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Narrative Review

Orthobiologics for the Hip Region: A Narrative Review

Kelly C. McInnis, DO, Eric T. Chen, MD, Jonathan T. Finnoff, DO, Eugene Y. Roh, MD, Joanne Borg Stein, MD

Abstract

Management of hip region disorders is challenging. Orthobiologic treatments including platelet rich plasma (PRP), mesenchymal stem cells, and amniotic injectables have gained popularity as promising treatments despite a lack of robust evidence for their effectiveness. We review rationale and current evidence for orthobiologics for three common hip region conditions: hip osteoarthritis, gluteal tendinopathy, and proximal hamstring tendinopathy. Overall, the current state of evidence is extremely limited for orthobiologic treatments and is predominantly relevant to PRP injections. There is currently a lack of data to support the use of mesenchymal stem cells or amniotic injectables in these conditions of the hip.

Introduction

Orthobiologic treatments are defined as biological materials used to improve the healing of injured bone, cartilage, muscle, tendon, and ligament.[1] Treatments including platelet rich plasma (PRP), mesenchymal stem cells, and amniotic injectables have gained popularity as promising alternative nonoperative treatment options in the field of musculoskeletal and sports medicine. These treatments are theorized to promote healing and reduce pain through the release of growth factors and cell-signaling molecules implicated in healing and inflammation.[2,3] The rationale for the use of these treatments in hip conditions is based heavily on translational studies or frequently extrapolated from existing clinical evidence in other musculoskeletal conditions. Published reports support that these procedures are safe.[4–7] However, data regarding their efficacy have remained mixed.

Despite a lack of high-quality clinical evidence, mainstream use of orthobiologics in the management of musculoskeletal injuries continues to grow. Clinicians and patients may turn to orthobiologics for hip region disorders due to a lack of nonsurgical alternatives when conservative measures fail. This narrative review provides an overview of the rationale for orthobiologic treatments and discusses the latest clinically relevant evidence for the use of orthobiologics in the treatment of three common diagnoses affecting the hip region: osteoarthritis (OA), gluteal tendinopathy, and proximal hamstring tendinopathy (PHT).

Methods

A review was conducted of PubMed and Medline articles from January 2000 to June 2019 with search terms including hip, osteoarthritis, gluteal tendonitis, hamstring tendonitis, tendinosis, tendinopathy, platelet rich plasma, mesenchymal stem cell, amniotic stem cell, and amniotic injectables. Randomized controlled trials, case series, systematic reviews, and meta-analyses were reviewed. Only studies investigating chronic refractory tendinopathy and osteoarthritis were included. We did not include studies investigating acute muscle, myotendinous injury, acetabular labral pathology, or focal osteochondral lesion.

Platelet Rich Plasma

PRP is an autologous plasma concentrate containing platelets above physiologic concentrations in whole blood. Platelets are thought to initiate the healing cascade by forming a fibrin matrix, which serves as a tissue

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scaffold for the sustained release of growth factors and cytokines.[2,8] Platelet degranulation results in release of numerous growth factors implicated in cell proliferation and collagen synthesis at the site of injury, including platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and insulin-like growth factor 1 (IGF-1).[9] Platelets are also theorized to promote healing through the release of hepatocyte growth factor (HGF), which reduces downstream production of pro-inflammatory mediators such cyclooxygenase (COX) and prostaglandins.[2,3] Platelets signal migration of mesenchymal stem cells, which may promote healing and decrease inflammation.[10] Platelets also attract macrophages and fibroblasts, which promote removal of degenerative and necrotic tissue.[10] Finally, platelets may play a role in bone and soft tissue remodeling, angiogenesis, coagulation, and cell differentiation.[2]

PRP injections may be safer than many oral and injectable medications, because PRP is derived from the patient's own autologous blood, thereby avoiding many adverse effects and drug interactions.[2,8,11] Minor adverse effects include injection site pain, bruising, swelling, and bleeding.[12]

Aspirin and other COX inhibitors may limit platelet release of growth factors. Jayaram et al[13] found that PRP isolated from participants taking daily low dose aspirin exhibited reduced expression of TGF-β, PDGF, and VEGF when activated in vitro. However, the clinical effects of COX inhibitors on PRP injection in vivo at the site of injury are not yet clear.

PRP for Osteoarthritis

OA is recognized as a consequence of both mechanical overload of the joint and an imbalance in inflammatory mediators resulting in cartilage loss and chondrocyte apoptosis. A number of mechanisms for inflammation in OA have been proposed. However, the most widely accepted mechanism posits that degraded cartilage fragments induce an inflammatory response by the synovium leading to matrix metalloprotease (MMP) production, synovitis, and further cartilage degradation.[14]

Standard nonoperative care for hip OA consists of activity modification, patient education, weight loss, physical therapy, and nonsteroidal anti-inflammatory drugs (NSAIDs). Intra-articular corticosteroid injections have been shown to reduce pain in patients for up to 3 months.[15-17] Risks of corticosteroid injections include local fat atrophy, injection site pain, hyperglycemia, infection, and hormonal dysregulation.[18] In vitro studies have shown a toxic effect of corticosteroids and local anesthetics on human chondrocytes.[19] Corticosteroid injections may also contribute to cartilage loss in vivo.[20-23] Alternatively, hyaluronic acid (HA) injection may reduce pain in some patients with OA. However, the evidence supporting its use in hip OA is less convincing.[24,25] Total hip arthroplasty is reserved for patients with persistent symptoms and unacceptable quality of life despite nonoperative management strategies.

Basic science studies that show increased rate of chondrocyte proliferation when cultured with human platelet supernatant provides the initial rationale for application of PRP in OA.[26,27] However, the effects of PRP when applied to animal models have shown mixed results.[28-30]

PRP has been studied most rigorously in the setting of knee OA, and this evidence has been extrapolated to other joints. Bennell et al[11] reviewed 15 randomized control trials (RCTs) involving the treatment of knee OA with PRP. Only three studies compared PRP injection to saline control. These three studies demonstrated significant pain reduction in patients treated with PRP injection up to 12 months after treatment compared to saline controls. The authors of the review concluded that intra-articular PRP injection is a generally safe procedure with the potential to provide pain relief up to 12 months. However, no definitive conclusions could be drawn on the effect of PRP in knee OA due to low methodologic quality including small sample sizes, lack of blinding, and heterogeneous treatment protocols. Bennell et al also included three RCTs[31-33] involving the treatment of hip OA in PRP in their review. These studies are discussed below and also included in the meta-analysis by Ye et al.[34]

Evidence for PRP in Hip Osteoarthritis

The evidence supporting PRP in the treatment of hip OA includes four RCTs comparing intra-articular PRP injection to HA treatments (Table 1). All four studies compared a series of three intra-articular PRP injections to a series of three HA injections. None of the studies found a significant difference between PRP and HA groups, although all studies found short-term improvement from baseline in patients treated with PRP. Ye et al[34] performed a meta-analysis of these studies, totaling 303 participants, and found that PRP treatment resulted in a greater reduction in visual analog scale (VAS) pain scores at 2 months, but was equivalent to HA at 6 and 12 months. There was no significant difference in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or Harris Hip Scores (HHS) when comparing the two groups at any time point. These results were limited by a number of methodological issues including lack of blinding, small sample sizes of individual RCTs, and heterogenous treatment protocols between studies.

PRP for Tendinopathy

There is a growing body of evidence involving humans and animal models that suggest PRP may promote processes associated with enhanced tendon healing and function. de Mos et al[36] found that proliferation of human hamstring tendon tenocytes increased when cultured in PRP. Another study reported increased fibroblast proliferation and VEGF expression by human tenocytes when

Table 1
Randomized controlled trials of PRP versus HA in hip osteoarthritis

	Level of Evidence*	Sample Size	Treatment	Disease Severity	Leukocyte Concentration	Posttreatment Protocol	Outcome
Battaglia et al[31]	II	n = 100	Series of 3 PRP versus 3 HA injections every 2 wk	KL grades 1 to 4	Reduced	Limit use for a few days	No statistically significant difference between PRP and HA groups in HHS or VAS at 12 mo.
Di Sante et al[32]	II	n = 43	Series of 3 PRP versus 3 HA injections weekly	KL grades 1 to 4	Reduced	Rest for 1 d.	No statistically significant difference between PRP or HA groups in WOMAC or VAS at 16 wk.
Dallari et al[33]	I	n = 80	Series of 3 PRP versus 3HA injections weekly	KL grades 2 to 3	NR	Restrict use for a few days. Avoid functional overload	Statistically significant reduction in VAS at 6 mo: PRP group 21 (95% CI, 15-28) HA 44 (95% CI, 36-52) $P < .0005$ [PRP vs. HA] No statistically significant difference in WOMAC or HHS.
Doria et al[35]	II	n = 80	Series of 3 PRP versus 3 HA injections weekly	KL grades 0 to 2	NR	NR	No statistically significant difference between PRP or HA groups in WOMAC, VAS, or HHS at 6 or 12 mo.

PRP = platelet rich plasma; HA = hyaluronic acid; KL = Kellgren-Lawrence; NR = not reported; Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); HHS = Harris Hip Score; VAS = visual analog scale.
*All cited studies were assigned a level of evidence based on criteria adopted by the American Academy of Physical Medicine and Rehabilitation and originally proposed in the *Journal of Bone and Joint Surgery*.

cultured in vitro with PRP.[37] Finally, PRP also appears to have an anabolic effect on tendon structure by increasing total collagen, enhancing matrix synthesis, and upregulating important tenogenic proteoglycans, including decorin, cartilage oligomeric matrix protein (COMP), and tenascin-C.[38-40]

Fitzpatrick et al[41] reviewed 18 studies that investigated the efficacy of PRP injection therapy for treatment of refractory tendinopathy of several different regions. The authors concluded that there is strong evidence that leukocyte-rich PRP improves outcomes in tendinopathy. However, the studies included were at high risk for bias and included various different regions of tendinopathy.

PRP for Gluteal Tendinopathy

Gluteal tendinopathy, affecting the gluteus medius and minimus, is the primary pathology in peritrochanteric pain and the most prevalent lower-extremity tendinopathy.[42] This condition can be associated with significant morbidity, similar to severe hip OA in disability and economic impact.[43]

Gluteal tendinopathy is typically managed nonoperatively with activity modification, NSAIDs, and physical therapy. There is also some evidence to support extracorporeal shockwave treatment (ESWT) for the nonoperative treatment of greater trochanteric pain.[44,45] Corticosteroid injections have historically been used in the treatment of trochanteric pain. Although patients generally experience early reduction in pain (55% average pain reduction), the effect is not sustained at 1 year compared to those receiving no injection.[46,47] Moreover, basic science and clinical evidence suggest that corticosteroid injections are detrimental to tendon tissue, eventually progressing from collagen disorganization to necrosis, reducing mechanical properties and leading to worse outcomes in conditions such as lateral epicondylosis.[48-50]

Surgical repair is an option for cases of gluteal tendon partial- and full-thickness tears that are not responsive to nonoperative management. Good to excellent pain reduction and functional outcomes have been reported with both endoscopic and open abductor tendon repair. However, there are complications with both approaches, including tendon re-tear, greater trochanter fracture, and infection.[51]

A number of investigators have reported positive results for the use of PRP in gluteal tendinopathy (Table 2). Fitzpatrick et al[52,55] conducted a randomized controlled trial comparing a single ultrasound-guided intratendinous leukocyte-rich PRP injection to a single corticosteroid injection. Eighty patients with either gluteal tendinosis or partial tendon tear and symptoms for at least 4 months were included. Pain and function measured by modified Harris Hip Score (mHHS) was significantly improved in the PRP group at 12 weeks compared to the corticosteroid injection group.

Table 2
Platelet rich plasma for gluteal tendinopathy

	Level of Evidence	Sample Size	Disease Severity	Treatment	Leukocyte Concentrate	Posttreatment Protocol	Outcome
Fitzpatrick et al[52,55]	I	N = 80	Tendinosis with or without partial thickness tear	Single PRP without tenotomy versus single cortisone injection	Rich	Unsupervised rehabilitation: 4 wk relative rest, 6 wk progressive walking program	mHHS in PRP group 74.05 ± 13.92 improved compared to control 67.13 +/− 16.04 at 12 wk (P = .048). MCID achieved in PRP group (82%) compared to corticosteroid (56.7%) (P = .16).
Lee et al[53]	IV	N = 21	Tendinosis with or without partial thickness tear	Single PRP injection with tenotomy	Rich	2 wk relative rest followed by non-standard rehab focused on eccentric strengthening	Statistically significant improvement at average 19.7 mo follow up: mHHS 56.73 to 74.17 (P < .001):HOS-ADL 68.93 to 84.14 (P < .001): HOS-Sport 45.54 to 66.72 (P < .001): iHOT-33 34.06 to 66.3 (P < .001):
Jacobson et al[54]	II	N = 30	Tendinosis with <50% tear	Single PRP injection versus fenestration alone	Rich	Relative rest × 1 wk followed by progression of activity as tolerated	No statistically significant difference in pain score between groups at average 92 d follow up.

PRP = platelet rich plasma; mHHS = modified Harris Hip Score; MCID = minimal clinically important difference; HOS = Hip Outcome Score; iHOT-33 = Hip Outcome Tool-33.

A small cohort study by Lee et al[53] prospectively evaluated 21 patients with recalcitrant gluteal tendinopathy after one leukocyte-rich PRP injection. The authors reported improvements in functional outcome measures including mHHS, Hip Outcome Score (HOS), and International Hip Outcome Tool-33 (iHOT-33) at a mean follow-up of 19.7 months. These outcomes do not include a comparison or control group.

Finally, Jacobson et al[54] performed a single-blinded prospective clinical trial that did not find a significant difference between 30 patients with chronic refractory gluteal tendinopathy treated with either percutaneous needle fenestration or PRP infiltration. Patients were blinded to the treatment arm. Significant pain score improvement was seen at 1 and 2 weeks compared to baseline in both groups. No significant difference was seen between groups at a mean follow-up of 92 days.

PRP for Proximal Hamstring Tendinopathy

Proximal hamstring tendinopathy (PHT) is a common overuse injury that can cause significant dysfunction and be challenging to treat.[56,57] Although it has been described in less active individuals, it primarily affects athletic populations, especially endurance runners, sprinters, and hurdlers.[56,58,59] Similar to gluteal tendinopathy, the primary pathology of PHT is degenerative tendinosis and partial tear due to cumulative microtrauma.[58]

Standard management of PHT is nonoperative, with initial treatment focused on relative rest from provocative activities and often a period of complete restriction from running. Physical therapy is utilized for eccentric hamstring strengthening and pelvic stabilization.[59-63] Corticosteroid injections may provide temporary relief, with the aforementioned risk of long-term detriment to tendon architectural integrity and strength.[49,64,65] Notably, ESWT has also been described as a promising noninvasive treatment option for PHT.[66,67] There is a paucity of data on the efficacy of surgical intervention for degenerative PHT and partial tearing. Different surgical techniques have been described with positive outcomes regarding symptom burden and return to activity.[58,68-70] However, complications may include wound infection, worsening sitting intolerance, hamstring tightness and cramping, and nerve injury. There is generally longer associated postoperative recovery time compared to nonoperative treatment.[68,70]

Clinical trials investigating PRP as an alternative treatment option for chronic refractory PHT demonstrate mixed results (Table 3). Davenport et al[71] conducted the only double-blinded RCT comparing one ultrasound-guided intratendinous leukocyte-rich PRP injection (11 patients) to one autologous whole blood injection (6 patients) in patients with tendinosis or less than 50% partial thickness tearing. Patients were required to have at least 6 weeks of symptoms recalcitrant to conservative management, which included eccentric hamstring

Table 3
PRP for proximal hamstring tendinopathy

	Level of Evidence	Sample Size	Treatment	Disease Severity	Leukocyte Concentrate	Postinjection protocol	Outcome
Davenport et al[71]	I	n = 17	Single PRP versus autologous whole blood injection (with tenotomy)	Tendinosis <50% tear with symptoms >6 mo	Rich	None	No statistically significant difference between PRP or whole blood groups at 6 mo in HHS, iHOT33, or HOS.
Levy et al[72]	IV	n = 29	Single PRP injection	Tendinosis <50% tear with symptoms >6 mo	Reduced	NR	No statistically significant difference in VISA-H at 8 wk follow up.
Fader et al[73]	IV	n = 18	Single PRP injection	Tendinosis without complete tear Symptoms >6 mo	Reduced	No strenuous activity × 1 wk. Jogging allowed at 3 wk.	10 of 18 patients reported 80% subjective improvement in pain at 6 mo.
Krauss et al[74]	IV	n = 14	Single PRP injection (with tenotomy)	Tendinosis with or without marrow edema	Rich	NWB × 2 d, relative rest × 1 wk	Statistically significant improvement in LEFS (49.5 increased to 62.6) (P = .02) and VAS (4.9 decreased to 2.5) (P = .01) at 12 wk.
Wetzel et al[75]	IV	N = 12	Single PRP Injection (non-US guided)	Persistent symptoms despite 6-12 wk of physical therapy and 1 wk of scheduled NSAIDs	NR	Protected weight bearing 3 wk post injection. No hip flexion beyond 30°.	All returned to sport at 4.5 mo. VAS improved from 8.2 to 0.7 (P < .01) at average 4.5 mo follow up. NPRS improved from 5.5 to 1.5 (P < .01) at average 4.5 mo follow up.

PRP = platelet rich plasma; NWB = non-wieght-bearing; NSAIDs = non-steriodal anti-inflammatory drugs; NR = not reported; NPRS = Nirschl Phase Rating Score; VAS = Visual Analog Scale; mHHS = Modified Harris Hip Score; LEFS = Lower Extremity Function Score; iHOT = International Hip Outcome Tool; VISA-H = Victorian Institute of Sport Assessment; HOS = Hip Outcome Score.

strengthening. The clinical diagnosis of PHT was confirmed with either diagnostic ultrasound or magnetic resonance imaging. Although both whole blood injection and PRP groups improved over time, the PRP group showed significant improvements in HOS and iHOT-33 scores at 6 months compared to baseline, but there was no significant difference observed when comparing PRP to whole blood injection at any time point. Due to a small sample size, the authors of the study could not conclusively determine the efficacy of either whole blood injection or PRP for recalcitrant PHT.

Levy et al[72] conducted a retrospective case series, including 29 patients with PHT with mild-to-severe tendinopathy who received one ultrasound-guided leukocyte-poor PRP injection. This study used a validated proximal hamstring-specific functional outcome measure, the Victorian Institute Sport Assessment-Proximal Hamstring Tendons (VISA-H) questionnaire.[76] No restrictions were imposed on volume or intensity of physical activity postprocedure. At 8-week follow-up, there was no significant improvement in VISA-H compared to baseline, and no significant difference in outcome across severity of tendinopathy.[72]

A number of additional small case series have been published that suggest PRP may be useful for the management of PHT (Table 3). Fader et al[73] reported that 10 of 18 patients had 80% or greater improvement in pain scores (mean subjective improvement 63%) at 6 months after single PRP injection. Krauss et al[74] found significant pain reduction and improved Lower Extremity Function Score among 14 patients with chronic PHT (mean duration 4.1 years) 12 weeks after a single leukocyte-rich PRP injection. Finally, a retrospective review by Wetzel et al[75] found a significant reduction in pain in 10 patients treated with one palpation-guided PRP injection compared to 5 patients treated with physical therapy and NSAIDs.

Mesenchymal Stem Cells or "Medicinal Signaling Cells"

Mesenchymal stem cells are defined as multipotent cells with the ability to differentiate into a variety of specific tissues including muscle, bone, tendons, and ligaments.[77] They exist in tissue throughout the body including bone marrow, adipose, and placental tissue.[78] Mesenchymal stem cells have been isolated from perivascular cell populations, leading to the hypothesis that a subset of mesenchymal stem cells play a role as pericytes, cells that contribute to angiogenesis and endothelial cell regulation.[79]

Although mesenchymal stem cells have been promoted for their potential to differentiate into a variety of cell types in vitro, this does not appear to occur in vivo.[80] We refer to mesenchymal stem cells as "medicinal signaling cells"(MSCs) to emphasize their paracrine role rather than their potential for cell-line differentiation.[80]

MSCs promote angiogenesis, attract other signaling cells, and stimulate local precursor cells to replicate

and differentiate.[77,81-83] In addition to releasing numerous cytokines and chemokines that facilitate the differentiation of local progenitor cells, MSCs also inhibit monocyte differentiation and reduce T-cell proliferation, which modulates autoimmune regulation of cells undergoing rapid division.[82,84-87] Finally, MSCs play an anti-inflammatory role through the release of a tissue inhibitor of MMP, which mediates MMP damage.[88]

Bone marrow and adipose tissue are the most common sources for acquisition of MSCs in clinical practice. Overall, the literature suggests that MSC injections are safe. Centeno et al[4] prospectively followed more than 2300 patients who collectively received more than 3000 autologous MSC injections. During an average follow-up period of 2.2 years, the most common nonserious adverse event was postprocedure pain (3.9%). Thirty-six serious adverse events were reported; 33 were deemed not related or unlikely to be related to MSCs. None of the events were deemed definitely related to MSCs. The most common serious events reported were neoplasm, neurologic, and vascular events, respectively. Notably, the incidence of neoplasm was lower than the annual incidence in the U.S. population. Another study also found no increased cancer risk in a cohort of 1873 patients who received autologous cell-based therapy, such as bone marrow aspirate concentrate (BMAC), with a mean follow-up of 12.5 years.[5]

MSCs in Osteoarthritis

The rationale for the use of MSCs in the treatment of OA is based, in part, on their ability to alter the local chemical milieu, modulating pain and inflammation. The TGF-β cytokine family has been shown to induce chondrogenic differentiation of MSCs in culture.[89] MSCs cultured in the presence of TGF-β synthesize important components of articular cartilage including aggrecan, fibromodulin, COMP, decorin, and chondroadherin.[89] Cartilage fragments from osteoarthritic knees were also shown to induce MSC chondrocyte differentiation and increase type-2 collagen production.[90] However, the potential for MSCs to promote cartilage regeneration has not been demonstrated in vivo.

Application of MSCs in animal models of OA has shown promise.[91,92] Human MSC transplantation in a suspension of HA resulted in partial cartilage repair and increased type-2 collagen production in a guinea pig model of OA.[93] Injection of culture-expanded MSCs resulted in marked medial meniscus regeneration and reduced degeneration of articular cartilage in goats with surgically induced OA.[94]

Preliminary data suggest that culture-expanded MSCs are safe and efficacious.[95-97] However, culture expansion is considered more than minimal manipulation and falls outside of regulatory guidelines in the United States.

As in the PRP literature, clinical trials of MSC treatments in humans have focused primarily on knee OA. Trials of BMAC (not culture-expanded), in knee OA have been less positive. A level 2 RCT by Shapiro et al[98] found no significant difference in pain or function in patients with knee OA treated with intra-articular BMAC injection compared to saline control. Rodriguez-Fontan et al[99] reported that minimal clinically important difference (MCID) was achieved in 12 of 19 patients with mild to moderate knee and hip OA, including 10 knees and 15 hips, treated with single BMAC injection at 6 months. Finally, Sampson et al[100] reported patient satisfaction in 90% of patients in a retrospective review of 125 patients with moderate-to-severe OA of primarily the knee, hip, and shoulder treated with a single BMAC injection followed by PRP injection 8 weeks later.

MSCs in Hip Osteoarthritis.

There are currently no level 1 RCTs investigating the use of MSCs for the treatment of hip OA. Although a number of small case series report encouraging results for the use of bone marrow–derived MSCs (Table 4), there is insufficient evidence to draw conclusions about the efficacy of MSCs for the treatment of hip OA at this time.

MSCs in Tendinopathy

There is a limited body of evidence investigating the use of MSCs in chronic tendinopathy. A review by Lui and Ng identified nine preclinical studies that reported decreased angiogenesis, increased type-1 collagen expression, and improved tendon histology in tendons treated with cell therapy.[104] These studies included several different animal species, tendon regions, and sources of cell therapies including only culture-expanded bone marrow, adipose-derived MSCs, and autologous tenocyte cell injection.

Pas et al[105] performed a systematic literature review of clinical trials investigating the use of MSCs in human tendon disorders. Four studies met inclusion criteria, which included three case series and one matched, nonrandomized trial. No studies utilized culture-expanded cells. The authors concluded that there is currently no evidence to support the use of MSC therapy for tendon disorders.[105]

Our review of the literature found no RCTs or case series investigating the use of MSCs specific to the treatment of gluteal or proximal hamstring tendinopathy. Therefore, there is insufficient evidence to draw conclusions about the efficacy of MSCs for gluteal tendinopathy or PHT at this time.

Amniotic Injectables

Amniotic injectables are a class of orthobiologics derived from the human amniotic membrane, amniotic fluid, umbilical cord, or other placental tissues that would otherwise be discarded after childbirth. During human fetal development, the fetal membranes are composed of two layers: the outer maternal chorion and the inner fetal amnion. The amniotic membrane itself consists of

Table 4
Bone marrow aspirate and adipose-derived MSCs for hip osteoarthritis

	Level of Evidence*	Sample Size	Treatment	Culture Expanded	Post Treatment Protocol	Result
Darrow et al[101]	IV	4	BMAC injection × 4	No	NR	Patients reported average 72.4% subjective overall improvement
Mardones et al[102]	IV	13	BMAC × 3 weekly	Yes	NR	Statistically significant improvement in VAS 4.2 to 1.1 (P = .00001) HHS improved 61.9 to 85.7 (P = .003) No statistically significant improvement in VAIL or HHS No change in Tonnis grade
Dall'Oca et al[103]	IV	6	Single micro-fragmented adipose transfer	No	NWB 7-10 d	Statistically significant improvement at 6 mo in: HHS 67.2 ± 3.4 to 84.6 ± 6.3 (P < .0001) WOMAC 19.8 ± 3.4 to 36.3 ± 4.7 (P < .0001) VAS 4.6 ± 0.8 to 1.5 ± 0.5 (P < .0001)

BMAC = boone marrow aspirate concentrate; HHS = Harris Hip Score; VAS = Visual Analog Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; NR = not reported; NSAIDs = non-steroidal anti-inflammatories; US = ultrasound; NWB = non-weight-bearing.
*All cited studies were assigned a level of evidence based on criteria adopted by the American Academy of Physical Medicine and Rehabilitation and originally proposed in the *Journal of Bone and Joint Surgery*.

two important cell layers where MSCs are thought to reside: the amniotic epithelial cell layer and amniotic mesenchymal layer.[6] Amniotic epithelial cells are attached to a thick basement cell layer, which itself may provide therapeutic benefit as a bioscaffold.[6] Placental tissues may be processed by cryopreservation or a freeze-drying method called lyophilization, preserving tissues to be later reconstituted at the time of administration.

Amniotic injectables should be considered as a source of growth factors and cytokines as opposed to a viable source of MSCs. Although amniotic epithelial cells have been shown to produce numerous cell proliferative and anti-inflammatory factors including TGF-β, bFGF, EGF, and HGF, Panero et al[106] was unable to isolate any MSCs from three different commercially available amniotic fluid preparations, suggesting that MSCs may not remain viable after the cryopreservation process.[107]

The safety profile of amniotic injectables appears to be encouraging in the published literature, with no reported treatment-related adverse effects in humans other than injection site pain.[6,7]

Overall, clinical and preclinical studies of amniotic injectables are limited. Promising clinical results have been observed in the treatment of plantar fasciitis and medial and lateral epicondylopathy.[7,108,109] Gellhorn and Han[7] reported reduced pain and functional impairments in a cohort of 40 patients with chronic tendinopathy or arthropathy treated with dehydrated human amnion/chorion membrane. However, only two hip joints and two gluteal tendons were included. Our review yielded no RCTs or other case series specific to the use of amniotic injectables in the treatment of hip OA, gluteal tendinopathy, or PHT. Therefore, we can draw no conclusions regarding the efficacy of their use in these conditions.

Conclusion

Orthobiologic interventions are a new treatment option for degenerative conditions affecting the hip region including OA and gluteal and hamstring tendinopathy. However, clinical evidence is extremely limited, predominantly involves PRP injections, and lacks high quality RCTs. Although published case series suggest that MSCs and amniotic injectables are safe in the short term, there is a lack of data on long-term safety. There is a lack of evidence to support the use of MSCs or amniotic injectables in these hip conditions.

Directions for future research are numerous. Defining the optimal cellular milieu and formulation of each orthobiologic treatment for specific pathology and subgroups of patients is essential. Adequately powered, multicenter RCTs using validated outcome measures are necessary to determine the efficacy of orthobiologics.

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K.C.M. Department of Physical Medicine and Rehabilitation, Harvard Medical School, Boston, MA
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E.T.C. Department of Rehabilitation Medicine, University of Washington, Seattle, WA. Address correspondence to: E.T.C.; Department of Rehabilitation Medicine, University of Washington, 325 9th Ave, Box 359721, Seattle, WA 98104. e-mail: ericch1@uw.edu
Disclosure: None

J.T.F. Department of Physical Medicine and Rehabilitation, Mayo Clinic College of Medicine and Science, Rochester, MN
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E.Y.R. Department of Orthopedic Surgery, Physical Medicine and Rehabilitation, Stanford University, Redwood City, CA
Disclosure: None

J.B.S. Department of Physical Medicine and Rehabilitation, Harvard Medical School, Boston, MA
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