The Role of Placental Membrane Allografts in the Surgical Treatment of Tendinopathies

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KEYWORDS

• Amniotic graft • Placental membrane graft • Tendon repair • Tendinopathy

KEY POINTS

- Surgeons have recently started to implant placental membrane grafts in a variety of surgical procedures.
- When used for tendinopathies, placental membrane grafts may allow for increased angiogenesis and decreased scar tissue formation.
- The scientific literature supports use of placental membranes to reduce inflammation and scarring.
- Although current literature for placental membrane graft use is promising, more high-level clinical trials are required.

INTRODUCTION

Placental membrane grafts have been used in the treatment of lower extremity pathologies for more than a century. The earliest documented use of human placental membrane for treatment of wounds was in 1910 when a general surgeon at John Hopkins Hospital used amniotic grafts to supplement skin transplants.[1] In 1913, amniotic membrane grafts were trialed on burn wounds because their use eliminated the need for a donor site.[2] Subsequently in 1940, an ophthalmologist applied harvested placental membranes to conjunctiva and noted formation of new blood vessels as well as full incorporation of the graft into conjunctival tissue.[3] Despite early studies showing

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some benefit with the application of human placental grafts, the increased risk of disease transmission prevented their widespread use. This increased risk was primarily due to the crude methods of harvesting as well as the lack of adequate health screenings for donors. Suboptimal graft harvesting and processing also led to the unintentional removal and destruction of live mesenchymal stem cells, decreasing the efficacy of the graft itself. In the past decade, harvesting, processing, and preservation methods have significantly improved. Placental membrane grafts are now obtained from volunteer donors, all of whom undergo significant screening protocols for hepatitis B and hepatitis C, syphilis, cytomegalovirus, HIV, and tuberculosis.[4] Once the placental membranes are harvested, they undergo a thorough sterilization process prior to preservation. Numerous companies are now manufacturing placental membrane grafts, with a wide variety of product types available for physicians to choose from.

One clarification is required prior to further discussion about grafts. The term, *amniotic graft*, has often been used as a catch-all phrase for any product derived from the placental membrane. This phrase can be confusing for physicians attempting to delineate one product from another. The placental membrane consists of 3 primary layers: the amnion, the chorion, and the uterine decidual tissue.[5] The amnion layer, which in utero is in direct contact with the embryo, is composed of 5 distinct layers: the epithelium, basement membrane, compact layer, fibroblast layer, and intermediate/spongy layer.[6] The chorion layer, which is 3 times to 4 times thicker than the amnion, consists of a cellular layer, a reticular layer, a pseudobasement membrane, and a trophoblast layer.[6] Placental membrane grafts are derived from 1 or both of these 2 layers. There are grafts that contain just the amnion layer and, strictly speaking, only these should be called amniotic grafts. Other products contain just the chorion layer, whereas some contain both the amnion and chorion layer. For the purpose of this article, the term, *placental membrane graft,* is used as an all-encompassing phrase, whereas the term, *amniotic graft,* refers exclusively to products containing just the amnion layer.

The amnion and chorion layers contain multiple growth factors, mesenchymal stem cells, and collagen, which all contribute to the healing process. Specific growth factors found in the grafts include epidermal growth factor, basic fibroblast growth factor, keratinocyte growth factor, vascular endothelial growth factor, transforming growth factor (TGF), nerve growth factor, as well as several other chemokines and cytokines.[6] A majority of these growth factors have been found within the chorion layer.[7] A recent article by Dinh and colleagues[8] provides an excellent overview of each growth factor and its particular role in the healing cycle.

Although research regarding the specific physiologic processes triggered by placental membrane grafts is ongoing, many investigators have noted numerous regenerative benefits of these grafts. First, in vitro and in vivo applications have shown increased native stem cell recruitment.[9,10] Although newer research has shown that mesenchymal stem cells do not themselves differentiate into native host tissue, the mesenchymal stem cells are nevertheless able to attract the host stem cells to the desired area.[11] These host cells then differentiate locally as needed for healing. Second, placental membrane grafts promote angiogenesis. After application of amniotic grafts on chronic wounds, for example, significant new blood vessel formation was noted with both histologic and immunohistologic evaluation.[12] Third, placental membrane grafts are immune privileged and have shown the ability to down-regulate local inflammation. These characteristics are believed secondary to high levels of tissue inhibitor of metalloproteinase, interleukin 10, and interleukin 1RA found in grafts.[13] These cytokines reduce metalloproteinase activity and, therefore, down-regulate the