https://doi.org/10.5114/oku/191664 (Research Paper)

Received: 31.03.2024 Accepted: 06.05.2024

Applications of Amniotic Membrane in Ophthalmology – New Perspectives in the Treatment of Eye Diseases

Larysa Krajewska-Węglewicz

Department of Ophthalmology, National Institute of Medicine of the Ministry of Interior and Administration in Warsaw, Poland
Head: Joanna Sempińska-Szewczyk, MD, PhD

Summary: Amniotic membrane, a natural protective barrier surrounding the fetus, possesses unique biological properties, making it a promising tool in regenerative medicine. It contains pluripotent cells, collagen, anti-inflammatory cytokines, and growth factors. This article aims to present the current state of knowledge regarding the potential applications of amniotic membrane in ophthalmology, as well as the benefits and challenges associated with this promising therapy. Amniotic membrane, used in the form of a graft or extract, exhibits anti-inflammatory effects, accelerates tissue healing, and regenerates corneal epithelium. In ophthalmology, amniotic membrane is used in the treatment of corneal ulcers, limbal stem cell deficiency, burns, strabismus, glaucoma, and neoplastic changes. It can also be used in the reconstruction of the ocular surface and in vitreoretinal surgery. Studies demonstrate its effectiveness in improving symptoms of dry eye syndrome. Additionally, new methods of combining amniotic membrane with the ocular surface are being introduced. Amniotic membrane is also used as a carrier in stem cell culture. The development of technology and research on amniotic membrane lead to the discovery of new applications and the improvement of surgical techniques, opening up prospects for even broader utilization of its potential in the future.

Key words: amnion, amniotic membrane, ophthalmology, cornea, pterygium.

Introduction

Amniotic membrane (AM), a thin yet sturdy layer enveloping the fetus in utero, serves as a natural protective barrier. Because of its unique biological characteristics, such as the capacity to expedite tissue healing and anti-inflammatory properties, AM plays an important role in regenerative medicine. AM contains pluripotent cells, highly organized collagen, antifibrotic and anti-inflammatory cytokines, immunomodulators, growth factors, and matrix proteins. The first documented use of amniotic membrane in tissue treatment dates back to 1910, when Davis used AM in a skin graft procedure [1]. De Roth was the first to utilize amniotic membrane in the treatment of chemical burn [2], but the applications of AM in ophthalmology were discontinued until the early 1990s, when Batlle documented the use of amniotic membrane in conjunctival injury [3], while Kim and Tseng reported the application of AM in ocular surface reconstruction [4]. Since then, amniotic membrane has emerged as a promising therapeutic option in ophthalmology, holding potential benefits for the treatment of many eye diseases. AM is used primarily in the form of a film covering a damaged area. However, recently, AM extract and AM extract eye drops have shown successful clinical applications, for example in treating conditions like dry eye syndrome and chemical burns. Researchers are continually uncovering novel properties of amniotic membrane, driving the search for innovative applications of AM in ophthalmology. This article aims to present the current state of knowledge regarding the applications of AM in ophthalmology.

Classification and properties of amniotic membrane

Amniotic membrane is a component of the chorion, consisting of a single layer of epithelial cells, basement membrane, and connective tissue matrix devoid of blood vessels. It is surrounded by amniotic fluid [5]. AM contains a rich extracellular matrix, which includes collagen, laminins, signaling proteins (cytokines), and growth factors. It exhibits anti-inflammatory, anti-angiogenic, immunomodulatory, antibacterial, angiomodulatory, and anti-cicatricial properties [6]. The most important beneficial effects of AM can be attributed to the presence of molecules such as transforming growth factor (TGF), hepatocyte growth factor (HGF), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), fibronectin, and collagen types I, III, IV, and V, which contribute significantly to corneal regeneration [7]. They facilitate the migration, adhesion, and differentiation of the corneal epithelium while inhibiting apoptosis. AM has an effect on reducing the expression of cell surface markers including CD80, CD86, and class 2 antigens of the major histocompatibility complex, which modulate the immune response. In addition, AM decreases the secretion of pro-inflammatory cytokines like tumor necrosis factor alpha and IL-6, while increasing the production of anti-inflammatory cytokines such as IL-10. As a result, inflammation is reduced, while lower levels of TGF-1 and TGF-2 inhibit the fibrosis process [8]. Together, these mechanisms contribute to promoting wound healing and regeneration.

In ophthalmology, AM is frequently employed for amniotic membrane transplantation (AMT). The procedure typically relies on fresh membrane, frozen at -80°C. However, AM can also be freeze-dried, stored, and subsequently rehydrated before use.

Amniotic Membrane Extract (AME)

AME shares many properties with cryopreserved amnion [7].

Similarly to AM, AME contains high levels of multiple growth factors such as EGF, HGF, bFGF, protease inhibitors, and a novel matrix component HC-HA/PTX3 which helps prevent inflammation, angiogenesis, and scarring [6].

AME exhibits anti-inflammatory properties through the down-regulation and induction of apoptosis in macrophages [9].

AME can be combined with umbilical cord blood (UCB). The combination may be beneficial because UCB contains higher levels of the HC-HA/PTX3 complex, which is responsible

ISSN 1505-2753

for the anti-inflammatory effects of AM. Additionally, UCB is known to be more effective than AM in inhibiting inflammatory markers [10]. AME can also be used to formulate eye drops known as Amniotic Membrane Extract Eye Drops (AMEED). There are numerous small studies describing various applications of AME and AMEED. AMEED shows promise in treating corneal damage leading to persistent epithelial defects (PEDs). Eye drops containing morselized cryopreserved amnion and umbilical cord serum (AMUC) were found to promote epithelial regeneration in a murine corneal abrasion model [10]. AMUC also demonstrated therapeutic efficacy in promoting healing of PEDs in patients with cicatrizing ocular surface diseases [11].

Furthermore, AMEED can be beneficial in treating various conditions including partial limbal stem cell deficiency, bullous keratopathy, corneoscleral ulcers, and during the acute phase of chemical burns [6].

AMEED may extend the treatment duration post-application of AM by delivering active growth factors and compounds to damaged corneal cells over a prolonged period. When used in combination, AM and AMEED can synergistically support ocular surface stability, stimulate stem cell growth, and promote corneal epithelial differentiation [6]. A potential drawback of AMEED is that it does not retain the structural properties of AM.

Amniotic fluid (AF)

AF contains electrolytes, growth factors, carbohydrates, lipids, proteins, amino acids, lactate, pyruvate, enzymes, and hormones [12].

The presence of multiple growth factors, including vascular endothelial growth factor, TGF-β1, TGF-β3, and growth differentiation factor-11, may facilitate cell growth and promote the regeneration of healthy collagen types I, II, III, IV, V, and VI, thereby supporting the healing process.

PLP is recognized as immune-privileged [12]. Even though the composition of PLP changes significantly as pregnancy progresses, influenced by factors such as increasing fetal urine output and pulmonary secretion, pluripotent stem cells have been isolated from AF throughout the entire pregnancy.

Ocular surface reconstruction

Ocular surface reconstruction using AM can be performed through three methods:

1. Graft or inlay technique. It involves positioning AM with the basement membrane facing upward. AM serves as a substrate for epithelial cell growth and becomes integrated into host tissues [13, 14];
2. Patch or overlay technique. In this application, the purpose of AM is to serve as a biological dressing to cover the surface [15];
3. Layered or sandwich technique. It entails placing small pieces of AM in the ulcer and subsequently overlaying it with AM graft [16].

The efficacy of the three techniques in treating corneal ulcers was evaluated by Lui et al. in a meta-analysis of 18 studies. The highest rate of epithelial healing was found in the group treated with the sandwich method. However, the technique resulted in the least improvement in visual acuity, which complicates the choice of an appropriate modality [17].

Advanced methods for attaching AM to the ocular surface

Typically, AM is fixated using sutures. However, this technique may potentially lead to damage to the surface of the eye, bleeding or scarring. Sutureless techniques involve the use of tissue adhesive [18], chemical bioadhesive agents [19], photoactivated rose Bengal dye [20], or medical devices like Prokera or AmnioClip [21]. Tissue adhesive can serve as a convenient alternative for AM fixation at the bedside [22]. Ma et al. introduced a technique involving suturing AM to the upper eyelid, positioning the amnion on the ocular surface and securing it with a ring attached to the fornices. The aim of the method is to reduce damage to the ocular surface in patients with Stevens-Johnson syndrome [23].

Amniotic membrane in the treatment of corneal diseases

The cornea is the thin, clear, front part of the eye, crucial for the process of vision. Damage to the cornea, regardless of its cause, can severely impair visual acuity. Traditionally, treatment options for such conditions have involved either corneal transplantation or the application of therapeutic contact lenses. However, the use of amniotic membrane in the treatment of corneal diseases presents several advantages.

Corneal ulcers

A retrospective analysis conducted by Schuerch et al. [24] involved 149 eyes with non-epithelializing corneal ulcers that were refractory to standard medical treatments. It needs to be noted that the study included patients with ulcers caused by various factors, primarily herpetic infections or a history of previous penetrating keratoplasty. The highest rates of epithelialization in corneal defects were observed in ulcers resulting from bullous keratopathy (79%), bacterial ulcers (80%), herpetic ulcers (85%), and neurotrophic ulcers (93%), primarily within the first three months following AM transplantation. It is important to note that ulcers associated with rheumatic diseases achieved epithelialization in only 52.5% of cases.

Tabatabaei et al. conducted a comparative study of 99 eyes diagnosed with bacterial keratitis. Treatment was started with topical antibiotics. After two to five days, in the study group, AM was affixed with sutures, with standard treatment continued in both groups. The AM graft was deemed safe and demonstrated superior visual acuity outcomes at six months ($p < 0.001$) compared to the group receiving conservative treatment [25]. Other studies show positive outcomes in terms of reducing pain and promoting epithelial healing when early AMT intervention (within 48 hours) is combined with topical steroids (initiated after 72 hours). Randomized controlled studies by Fuchsluger et al. [26] and Khokhar et al. [27] evaluating the application of AM in ulcers associated with neurotrophic keratopathy found AM to have comparable efficacy to therapeutic contact lenses or tarsorrhaphy. Amniotic membrane can also be used following procedures performed to remove band keratopathy [28] or to alleviate pain associated with bullous keratopathy [29]. The efficacy of reducing pain in bullous keratopathy was demonstrated in a study involving 55 patients who underwent corneal epithelial removal followed by fixation of amniotic membrane [30].

Limbal stem cell deficiency

Broad applications of AM in limbal stem cell deficiency encompass a range of cicatrizing conditions, including Stevens-Johnson syndrome, chemical and thermal burns, and cicatricial ocular pemphigoid. In such cases, transplantation of limbal stem cells on an AM carrier is performed [31].

Cell-free AM serves as a substrate for ex vivo culture of limbal epithelial cells. Subsequently, AM containing cultured cells is transplanted onto the corneal surface [32].

Treatment outcomes are worse in patients with progressive scarring, such as Stevens-Johnson syndrome and cicatricial ocular pemphigoid, compared to patients with chemical burns.

Chemical and thermal burns

Because of its biological properties, AM supports treatment after burns. It demonstrates epitheliotropic and anti-inflammatory effects, and inhibits vascular tumorigenesis. In addition, AM increases oxygen permeability, reduces epithelial abrasion caused by eyelid friction, and relieves pain. In a randomized controlled trial conducted by Tandon in patients with chemical burns, AM was transplanted with the epithelium-side down within seven days of injury. The study involved 100 patients. AM was found to significantly enhance epithelialization in moderate burns (grades II–III according to the Roper-Hall classification). However, no benefit of amniotic membrane (AM) was observed in terms of final visual acuity, symblepharon formation, neovascularization, or corneal transparency [33]. Similarly, Sharma et al. found that AM promoted faster epithelialization but did not improve ultimate outcomes including final visual acuity, symblepharon formation, tear film quality, or eyelid disorders [34]. Nevertheless, no effect on accelerating epithelialization was achieved in patients with Roper-Hall grade IV burns [35]. In conclusion, AM can help heal milder burns and relieve pain and inflammation when applied within the first week after injury. Nevertheless, its effect on the final treatment outcomes is limited. The anti-inflammatory properties demonstrated by AM may be insufficient to counteract the effects of limbal stem cell deficiency, and its anti-angiogenic characteristics could potentially be detrimental in certain cases by inhibiting therapeutic angiogenesis.

Oculoplasty

In oculoplastic surgery, AM may be an alternative to mucosal grafts, particularly when obtaining the patient's own mucosa is challenging or not feasible. AM has applications in eyelid surgery and fornix reconstruction [36], and in covering the orbital surface, e.g. in anophthalmia [37], cryptophthalmos [38], and symblepharon repair. Treatment outcomes can be improved by using mitomycin C [39].

There are reported cases of using AM in the surgical treatment of cicatricial entropion, with AM applied to cover the tarsus after anterior lamella recession procedure [40]. At one-year follow-up, in 88% of patients there were no lashes touching the globe.

AM was also used in the Hughes procedure following the resection of conjunctival melanoma involving the fornix [41].

In patients with cicatricial pemphigoid, attempts have been undertaken to use AM for conjunctival reconstruction [42]. In their study, Barabino et al. additionally used systemic treatment with immunosuppressive drugs and steroids for a period of six months. At 28 weeks after the procedure, adequate fornix depth was achieved. However, with time, fornix shallowing was observed [42]. Similar outcomes were achieved in the treatment of patients with Stevens-Johnson syndrome [43].

Cancerous lesions

AM can be used for reconstructing the ocular surface following the removal of benign or malignant tumors. AM is hypothesized to possess anti-neoplastic effects, though the precise mechanism of action remains unclear. AM is known to contain interleukins (IL-2, IL-3, IL-4) and express cytotoxic cytokines [44]. The application of AM in reconstructive procedures after melanoma excision was shown to accelerate healing and minimize the occurrence of symblepharon, granulation tissue, and scarring [45]. Some authors highlight the advantage of AM over oral mucosa transplants in monitoring recurrence of the neoplastic process, which is attributed to the greater transparency of AM and superior esthetic outcomes [46].

Pterygium

A Cochrane meta-analysis showed that pterygium removal surgery combined with autologous conjunctival transplantation was associated with the highest therapeutic efficacy [47]. In patients after conjunctival transplantation, fewer recurrences of pterygium were observed at six months compared to patients treated with AM, including cases of recurrent pterygium [47] and double-head pterygium (nasal and temporal) [48, 49]. An advantage of using AM is that there is no damage to the donor site.

Strabismus

In strabismus surgery, AM is used to prevent fibrosis and to cover defects. There is no conclusive information on the optimal orientation of amniotic membrane. Also, no agreement exists regarding the superiority of either method [50]. Currently, there are no multicenter studies comparing the suture-assisted and sutureless techniques of AM fixation. Kassem argues that the sutureless method provides greater advantages by reducing the inflammatory reaction and shortening the duration of the procedure [51]. Indications for the use of AM include cases of complicated strabismus, e.g. correction of diplopia after vitrectomy [52], congenital fibrosis of extraocular muscles [53], and recurrent strabismus [54].

Dry eye syndrome

AM is effective in the treatment of severe dry eye syndrome, reducing patient discomfort and alleviating clinical symptoms [55]. It was found that wearing Prokera for five days a week led to a four-month improvement in symptoms, manifested as reduced corneal and conjunctival staining, as well as improved visual acuity [56]. AM was also shown to improve the density of corneal nerves [57], which may potentially improve the condition of the ocular surface.

Glaucoma

In the treatment of glaucoma, the most frequent application of amniotic membrane is during trabeculectomy procedures. Meta-analysis findings suggest a more substantial decrease in intraocular pressure following trabeculectomy with AM compared to trabeculectomy alone, both in primary procedures [58] and in repeat trabeculectomies. Sheha found that combining AM with mitomycin C improved the therapeutic efficacy of trabeculectomy in refractory glaucoma. The approach achieved an intraocular pressure below 22 mmHg without the need for topical drugs in 93.7% of patients [59]. However, in Bochmann's meta-analysis on interventions for persistent filtering bleb leaks after trabeculectomy, there was no observed advantage of AM over conjunctival advancement [60].

AM can be attached over bare sclera to replace lost or damaged conjunctiva. It is also used in procedures involving drainage devices [61] and in the management of complications following procedures with drainage devices and minimally invasive glaucoma surgeries [62].

Vitreoretinal surgery

The use of AM in vitreoretinal surgery represents a novel and promising indication. To close macular holes, AM plugs can be implanted under the retina [63]. Retinal pigment epithelium cells were observed to cover AM within 24 hours of implantation. They proliferate on its surface, forming a layer of tightly packed cells with well-developed intercellular interactions, secreting growth factors [64]. Caporossi conducted a study involving 16 myopic eyes with a macular hole, treated by pars plana vitrectomy combined with AM implantation. Macular hole closure was achieved in all cases; one patient required reoperation [63]. Caporossi also documented two cases of patients with retinal detachment and a macular tear. The author performed pars plana vitrectomy with AM and silicone oil, achieving improved visual acuity and coverage of the AM plug by neurosensory retina [65].

Conclusions

The article provides an overview of the current knowledge regarding the applications of AM in ophthalmology. The precise mechanisms of action of AM are still not completely understood. The list of indications for AM application is growing as medicine progresses. At the same time, as more studies involve larger participant groups and longer observation periods, the understanding of the effectiveness of AM in current applications is steadily expanding. The future appears promising for this innovative therapy in ophthalmology.

Disclosure
Conflict of interests: none declared
Funding: no external funding
Ethics approval: Not applicable.

References:

1. Davis JS: *Skin Grafting at the Johns Hopkins Hospital*. Annals of Surgery. 1909; 50(3): 542–549. doi:10.1097/00000658-190909000-00002
2. de Rotth A: *Plastic Repair of Conjunctival Defects with Fetal Membranes*. Archives of Ophthalmology. 1940; 23(3): 522–525. doi:10.1001/archopht.1940.00860130586006
3. Batlle JF, Perdomo FJ: *Placental membranes as a conjunctival substitute*. Ophthalmology. Published online 1993.
4. Kim JC, Tseng SC: *Transplantation of preserved human amniotic membrane for surface reconstruction in severely damaged rabbit corneas*. Cornea. 1995; 14(5): 473–484.
5. Koob TJ, Lim JJ, Zabek N, et al.: *Cytokines in single layer amnion allografts compared to multilayer amnion/chorion allografts for wound healing*. J Biomed Mater Res B Appl Biomater. 2015; 103(5): 1133–1140. doi:10.1002/jbm.b.33265
6. Baradaran-Rafii A, Asl NS, Ebrahimi M, et al.: *The role of amniotic membrane extract eye drop (AMEED) in in vivo cultivation of limbal stem cells*. Ocul Surf. 2018; 16(1): 146–153. doi:10.1016/j.jtos.2017.11.001
7. Dudok DV, Nagdee I, Cheung K, et al.: *Effects of amniotic membrane extract on primary human corneal epithelial and limbal cells*. Clin Exp Ophthalmol. 2015; 43(5): 443–448. doi:10.1111/ceo.12480
8. Dua HS, Rahman I, Miri A, et al.: Said DG: *Variations in amniotic membrane: relevance for clinical applications*. Br J Ophthalmol. 2010; 94(8): 963–964. doi:10.1136/bjo.2009.157941
9. He H, Li W, Chen SY, et al.: *Suppression of activation and induction of apoptosis in RAW264.7 cells by amniotic membrane extract*. Invest Ophthalmol Vis Sci. 2008; 49(10): 4468–4475. doi:10.1167/iovs.08-1781
10. Tighe S, Moein HR, Chua L, et al.: *Topical Cryopreserved Amniotic Membrane and Umbilical Cord Eye Drops Promote Re-Epithelialization in a Murine Corneal Abrasion Model*. Invest Ophthalmol Vis Sci. 2017; 58(3): 1586–1593. doi:10.1167/iovs.16-20834
11. Cheng AMS, Chua L, Casas V, et al.: *Morselized Amniotic Membrane Tissue for Refractory Corneal Epithelial Defects in Cicatricial Ocular Surface Diseases*. Trans Vis Sci Tech. 2016; 5(3): 9. doi:10.1167/tvst.5.3.9
12. Rennie K, Gruslin A, Hengstschläger M, et al.: *Applications of amniotic membrane and fluid in stem cell biology and regenerative medicine*. Stem Cells Int. 2012; 2012: 721538. doi:10.1155/2012/721538
13. Röck T, Bartz-Schmidt KU, Landenberger J, et al.: *Amniotic Membrane Transplantation in Reconstructive and Regenerative Ophthalmology*. Ann Transplant. 2018; 23: 160–165. doi:10.12659/AOT.906856
14. Jirsova K, Jones GLA: *Amniotic membrane in ophthalmology: properties, preparation, storage and indications for grafting – a review*. Cell Tissue Bank. 2017; 18(2): 193–204. doi:10.1007/s10561-017-9618-5
15. Malhotra C, Jain AK: *Human amniotic membrane transplantation: Different modalities of its use in ophthalmology*. WJT. 2014; 4(2): 111. doi:10.5500/wjt.v4.i2.111
16. Dua HS, Gomes JAP, King AJ, et al.: *The amniotic membrane in ophthalmology*. Survey of Ophthalmology. 2004; 49(1): 51–77. doi:10.1016/j.survophthal.2003.10.004
17. Liu J, Li L, Li X: *Effectiveness of Cryopreserved Amniotic Membrane Transplantation in Corneal Ulceration: A Meta-Analysis*. Cornea. 2019; 38(4): 454– 462. doi:10.1097/ICO.0000000000001866
18. Hick S, Demers PE, Brunette I, et al.: *Amniotic membrane transplantation and fibrin glue in the management of corneal ulcers and perforations: a review of 33 cases*. Cornea. 2005; 24(4): 369–377. doi:10.1097/01.ico.0000151547.08113.d1
19. Takaoka M, Nakamura T, Sugai H, et al.: *Sutureless amniotic membrane transplantation for ocular surface reconstruction with a chemically defined bioadhesive*. Biomaterials. 2008; 29(19): 2923–2931. doi:10.1016/j.biomaterials.2008.03.027
20. Soeken TA, Zhu H, DeMartelaere S, et al.: *Sealing of Corneal Lacerations Using Photoactivated Rose Bengal Dye and Amniotic Membrane*. Cornea. 2018; 37(2): 211–217. doi:10.1097/ICO.0000000000001389
21. Kotomin I, Valtink M, Hofmann K, et al.: *Sutureless fixation of amniotic membrane for therapy of ocular surface disorders*. PLoS One. 2015; 10(5): e0125035. doi:10.1371/journal.pone.0125035
22. Shanbhag SS, Chodosh J, Saeed HN: *Sutureless amniotic membrane transplantation with cyanoacrylate glue for acute Stevens-Johnson syndrome/toxic epidermal necrolysis*. Ocul Surf. 2019; 17(3): 560–564. doi:10.1016/j.jtos.2019.03.001
23. Ma KN, Thanos A, Chodosh J, et al.: *A Novel Technique for Amniotic Membrane Transplantation in Patients with Acute Stevens-Johnson Syndrome*. Ocul Surf. 2016; 14(1): 31–36. doi:10.1016/j.jtos.2015.07.002
24. Schuerch K, Baeriswyl A, Frueh BE, et al.: *Efficacy of Amniotic Membrane Transplantation for the Treatment of Corneal Ulcers*. Cornea. 2020; 39(4): 479–483. doi:10.1097/ICO.0000000000002179
25. Tabatabaei SA, Soleimani M, Behrouz MJ, et al.: *A randomized clinical trial to evaluate the usefulness of amniotic membrane transplantation in bacterial keratitis healing*. Ocul Surf. 2017; 15(2): 218–226. doi:10.1016/j.jtos.2017.01.004
26. Fuchsluger T, Tuerkeli E, Westekemper H, et al.: *Rate of epithelialisation and re-operations in corneal ulcers treated with amniotic membrane transplantation combined with botulinum toxin-induced ptosis*. Graefes Arch Clin Exp Ophthalmol. 2007; 245(7): 955–964. doi:10.1007/s00417-006-0493-1
27. Khokhar S, Natung T, Sony P, et al.: *Amniotic Membrane Transplantation in Refractory Neurotrophic Corneal Ulcers: A Randomized, Controlled Clinical Trial*. Cornea. 2005; 24(6): 654–660. doi:10.1097/01.ico.0000153102.19776.80
28. Anderson DF, Prabhasawat P, Alfonso E, et al.: *Amniotic Membrane Transplantation After the Primary Surgical Management of Band Keratopathy*. Cornea. 2001; 20(4): 354–361. doi:10.1097/00003226-200105000-00004
29. Altiparmak UE, Oflu Y, Yildiz EH, et al.: *Prospective Comparison of Two Suturing Techniques of Amniotic Membrane Transplantation for Symptomatic Bullous Keratopathy*. American Journal of Ophthalmology. 2009; 147(3): 442–446.e1. doi:10.1016/j.ajo.2008.08.036
30. Pires RT, Tseng SC, Prabhasawat P, et al.: *Amniotic membrane transplantation for symptomatic bullous keratopathy*. Arch Ophthalmol. 1999; 117(10): 1291–1297. doi:10.1001/archopht.117.10.1291
31. Koizumi N, Sakamoto Y, Okumura N, et al.: *Cultivated corneal endothelial cell sheet transplantation in a primate model*. Invest Ophthalmol Vis Sci. 2007; 48(10): 4519–4526. doi:10.1167/iovs.07-0567
32. Fernandez-Buenaga R, Aiello F, Zaher SS, et al.: *Twenty years of limbal epithelial therapy: an update on managing limbal stem cell deficiency*. BMJ Open Ophthalmol. 2018; 3(1):e000164. doi:10.1136/bmjophth-2018-000164
33. Tandon R, Gupta N, Kalaivani M, et al.: *Amniotic membrane transplantation as an adjunct to medical therapy in acute ocular burns*. Br J Ophthalmol. 2011; 95(2): 199–204. doi:10.1136/bjo.2009.173716
34. Sharma N, Singh D, Maharana PK, et al.: *Comparison of Amniotic Membrane Transplantation and Umbilical Cord Serum in Acute Ocular Chemical Burns: A Randomized Controlled Trial*. Am J Ophthalmol. 2016; 168: 157–163. doi:10.1016/j.ajo.2016.05.010
35. Eslani M, Baradaran-Rafii A, Cheung AY, et al.: *Amniotic Membrane Transplantation in Acute Severe Ocular Chemical Injury: A Randomized Clinical Trial*. Am J Ophthalmol. 2019; 199: 209–215. doi:10.1016/j.ajo.2018.11.001
36. Oliphant H, Rajak SN: *Dried amniotic membrane in fornix reconstruction*. Clin Exp Ophthalmol. 2019; 47(8): 1090–1091. doi:10.1111/ceo.13566
37. Thatte S, Jain J: *Fornix Reconstruction with Amniotic Membrane Transplantation: A Cosmetic Remedy for Blind Patients*. J Ophthalmic Vis Res. 2016; 11(2): 193–197. doi:10.4103/2008-322X.183916
38. Ding J, Hou Z, Li Y, et al.: *Eyelid and fornix reconstruction in abortive cryptophthalmos: a single-center experience over 12 years*. Eye (Lond). 2017; 31(11): 1576–1581. doi:10.1038/eye.2017.94
39. Tseng S, Dipascuale M, Liu D, et al.: *Intraoperative Mitomycin C and Amniotic Membrane Transplantation for Fornix Reconstruction in Seve-*

re Cicatricial Ocular Surface Diseases. Ophthalmology. 2005; 112(5): 896–903.e1. doi:10.1016/j.ophtha.2004.11.041
40. Ti SE, Tow SL, Chee SP: *Amniotic membrane transplantation in entropion surgery*. Ophthalmology. 2001; 108(7): 1209–1217. doi:10.1016/s0161-6420(01)00599-1
41. Becerra EM, Blanco G, Saornil MA, et al.: *Hughes technique, amniotic membrane allograft, and topical chemotherapy in conjunctival melanoma with eyelid involvement*. Ophthalmic Plast Reconstr Surg. 2005; 21(3): 238–240. doi:10.1097/01.iop.0000161993.33230.a8
42. Barabino S, Rolando M, Bentivoglio G, et al.: *Role of amniotic membrane transplantation for conjunctival reconstruction in ocular-cicatricial pemphigoid*. Ophthalmology. 2003; 110(3): 474–480. doi:10.1016/S0161-6420(02)01892-4
43. Honavar SG, Bansal AK, Sangwan VS, et al.: *Amniotic membrane transplantation for ocular surface reconstruction in Stevens-Johnson syndrome*. Ophthalmology. 2000; 107(5): 975–979. doi:10.1016/s0161-6420(00)00026-9
44. Niknejad H, Yazdanpanah G: *Anticancer effects of human amniotic membrane and its epithelial cells*. Med Hypotheses. 2014; 82(4): 488–489. doi:10.1016/j.mehy.2014.01.034
45. Agraval U, Rundle P, Rennie IG, et al.: *Fresh frozen amniotic membrane for conjunctival reconstruction after excision of neoplastic and presumed neoplastic conjunctival lesions*. Eye (Lond). 2017; 31(6): 884–889. doi:10.1038/eye.2016.322
46. Paridaens D, Beekhuis H, van Den Bosch W, et al.: *Amniotic membrane transplantation in the management of conjunctival malignant melanoma and primary acquired melanosis with atypia*. Br J Ophthalmol. 2001; 85(6): 658–661. doi:10.1136/bjo.85.6.658
47. Clearfield E, Muthappan V, Wang X, et al.: *Conjunctival autograft for pterygium*. Cochrane Database Syst Rev. 2016; 2(2): CD011349. doi:10.1002/14651858.CD011349.pub2
48. Akbari M, Soltani-Moghadam R, Elmi R, et al.: *Comparison of free conjunctival autograft versus amniotic membrane transplantation for pterygium surgery*. J Curr Ophthalmol. 2017; 29(4): 282–286. doi:10.1016/j.joco.2017.08.003
49. Prajna NV, Devi L, Seeniraj SK, et al.: *Conjunctival Autograft Versus Amniotic Membrane Transplantation After Double Pterygium Excision: A Randomized Trial*. Cornea. 2016; 35(6): 823–826. doi:10.1097/ICO.0000000000000812
50. Kassem RR, El-Mofty RMAM, Khodeir MM, et al.: *A comparative study of different amniotic membrane orientations during extraocular muscle surgery in rabbits*. Curr Eye Res. 2018; 43(3): 325–332. doi:10.1080/02713683.2017.1401645
51. Kassem RR, El-Mofty RMAM: *Amniotic Membrane Transplantation in Strabismus Surgery*. Curr Eye Res. 2019; 44(5): 451–464. doi:10.1080/02713683.2018.1562555
52. Yamada M, Shinoda K, Hatakeyama A, et al.: *Fat adherence syndrome after retinal surgery treated with amniotic membrane transplantation*. Am J Ophthalmol. 2001; 132(2): 280–282. doi:10.1016/s0002-9394(01)00930-8
53. Kersey JP, Vivian AJ: *Mitomycin and amniotic membrane: a new method of reducing adhesions and fibrosis in strabismus surgery*. Strabismus. 2008; 16(3): 116–118. doi:10.1080/09273970802405493
54. Tugcu B, Helvacioglu F, Yuzbasioglu E, et al.: *Amniotic membrane in the management of strabismus reoperations*. Jpn J Ophthalmol. 2013; 57(2): 239–244. doi:10.1007/s10384-012-0217-5
55. Craig JP, Nelson JD, Azar DT, et al.: *TFOS DEWS II Report Executive Summary*. The Ocular Surface. 2017; 15(4): 802–812. doi:10.1016/j.jtos.2017.08.003
56. McDonald MB, Sheha H, Tighe S, et al.: *Treatment outcomes in the DRy Eye Amniotic Membrane (DREAM) study*. Clin Ophthalmol. 2018; 12: 677–681. doi:10.2147/OPTH.S162203
57. John T, Tighe S, Sheha H, et al.: *Corneal Nerve Regeneration after Self--Retained Cryopreserved Amniotic Membrane in Dry Eye Disease*. Journal of Ophthalmology. 2017; 2017: 1–10. doi:10.1155/2017/6404918
58. Wang X, Khan R, Coleman A: *Device-modified trabeculectomy for glaucoma*. Cochrane Database Syst Rev. 2015; 2015(12): CD010472. doi:10.1002/14651858.CD010472.pub2
59. Sheha H, Kheirkhah A, Taha H: *Amniotic Membrane Transplantation in Trabeculectomy With Mitomycin C for Refractory Glaucoma*. Journal of Glaucoma. 2008; 17(4): 303–307. doi:10.1097/IJG.0b013e31815c3a47
60. Bochmann F, Azuara-Blanco A: *Interventions for late trabeculectomy bleb leak*. Cochrane Database Syst Rev. 2012; (9): CD006769. doi:10.1002/14651858.CD006769.pub2
61. Yazdani S, Mahboobipour H, Pakravan M, et al.: *Adjunctive Mitomycin C or Amniotic Membrane Transplantation for Ahmed Glaucoma Valve Implantation: A Randomized Clinical Trial*. Journal of Glaucoma. 2016; 25(5): 415–421. doi:10.1097/IJG.0000000000000256
62. Arnould L, Theillac V, Moran S, et al.: *Recurrent Exposure of XEN Gel Stent Implant and Conjunctival Erosion*. Journal of Glaucoma. 2019; 28(3): e37–e40. doi:10.1097/IJG.0000000000001146
63. Caporossi T, Pacini B, de Angelis L, et al.: *Human Amniotic Membrane To Close Recurrent, High Myopic Macular Holes in Pathologic Myopia with Axial Length of ≥30 mm*. Retina. 2020; 40(10): 1946–1954. doi:10.1097/IAE.0000000000002699
64. Ohno-Matsui K, Ichinose S, Nakahama Kichi, et al.: *The effects of amniotic membrane on retinal pigment epithelial cell differentiation*. Mol Vis. 2005; 11: 1–10.
65. Caporossi T, Tartaro R, de Angelis L, et al.: *A human amniotic membrane plug to repair retinal detachment associated with large macular tear*. Acta Ophthalmologica. 2019; 97(8): 821–823. doi:10.1111/aos.14109

Contact and reprint request:
Larysa Krajewska-Węglewicz, MD, PhD (email: larysa.krajewska@gmail.com)
Department of Ophthalmology, National Institute of Medicine of the Ministry of Interior and Administration in Warsaw, Poland