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THE HISTORY AND FUTURE OF AMNIOTIC MEMBRANE USE IN MEDICINE

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ABSTRACT

The use of amniotic membrane in medicine is expanding in many specialty areas of medicine including ocular applications. Although the history of the use of this tissue showed modest success in the early 1900s, newer methods of storage have made the membrane more available and expanded its use. The future of this tissue in eye care lies in the development of a drop form containing key biologics to treat patients more easily and persistently over time.

Human amniotic membrane (AM) has been used for over a century in medicine as a way to treat wounds. AM is a source of stem cells and has shown regenerative, anti-inflammatory, and anti-scarring properties while being immunologically inert when transplanted. While wound care remains the mainstay of AM use in medicine, in recent decades the use of AM has expanded, not only in the field of eye care, but in dentistry, podiatry, gynecology, plastics, urology, and orthopedics.[1]

The first documented use of AM was in a 1910 Johns Hopkins publication where Davis reported attempting to use the lining of the amniotic sac as a skin graft - at the suggestion of a fourth-year medical student – but was "unable to report favorable results." He commented that the "material is well worth a trial, and if a technic (sic) is developed by which favorable results can be obtained, it may be of great use."[2]

In 1913, two separate doctors reported using AM in skin grafting with slightly different techniques. The logic in their attempts was straightforward. "Amnion is essentially an embryonic offshoot of the skin"[3] and therefore may have applications in skin grafting. It was reasoned that patients who had large wounds where autologous grafts would be impossible would benefit most.[4] Screening for disease was by visual inspection and history: "any abnormality or diseased portion or ulcerations, and question the patient from whom these organs are obtained as to her previous history. If such caution is observed, there will be no chance of infecting the patient."[4] They preserved the membranes in either petrolatum or in saline and used within 48–72 hours of harvesting. Their results were successful and similar to using autologous skin grafts.

The use of AMs has expanded from wound coverage to include applications across disciplines and disease processes. Modern examples include orthopedic utilization for post-surgical wound covering, dental utilization as a matrix for gingival recession, gastrointestinal utilization for the reduction of adhesions, and gynecological utilization during vaginal reconstruction. Interesting future use in medical research includes in-utero repair of myelomenigocele (spina bifida), a matrix for engineering blood vessels, enhancing fracture repair, and repairing cleft palate. In these applications, the actual membrane is often used as a matrix upon which healthy tissue can grow or as a barrier to scar tissue and adhesions.[5]

The first documentation of fetal membranes used in the eye was in 1940 by De Rotth who used the chorion and the amnion together rather than dissecting the chorion away. He obtained these membranes during cesarean sections of women who had a negative Wassermann reaction (syphilis test), kept them in Locke solution, and used within 15 hours of having harvesting. He employed them in a total of 10 patient cases: including eight symblepharons. He considered all but one case failures due to the shrinkage of the membrane. In the one successful case, the patient was being treated due to a chemical burn via an AM used as a conjunctival-limbal allograft. He noted that the new vessel growth in the graft showed a course similar to normal conjunctiva. This had not been observed in other graft materials (i.e., conjunctiva, inner surface of lips, rabbit peritoneum, and skin) that had been used for the conjunctiva up to that point.[6] Sorsby followed in the mid-1940s with a report on 58 cases of chemical burns where AM was used successfully as a splint for the proliferation of tissue and as a barrier of the burned tissue to form symblepharon.[7]

Literature publications for the use of AMs in eye care went quiet until the early 1990s when news came out that Soviet doctors were using a mysterious tissue for ocular transplantation that was very successful in terms of patient outcomes. Dr. Juan Batlle, an ophthalmologist trained at Bascom Palmer Eye Institute, obtained samples of this product, labelled "Allotransplantation for Conjunctiviplasty," and saw firsthand its benefits after utilizing this tissue on his own patient cases.[8] He and his colleague, Dr. Francisco J. Perdomo, conducted a variety of tests and determined that the material was histologically similar to placental membranes.[9]

At Bascom Palmer Eye Institute's 1992 annual research meeting, Dr. Batlle presented his findings and sparked the interested of Dr. Scheffer Tseng.[10] AM applications in the eye became Dr. Tseng's research interest and eventually led to the creation of his company Bio-Tissue in 1997. Bio-Tissue has created the only cryo-preserved AM (Prokera) that is fastened within an ophthalmic conformer ring; meaning no glue or sutures are necessary. Other companies, including IOP Ophthalmics (AmbioDisc) and BioD (BioDOptix), offer freeze-dried membranes, which can be held on the cornea with the help of a bandage contact lens. Due to preservation methods, these membranes are able to be stored for years.

Ophthalmological applications include any disease process where there is the potential for corneal scarring (such as microbial keratitis), any disease restricting nerve regeneration (such as neurotrophic keratitis). Newer applications include the use of AM for dry eye and other ocular surface diseases.

One drawback of using an AM in eye care is the inability for the active ingredients of the AM to persist on the eye without a membrane on the eye. The membrane itself is arguably not vital (unless replacing the conjunctiva) rather the benefits for most uses are gained by the biologics contained within the membrane. Therefore, access to these biologics in a drop form would allow for consistent treatment over time and better, more persistent outcomes in chronic disease such as dry eye and cicatricial disease. Bio-Tissue is developing a morselized AM tissue eye drop in order to allow for easier and persistent treatment of the ocular surface.[11] Another company, Ocular Science, markets a drop they term an AM cytokine extract. This drop contains cytokines, growth factors, and anti-inflammatory molecules.[12] As with all biologics companies, the method of extraction and sterilization is proprietary. There is a lack of prospective, placebo-controlled studies with either of these drops at this time.

Regenerative Network International, is marketing a human amniotic fluid (HAF) drop for the treatment of dry eye disease. HAF has been found to contain stem cells and amniocytes which have been proven to accelerate wound healing in an animal model and thought to contain substances similar to AM.[13] However, studies looking at wound healing typically use donated HAF from genetic testing laboratories that are conducting amniocentesis. Therefore, the HAF used in these studies is harvested much earlier in gestation than the HAF being used by Regenerative Network International and others that may come to market which are harvested at the time of delivery. HAF components change dramatically as the pregnancy progresses. For example, an incision made to a fetus early in the pregnancy results in no scar at the incision site, while incisions late in gestation lead to

scarring. This is thought to be due to the different levels of hyaluronic acid in HAF in the first half of gestation compared to the second half.[14]

Great strides have been made in protecting patients from infectious disease secondary to the use of badly sourced AMs. Companies marketing human AM products follow the American Association of Tissue Banks for safety protocol and disease prevention. Membranes are harvested from live births when babies are delivered by cesarean section. Diseases prescreened for include human immunodeficiency virus, hepatitis B, hepatitis C, syphilis, cytomegalovirus, and tuberculosis.[15] The National Organ Transplant Act in the United States established that is unlawful for mothers to be compensated for these donations.

In conclusion, the use of AM in medicine is expanding in many specialty areas including ocular applications. Although the history of the use of this tissue showed modest success in the early 1900s, newer methods of storage have made the membrane more available and expanded its use. The future of this tissue in eye care lies in the development of a drop form containing key biologics to treat patients more easily and persistently over time.

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