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MINI REVIEW

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## Amniotic Membrane Transplantation for Ocular Surface Reconstruction

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The use of amniotic membrane (or amnion) for transplantation as graft in ocular surface reconstruction is reviewed. This technique has become widespread because of the availability of the amnion, convenience and ease of use, and high and reproducible success rates. The mechanisms of action of the transplantation are varied and include the prolongation and clonogenic maintenance of epithelial progenitor cells, promotion of goblet and non-goblet cell differentiation, exclusion of inflammatory cells with anti-protease activities, suppression of Transforming Growth Factor  $\beta$  signaling and myoblast differentiation of normal fibroblasts. The observed clinical effects include facilitation of epithelialization, maintenance of normal phenotypes, and reduction of inflammation, vascularization and scarring. Amniotic membrane transplantation is being increasingly used as graft for various conjunctival and corneal diseases and as a patch in cases of chemical and thermal burns, refractory and recalcitrant keratitis, and most recently as an excellent substrate for expanding epithelial stem cells *ex vivo*.

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**KEY WORDS:** Amniotic membrane; conjunctival surface reconstruction; corneal surface reconstruction; ocular surface patch; substrate for stem cell growth.

### HISTORY OF AMNIOTIC MEMBRANE TRANSPLANTATION

Amniotic membrane, or amnion, is the innermost layer of the placenta and consists of a thick basement membrane and an avascular stromal matrix. Amniotic membrane transplantation has been used as a graft or as a dressing (patch) in different surgical subspecialties in early literature (for review see [1]). In English literature, a *live* fetal membrane including both amnion and chorion was first used by De Roth in 1940 as a graft for conjunctival surface reconstruction [2]. Probably due to the inclusion of live cells and the chorion the success rate was low, i.e., one out of six cases, of treating symblepharon and conjunctival defect. Brown [3] in 1940 proposed the use of rabbit peritoneum as a temporary patch to cover the acutely burned ocular surface so as to promote healing and prevent spread of necrosis. Taking from this idea, Sorsby *et al.* [4, 5] in 1946 and 1947 used chemically processed “dry” amniotic membrane, termed “aminoplastin”, as a temporary patch for treating acute ocular burns. They showed that the earlier intervention, the shorter the hospitalization. Although a remarkable success was noted, aminoplastin had to be repetitively

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applied. For reasons still not clear the use of amniotic membrane disappeared from the literature. As early as 1956 Roper-Hall [6] reviewed the subject of chemical burns and concluded that “other materials have been advocated from time to time as a temporary graft with varying enthusiasm”.

In 1995 Kim and Tseng [7] reintroduced amniotic membrane for ophthalmic uses. In a rabbit model they showed that 40% of corneas with total limbal deficiency can be reconstructed by replacing the conjunctivalized surface with a preserved human amniotic membrane. As will be described in detail below, encouraging results have since been reported by a number of investigators (see Fig. 1). We attribute such a surge of interest in this new surgical procedure to an improved method of processing and preservation, which has maintained the inherent properties of the amnion.

### ACTION MECHANISMS

The guidelines and operation standards concerning the procurement, processing and distribution of such a tissue as amniotic membrane are reported by the American Food and Drug Administration (Final Rule: Screening and Testing of Donors of Human Tissue Intended for Transplantation (July 29, 1997), and recently reviewed by Dua [8]. When appropriately processed and preserved (see Fig. 2), the amniotic membrane can be used for a number of indications, either as a graft to replace the damaged ocular surface stromal matrix or as a patch (dressing) to prevent unwanted inflammatory insults from gaining access to the damaged ocular surface, or a combination of both. Recent reports indicate that potential action mechanisms might include the following, which are summarized in Table 1.

Compositionally, the basement membrane component of the amniotic membrane resembles that of the conjunctiva [9]. The basement side of the membrane is an ideal substrate for supporting the growth of epithelial progenitor cells by prolonging their life span and maintaining their clonogenicity. This action supports why amniotic membrane transplantation can be used to expand the remaining limbal

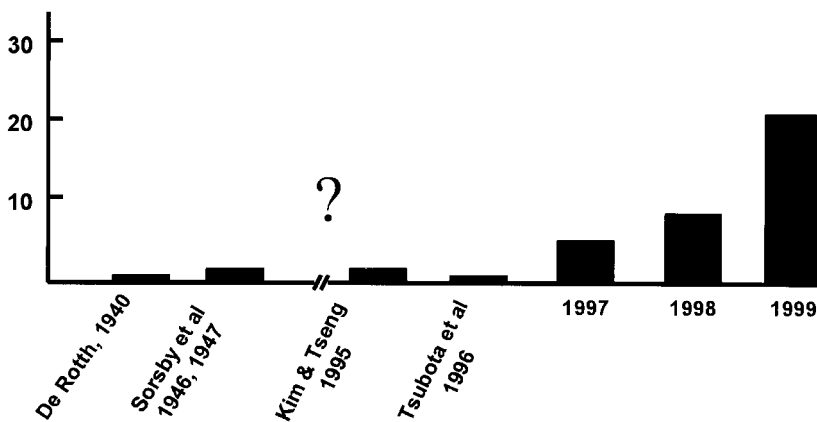
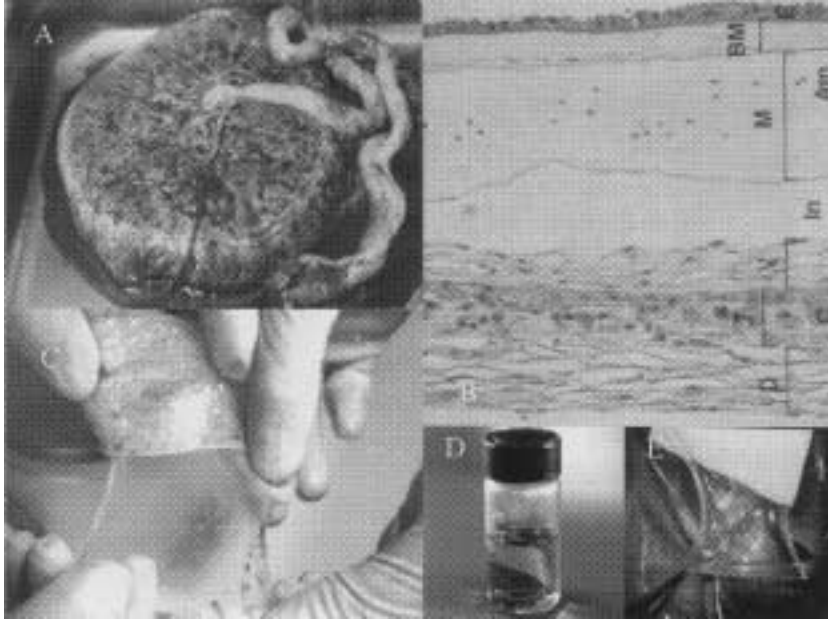


Fig. 1. History of English literature of amniotic membrane transplantation in ophthalmology.



**Fig. 2.** *Histology and preparation of amniotic membrane.* Amniotic membrane (Am) is the innermost layer of the placenta [A] and consists of a thick basement membrane (BM) and an avascular stromal matrix (M), which is apposed to vascularized chorion (C).

stem cells and corneal transient amplifying cells during the treatment of partial limbal deficiency [10] and to facilitate epithelialization for persistent corneal epithelial defects with stromal ulceration [11–13]. In tissue cultures, amniotic membrane supports epithelial cell grown from explant cultures [14–16] or other cultures [17, 18], and maintains their normal epithelial morphology and differentiation [14, 15]. The resultant epithelial cells–amniotic membrane can be transplanted back to reconstruct the damaged corneal surface in humans [17, 19] and in rabbits [16, 17]. The amniotic

**Table 1.** Action Mechanisms and Observed Effects of Amniotic Membrane Transplantation

*Action Mechanisms*

- Prolong life span and maintain clonogenicity of epithelial progenitor cells
- Promote non-goblet cell epithelial differentiation
- Promote goblet cell differentiation when combined with conjunctival fibroblasts
- Exclude inflammatory cells with anti-protease activities
- Suppress TGF- $\beta$  signaling system and myofibroblast differentiation of normal fibroblasts

*Observed Clinical Effects*

- Facilitate epithelialization
- Maintain normal epithelial phenotype
- Reduce inflammation
- Reduce vascularization
- Reduce scarring

*Note:* TGF- $\beta$ : transforming growth factor  $\beta$ .

membrane can also be used to promote non-goblet cell differentiation of the conjunctival epithelium [15]. This data supports why conjunctival goblet cell density is promoted following amniotic membrane transplantation *in vivo* [20].

The stromal side of the membrane contains a unique matrix component that suppresses TGF- $\beta$  signaling, and proliferation and myofibroblast differentiation of normal human corneal and limbal fibroblasts [21] and of normal conjunctival fibroblasts and pterygium body fibroblasts [22]. This action explains why amniotic membrane transplantation reduces scars during conjunctival surface reconstruction [23, 24], prevents recurrent scarring after pterygium removal [25–29] and reduces corneal haze following phototherapeutic keratectomy (PTK) and photorefractive keratectomy (PRK) [30–32]. Although such an action is more potent when fibroblasts are in contact with the stromal matrix, a lesser effect is also noted when fibroblasts are separated from the membrane by a distance [21], suggesting that some diffusible factors might also be involved besides the insoluble matrix components in the membrane. In line with this thinking, several growth factors have been identified in the amniotic membrane [33]. The stromal matrix of the membrane can also exclude inflammatory cells by stimulating them into rapid apoptosis [31, 32] and contains various forms of protease inhibitors [34]. This action explains why stromal inflammation is reduced after amniotic membrane transplantation [11, 23] and corneal neovascularization is mitigated [35], actions important for preparing the stroma for supporting limbal stem cells to be transplanted either at the same time or later [10, 26, 36–39]. This action also explains why keratocyte apoptosis can be reduced and hence stromal haze is prevented in PRK or PTK by amniotic membrane [30–32]. Future studies are needed to resolve the exact action mechanism.

## CLINICAL INDICATIONS

Based on the action mechanisms and observed clinical effects summarized in Table 1, amniotic membrane has been used in the following indications summarized in Table 2.

### AMNIOTIC MEMBRANE AS A GRAFT FOR CONJUNCTIVAL SURFACE RECONSTRUCTION

The above action mechanisms summarized in Table 1 help explain why amniotic membrane transplantation can facilitate epithelialization, maintain normal epithelial phenotype (with goblet cells when performed on conjunctiva [20]), and reduce inflammation, vascularization and scarring. Based on these therapeutic effects, one can envision that amniotic membrane transplantation can be used for conjunctival surface reconstruction to restore normal stroma and provide a healthy basement membrane for renewed epithelial proliferation and differentiation. The reported literature shows that amniotic membrane transplantation can be used to reconstruct the conjunctival surface as an alternative to conjunctival graft following removal of large conjunctival lesions such as pterygium [25–29] conjunctival intraepithelial neoplasia and tumors [23], scars and symblepharon [23, 24, 27], and conjunctivochalasis [40]. These results indicate that the reconstructed area can be very large so long

**Table 2.** Surgical Indications of Amniotic Membrane Transplantation*As a Graft for Conjunctival Diseases*

- Pterygium
- Bulbar Conjunctival Reconstruction after Removal of Large Lesions or Scars
- Symblepharon Lysis
- Conjunctivochalasis
- With or without preserved sclera or pericardium  
for
- Bleb Leakage or Revision
- Scleral Melt
- Lid Reconstruction
- Orbit Reconstruction

*As a Graft for Corneal Diseases*

- Persistent Corneal Epithelial Defect with or without Ulceration
- Partial Limbal Stem Cell Deficiency
- Total Limbal Stem Cell Deficiency (with Limbal Transplantation)
- For Chemical burns, Stevens–Johnson Syndrome
- Painful Bullous Keratopathy with Erosion
- Band Keratopathy

*As a Patch*

- Acute Stage of Chemical or Thermal burns, Stevens–Johnson Syndrome
- Preventing Scar after PRK or PTK
- Refractory or Recalcitrant Inflammatory or Ulcerative Keratitis: HSV, HZO, and Vernal

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As a Carrier for Expanding Epithelial Stem Cells *Ex Vivo*.

as the underlying bed is not ischemic and the bordered conjunctiva has a normal epithelium and subconjunctival stroma. In conjunction with scleral patch graft, amniotic membrane has successfully been used to repair scleral perforation in Marfan's syndrome [41]. As a graft to substitute conjunctival autograft, amniotic membrane can also be used to repair leaking filtration blebs [42]. Because amniotic membrane may substitute conjunctival autograft and thus may be a better alternative to mucous membrane graft in plastic correction of lid abnormality and orbic reconstruction.

### AMNIOTIC MEMBRANE AS A GRAFT FOR CORNEAL SURFACE RECONSTRUCTION

Following diagnosis of limbal deficiency, new strategies include the use of amniotic membrane transplantation and limbal stem cell transplantation [10, 36, 37]. The former is intended to restore the damaged limbal stromal environment, and the latter is to restore the limbal stem cell population. Reported clinical experience showed that this combined approach is effective in treating various extents of limbal deficiency according to the parameters: the extent of limbal deficiency, presence or absence of the central corneal transient amplifying cells (TAC), and depth of central corneal involvement [10].

One major advance made by amniotic membrane transplantation is that partial limbal deficiency can now be reconstructed by this technique without the use of

limbal transplantation [10]. This result, first observed in rabbit experiments at the time when no explanation was available [7], indicates that patients with partial limbal deficiency can now be treated without long-term use of oral cyclosporin. The second advance is the extremely low incidence of limbal allograft rejection, when systemic cyclosporin is concomitantly used when amniotic membrane transplantation is performed as the first stage procedure to restore the limbal stromal environment. This effect is presumably attributed to the restoration of a non-inflamed limbal stroma. Because of these reasons we thus advise performing a limbal allograft but not an autograft as a first attempt to treat unilateral total limbal deficiency or bilateral limbal deficiency with asymmetrical involvement. However, if the limbal allograft fails due to rejection, limbal autograft can then be used as the last resort. In the latter situation, amniotic membrane is ideal for helping both transplanted limbal stem cells expand on the recipient eye and the residual stem cells expand in the donor eye. The remaining difficulty remains in those patients who suffer from severe and deep limbal deficiency leading to concomitant transplantation of corneal grafts. We continued to observe a high rate of rejection [10].

Amniotic membrane can also be applied to treat corneal surface diseases as a graft. When used as a graft or a patch, amniotic membrane can promote healing of persistent corneal ulcers from different causes including neurotrophic keratopathy caused by various underlying etiologies [11–13, 27], and band keratopathy [11]. This approach is superior to conjunctival flaps or tarsorrhaphy as it preserves a cosmetically more acceptable appearance. A recent multi-center trial shows that amniotic membrane transplantation can be used to treat symptomatic bullous keratopathy caused by aphakia, pseudophakia or failed corneal grafts [43]. These patients suffered from pain, recurrent erosion and infection. Although it was advocated for patients without visual potentials, it may help eliminate pain from those who are on the waiting list for corneal transplantation.

### **AMNIOTIC MEMBRANE AS A PATCH**

Amniotic membrane can also be used as a patch in a temporary or prolonged manner. Experimentally, when used as a patch on a temporary basis this membrane has been shown to reduce corneal haze following PRK or PTK [30, 31], an effect verified in human patients [27, 44]. As a temporary patch, amniotic membrane can reduce inflammation, facilitate epithelialization and prevent scarring caused by acute chemical burns in a rabbit model [44] and in human patients [45]. Based on these actions, amniotic membrane as a patch was also used successfully in the acute stage of Stevens Johnson syndrome [46] and to suppress refractory inflammation in various ocular surface disorders [47]. Further research in this area may uncover additional applications of using amniotic membrane as a patch.

### **AM AS A CARRIER FOR SUPPORTING AND EXPANDING LIMBAL EPITHELIAL STEM CELLS *EX VIVO* FOR TREATING TOTAL LIMBAL STEM CELL DEFICIENCY**

The fact that the amniotic membrane can help preserve and expand limbal epithelial stem cells indicates that it can also be used as a carrier to expand them *in*

*vitro* culture. This new approach is applicable to those patients with limited limbal reserve or who are concerned about having a large part of the healthy limbus removed from the fellow eye or from a living-related donor. In this case, a small limbal biopsy will be performed and the sample will be placed on the amniotic membrane and appropriately cultured. Within three to four weeks, such an *ex vivo* expanded culture together with the amniotic membrane can then be transplanted to restore the normal corneal surface on limbal deficient corneas. The feasibility of this new approach based on an autologous source has been demonstrated in a short-term rabbit study [16] and in long-term human patients [17, 19, 48]. This new approach paves the way to use amniotic membrane as a tissue engineering substrate and may open up new therapeutics by incorporating gene therapies in the future.

### LIMITATIONS

One should recognize that amniotic membrane transplantation is a substrate transplantation and thus cannot be used to treat ocular surface disorders that are characterized with a total loss of limbal epithelial stem cells or conjunctival epithelial stem cells. Because amniotic membrane transplantation still relies on the host tissue to supply epithelial and mesenchymal cells, it cannot be used to reconstruct the ocular surface that has severe aqueous tear deficiency, diffuse keratinization [39], absence of blinking in severe neurotrophic state, and stromal ischemia. If not overcome, these conditions present as contraindication for amniotic membrane transplantation.

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