Operative Applications of Placental Tissue Matrix in Orthopaedic Sports Injuries: A Review of the Literature

ABSTRACT

Introduction: Placental and amniotic membrane-based tissues have gained widespread popularity for their ability to promote healing and tissue regeneration and have manifested multiple applications in wound care, burn treatment, and management of various ocular conditions. Recently, there have been multiple studies that investigated the nonoperative uses of placental tissue-based products in orthopaedic sports injuries. However, there is a relative paucity of studies that have attempted to evaluate their adjuvant operative uses. Therefore, the aim of this review was to evaluate the use of placental and amniotic tissue-based products as an adjuvant treatment to the operative management of orthopaedic sports injuries.

Materials and Methods: A comprehensive literature search was performed on PubMed, EBSCO Host, EMBASE, and SCOPUS. Studies published between January 1, 2000 and June 1, 2018 were reviewed. Inclusion
Placental and amniotic membrane-based tissues have gained widespread popularity for their ability to promote healing and tissue regeneration, and they have manifested multiple applications in wound care, burn treatment, and management of various ocular conditions. More recently, several in-vitro and animal studies have demonstrated that these tissues have strong regenerative potentials through their rich content of growth factors, extracellular matrix scaffolds, and cytokines. It has been shown that its content with pluripotent mesenchymal stem cells may expand their applications to various tissue healing processes. Low immunogenicity has also been demonstrated.

Results: Current evidence has led to investigation of various placental and amniotic membrane products used as an adjuvant treatment to surgical reconstruction of various types of tendon injuries, with a demonstrated effectiveness found mostly in the short-term, with follow up ranging between five weeks and two years. In addition, their safety and minimal complication profile have been demonstrated. Marked differences exist among the currently available products due to variations in their formulations, tissue source, processing methodology, sterilization method, preservation and storage methods, indications for use, and FDA regulation.

Conclusion: Operative uses of placental and amniotic membrane-derived tissues appear to be safe when utilized as an adjuvant or augmentation option along with surgical reconstruction. However, several factors may come into play when considering the diversity of commercially available products. Future clinical trials will need to confirm the safety and demonstrate clearer indications and specific guidelines for use in each clinical scenario involving operative management of tendon injuries. Nevertheless, this review will serve as an up-to-date reference and provide an impetus for future investigations.
products as an adjuvant treatment to the operative management of orthopaedic sports injuries.

MATERIALS AND METHODS

A comprehensive literature review was performed by searching the following databases: PubMed; EMBASE; EBSCO Host; and SCOPUS. Studies published between January 1, 2000 and June 1, 2018. The following keywords were used in combination with Boolean operators AND or OR for the literature search; “Placental,” “Tissue,” “Matrix,” “Orthopaedic,” “Sports Injuries,” “Clinical,” “Outcomes,” “Indications,” and “Human.” Inclusion criteria that was utilized were those studies that reported on: 1) Operative uses of placental tissue matrix (PTM) therapy in tendons and ligaments injuries; and 2) clinical outcomes; in 3) human subjects. In addition, the following studies were excluded: 1) animal studies; 2) basic science studies; 3) non-English language literature; 4) review articles; and 5) duplicate studies across databases.

The initial database search yielded 31 reports that were screened for relevant studies. This resulted in 19 reports, and the abstracts were thoroughly reviewed for eligibility according to the inclusion and exclusion criteria, including scanning the reference lists, which in turn led to four studies that were included in our final analysis. Three of these studies were level IV evidence, while one study was a technical note (Level V). These studies reported on a total of 146 patients. Three of these studies reported on the clinical outcomes consisting mainly of pain and physical functions scores with follow up ranging between five weeks and two years, with one study that did not report on the follow up. This selection process is summarized in Figure 1.

Additionally, to determine the various product compositions and indications for use, we searched publicly available manufacturer’s website content, marketing literature, FDA registration documents, and the Center for Medicare and Medicaid Services submissions to assess the key differences for each of the products. This is summarized in Table I.

![Flow chart demonstrating the selection process for clinical reports in this review.](image)

### Table I

<table>
<thead>
<tr>
<th>Study</th>
<th>Product Description</th>
<th>Manufacturer</th>
<th>Tissue Source</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warner and Lasyone</td>
<td>CLARIX-CORD 1K</td>
<td>Amniox Medical, Inc. (Atlanta, GA)</td>
<td>Cryopreserved human amniotic membrane and umbilical cord</td>
<td>Augmentation of foot and ankle tendon surgical repair</td>
</tr>
<tr>
<td>Ang et al.</td>
<td>Amniotic membrane graft</td>
<td>N/A</td>
<td>Amniotic membrane</td>
<td>Prevention of scarring and promoting healing after peroneal and Achilles tendon repair</td>
</tr>
<tr>
<td>DeMil et al.</td>
<td>Pending</td>
<td>Pending</td>
<td>Cryopreserved human amniotic membrane and umbilical cord</td>
<td>Augmenting foot and ankle tendon repairs. Safety assessment showed very low complication profile and all patients achieved satisfactory wound healing</td>
</tr>
<tr>
<td>Woodall et al.</td>
<td>Amnion matrix thick graft</td>
<td>Arthrex GmbH (Munich, Germany)</td>
<td>Amniotic membrane derived</td>
<td>Augmentation of ACL reconstruction, enhancement of tendon graft to bone integration and graft healing</td>
</tr>
</tbody>
</table>
RESULTS

In a retrospective case series by Warner and Lasyone,10 14 patients underwent surgical reconstruction for a variety of foot and ankle tendon injuries and simultaneously received cryopreserved human amniotic membrane and umbilical cord (cHAM/UC). Of these patients, nine underwent revision procedures. Outcomes were assessed using the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale and visual analogue pain scale (VAS) scores. At 15-week mean follow up (range, 4 to 32 weeks), mean postoperative AOFAS and VAS scores improved significantly when compared with preoperative scores. No adverse events were reported to be related to the use of cryopreserved human amniotic membrane and umbilical cord.

Ang et al.25 reported on two cases that underwent surgical repair for tendon injuries with intraoperative adjuvant amniotic membrane augmentation of repair. One case had peroneus brevis tendon split tear while the second had traumatic partial Achilles tendon tear due to a fall with concurrent retrocalcaneal exostosis. Clinical outcomes were reported using pain and return to activity. Both patients demonstrated minimal pain and were able to return to normal activity at the last follow up of two years and two months, respectively.

DeMil et al.26 reported on 124 consecutive patients who underwent various foot and ankle surgical procedures that involved tendon repairs and the intraoperative use of cHAM/UC. The cHAM/UC tissues were applied to the repaired tendons at the end of the procedure. The authors specifically assessed the safety profile by evaluating the occurrence of various complications at a minimum follow up of three months. They evaluated postoperative incidence of infections, delayed or nonhealing wounds, adverse surgical site reactions, and the need for an irrigation and debridement. They reported an overall complication rate of approximately 6% and a 1.6% (2/124) reoperation rate for irrigation and debridement. At the final follow up, all patients achieved successful wound healing with no other complications reported. The authors concluded that the cHAM/UC had an excellent safety profile in the short-term.

Woodall et al.23 have reported on augmenting anterior cruciate ligament (ACL) reconstruction by using amnion-based graft sutured to the entire length of the tendon graft aiming to enhance bony incorporation of the graft and healing. The authors recommended placing the cHAM/UC graft with the epithelial layer facing the tendon graft. Standard postoperative rehabilitation with a functional brace, in extension with gradual advancement of flexion range-of-motion (ROM) to a maximum of 90° over 48 to 72 hours, is then performed. Although the authors detailed the technique, they did not report follow-up data for this particular patient. However, no intraoperative or immediate postoperative complications were reported.

DISCUSSION

Placental and amniotic tissue-based products have shown promising results in multiple cell culture and animal studies indicative of their regenerative capacity and potential for use to promote healing of injured tendons. This has also been demonstrated clinically in multiple studies that examined their role as a sole agent for nonoperative treatment in various acute and chronic tendon injuries. In this review, we attempted to investigate their use as an adjuvant treatment to operative tendons reconstruction. Overall, the current evidence suggests that these products may have a strong potential for wide application in operative settings, with an excellent safety profile in the short term.

This review is not without limitations. Our findings are based on the quantity and quality of the published literature. To date, only the studies included in this review have reported on the operative uses and all of them are low level of evidence. However, we aimed to provide an up-to-date reference and educate the orthopaedic community on an emerging treatment modality which has consistently demonstrated good potential in cell-based, animal, and nonoperative human studies. Additionally, current studies reported outcomes in the short-term. However, all of the studies demonstrated an excellent safety profile of the used products without any deleterious effect on graft or wound healing.

There have been various studies investigating the nonoperative utility of placental tissue matrix therapy for various sports injuries and all have shown promising results. Hanselman et al.22 conducted a randomized, controlled, double-blind study comparing corticosteroid injections to cryopreserved human amniotic membrane (c-hAM) in patients with plantar fasciitis. Results showed that patients randomized to the c-hAM injection group had significantly lower pain scores on the Foot Health Status Questionnaire (FHSQ). Another prospective randomized study conducted by Zelen et al.29 investigated the use of micronized, acellular dehydrated human amniotic/chorionic membrane (mDHACM) versus placebo (saline injection) in 45 patients with plantar fasciitis. They found significantly higher American Orthopaedic Foot and Ankle Society (AOFAS) scores at eight weeks' follow up in the mDHACM group.

PTM injection has also shown promise in various other tendinopathies. Luuvel et al.31 reviewed 10 patients who received PTM injections for injuries such as posterior tibial tendinitis and Achilles tendinitis. Using the VAS, this study found that 100% of patients in the series were pain-free at five weeks following injection with PTM. Werber18 analyzed 44 patients with Achilles tendinitis and plantar fasciitis who were refractory to standard treatment for six months prior to injection. Following treatment with a product consisting of cryopreserved human amniotic membrane and amniotic fluid derived cells, all patients rated their pain levels <4 on the VAS scale at 12 weeks' follow up. Lastly, Gellhorn et al.17 investigated the results of mDHACM injections in a series of 40 patients with various tendinopathies ranging from tennis elbow to Achilles and patellar tendinitis. At three months, the authors found a statistically significant decrease in pain scores and frequency of pain medication use. Placental tissue matrix therapy has shown compelling benefits in a nonoperative setting as demonstrated by these studies and could be a promising adjuvant to operative treatment for various orthopaedic injuries in the near future.

With increasing utilization and growing interest in these products, orthopaedic surgeons should be aware of the presence of marked differences
that exist among the currently available amniotic and placental tissue-based products. The differences are due to formulations, variations in tissue source, processing methods, sterilization, preservation and storage methods, indications for use, and FDA regulation (Table 1). Amniotic and placental tissue-based products are usually obtained through harvesting human placentas during elective cesarean section procedures. The final products are made through a series of aseptic techniques, and then most are terminally sterilized post-packaging. Sterilization is used to reduce the risk of infection and blood-borne pathogens; however, this is not a requirement for human tissue products like it is for most medical devices. Not all amniotic and placental products are sterilized, and the clinical evidence has shown no advantage to an unsterile product to justify the potential increased safety risk. Product constituents are also distinctive among various products. While some may contain a broad range of growth factors and extracellular matrix components of the harvested placental tissue, others are based on providing stem cells or a richer complete connective tissue matrix biologic scaffold. Newer evolving processing technologies have allowed near-complete preservation of biologically rich placental connective tissue while maximizing sterilization through advanced techniques with promising fab results (BioECM, Sky Biologicals, El Segundo, California).

Another factor to be examined by orthopaedic surgeons when considering the operative use of placental and amniotic membrane products is to ensure on-label application, as this could potentially raise concerns of legal liability. Most of the products reported in the current review, as well as those used for nonoperative indications, are indicated for use as wound coverings and, therefore, their use for tendon injuries is off-label per current FDA-regulations.

**CONCLUSION**

Operative applications of placental and amniotic membrane-derived tissues appear to be safe when used as an adjuvant or augmentation option along with surgical reconstruction. However, several factors may come into play when considering the diversity of commercially available products. Future clinical trials will need to confirm the safety and demonstrate clearer indications and specific guidelines for use in each clinical scenario involving operative management of tendon injuries. Nevertheless, this review will serve as an up-to-date reference and provide an impetus for future investigations.

**AUTHORS’ DISCLOSURES**

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All other authors have no conflicts of interest to disclose.

**REFERENCES**