to regenerate, including mesenchymal stem cells, which can differentiate into several cell types [9]. Since the lack of tissue donors for transplantation is the chief challenge, resulting from the unwillingness of donor individuals and the risk of severe immune responses that lead to graft rejection, using these waste materials can be a promising approach in tissue engineering and regenerative medicine. Unlike obtaining the donation tissue from cadaveric or fetal tissue, these tissues are post-partum obtained from healthy

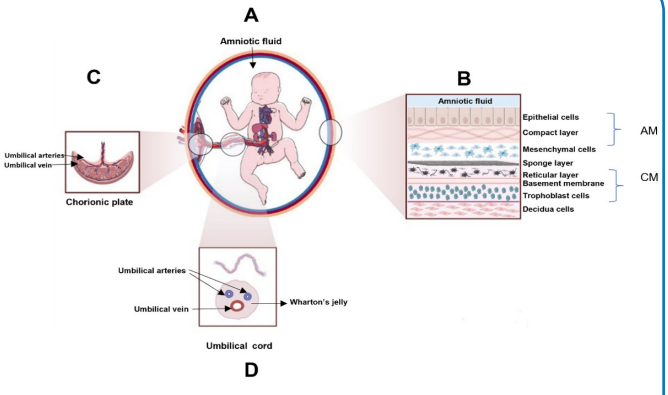

Figure 2: *(A). The whole fetus with different post-partum waste materials floating in the amniotic fluid; (B). The placental membrane layers contain three layers: amniotic membrane, sponge layer, and chorion membrane; (C). The chorionic plate; (D). The umbilical cord contains two umbilical arteries, an umbilical vein, and Wharton's jelly.*

individuals who willingly donate them. These tissues are typically classified as medical waste and can be collected without causing any harm to the donor or the fetus, thereby minimizing ethical and legal concerns [2].

Some of these waste materials originate from Placental Membranes (PM). Placental membranes are composed of a fetal component and a maternal component [10]. Fetal membranes have two layers: the outer and the inner layers, which separate the fetus from the endometrium [10]. The former and latter are called chorion and Amniotic Membrane (AM), respectively. Despite their tight adherence, the amniotic and chorionic layers of the placental membrane do not blend and maintain distinct histological characteristics [11].

Some works of literature mentioned that PM consists of three primary layers: the amnion, which faces the fetus, the chorion, which faces the mother, and an intermediate

layer that lies between them [12]. The intermediate layer, composed of a sponge-like network of collagens and proteoglycans, serves as a physical barrier between the amnion and chorion. The arrangement of this particular layer facilitates the motion of the amnion over the chorion by benefiting from the abundant presence of Hyaluronic Acid (HA), which serves to moisturize and provide lubrication to the tissue [13]. There is a mixture of collagens, laminin, fibronectin, HA, vitronectin, elastin, and proteoglycans in the PM, but each layer of the PM has a distinct structural composition tailored to its specific function [14-15]. While the ECM of the amnion contains collagens(types I, III, IV, V, and VI), elastin, fibronectin, laminin, HA, and sulfated proteoglycans; the chorion ECM consists of collagens(types I, III, IV, V, and VI), elastin, fibronectin, laminin, and HA [15]. In contrast, the intermediate layer is composed of collagen types I, III, and IV, sulfated proteoglycans, and glycoproteins.

In addition to the unique biological properties of perinatal-derived biomaterials, such as their immunological privilege, anti-inflammatory, anti-microbial, and antigenicity, these tissues are used for innovative purposes in various medical specialties [16]. In 1910, Davis, at Johns Hopkins Hospital, pioneered the utilization of perinatal-derived biomaterials to promote the healing of skin wounds. The scope of these biomaterials' clinical and research uses has expanded recently to encompass roles in tissue engineering, regenerative medicine, and cell-based therapies [17].

Overall, exploring postpartum waste materials in tissue engineering represents an exciting avenue for research and innovation, with the potential to contribute to advancements in regenerative medicine and improve patient outcomes in the future. Here, we review and discuss the advances in the use of these tissues in the exciting field of tissue engineering and regenerative medicine.

LITERATURE REVIEW

A Glance at General Structural and Functional Aspects of these Post-Partum Waste Materials

Placental Disk

The typical perception of the human placenta is that it is a form of biological refuse. However, it is consistently obtainable from births that reach full-term, and it also serves as a reservoir of mesenchymal stem cells, growth factors, and proteins found in the extracellular matrix [18,19].

The placental disc is an essential component of the placenta, the organ that develops in the uterus during pregnancy. The placenta, named after its disc-like shape, is the primary connection between the mother and the developing fetus [19]. The design facilitates optimal surface area for efficient exchange of nutrients and oxygen from the mother to the fetus, while also facilitating the elimination of waste materials [9]. The mature placenta, weighing about 500 gm, is in a disk-shaped form and has a thickness and diameter of 3 cm and about 20 cm, respectively [20]. The placenta has two distinct sides: the maternal and fetal sides. The former, which adheres to the uterine wall, is dull and comprises as many as 35 lobes and grooves. Grooves are distances among these lobes, and placental septa are located within grooves among distances of these lobes. Several cotyledons with main stem villus and branches have been located within a placental lobe.

Additionally, the intervillous space in each lobe represents a nearly isolated compartment of the maternal circulation to the placenta [20]. The latter (fetal side), being shiny due to the amniotic membrane is linked to the baby by the umbilical cord. Nutrient and waste transfer between maternal and fetal blood occurs through the villi, which are fetal placental structures characterized by tiny and finger-like projections [19,21]. Following the baby's birth, the placental disc is discharged from the uterus during the last phase of labor. The removal of the placenta is an essential and inherent procedure, as it has served its purpose with the delivery of the infant, and its extraction is important to prevent any difficulties after childbirth [19,22]. The placental disc is abundantly supplied with blood arteries, specifically fetal blood vessels extending from the umbilical cord and interweaving with the villi [23]. These villi are tiny, finger-like projections that enhance the surface area available for exchange.

In contrast, the maternal blood is transported to the intervillous area, which surrounds and nourishes the villi [11]. Oxygen and nutrients, including glucose, amino acids, vitamins, and minerals, passively flow from the maternal blood supply into the fetal arteries. At the same time, carbon dioxide and waste products undergo movement in the reverse direction [22,24,25]. In addition to facilitating the transmission of nutrients, the placental disc also serves as a highly active endocrine organ, secreting hormones such as hCG, estrogen, and progesterone. These hormones are essential since they sustain the pregnancy by preserving the uterine lining, promoting fetal growth, and preparing the body for labor [26-28]. The placental disc also affects the immune system [29], resulting from the generation of neurokinin B, which helps regulate the maternal immune system and prevents the mother from rejecting the genetically distinct fetus [30].

The placenta has a specified Extracellular Matrix

(ECM) like other adult tissue. The placenta's ECM is not a static entity but a dynamic and flexible component of the placental organ. It plays a crucial function in facilitating the interchange of gasses and nutrients, supporting the growth of the fetus, and permitting the necessary adjustments for a successful pregnancy [31]. The placental disc's ECM plays a vital role by providing mechanical support and enabling various necessary physiological processes for the growth and well-being of the growing embryo [32]. This ECM has specialized aspects associated with the placenta like other ECM. Collagen, elastin, fibronectin, laminins, and proteoglycans are its components in addition to other components. Collagens serve as the main structural framework in the ECM, providing it with the ability to withstand tension [33]. In addition to collagen, elastin is one of the structural elements that provides the placental tissues with the required resilience and flexibility [34]. It enables the tissues to stretch and bounce back, which becomes more crucial as the placenta grows with the fetus [35]. Fibronectin, a versatile glycoprotein found in the extracellular matrix, interacts with integrins on the cell surface, regulating several cellular processes such as adhesion, proliferation, and migration [36]. These interactions play a crucial role in the invasion of trophoblasts and the general maintenance of placental integrity [2]. Laminins, which are found within this matrix, have a crucial function in the assembly of the basement membrane [2]. They have a significant impact on cell differentiation, survival, and migration, all of which are necessary for the development and maintenance of the fetal-maternal interface. Proteoglycans, which consist of core proteins with glycosaminoglycan chains attached, function as fillers in the ECM [24,37]. They play a crucial role in maintaining the viscoelastic properties of the ECM, facilitating the movement of growth factors, and regulating the filtration of nutrients and waste products between the mother and fetus [38]. The ECM's dynamic nature is demonstrated by the continuous remodeling activity controlled by trophoblast cells. These cells utilize enzymes such as Matrix Metalloproteinases (MMPs) to carefully adjust the matrix, guaranteeing that the placenta can adapt to the changing demands of pregnancy [39].

The Umbilical Cord

The umbilical cord, being a structure critical to the growth of the fetus during gestation, is a structure with an average length of 50-60 cm at term [40,41]. It, providing a duct for blood transportation from the placental to the fetus, is one of the most applicable postpartum waste materials in tissue engineering in recent years [40]. The umbilical cord was identified initially by Aristotle as the connection between the mother and the unborn fetus [40]. However, its importance in different sciences has increased, attributing to its structures.

Structurally, the fully developed umbilical cord typically contains three blood vessels (two umbilical arteries and one umbilical vein) and the remnant of the allantois [40,42]. All these are embedded in a connective tissue called Wharton's Jelly (WJ) and surrounded by a single layer of amnion [40]. Notably, these vessels have different structures from their counterparts throughout the fetal body. While the walls of blood circulation arteries have elastic lamina (internal and external) and the adventitia, those of the umbilical cord arteries lack an elastic lamina (internal and external) and the adventitia and are replaced by mucous connective tissue. In contrast, the umbilical cord vein has a thickened muscular layer with interwoven smooth muscle fibers (circular, longitudinal, and oblique) and an internal elastic lamina [40]. Not only are these vessels structurally different, but they are also functionally different. In other words, the umbilical cord arteries, returning oxygen-depleted blood to the placenta, are different from other arteries that deliver oxygen to the tissue and organs of the fetus. In addition, this difference is seen in the umbilical vein. While the whole veins in the fetal circulation carry the unoxygenated blood, the umbilical cord vein transports oxygenated blood to the fetal heart [40].

As arterial adventitia, being the external layer of the blood vessel wall consists of connective tissue and has a critical role in vascular health; its absence may expose the umbilical arteries to the risk of damage [42,43]. However, this loss was compensated with a rigid structure called Wharton's jelly, which plays the role of the adventitia for the umbilical cord arteries [42]. WJ is a connective tissue located within the umbilical cord with some components similar to connective tissue [44]. The WJ consists of an ECM-based backbone like the chief constituents of connective tissue, the ECM [45]. Like the ECM within the most connective tissues, which consists of different combinations of protein fibers, including collagen and elastic fibers, this umbilical cord-based ECM (WJ) is made of collagen and elastin fibers, which play essential roles in the firmness of the intact cord [42,45]. In addition, this umbilical cord-based ECM has a ground substance similar to that of the most common connective tissues [45]. The ground substance of the ECM is a highly hydrated, transparent, and complex mixture of three major kinds of macromolecules: Glycosaminoglycans (GAGs), proteoglycans, and glycoproteins [45]. GAGs, so-called mucopolysaccharides, are long polymers with repeating disaccharide units. Among all GAGs, the largest and most ubiquitous GAG, hyaluronan (hyaluronate or hyaluronic acid) is located in the ECM of WJ [42,45].

In other words, the ECM of WJ is chiefly composed of hyaluronic acid and chondroitin sulfate [45].

Amniotic Membrane

The amnion or AM, the inner layer of the PM, is a translucent biological structure, lacking nerves, muscles, or lymph vessels [11,13,22]. This inner layer, being a crucial structure, plays a significant role in fetal development. It creates a protective sac around the developing embryo and fetus, defining the amniotic cavity filled with amniotic fluid [11,22]. The amnion primarily serves to provide a protective barrier and create a fluid-filled environment conducive to the development of the fetus. However, there exists supporting data indicating its potential role in immunoregulatory processes [46]. It has different thickness, varying from 0.2 mm to 0.5 mm. In addition, it consists of three main histological layers: the epithelial layer, the thick basement membrane, and the avascular mesenchymal tissue. The inner layer, adjacent to the amniotic fluid is a single homogeneous layer of cuboidal epithelial cells, which are firmly fixed to the basement membrane, which is, in turn, attached to a condensed acellular layer composed of collagen type I, II, and V [13]. Amniotic epithelial cells have many microvilli at their apical surface. These cells have an active secretory function and intra-cellular and trans-cellular transport functions. These epithelial cells express epidermal markers, including glycoprotein CA125 and oxytocin receptors. In addition, they are also positive for antigen CD44 and desmin. Most importantly, Erythropoietin and its receptors are expressed in human amniotic epithelial cells. Although the functions of Erythropoietin are still unknown in the AM, the differentiation, proliferation, and survival of erythroid precursors and their production are stimulated by these cells and regulated by the oxygen level of blood [13]. The basement membrane contains large amounts of proteoglycans, rich in heparan sulfate, and serves as a permeable barrier to amniotic macromolecules and several molecules [13]. These molecules are actin, α-actinin, spectrin, ezrin, several cytokeratins, vimentin, desmoplakin, and laminin, having structural functions that enable the maintenance of membrane integrity [13]. The outer layer is composed of mesenchymal fibroblast-like cells. This mesenchymal layer is rich in collagen, contributing to an increase in the tensile strength of the layer. However, some authors mention that this AM has another layer, called the zona spongiosa, which is the outermost layer of the amnion. This naming results from its abundant content of proteoglycans and glycoproteins, producing a spongy appearance in histological preparations. This layer, lying adjacent to the chorion laeve, is an almost acellular structure and contains a nonfibrillar meshwork mostly of type III collagen [13].

Additionally, the amnion, a vital constituent of the extraembryonic membranes, exhibits a distinctive composition of ECM that serves a pivotal function in preserving this membrane's structural integrity and functionality during embryonic development [47]. ECM of the amnion consists of an intricate arrangement of proteins, glycoproteins, and polysaccharides, which collectively establish a conducive milieu for the developing fetus. The ECM of the amnion contains a significant amount of collagen, including type I, II, IV, and VII collagen. In addition, fibronectin, laminin, and tenascin are glycoproteins that significantly facilitate cell adhesion, migration, and overall tissue structure within the amnion [13,48,49]. Proteoglycans, including hyaluronic acid, play a crucial role in preserving hydration and contributing to the viscoelastic characteristics of the ECM in the amniotic environment [50]. Comprehending the complexities of the amnion's ECM composition is crucial to acquire a deeper understanding of its biomechanical characteristics and function in facilitating embryonic development.

Chorion Membrane

The chorion, one of the main layers of PM, acts as a protective barrier and separates the fetus's environment from the mother's immune system [51]. After the third month of gestation, the amnion becomes visibly distinct from the chorion laeve, which is the precursor to the chorion, due to the presence of the chorionic cavity. As the amniotic sac fills with fluid and expands, the amnion adheres to the innermost surface of the chorion, and the chorionic cavity disappears. Even though they are closely attached, the amniotic and chorionic layers of the PM do not merge and remain distinct in terms of their histological structure [52]. This layer (chorion membrane), which is the layer that faces the mother and comes into contact with the maternal decidua is composed of three layers: the reticular layer, a basement membrane, and a trophoblast layer [12,53]. The reticular layer serves as a framework for the chorion, featuring a network of fibers and housing mesenchymal cells similar to those found in the fibroblast layer of the amnion [54]. The basement membrane situated between the reticular layer and the trophoblasts, enhances the structural stability of the chorion by offering a cellular framework for the trophoblast layer and contributes to the immune-protective properties of the tissue [55]. The trophoblast layer, positioned on the outermost surface of the chorion, comprises trophoblasts, myofibroblasts, and macrophages [51]. The chorion's ECM comprises various components, including collagen types I, III, IV, V, and VI, elastin, fibronectin, laminin, and HA [56].

Collagen in the trophoblast layer of the chorion plays a role in anchoring the PM to the maternal decidua [12,14]. The structural aspects of these bio-based materials are portrayed in Figure 2(A, B, C, and D).

The Positive Aspects of these Post-Partum Waste Materials for Tissue Engineering-Based Approaches

The emergence of tissue engineering and regenerative medicine has brought inspiring approaches for troubleshooting different issues associated with various diseases and tissues. In addition, it provides an opportunity to apply postpartum waste materials, including the umbilical cord, placental, and amniotic membrane. However, a question was raised. What aspects of these waste materials made them applicable in tissue engineering? To answer this question, the positive aspects of these natural-based materials for tissue engineering-based approaches are discussed in the following, followed by elaborating their applications in different studies in the next section.

Placental Disk

The placental disc's adaptability extends beyond its main role in supporting fetal development; it is becoming acknowledged for its significant implications in the field of regenerative medicine. The interest arises from the existence of various types of stem cells and a plentiful ECM within the placental tissue.

The placental disc contains stem cells, including Mesenchymal Stem Cells (MSCs), which have a remarkable ability to regenerate tissues. These cells can undergo morphological changes and differentiate into a diverse range of cell types, offering potential for therapeutic applications and tissue regeneration [57,58]. MSCs, renowned for their minimal immunogenicity and immunomodulatory properties, are currently undergoing intensive investigation for their regenerative potential in bone, cartilage, and cardiac tissues [59].

As mentioned, the ECM of the placental disc comprises essential proteins, including collagen, fibronectin, and laminin. These proteins not only provide structural support but also actively participate in cellular communication. The ECM plays a crucial role in tissue engineering by enabling the development of scaffolds that facilitate the adhesion, growth, and differentiation of stem cells, hence promoting the regeneration of injured tissues [22]. Moreover, utilizing the placental disc for regenerative applications is a viable alternative with diminished ethical considerations, as the material is obtained from a source that is otherwise disposed away, hence causing no harm or danger to the donor.

Amniotic Membrane

The application of amniotic membrane in the field of tissue engineering offers significant benefits and poses certain obstacles. The amniotic membrane possesses inherent biocompatibility, demonstrating anti-inflammatory characteristics and serving as a plentiful reservoir of growth factors that facilitate the process of tissue regeneration [60]. The adaptability of this substance enables its use in diverse tissue types, and it has exhibited effectiveness in diminishing scar formation and facilitating the growth of new blood vessels. Nevertheless, there are some obstacles that need to be addressed in this context. These challenges encompass the varying quality observed across different donors, concerns regarding the potential immunogenicity associated with prolonged exposure, and limitations in terms of mechanical strength specifically for load-bearing tissues. It is imperative to thoroughly address concerns pertaining to storage, regulatory standards, and the potential for disease transmission [61].

Some of the positive roles associated with this postpartum membrane are innate biocompatibility [61], anti-inflammatory properties [62], growth factor richness [63], versatility [64], scar reduction [65], ease of handling [60], abundant availability [66], angiogenesis promotion [67].

The amniotic membrane possesses several antiinflammatory qualities, making it a promising candidate for therapeutic interventions in conditions characterized by inflammation. The complex chemical composition of amnion, containing cytokine inhibitors, growth factors, and immunomodulatory chemicals, is thought to be responsible for the amnion's anti-inflammatory properties. Some of these anti-inflammatory traits are highlighted here.

- **Cytokine Inhibition:** The presence of cytokine inhibitors within the amniotic membrane is of significant importance since they actively regulate the inflammatory response. The activity of pro-inflammatory cytokines, such as Tumor necrosis Factor-alpha (TNF-α) and Interleukin-1 beta (IL-1β), can be suppressed by these inhibitors. The amniotic membrane aids in the mitigation of the inflammatory cascade by reducing the activity of certain inflammatory cytokines.
- **Anti-Inflammatory Cytokines:** The amniotic membrane exhibits an active secretion of anti-inflammatory cytokines, including interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). Cytokines are of paramount importance in the modulation of the immune response and the inhibition of inflammatory processes. Interleukin-10

(IL-10), specifically, is renowned for its robust anti-inflammatory characteristics [68].

- **Immune Cell Modulation:** Research has demonstrated that immune cell function can be influenced by cells coming from the amniotic membrane. This encompasses the inhibition of T-cell proliferation and the stimulation of regulatory T cells (Tregs). Tregs are crucial to establishing and preserving immunological tolerance through their ability to dampen exaggerated immune reactions and uphold immune equilibrium [69].
- **Reduced Production of Inflammatory Mediators:** Cells generated from the amniotic membrane have the ability to decrease the synthesis of inflammatory mediators, including prostaglandins and nitric oxide. Prostaglandins and nitric oxide are recognized as significant factors in the process of inflammation, and their inhibition plays a crucial role in establishing an environment that is conducive to reducing inflammation [19,70].
- **Suppression of Reactive Oxygen Species (ROS):** The constituents of the amniotic membrane possess the ability to inhibit the production of reactive oxygen species. Reactive Oxygen Species (ROS) are molecular entities that play a significant role in the processes associated with oxidative stress and inflammation. The amniotic membrane exerts an anti-inflammatory impact by decreasing the formation of reactive oxygen species [71].

Chorion Membrane

The PM, which functions as a protective barrier against bacterial infections throughout pregnancy, includes various layers of antimicrobial peptides, encompassing human defensins, elafin, Secretory Leukocyte Protease Inhibitor (SLPI), as well as histones H2A and H2B [72,73]. Notably, the maternal-facing chorion demonstrates more substantial levels of bacterial inhibition in comparison to the fetal-facing amnion, underscoring the importance of the chorion as a pivotal protective layer in preventing infections and immune rejection [74]. In addition, analyzing the content of cytokines and growth factors in the chorion is of interest for various applications of the tissue [75,76]. The amnion and chorion exhibit similarities between the types of cytokines they contain, but they vary in their distribution and concentration [76]. Specific attention has been given to growth factors, such as Epithelial Growth Factor (EGF), Fibroblast Growth Factors (FGFs), Vascular Endothelial Growth Factor (VEGF), Transforming Growth Factor Alpha (TGFα), Transforming Growth Factor Beta (TGFβ), Keratinocyte Growth Factor (KGF), Hepatocyte Growth Factor (HGF), and Platelet-Derived Growth Factors (PDGFs), as well as interleukins (ILs) like IL-4, IL-6, IL-8, and IL-10, interferons (IFNs), and protease inhibitors, including tissue inhibitors of metalloproteinases (TIMPs) such as TIMP-1, TIMP-2, and TIMP-4. These components have potential applications in therapeutic contexts [56,77]. They play crucial roles in regulating various aspects of the healing process, including angiogenesis, inflammation, and tissue remodeling [14,76]. Despite the utilization of certain placenta-derived products in tissue regeneration, there has been limited investigation into the potential of the Human Chorion Membrane (HCM) on its own.

Umbilical Cord and Its Wharton's Jelly

One of the aspects that makes these postpartum waste materials usable is the ease of access to Wharton's jelly. In addition, it is associated with primitive mesenchymal stem cells within the Wharton's jelly. These mesenchymal stem cells are perinatal stem cells, resembling embryonic stem cells and retaining many characteristics of adult mesenchymal stem cells [44]. As Wharton's Jelly-derived Mesenchymal Stem Cells (WJMSCs) express markers of pluripotent stem cells at a lower level than those of embryonic stem cells, it can be said that they are highly multipotent [44]. Therefore, an opportunity for harvesting these highly multipotent mesenchymal stem cells is provided by each birth delivery in a way that the highest concentration of mesenchymal stem cells is within WJ per milliliter compared to other tissues, being rich in components of ECM [44].

Furthermore, the healing capability of these postpartum products makes them attractive for regenerative medicine. This capability is attributed to the presence of stem cell, growth factors, cytokines, hyaluronic acid, and/or extracellular vesicles within these products [44,78]. Gupta *et al.* revealed that there are a clinically relevant quantity of growth factors, cytokines, and extracellular vesicles within Wharton's jelly, playing a role in reducing inflammation and pain at high quantity. Additionally, these agents can promote the healing of musculoskeletal injuries [44].

It is worth mentioning that these positive aspects mentioned can be a part of the infinite sea and there are still some aspects that are still unknown.

The Application of this Postpartum Waste Material In Studies Associated with Tissue Engineering

The utilization of these post-partum waste materials has gained significant attention in the different fields of tissue engineering and regenerative medicine, including

cardiovascular, skin, cartilage, gingival, corneal, and other various tissues. These postpartum-derived materials can be served as a scaffold or matrix for cell attachment and growth in different forms, including decellularized tissue-derived powder and hydrogels, and nanofibers, for the engineering of different tissues, such as the heart, skin, ear, and so on. For example, researchers have investigated decellularization techniques using different concentrations of decellularization agents, including Sodium dodecyl sulfate and Triton X-100, whether alone or in combination, to remove cellular components from the placental tissue while preserving its extracellular matrix. This decellularized placental tissue can then be repopulated with patient-specific cells or used as a template for tissue regeneration [79,80].

Scaffolds, playing a unique role in tissue regeneration and regenerative medicine, are defined as three-dimensional porous structures with some or all functionality aspects designed from biomaterials [81]. Scaffolds are classified into two general types: solid and fluid, in which the formers and latter have different subsets. Solid scaffold subsets include sponges, foams, fibers, membranes, and tubes, revealing a stable and well-defined 3D porous structure [82]. The latter, fluid-based scaffolds, being in the form of hydrogels have been a promising approach in the drug delivery system, resulting their minimally invasive application. These scaffolds are usually flat hydrogels, microparticles, or nanoparticle hydrogels [82]. To fabricate these constructs, different methods have been revealed in different studies are used, including freeze-drying [83,84], electrospinning [85-87], and three-dimensional printing [88]. Additionally, decellularization-based approaches attracted a great deal of attention to fabricate biologically-based scaffolds [89-91].

As the basis of tissue engineering is on triad components (cells and scaffolds), the application of this postpartum waste material in studies associated with tissue engineering and regenerative medicine will be elaborated around these components [92,93]. In other words, some of the post-partum-based scaffolds designed in different studies were described to catch the importance of these postpartum waste materials in this novel emerging field of study. In addition, the application of post-partum tissue-derived cells will be mentioned.

The Warthon's Jelly

In recent years, WJ, which is a connective tissue located within the umbilical cord are used in different forms of scaffolds, including hydrogels, spongy scaffolds, nanofibers, etc [44]. For example, Cristian *et al.* designed a novel bio composite based on the combination of WJ, bioceramic, and bioactive glass particles [94,95]. The application of biopolymers or bioceramics composite in this construct can be attributed to their biocompatibility, nontoxicity, controlled degradation, mechanical properties, and tissue regeneration induction. They implanted this construct in the hematopoietic bone marrow compartment of both tibiae related to rats, parallel to their longest axis, without administration of antibiotic therapy, and revealed that it had high toughness, being suitable for tissue regeneration and lamellar bone formation [95].

Beiki *et al.* fabricated a three-dimensional spongy scaffold using an extracellular matrix derived from the decellularization of human Wharton's jelly, followed by its crosslinking with NHS/EDC to promote skin regeneration. Positive physical aspects of this construct were revealed by the corresponding results. In addition, the efficacy of WJ-derived scaffolds in the regeneration of full-thickness wounds assessed through an *in vivo* experiment on mice (areas between shoulders) demonstrated that the scaffolds were well integrated into the mouse tissue and absorbed the exudates after one week. In addition, it was revealed that there was not only complete wound closing and disappearance of the scab in the WJ group compared to the control group, but also complete reepithelialization, newly generated epidermal layers and appendages after 12 days of implantation. Additionally, the wound closing was accelerated and no inflammatory responses observed [96].

Li *et al.* also fabricated a biomimetic scaffold in two forms to investigate the efficacy of these constructs in the expansion of CD34 cells (Umbilical Cord Blood (UCB) CD3 cells). The first one contained the combination of the matrix derived from decellularization of human WJ and human Bone Marrow (BM)-derived Mesenchymal Stromal Cells (MSCs), within which the former was used as an ECM-based scaffold and the latter was as supporting niche cells. The second construct was a matrix derived from DHWJ (MDHWJ) free from BMMSCs. Based on the obtained results, they revealed that the MDHWJ-based scaffold had a significant effect on the expansion of CD34 cells. In contrast, the presence of BMMSCs in the scaffold impaired the cell transmigration of CD34 [97]. All in all, they revealed that the DWJM-based scaffold could be a novel approach for supporting the proliferation of UCB CD34 cells, which can open a new promising window for enhancing future clinical applications of DWJM in tissue regeneration and UCB transplantation.

Najafi *et al.* developed a novel 3-layered composite containing polymeric matrix-based nanofiber plus ECM-based hydrogels derived from decellularized Wharton's Jelly for tissue engineering of Tympanic Membrane

Perforations (TMPs). In the following based on *in vitro* studies, they applied the optimized composite *in vivo* study and demonstrated that the optimal composite stimulated the healing of TMPs. Additionally, it could shorten the healing period, which revealed that this ECM-based construct could be a promising regenerative platform for TMPs [98].

As above-mentioned, the healing capability of these postpartum products is attributed to the presence of stem cells, growth factors, cytokines, hyaluronic acid, and/or extracellular vesicles within these products [44,78].

In addition to the application of WJ in different forms of scaffolds, cells isolated from this kind of connective tissue have also therapeutic applications. Among different available sources to obtain MSCs, extraembryonic tissues, such as the WJ, represent a money-saving, workable, and non-invasive method to isolate MSCs. In addition, stem cells obtained from this source are beneficial, which can be attributed to their higher proliferative capacity with no signs of senescence over serial passages compared to bone marrow MSCs [99]. Additionally, the derived from WJ are less immunogenic than their adult tissue counterparts and also possess potent immunomodulatory properties due to the release of large amounts of anti-inflammatory molecules, including TGFβ and IL-10 compared to bone marrow-derived MSCs [99]. Furthermore, studies on umbilical cord Wharton's jelly-derived mesenchymal stem cells have demonstrated that they represent a high-yield source of young, nontumorigenic, and immunomodulatory cells that may be allo-transplanted to regenerate liver, heart, bone, cartilage, fat, pancreas, neural, vascular/endothelial, and skin components [100]. The skin regenerative capability of MSCs derived from human WJ has been shown in such a way that they differentiate into sweat gland-like cells, which in turn may promote skin regeneration [100]. Arno *et al.* isolated human WJ- derived MSCs and skin fibroblasts from umbilical cords and intact adult human skin. In the following, they treated fibroblasts with condition media related to WJ- derived MSCs or no conditioned medium and demonstrated that the proliferation and migration of fibroblasts treated with condition media enhanced, and wound healing in an excisional full-thickness skin murine model promoted. This event could be attributed to paracrine signaling of WJ- derived MSCs in culture conditions [100].

Millán-Rivero *et al.* fabricated electrospun silk fibroin-based scaffolds, cell-seeded with human Wharton's jelly-derived MSCs to investigate the wound healing effects of scaffolds in a murine excisional wound-splinting model [99]. Based on their corresponding results, they revealed that Wharton's jelly-derived MSCs transplanted in the wound bed on a silk fibroin scaffold could contribute to the generation of vascularized granulation tissue, promote reepithelization of the wound, and decline the formation of fibrotic scar tissue. All of these could be an acceptable justification for the potential therapeutic effects of tissue engineering-based approaches focused on Wharton's jelly-derived MSCs to treat non-healing wounds [99].

It has also been revealed that MSCs derived from human WJ have the ability to regenerate the liver and they can decrease fibrosis associated with the liver, lung, and kidney [100]. Su *et al.* fabricated polymeric scaffolds (Poly (3-hydroxybutyrate-co-3-hydroxyvalerate-co-3-hydroxyhexanoate) (PHBVHHx), loaded with umbilical cord-derived mesenchymal stem cells (UCDMSM) or hepatocyte-like cells differentiated from these cells for liver tissue engineering. In the following, they applied this cell/polymeric-based construct in a liver-injured mouse model and revealed that livers had a similar tissue structure to normal livers in scaffolds loaded with both cells on day 28 post-transplantation [101].

Amniotic Membrane

Like WJ, this membrane has also been used in tissue engineering as different forms of scaffolds and cells. Sabouri *et al.* decellularized the human amniotic membrane and mineralized it by the double diffusion method. During *in vivo* studies, they showed that fabricated mineralized amniotic membrane cell-seeded with Adipose-Derived Mesenchymal Stem Cells (ADMSCs) could promote bone regeneration in calvarial defects of rats, which would be considered as a promising biomaterial candidate for bone regeneration in tissue engineering applications [102].

Hosseini *et al.* fabricated a biocomposite from the decellularized human amniotic membrane, which was solubilized and impregnated it with copper- and Cobalt-Doped 13-93B3 MBGs (CuCo-MBGs). The incorporation of the MBG and CuCo-MBG into this decellularized membrane promoted the antibacterial activity of this construct, which would be the next generation of wound dressings after performing *in vivo* experiments [103].

John *et al.* de-epithelialized the human amniotic membrane and developed an air/liquid interface cell culture, using a serum-containing keratinocyte-based growth medium to cultivate keratinocytes and fibroblasts on the de-epithelialized membrane, which resulted in a mostly keratinized surface and can be used as a tissue-engineered skin substitute [104].

Sarumathi *et al.* crosslinked a decellularized amniotic membrane by genipin to fabricate a crosslinked bioscaffold and revealed that this bio scaffold had better biocompatibility

and biostability compared to the native and decellularized membrane, indicating its suitability as a scaffold for various tissue engineering applications [105].

Khorramirouz *et al.* fabricated a construct using decellularized human AM and seeded it with adipose-derived mesenchymal stem cells. In the following, they implanted this cell-seeded construct in the infarcted hearts and revealed that it had significant potential for cardiomyocyte regeneration and cardiac neovascularization [106].

Verdes *et al.* investigated the use of mesenchymal stem cells derived from human amniotic membrane and human WJ for nerve regeneration. In addition, they studied the epithelial stem cells derived from human amniotics. For this investigation, they differentiated these cells into neural-like cells and seeded them on the decellularized human amniotic membrane as substrate, which revealed their potential application for the regeneration of neurodegenerative diseases [107].

Zhang *et al.* developed an Ultra-Thin Amniotic Membrane (UTAM), followed by generating engineered Rabbit Corneal Epithelial Cell (RCEC) sheets through the expansion of limbal epithelial cells on ultra-thin amniotic membrane. *In vivo* study revealed that two weeks after surgery, the cornea grafted with UTAM-based cell sheets showed higher transparency and more stratified epithelium than the cornea grafted with the epithelial denuded AM-based cell sheets, which might be a promising scaffold for corneal epithelial tissue engineering [108].

Esmaeili *et al.* fabricated a bilayer corneal wound dressing membrane via decellularization of AM, which was covered with an ultrathin layer of Poly-dimethylsiloxane (PDMS) through a spinning method. Their corresponding studies revealed the application of this dressing in corneal healing. In addition, they showed the improved mechanical behavior and transparency of these constructs [109].

Hussin *et al.* fabricated a new 3D scaffold using the blending of the human amniotic membrane and fibrin, cell-seeded with bovine chondrocytes, and revealed that it had good biodegradation characteristics and could be a proper substrate for chondrocyte proliferation in 3D form, confirming its suitability for cartilage tissue engineering applications [110]. Toniato *et al.* created a hybrid hydrogel combining solubilized chitosan and ECM-derived from decellularized amniotic membranes, which had potential application for articular cartilage tissue engineering application [111].

Chorion Membrane

ECM-based hydrogels from decellularized tissues have attracted a great deal of attention to promote the endothelialization of vascular grafts, resulting from mimicking the ECM composition of tissues and promoting stem cell homing. As chorionic tissue contains considerable amounts of basal lamina proteins, which mediate endothelial cell adhesion and function, Rohringer *et al.* coated the surface of polytetrafluorethylene vascular graft by the solubilized chorion-derived extracellular matrix to improve endothelialization. In the following, they cell seeded the surface of this modified graft by Human Umbilical Vein Endothelial Cells (HUVECs) and revealed that this modification could induce a significantly higher endothelial cell adhesion to this graft, representing a possible alternative for vascular graft modification to improve endothelialization [112].

Frazão *et al.* fabricated a decellularized human chorion membrane vascular graft and assessed the ability of this decellularized membrane to promote the formation of capillary-like structures *in vitro* by seeding HUVECs in both sides of the membrane (reticular and trophoblast layer sides). They revealed that both sides of this membrane were compatible with seeded cells regarding blood compatibility, and both sides had antibacterial properties against S. aureus adherence and adhesion. A faster reendothelization, lower platelet adhesion and activation, and better hemocompatibility were allocated to the reticular layer side. Therefore, they fabricated a decellularized membrane-based tube with the reticular layer side as a vascular graft and revealed that its mechanical properties were similar to the ones of the saphenous vein, being the gold standard for autologous small-diameter vessel replacement [113].

Francis *et al.* demonstrated that a hydrogel from human chorion could reduce scarring after cardiac ischemia in animal model studies [112].

Both chorion and amnion membranes are also used as a profitable allogenic substitute for the connective tissue autograft to promote periodontal reconstruction. George *et al.* used freeze-dried irradiated amnion and chorion membranes and evaluated the biomechanical properties of both membranes regarding their potential application as a substitute in root coverage procedures. Mechanical testing of these membranes demonstrated that they are elastic in nature. Amnion is more elastic with higher tensile strength, Young's modulus, and extension at break than chorion. Regarding *in vitro* degradation, it was revealed that amnion membranes were more resistant than chorion membranes, resulting from the lack of whole degradation at the end of four weeks. It was worth mentioning that amnion membranes could bear more load during suturing, investigated by

the suture retention test [114]. Gulameabasse *et al.* also revealed the clinical applications of Chorion Membrane (CM) and Amnion Chorion Membrane (ACM) for oral soft and hard tissue regeneration in a systematic review. In this review, seven clinical applications of CM and ACM in oral and periodontal surgery were identified: gingival recession treatment, intrabony, and furcation defect treatment, alveolar ridge preservation, keratinized gum width augmentation around dental implants, maxillary sinus membrane repair, and large bone defect reconstruction [115]. For example, Veerabadran Loganathan *et al.* demonstrated the treatment of gingival recession defects using Lyophilized Chorion Membrane (LCM) in smokers. In other words, they revealed the role of LCM allograft as a scaffold to promote soft tissue regeneration, especially in root coverage procedures in smokers [116].

Currently, mesenchymal stem cells derived from human chorionic membranes has been emerged as the best choice source of transplanted cells for regenerative therapy due to their non-invasive isolation and simple method with high proliferative capabilities. Zhou *et al*. used mesenchymal stem cells derived from the human chorionic membrane, investigated the therapeutic potential and mechanism of intravenous transplantation of these cells in a rat model with Traumatic Brain Injury (TBI), and revealed that these stem cells exhibited efficient therapeutic efficacy in a TBI model, resulting from reducing in the inflammation, apoptosis, and the blood-brain barrier disruption, and promoting angiogenesis and neurogenesis [117].

Placenta

Fan *et al.* decellularized the human placenta, human placenta-derived ECM, and physically incorporated the ECM into synthetic poly (ethylene glycol) (PEG)-based hydrogels via UV-initiated Thiol-ene Coupling (TEC). In the following, they applied these ECM-based hydrogels for a porcine skin wound and a bone void in a porcine metacarpal, and revealed that these ECM-based hydrogel could be easily applied to and cured within porcine skin and bone wounds, after which its adhesion to these substrates prevented the hydrogels from being dislodged. In other words, in situ application of the hydrogel was achieved. Additionally, the 3D printability of the hydrogels with complex topology was proved using a commercial SLA 3D printer [118].

Schneider *et al.* decellularized the placenta vessels and reendothelialized the decellularized vascular scaffolds by human endothelial cells isolated from the umbilical cord vein (HUVECs). They revealed that the cell-seeded luminal surface of a decellularized vessel graft performed endothelialization and high viability of the cells, indicating a lack of toxic effects from residues of the chemicals used during the decellularization process [18].

Choi *et al.* created a new dermal substitute in the form of ECM-based sheets (15 mm diameter and 10 mm thickness) via the decellularization of human placentas for full-thickness wound healing. They used these sterilized and decellularized sheets hydrated *in vivo* and revealed that this ECM-based sheet efficiently absorbed wound exudates and tightly attached to the wound surface. In addition, they observed that the wound was completely contracted, epidermic cells were well arranged, and the bilayer structure of the epidermis and dermis was recovered [119].

Asghari *et al.* investigated different decellularization procedures to choose the optimum approach and fabricate a three-dimensional substrate for the colony formation capacity of mouse spermatogonial stem cells. Following the subcutaneous implantation of decellularized scaffolds, they revealed that the cells could infiltrate into the scaffold on days 7 and 30 post-implantation with no sign of rejection, revealing its application for tissue engineering and reproductive biology applications [79].

DaShun *et al.* fabricated an engineered cartilage by combining Human Placenta-Derived Stem Cells (hPDSCs) with a collagen-based scaffold. They revealed that these cells have the potential to differentiate into functional cartilage cells *in vitro* when combined with a collagen sponge. However, hPDSCs maintained proliferation *in vitro* for over 30 passages while remaining undifferentiated.

Jin *et al.* evaluated the potential of a Silk Fibroin/Hydroxyapatite (SF/HA) porous scaffold as a delivery system for human Placenta-Derived Mesenchymal Stem Cells (PMSCs) in a radius defect of rabbit model and revealed that fracture healing in the experimental group was significantly improved over the control group, demonstrating evidence for the application of human placenta as a potential source of stem cells for bone tissue engineering.

CONCLUSION

In conclusion, the potential of postpartum waste materials : the amniotic membrane, chorion membrane, placental disk, and umbilical cord to propel the fields of tissue engineering and regenerative medicine is undeniable. These readily available and biologically diverse sources offer a treasure trove of natural scaffolds, bioactive molecules, and stem cells, each holding the key to unlocking novel therapeutic approaches. Their inherent properties ,from the extracellular matrix composition of the amnion to the mesenchymal stem cell richness of the cord, provide a unique platform for

tissue regeneration and hold immense promise for treating various conditions, from chronic wounds to organ failure.

However, this exciting journey necessitates a meticulous and responsible approach. Rigorous characterization studies are crucial to understand the intricate composition and function of each material. Standardized processing protocols are essential for ensuring their consistent quality and safety. Extensive preclinical assessments, conducted with adherence to ethical guidelines, are paramount to validate their therapeutic potential and address potential immunomodulatory effects. Only through such disciplined exploration can we unlock the true potential of these materials and translate them into safe and effective clinical applications.

The future of tissue engineering and regenerative medicine hinges on embracing these sustainable and readily available resources. By integrating them responsibly and ethically, we pave the way for innovative biomedical solutions that address unmet clinical needs and ultimately improve patient care outcomes. The potential is boundless, and the journey towards realizing it demands a collaborative and disciplined effort from scientists, medical professionals, and regulatory bodies alike. This is not just about utilizing waste; it's about harnessing the power of nature's regenerative toolkit to empower healing and improve lives.

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