GENERAL GYNECOLOGY

# Stem cells in gynecology

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Stem cell based therapies hold promise for the obstetrician and gynecologist. This article reviews the history of stem cells and some of their current applications in gynecology. Currently, mesenchymal and muscle-derived stem cells are being explored for the treatment of urinary and anal incontinence. Potential stem cell treatments include fistula repair, vaginal tissue engineering, and graft material enhancement. Published animal and human pilot studies demonstrate improved histologic and functional outcomes in those receiving stem cells. Transplanted cells may improve function by local engraftment, trophic factors, or modulation of inflammation. Further clinical and safety studies are needed before clinical application.

**Key words:** gynecology, incontinence, mesenchymal, sphincter, stem cells

Dating back to ancient times, the Greeks recognized the human body's potential for regeneration. Their term for the liver, *hepar*, was derived from the word *hepaomai*, "to repair oneself." Furthermore, Aristotle published observations of animals that possessed the ability to regrow body parts including: the salamander's ability to regrow its tail and of deer to regrow antlers.[1] Attempts to more actively partake in and control this regenerative capacity on a cellular level can be traced to the early 1900s. In 1912, Alexis Carrel developed an "immortal" cell line from a chick embryo, and continued to culture this cell line for years to follow. In 1963, Ernest A. McCulloch and James E. Till solidified the concept of stem cells in their landmark Nature publication.[1] They transplanted bone marrow cells into irradiated mice and demonstrated that these same cells developed into colonies within the spleen. Gail Martin and Martin Evans, in 1981, developed a line of mouse cells with the capacity to become any tissue in the adult mouse. From this cellular line, the term *embryonic stem cells* was coined. James Thomson subsequently developed the first line of human embryonic stem cells in 1998.[1] Exciting investigations of medical applications have since exploded and brought us into the realm of research and therapeutic potentials existing today.

The study and use of stem cells has made strides across many fields of medicine. This has included work in hematology, ophthalmology, spinal cord injury, burn therapy, cardiac ischemia, and, more recently, in pelvic floor dysfunction. In this review, we will focus on treatment potentials for urinary and anal incontinence. Much of the existing stem cell research in gynecology has focused on these aspects. Results are promising, but largely limited to animal studies. Clinical, human application remains an exciting goal, but one whose routine, widespread use is premature.

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## Stem cell sources

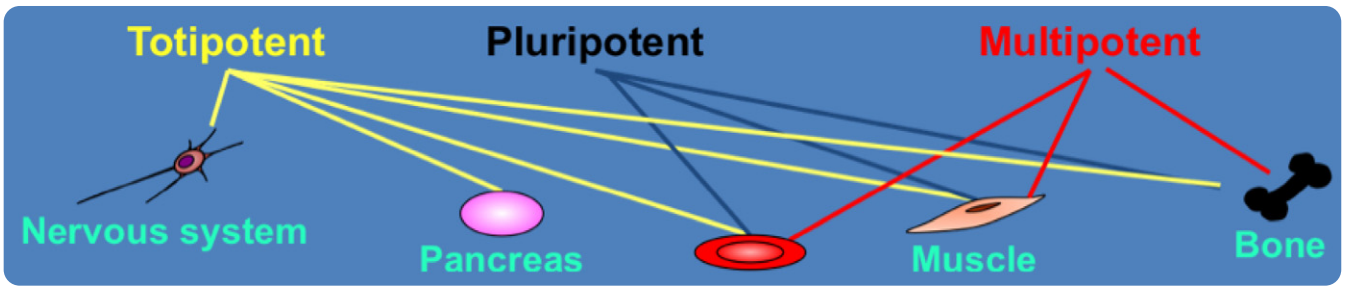
Stem cells are defined by their regenerative capacity and their ability to differentiate into 1 or more cell types. Hence, different stem cell types possess different abilities. Toti or pluripotent stem cells, typically embryonic or fetal in source, can differentiate into any cell type or germ cell layer. Multipotent, including mesenchymal stem cells (from blood, bone marrow, placenta, or adipose tissue), are capable of differentiating into multiple, but not all, cell types. Unipotent stem cells, of skin and muscle origin, are the most limited, capable of regeneration within only 1 cell type (Figure 1).[2]

Overall, stem cells can be derived from embryonic and nonembyronic tissue. Human embryonic stem cells (hESC) are obtained from the inner cell mass of blastocysts, are highly plastic and proliferate rapidly. They are theoretically totipotent and capable of differentiating into any germ cell layer. However, hESC require directed differentiation into specific determined high purity cell types.[3] This process is technically rigorous but necessary to improve engraftment and decrease tumorigenicity.[4] In addition, most readers are unaware that immune rejection can occur after hESC transplantation. These cell lines acquire human leukocyte antigens (HLA) as they mature and therefore recipients may need life-long immumosuppression.[5] These special requirements and the ethical debates, surrounding embryonic stem cell limit their current applications in gynecology. Nonembryonic stem cells on the other hand, can be readily derived from sources such as bone marrow, umbilical cord blood, and adipose tissue (multipotent cells), or from muscle (multi- and unipotent populations). The majority of these cell types can be autologously derived from the gynecologic patient. Adult stem cells can be identified by a variety of markers including CD45, CD34, Pax7, and MyoD. In preparation, cells are selected from biopsied tissue (ie, bone marrow, adipose, or muscle), expanded in culture, and passaged to achieve confluency until desired cell transplant numbers are achieved. Within animal studies, an identifying marker (ie, green fluorescent protein [GFP], BrdU, or PKH-26) is typically transduced to cells to assess for survival and/or integration.

## Origins of stem cell use in gynecology

Stem cell therapy for the treatment of urinary and anal incontinence is based on principles of skeletal muscle regeneration. The urethral and external anal

FIGURE 1
**Variation in potency of stem cell types**

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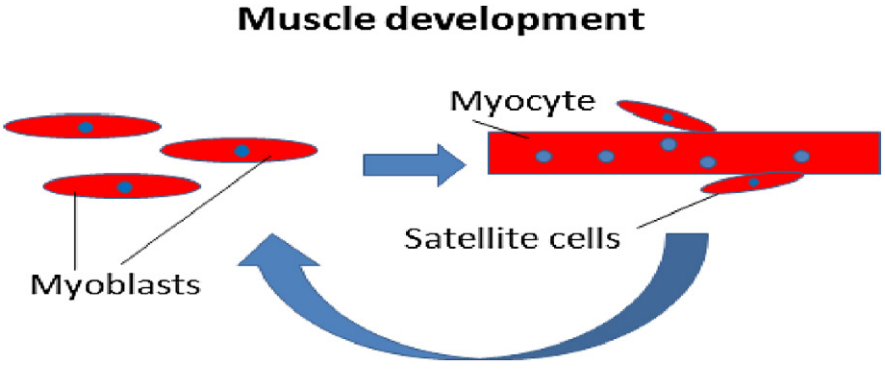
sphincters both contain skeletal muscle that contributes to effective continence. However, age-related changes, injury, and trauma can all lead to compromise in function. Skeletal muscle possesses the ability of inherent regeneration based on the presence of satellite cells. Satellite cells exist below the basal lamina in a dormant state, and on injury are activated and act as native reparative cells. Activated satellite cells produce myoblasts—unipotent muscle progenitor stem cells (Figure 2). Myoblasts fuse to form myotubes, and myotubes are packaged into sarcomeres and align to form myofibers. This process ultimately leads to muscle regeneration. Unfortunately, in the native state, the portion of satellite cells within skeletal muscle is quite small—unable to compensate for large or chronic injuries alone.[6]

Some of the earliest research using myoblasts was in the field of Duchenne Muscular Dystrophy. The concept of muscle biopsy, in vitro culture, and subsequent myoblast transplant to treat this degenerative disorder was proposed in 1978. Multiple animal studies ensued through the 1980s, and in 1990 the first human myoblast transplant occurred. Unfortunately, success was limited, possibly because of the nature of this systemic degenerative disorder and large burden of muscular dysfunction. In addition, transplanted cells presented an overwhelming challenge of rapid cell death and migration.[6] Incontinence models built on this concept, and possibly because they involve a smaller muscle burden, have demonstrated greater promise. Proof of concept of myoblast transplantation in a rat stress incontinence model was published in 2000.[7] Chancellor et al[7] demonstrated histologic evidence of cell survival and fusion of myoblasts to myotubes after periurethral injection. Translation to anal incontinence models ensued. Kang et al[8] and Lorenzi et al[9] published some of the earliest work transplanting stem cells into injured rat anal sphincters. Improved function was demonstrated.

FIGURE 2
**Native satellite cells produce myoblasts upon injury/activation**




In the natural state, satellite cells reside below the basal lamina of skeletal muscle. At times of injury, these cells are activated and produce unipotent myoblast cells which act as stem cells and aid in muscular regeneration.

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## Potential benefits of stem cell use in gynecology

Use of stem cells for the treatment of urinary and anal incontinence holds great promise especially when considering that existing options for both remain limited. Stress urinary incontinence (SUI) can be attributed to either loss of urethral support and resulting hypermobility, intrinsic deficiency within the urethral sphincter (ISD), or a combination of both. To date SUI can be effectively treated with surgical placement of a midurethral sling. Treatment of sphincteric dysfunction presents a greater challenge. Urethral bulking can help to restore coaptation, but long-term efficacy is lacking and local tissue reaction can occur.[10] Effective treatment options for anal incontinence are even more sparse. Physical therapy can provide modest benefit. Sphincteroplasty, bulking agents, and/or artificial sphincters have poor long-term outcomes and can pose significant risks of infection.[11]

As both SUI and anal incontinence (AI) can result from loss of muscular integrity and function, rebuilding muscle from a cellular level represents an ideal treatment concept. Numerous animal, along with a few human studies, have, in