Amniotic Fluid and Membrane Injections for Musculoskeletal Disease and Arthritis

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***We only use-Zimmer Biomet® Amnioflo® and since not all amniotic/chorionic membrane/fluid products are alike and results may vary widely between brands, the comments in this article do not apply to any other brands of similarly named products.**

(Zimmer Biomet® MiMedX® PURION processed dehydrated Human Amnion/Chorion Membrane dHACM)

Amniotic and chorionic products have been used successfully for over a century in the setting of problematic tissue healing and have enjoyed a stellar safety record. Following recent clinical success with treating orthopedic injuries, there has been renewed interest in the use of allograft tissue treatments for musculoskeletal disease and injury. An abundance of scientific and clinical evidence has demonstrated the relationship between the molecular healing mechanisms and the clinical success of treatment in the setting of chronic inflammation where amnionic/chorionic products have been used.

Scientific investigations have concluded that there may be a significant clinical role for amniotic fluid in the setting of osteoarthritis pain. A study presented in 2015 at the American Academy of Pain Medicine Meeting concluded that "Amniotic fluid may be a safe and effective alternative to hyaluronic acid (HA) for osteoarthritis pain."

Hyaluronic acid is FDA approved and indicated for knee osteoarthritis that has failed all other conservative treatment options. In spite of FDA approval, insurance coverage for hyaluronic acid injections has now become thin and cumbersome to obtain. Patients are often faced with out of pocket costs that may dictate what types of treatment they are able to obtain. What's most cost effective in terms of treatment for the insurance company is not necessarily in line with what's best for the patient. When considering out of pocket costs, amniotic fluid injections are often less expensive and more efficacious than hyaluronic acid. What's makes even less sense is that amniotic fluid injections already contain HA.

"Amnionic fluid demonstrated in this study to offer pain and functional improvement that is greater at 13 weeks than at 30 days; thus it appears to offer longer-lasting relief at a higher level [than hyaluronic acid]," said lead author Didier Demesmin, M.D., a pain management specialist with the University Pain Medicine Center in Somerset, N.J."It also demonstrated a much lower incidence of pain, swelling or inflammation compared to other injections," said Noreen Rana, M.P.H., research director at the center."

Hyaluronic acid injections, like the most recently direct to consumer marketed 'Gel-One®' (Zimmer Biomet®, Warsaw, Indiana) include a naturally occurring substance found in the synovial fluid, which lubricates the cartilage and reduces friction in the joint. The FDA approved HA knee injections starting in the 1990s, and they are frequently performed and reimbursed. While the scientific literature has shown some benefit, recent studies of cellular and molecular biologics have demonstrated clinical superiority for the treatment of arthritis pain and these treatments have become routine in some parts of the country. Studies have demonstrated that at best, the effects of HA usually decline after 7 weeks for a single injection and 12 weeks with multiple injections. Amnionic fluid, which is similar to synovial fluid in its ability to protect and lubricate, also provides cushioning for the knee much the same way as it cushions the fetus. HA treatments are only FDA cleared for use in the knee, while the amniotic injections are cleared for safety and can be used in any synovial joint.

Another interim report in 2015 presented data from the first 15 of 23 investigative sites looking at patients treated with amnionic fluid injections for osteoarthritis pain. Results observed in the first 170 amniotic fluid-treated patients showed their VAS and WOMAC scores (validated outcomes measurements of treatment success) improved an average of 68.1 percent (44mm) and 70.9 percent (812mm), respectively, at 30 days. Improvements increased at 90 days to 82 percent for WOMAC and 74 percent for VAS.

So while some authors aggressively point out that amniotic fluid products do not have any living stem cells-and we completely agree with that, we can't agree that it doesn't play an important clinical role. The fact that amniotic fluid doesn't have any living stem cells, however, shouldn't preclude us from acknowledging its potential value in treatment, given the excellent safety record and demonstrated scientific efficacy of the product when used in the correct setting. In some of our

clinic patients, amniotic fluid treatment has been the ideal tool to restore their ability to enjoy their recreational and vocational pursuits almost immediately after inejection and without surgery.

Human amniotic fluid is immune privileged, making it ideal for allograft procedures. The Zimmer® amniotic fluid product that we use has 226 key chemokines, signaling proteins and growth factors such as FGF, IGF-1, VEGF, TGFB1, TGFB3 and BMP11 that are known to promote cell growth and regeneration of healthy tissue collagens I, II, III, IV, V and VI. Anyone with a scientific/academic interest in biologics should add "*A Primer On Amniotic Membrane Regenerative Healing"* to their reading list. You may be able to order one here at no cost: http://www.mimedx.com/products.

We believe the value of the amniotic product may be in it's ability to neutralize the toxic healing environment of the degenerative joint and cause a shift from a catabolic back to an anabolic milieu. It has been clearly demonstrated that concentrations of tissue degrading enzymes (MMPs) that destroy cartilage and cause painful symptoms are elevated in arthritic joints. These harsh conditions are characterized by an altered pH and low concentration of tissue stem cells and progenitor cells (potentially making staged amniotic fluid/MSCT treatments a more viable option than MSCT alone) . Gene profile analysis confirms the presence of a distinctive set of cytokines that persist unopposed and create an environment contributing to T-lymphocyte (CD4) migration and sequestration at sites of inflammation-basically a death sentence for the cartilage cells and the joint. These findings are easily and reproducibly demonstrated using the Human Inflammatory Cytokine Panel (Multiplex) ELISA.

Inflammation is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. It is initiated by production of a cascade of chemicals and cytokines in the area of injury. Pro-Inflammatory mediators result in vasodilation, increased vascular permeability, influx of blood, plasma leakage, neutrophil and macrophage infiltration and activation. Tissues are in constant dynamic equilibrium. The reparative process in connective (mesenchymal) tissues involves cellular and ECM checks and balances that are maintained by cells with opposing genetic direction through complex protein signaling cascades. Tissue healing involves a delicate balance of the removal of necrotic tissue coupled with the rebuilding of the tissue structure and composition. When the balance becomes tilted too far in the direction of catabolism, the reparative mechanisms of the body can become overwhelmed, resulting in a state of chronic, unopposed inflammation. Restoration to an anabolic state can be the first step in tissue repair and regeneration.

Amnioflo® contains 226 known regulators of healing and inflammation. Once re-hydrated, this medium of beneficial molecules can enhance the tissue healing environment by stimulating proliferation of progenitor cells. These biologic facilitators help encourage tissue growth and healing. Components of the extracellular matrices can incorporate into natural scaffolds that may accelerate healing while limiting scar formation.

Amniotic fluid contains multiple excellent properties for promoting tissue regeneration and repair: The fluid contains growth factors which can help promote new tissue growth and also help to call in the body's stem cells. Amniotic fluid contains important anti-inflammatory properties from biochemicals called cytokines that help relieve pain. Amniotic fluid is heavily concentrated in important healing molecules, growth factors, hyaluronic acid, antimicrobial components and stem cell activators that are able to work in a anyone's body without producing an immunologic rejection response, often making it an ideal biologic treatment option either alone or used with other biologic treatment modalities.

In our patients, amniotic fluid treatment is often used at a specific time as a first stage before proceeding to mesenchymal stem cell injection with a patient's own stem cells, just one example of how our proprietary mesenchymal stem cell treatment program might make more sense than most of the other treatments being offered. All of our treatments are scientifically sound and clinically proven to work. Years of experience has given us the ability to predict which patients are likely to do best with each biologic treatment modality. If I don't think the treatments will help you or will not be money very well spent, I simply won't recommend or offer them.

To summarize, amniotic fluid can be an ideal option for some patients with musculoskeletal diseases, including arthritis and already contains hyaluronic acid. HA is also a prominent component of joint fluid, and is important for lubricating cartilage and promoting growth of new cartilage. Hyaluronic acid is the main component of viscosupplementation injections with Gel-one®, Synvisc®, Hyalgan®, Euflexxa and other injectable HA medications. While HA injections have been shown to provide excellent pain relief for upwards of six to twelve months, amniotic fluid injections may extend the relief of symptoms dramatically and lead to better patient outcomes. Amniotic Fluid is a source of concentrated stem cell activators. Due to

the immune privileged status of the amniotic membrane, amniotic fluid does not cause an immune or rejection reaction when injected into a patient. Amniotic fluid is intended for homologous use (does the same job it was designed by nature to do) to cushion, protect and provide lubrication for joints.

Amniotic fluid is contraindicated for injection into the spinal canal, vital organs and other areas of the cardiovascular system and CNS. It should not be used on areas with active or latent infection. It should not be used as a bone substitute or replacement or for ANY intravenous, intra-arterial or intrathecal applications.

Amniotic fluid is an allograft tissue from a human donor that is carefully screened and tested to minimize the risk of an disease transmission. However, as with ALL biological implants, an absolute guarantee of tissue safety is not possible.

I have not known any patients who would elect to undergo a total joint replacement, or any invasive surgery for that matter, when there was another reasonable option. Unfortunately, cost gets in the way and insurance companies force patients down the path of least expensive rather than best interest. Based on past performance, there is little hope that insurance companies will begin covering these treatments any time soon, no matter how many scientists, physicians, surgeons or patients demand better treatment strategies.

*AMNIOTIC FLUID DOES NOT CONTAIN LIVE STEM CELLS AND MARKETING FROM THE VAST MAJORITY OF “STEM CELL” WEBSITES IS MISLEADING. HOWEVER, THIS FACT DOES NOT REFLECT ON THE CLINICAL UTILITY OF AMNIOTIC FLUID AT ALL. WHAT’S THE REAL SCIENCE BEHIND THE TREATMENT OF ORTHOPEDIC AND MUSCULOSKELETAL PROBLEMS WITH AMNIOTIC FLUID?

WE WANT OUR PATIENTS TO BE FAMILIAR WITH ON ALL OF THE UP-TO-THE-MINUTE BIOLOGIC AND CONVENTIONAL TREATMENT OPTIONS AVAILABLE. OUR FIRST GOAL IS TO EDUCATE PATIENTS SO THAT THEY ARE EQUIPPED TO MAKE AN INFORMED DECISION ABOUT THEIR TREATMENT AND THERE’S NEVER A CHARGE FOR EDUCATION.

WE SUPPORT ANY TREATMENT DECISIONS OUR PATIENT’S MAKE, WHETHER THEY DECIDE TO UNDERGO TREATMENT WITH US OR NOT. OUR GOAL IS TO ENSURE THAT OUR PATIENTS GET THE BEST NON-SURGICAL AND SURGICAL TREATMENT AVAILABLE WORLDWIDE, WHETHER THEY HAVE TREATMENT WITH US OR NOT.

TAKING IT A STEP FURTHER, IF YOU’RE CONTEMPLATING HAVING BIOLOGIC TREATMENT FOR ANY MUSCULOSKELETAL ISSUES ANYWHERE IN THE COUNTRY OR THE WORLD, WE ARE HAPPY TO RECOMMEND WHAT WE THINK ARE THE BEST CLINICS PRACTICING LEGITIMATE MEDICINE AND THERE’S NO COST. SIMPLY CALL ME ON THE PHONE.

Austin Yeargan III MD is an orthopedic surgeon who was first described as a pioneer in the field of regenerative medicine in 2009, years after he first recognized the clinical value of harnessing human biology in the treatment of orthopedic and musculoskeletal disease. With an advanced chemistry degree, Doctor Yeargan is scientist and an orthopedic surgeon with fellowship training in sports medicine, adult knee, shoulder and elbow surgery. He completed his fellowship at the world-renowned Steadman Clinic in Vail, Colorado where the best athletes in the world go for treatment. He is an expert on the biologic management of orthopedic disease and was the first in the country to use biologics for orthopedic surgical procedures in the shoulder and knee.

Doctor Yeargan currently practices at the Regenerative Medicine Clinic in Wilmington, North Carolina. He has spent his entire science and orthopedic career looking for new alternatives to treat patients less invasively.

Doctor Yeargan has no relevant financial disclosures.

The Regenerative Medicine Clinic: www.regenmedclinic.com

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