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Regenerative Medicine in Urogynecology: Where We Are and Where We Want to Be

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Abstract

Pelvic floor disorders (PFDs) constitute a major public health issue given their negative effect on quality of life for millions of women worldwide and the associated economic burden. As the prevalence of PFDs continues to increase, novel therapeutic approaches for the effective treatment of these disorders are urgently needed. Regenerative medicine techniques, including cellular therapies, extracellular vesicles, secretomes, platelet-rich plasma, laser therapy, and bioinductive acellular biomaterial scaffolds, are emerging as viable clinical options to counteract urinary and fecal incontinence, as well as pelvic organ prolapse. This brief expert review explores the current state-of-science regarding application of these therapies for the treatment of PFDs. Although regenerative approaches have not been widely deployed in clinical care to date, these innovative techniques show a promising safety profile and potential to positively affect the quality of life of patients with PFDs. Furthermore, investigations focused on regeneration of the main constituents of the pelvic floor and lower urinary tract improve our understanding of the underlying pathophysiology of PFDs. Regenerative medicine techniques have a high potential not only to revolutionize treatment of PFDs but also to prevent these complex conditions.

Pelvic floor disorders (PFDs) are prevalent conditions that negatively affect individuals' quality of life. These disorders include pelvic organ prolapse (POP), stress urinary incontinence (SUI), urgency urinary incontinence, and fecal incontinence (FI). In addition, such ailments as irritative lower urinary tract (LUT) symptoms/voiding dysfunction, bladder pain syndrome/interstitial cystitis, myofascial pelvic pain, sexual dysfunction, pelvic floor dyssynergia, genitourinary syndrome of menopause (GSM), and recurrent urinary tract infections are also common in urogynecologic patients. The prevalence of PFDs increases with age and as our population ages, the disease burden is estimated to increase as well.[1] The current approaches to treating these conditions focus on restoring anatomy and compensating for the lost function after the development of bothersome symptoms, which does very little to address the pathophysiology underlying these disorders.

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Regenerative medicine approaches have a promise of addressing the underlying pathophysiology of the pelvic floor and LUT dysfunction. In urogynecology, multiple regenerative approaches have been studied, including stem cells (SCs), extracellular vesicles, secretomes, laser therapies, platelet-rich plasma (PRP), and bioinductive acellular biomaterial scaffolds. The unifying goal of all these treatments is to restore function by repairing or regenerating dysfunctional host tissues.

CELLULAR THERAPIES

Stem cells are generally thought to cause a therapeutic effect through releasing paracrine factors. Stem cells can be harvested from autologous sources such as adipose tissue, bone marrow, skeletal muscle, endometrium,[2] menstrual fluid,[3] and urine.[4] They have been used in animal models and clinically in small trials to treat a multitude of PFDs.[5]

Numerous preclinical models have been used to understand the role of SCs in the treatment of SUI. More than 2 decades ago, Yiou et al[6] demonstrated that injection of muscle progenitors, isolated from limb skeletal muscle, increased myofiber size and number in the murine urethral sphincter repair after injury with a myotoxic injection. Using a rat model of SUI achieved by electrocoagulation of the left hemisphincter, the same group showed that injection of muscle progenitors, isolated from the flexor brevis, into the injured urethral sphincters improved leak point pressure (LPP) and led to the formation of de novo myofibers 1 month after injection.[7] In a female cynomolgus monkey model of urinary sphincter deficiency, Badra et al[8] injected prelabeled muscle progenitors, isolated from the quad-riceps, into the urethra injured by cauterization of the pudendal nerve branches supplying the sphincter. The muscle and collagen content was restored to the uninjured levels 12 months after the injection.[8]

De Ligny et al[9] performed a comprehensive review of regenerative medicine applications for the treatment of FI, which includes 34 preclinical studies using varied models and interventions. Unfortunately, only 1 study by Montoya et al,[10] in which a myogenic SC-containing hydrogel was used for the regeneration of the injured external anal sphincter (EAS), was deemed to be of high quality. The EAS of 80 female rats was transected and either left untreated (sham), or injected with polyethylene glycol–based hydrogel, myogenic SC-containing hydrogel, or type I collagen. The contractile function was improved in animals treated with the SC-containing hydrogel, and these outcomes were sustained over 12 weeks with the additional benefit of increased muscle volume.[10]

Although much of the preclinical studies deploy SCs for regeneration of striated urethral and anal sphincters, Sesillo et al[11] examined the role of muscle stem cells (MuSCs) in pelvic floor muscle (PFM) regeneration after simulated birth injury (SBI) in a rat model. Pelvic floor muscle birth injury and subsequent dysfunction is one of the key risk factors for PFDs, especially POP. The investigators deployed radiation to induce DNA damage in MuSCs before SBI in the validated preclinical model. Pelvic floor muscles in animals with dysfunctional MuSCs did not recover, leading to profound muscle atrophy long-term, demonstrating the indispensable role of MuSCs in PFM regeneration after birth injury[11] and suggesting that MuSC delivery may be therapeutically beneficial in damaged PFMs.

Ben Menachem-Zidon et al[12] injected labeled MuSCs into the tail vein of young (10 weeks old) and old (12 months old) Sprague-Dawley rats after a full thickness colpotomy to promote healing of the vagina in order to assess the role of MuSCs in improving surgical outcomes. Vaginal tissue healing, assessed by measuring the maximal distance between wound edges, was improved in the treated relative to untreated injured old rats at 3 days postinjury, but the response of treated and untreated injured young rats was similar. At 30 days postinjury + MuSC injection, the transplanted cells promoted angiogenesis in both the young and old groups, indicating benefit in wound healing.[12]

A recent systematic review reported on the available clinical safety and efficacy data on the use of SCs as a therapeutic approach for PFDs.[13] Only 11 single-armed prospective clinical trials with a total of 155 women were included, with 7 deploying SCs for SUI and 4 for FI, without any studies of POP. In one of the earlier clinical studies by Kuismanen et al[14] in 2014, adipose-derived SCs, expanded over 3 weeks and seeded on bovine collagen gel, were injected transurethrally in 5 patients with SUI. Patients were followed for 12 months: 3/5 had a negative cough stress test result and 2/5 were satisfied with their treatment.[14] The most recent clinical study included in the review also used adipose-derived SCs injected transurethrally in 10 women with SUI. Half of the participants had >50% improvement in a 24-hour pad test 3 months after the treatment.[15] The largest of the studies reviewed included 39 patients, in whom SCs derived from umbilical cord blood were injected transurethrally. Greater than 50% improvement, measured by a patient satisfaction test, was reported by 72.2% of participants at 12 months.[16] Altogether, the available data indicate no major adverse events and infrequent occurrence of minor adverse events. Thus, despite significant heterogeneity, the existing trials trend toward positive patient outcomes with an excellent safety profile.[13] However, the overall conclusions are hindered by myriad study designs, indications for treatment, SC sources, procedures, lack of randomization, and outcomes used in the individual studies as well as the small number of participants and lack of head-to-head comparisons with existing treatment modalities.

The systematic review of SCs deployed for the treatment of FI included 4 clinical studies. The 2 single-arm prospective studies with a total of 43 women and 6 men demonstrated improvement in the FI quality of life scale at 1, 6, and 12 months and improved Wexner scores in 44% of participants at 12 months.[17–19] The most recent study reviewed was a placebo-controlled trial, in which 6 men and 12 women were randomized to adipose-derived SCs injected either into the internal anal sphincter or the EAS, depending on the defect presumed to be causative of FI, or placebo (lactated Ringer injection). The rate of FI did not differ between the groups up to 48 weeks after the injection.[20] The other double-blinded randomized controlled trial included 15 women and 3 men, injected with either adipose-derived SCs (n = 9) or saline (n = 9) into the EAS after sphincteroplasty. Two months after the intervention, endorectal ultrasonography showed an increased muscle area at the repair site and electromyo-graphy recording revealed normal action potentials in 5 of 9 patients in the treatment versus the control group; however, Wexner scores were similar between groups.[21]

The use of pluripotent adult SCs in other contexts has been shown to have serious risks, including rejection and tumorigenicity.[22,23] Although tumorigenicity of adult SCs is lower

than that of embryonic SCs or induce pluripotent SCs, it is still a risk that is important to consider, as most adult SCs must be expanded in vitro before transplantation.[24] These risks might not be acceptable to many women with non–life-threatening conditions such as PFDs. It is, therefore, of outmost importance to pursue long-term outcomes of cell-based therapies in female pelvic medicine. Taken together, despite the existing efforts, robust conclusions regarding safety and efficacy of SC therapies for PFDs cannot be drawn at this time, precluding wide adoption in clinical care.

EXTRACELLULAR VESICLES AND SECRETOMES

Given the hurdles associated with the use of SCs, scientists have chosen to explore the role of SC-secreted factors referred to as the secretome, which is a collection of soluble molecules (ie, growth factors, cytokines, chemokines, and hormones) and extracellular vesicles (EVs) that contain membrane-wrapped packages of proteins, lipids, and microRNAs.[5] EVs are further subdivided by size into exosomes (40–200 nm), microvesicles (100–200 nm), apoptotic bodies (200–4000 nm), and exomeres (35 nm).[25,26] EVs have a double-layered phospholipid membrane, which plays several important roles: it drives cell-binding properties dictated by the cell of origin, acts as protection from extracellular degradation, and enhances exocrine and paracrine effects by facilitating highly specific binding and internalization by the recipient cell, leading to changes in the target cells' function.[25]

Both secretomes and EVs contain a multitude of factors that exert autocrine and paracrine signals, important for the homing of progenitor cells to a site of injury, angiogenesis, immune modulation, and constructive tissue repair.[27] Application of secretomes and EVs as a treatment for PFDs is in its infancy; however, this is an important area of research because these approaches have many benefits of cell-based therapies, while being devoid of such serious risks as tumorigenesis.

The use of a chemokine, CXCL12, found in the SC secretome, has been found to play an important role in the homing of progenitor cells to a site of injury and had similar therapeutic effects to skeletal muscle progenitor cells in preclinical model of SUI. Williams et al[27] used a rat model of intrinsic sphincter deficiency, accomplished by cauterizing the innervation and vasculature to the bladder and removing the outer layer of skeletal muscle of the urethra, to show that treatment with skeletal muscle progenitors or CXCL12 restored normal architecture and thickness of the urethral sphincter. Notably, treatment with CXCL12 restored LPPs to the uninjured control levels, underscoring the critical role that secretomes play in tissue regeneration.[27]

Dissaranan et al[28] treated rats 1 week after serial vaginal distentions with either MuSCs injected intravenously or with MuSC-derived conditioned media, that is, secretome, injected periurethrally. Leak point pressure and elastin fiber density in the external urethral sphincter improved equally in both groups compared with untreated injured controls.[28] In a second study by the same group, rats underwent a dual birth injury—vaginal distension and pudendal nerve crush, followed by either intravenous MuSC or intraperitoneal MuSC-

derived secretome injection. Similar to the first study, increased periurethral elastin fiber density was noted in both treatment groups compared to untreated injured controls.[29]

With respect to the application of EVs for the treatment of PFDs, most investigations explored the role of exosomes. In a recent study, Rolland et al[30] used a porcine model of SUI, where a sphincter defect caused a significant manometric decrease in urethral pressure, to explore exosomes as an “off-the-shelf” acellular platform to restore urethral function. Seven days after injury, either collagen or collagen with platelet-derived exosomes, was injected deep into the urethral wall without any bulking effect noted on cystoscopy. The exosome therapy restored urethral sphincter function at 7 weeks posttreatment, whereas collagen alone did not affect function.[30]

Another potential source of EVs is from SCs recently isolated from urine, although their true source is still unknown. These EVs have many of the same properties as EVs derived from other sources and have a wide potential application in multiple organ systems. Urine-derived regenerative materials are advantageous given the noninvasive nature of collection, although some distinct disadvantages have been identified, including lack of standardization and potential for contamination, given the higher microbial load of the source.[31]

Although neither secretomes nor EVs have been used for POP treatment, these regenerative approaches are promising strategies for mitigating mesh-related complications that have stifled advancements in POP treatments. Kisby et al[32] used a porcine model to explore the role of exosomes in augmenting surgical repair of vaginal mesh exposure. Treatment with exosomes, derived from human apheresis blood, with or without surgical closure, resulted in partial to full mesh exposure resolution in areas measuring up to 3 × 3 cm.[32]

In addition to the advantages outlined previously, identification of potent proregenerative factors could eventually eliminate the need for autologous tissue or cell sourcing. Deciphering the mechanisms governing the in vivo function of these trophic factors and the sustainability of the therapeutic effects is a fruitful avenue for future investigations.[5,26]

PLATELET-RICH PLASMA

Platelet-rich plasma obtained by centrifugation of autologous blood[33] has been used in orthopedics, plastic surgery, ophthalmology, cardiac surgery, and urology.[34] The key proregenerative factors in PRP include platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), fibroblast growth factor (FGF), and insulin-like growth factor (IGF).[35] In orthopedics, PRP has been deployed to treat tendinopathies, cartilage pathology, acute muscle injuries, and to augment surgery to expedite recovery. PRP exerts its proregenerative effects through promoting angiogenesis, chemotaxis of mesenchymal SCs, osteoblastogenesis, and chondrocyte and MuSC differentiation.[34] In the treatment of PFDs, PRP has been used alone or in combination with laser therapy, as discussed below.

Nikolopoulos et al[36] used a rat model of SUI, produced by transecting the pubourethral ligaments, and injected the animals with PRP at the time of transection as well as a month after injury. Animals who received PRP (n = 10) had significantly higher LPP at 1 and

2 months after injury compared with the no-treatment group, which did not receive any additional intervention after injury (n = 10).[36] The lack of injection controls, that is, saline, limits the above findings. In a pilot clinical trial, Athanasiou et al[37] injected PRP twice at 4-to 6-week intervals into the anterior vaginal wall of 20 women with SUI. Subjective improvement was reported by 80% of participants, with 50% demonstrating reduction in the amount of leakage measured by a 1-hour pad test at 6 months.[37] Long et al[38] reported significant improvement in incontinence, assessed by the Urogenital Distress Inventory and Incontinence Impact questionnaire, up to 6 months after 3 monthly PRP injections into anterior vagina at the level of midurethra of 20 women with SUI. Chiang et al[39] injected PRP at 5 sites around the urethral meatus every 4 weeks for a total of 4 months' duration in 26 women with SUI/intrinsic sphincter deficiency refractory to standard therapies. The overall success rate was 50%, with 7 patients completely dry at 12 months as measured by the global response assessment.[39] Although the studies by Athanasiou, Long, and Chiang report some improvement in symptoms, none of the studies include a control group limiting their effect.

PRP application for POP has been explored as an adjunct to surgical interventions. Einarsson et al[40] injected a platelet gel—a combination of thrombin-rich serum and PRP—at the time of anterior colporrhaphy in 9 patients with POP. They showed significant improvement in the position of the anterior vaginal wall, based on the Aa and Ba Pelvic Organ Prolapse Quantification points, at 3 months, and in the position of the bladder neck, based on the Aa Pelvic Organ Prolapse Quantification points, at 20 months compared with preoperative examination.[40] The lack of a comparison group in the previous study similarly limits its conclusions. Gorlero et al[41] evaluated efficacy of the Vivostat system that prepares platelet-rich fibrin—an autologous fibrin matrix containing platelet- and leukocyte-derived cytokines—in 10 patients undergoing site-specific vaginal repairs of recurrent prolapse. At 24 months postoperatively, 80% of participants had stage 0 prolapse and 20% had stage 1 prolapse, with 100% improvement in patient-reported symptoms measured by a validated questionnaire.[41] The lack of a comparison group significantly limits conclusions of this study as well.

PRP is easy to obtain and has an excellent safety profile, with mostly minor adverse effects related to pain with injections. The results are overall promising, although there is significant heterogeneity in the preparation and application of PRP between studies that included a very small number of participants and lacked comparison groups[35] and, therefore, it is currently difficult to assess whether there is true efficacy. The two ongoing randomized controlled trials (NCT05390970[42] and NCT05112718[43]) evaluating the efficacy of PRP compared to placebo for SUI will provide rigorous data regarding the PRP's efficacy for this PFD.

LASER THERAPY

Lasers have been used in gynecology for decades with the first applications for treatment of cervical lesions. More recently, erbium:YAG lasers and CO_2 lasers have been deployed for LUT dysfunction, GSM, and vaginal aesthetics.[33] The proposed mechanism of action is that the laser causes thermal changes that lead to activation of the inflammatory healing cascade,

ultimately resulting in restoration and remodeling of the tissue as evidenced by increased collagen synthesis.[44,45]

A recent meta-analysis of erbium:YAG (used in the majority of studies) and CO_2 lasers for the treatment of SUI that included 16 studies with a total of 899 participants demonstrated a short-term improvement, assessed by a validated questionnaire at 6 months after a single treatment, although longer-term outcomes were only reported in 2 studies.[46] Lasers have also been used in combination with PRP because of the potential synergistic therapeutic effect. Behnia-Willison et al[44] performed a single-center prospective observational study that combined vaginal laser treatments with PRP in 62 women with SUI who received 3 laser treatments + PRP injections into the anterior distal third of the vagina and periurethral area 4–6 weeks apart. More than 60% of participants reported either occasional or no symptoms up to 24 months after the last treatment, but the study did not include an appropriate control group.[44]

Although the individual studies report minimal adverse effects, the U.S. Food and Drug Administration has issued a warning about the application of lasers for the treatment of vaginal symptoms related to “menopause, urinary incontinence, or sexual function,” highlighting numerous adverse events and the off-label use of the technology for these indications.[47] This underscores the importance of rigorous follow-up and reporting, as detailed in a recent excellent review by Burkett et al.[48]

Numerous studies have been published on the use of laser for GSM. Although these studies are outside of the scope of this short review, we would like to highlight that, despite the benefits reported in prospective observational studies, a recent sham-controlled double-blinded randomized controlled trial that included 60 women with GSM showed comparable outcomes 12 weeks after laser or sham treatment.[49] More research is certainly needed to understand the mechanisms of action and applicability of laser therapies for PFDs, and more randomized controlled trials in this area need to be performed to elucidate whether these new therapeutic approaches have true benefit.

ACELLULAR BIOMATERIAL SCAFFOLDS

Another promising approach to regenerative medicine is the use of biomaterial scaffolds to promote host cell infiltration and endogenous regeneration.[50] In particular, decellularized extracellular matrix (ECM) scaffolds have begun to be evaluated in urogynecology. Native ECM is an important component of the microenvironment that influences cell behavior, and decellularized ECM, wherein the cellular components have been stripped from a tissue, has been shown to support cell infiltration and promote a proremodeling as opposed to a proinflammatory immune response leading to tissue healing and regeneration.[51] Many products from xenogeneic sources are commercially available for indications such as hernia repair and for nonhealing diabetic foot ulcers.[52] Surgisis, a porcine small intestinal submucosa (SIS)–derived ECM product, has been used in POP repair. A randomized controlled trial by Feldner et al[53] compared anterior colporrhaphy with (n = 29) or without (n = 27) SIS graft. At 12 months postoperatively, the SIS group had an 86.2% anatomic cure rate, as defined by the International Continence Society, compared with a 59.3% anatomic

cure rate in the no SIS group, with no difference in quality of life, assessed by a validated questionnaire, between the groups.[53] In a case report published in 2014, a large vaginal mesh exposure after transvaginal mesh-augmented prolapse repair was successfully treated with SIS without resection of the underlying mesh.[54] This was in line with a previously published case series of mesh exposure where the mesh was first excised then covered with SIS with a 55% rate of complete re-epithelization.[55]

Commercial decellularized ECM products have been limited to patches and ground particulate; however, numerous preclinical studies and a phase I clinical trial have evaluated a hydrogel form, which is generated from partial enzymatic digestion of the decellularized ECM.[56] Upon injection or incubation at body temperature, the digested liquid ECM self-assembles into a porous and nanofibrous scaffold that likewise supports cell infiltration and promotes a proremodeling immune response.[57] Duran et al[58] studied the role of a porcine-derived skeletal muscle ECM hydrogel in the PFMs of a rat SBI model. They found that the injection of the ECM hydrogel increased the fiber area compared with untreated animals and animals injected with saline when injected either coincidentally with the SBI as well as 4 weeks later (simulating injection at the postpartum visit),[58] suggesting that this strategy could be used to prevent or treat postpartum PFM degeneration. In general, these bioinductive scaffolds show promise in improving the way that we approach PFDs, and provide options for managing complications associated with permanent synthetic materials.

CHALLENGES AND FUTURE DIRECTIONS

Application of regenerative medicine techniques is an exciting prospect in the realm of PFDs. However, several barriers to effective implementation in humans still exist. Stem cell therapies have been explored in multiple fields, but their implementation for the treatment of PFDs has been limited. First, the use of SCs is associated with serious adverse side effects, which may be unacceptable to patients with non–life-threatening conditions such as PFDs.[29,59] In addition, harvesting autologous cells is an invasive and time-consuming process that ultimately may yield inconsistent results as we are relying on the intrinsic function of the host SCs in a maladaptive environment that we do not fully understand. This is true of all proposed approaches, although the utilization of acellular interventions affords similar benefits while lowering potential undesired effects and allowing for an off-the-shelf product with easier shipping and storage. Many regenerative approaches are associated with substantial costs, which is likely to present a significant barrier to their wide adoption into clinical care, as insurers will be reluctant to cover such expensive treatments for conditions that do not directly cause mortality or severe disability. Fortunately, pragmatic lower cost regenerative strategies, such as ECM-based biomaterials, already exist. Finally, a multiscale understanding of the pathophysiology that leads to pelvic soft tissue dysfunction is an absolute prerequisite for effective implementation of regenerative techniques to prevent or treat PFDs. Discovery science investigations, followed by rigorous translational and randomized controlled clinical studies, are of outmost importance to promote our understanding of the tissue- and cell-level pathways underlying pelvic floor and LUT dysfunction, and to enable identification of patients who would benefit most from these approaches. Ultimately, this will enable a dramatic shift in the clinical paradigm—instead of relying on delayed compensatory treatments that do not address the underlying

pathophysiology, we will focus on preventing or mitigating PFDs by inhibiting maladaptive degenerative changes in the integral pelvic components along a woman's lifespan.

CONCLUSIONS

Regenerative medicine has a high potential to revolutionize the treatment and prevention of PFDs. Proregenerative therapeutics hold promise to address the underlying pathophysiology and restore function of the host tissues, and can be delivered via minimally invasive approaches (Fig. 1). Furthermore, many evolving regenerative approaches are devoid of significant risks, and some can be used as low-cost off-the-shelf products, circumventing various hurdles associated with their adoption in standard clinical care. It may take a creative combination of strategies to achieve our fundamental goal—to decrease the burden of PFDs and improve lives of millions of women worldwide.

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Simply Stated

Pelvic floor disorders (PFDs) are common conditions that negatively affect the quality of life of women worldwide. They include pelvic organ prolapse, urinary incontinence, and fecal incontinence. We currently treat these disorders by restoring anatomy and compensating for lost function after the development of bothersome symptoms. This narrative review aims to summarize the state-of-the-art of regenerative medicine in the treatment of PFDs. The reviewed regenerative approaches to treat these disorders by restoring the host tissues' structure and function include cellular therapies, extracellular vesicles, secretomes, platelet-rich plasma, laser therapy, and bioinductive acellular scaffolds.

WHY THIS MATTERS

Regenerative medicine in the treatment of pelvic floor disorders (PFDs) holds promise of better outcomes and less untoward effects, as the goal is to restore the normal physiology of the endogenous pelvic soft tissues to either prevent or treat PFDs. Regenerative approaches can be used as an adjunct or alternative to current compensatory treatments. This review highlights proregenerative therapeutics deployed in female pelvic medicine, while discussing the limitations and future directions for continued research and innovation. Ultimately, regenerative medicine has a high potential to revolutionize the treatment and prevention of PFDs.

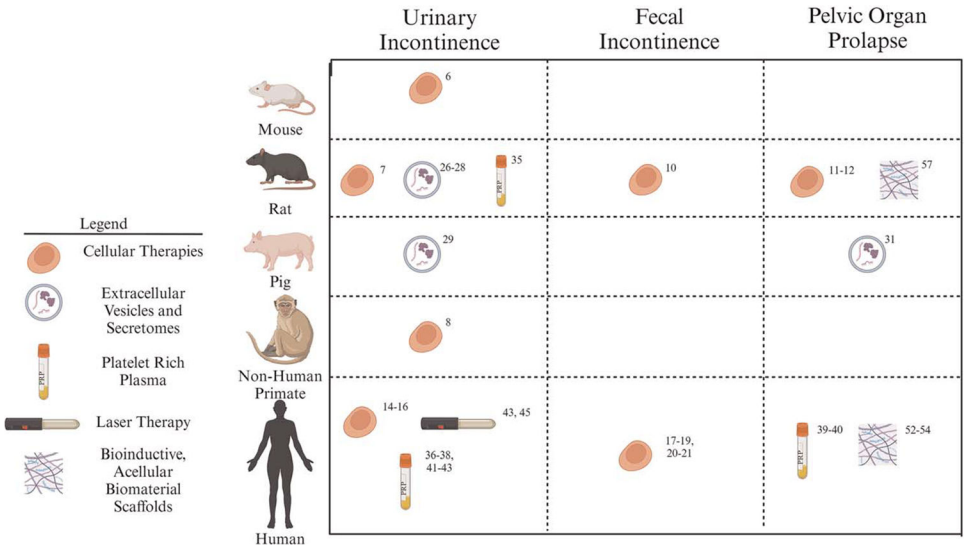

FIGURE 1.

Schematic summarizing clinical and preclinical studies focused on the regenerative medicine in female pelvic medicine that are included in this narrative review. Created with BioRender.com.