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*Editorial*

*Corresponding author
**Parveen Parasar, DVM, PhD**
Postdoctoral Research Fellow
Brigham and Women's Hospital
Boston Children's Hospital
Harvard Medical School
300 Longwood Avenue
Boston, MA 02115, USA
**E-mail:** suprovet@gmail.com

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# Endometriosis Research: Need for a Stem-Cell Based Experimental Model

**Parveen Parasar***

*Boston Center for Endometriosis, Brigham and Women's Hospital, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, USA*

## ABSTRACT

Endometriosis is a complex disease and not a single phenotype can be delineated in available *in vitro* models. A comparative analysis of pluripotent stem cells in normal endometrium and endometriosis will give an understanding of status of biomarkers in endometrium and endometriosis, respectively. Highly pluripotent stem cells are critically important constituents of endometrium and contribute to ectopic endometriotic implants as reported in various studies. Because stem cells are undifferentiated and possess tremendous regenerative capacity, they are candidate cellular system for modeling endometriosis.

**KEYWORDS:** Endometriosis; Stem cells; Experimental model.

## INTRODUCTION

Endometriosis is defined as the presence of endometrial glands and stroma like lesions outside of the uterus. A unique feature of the menstrual cycle in women and non-human primates is the retrograde menstruation – an outflow of the endometrial lining through the patent fallopian tubes into the pelvic space.[1] This retrograde flow, along with potential hematogenous or lymphatic circulation,[2] results in the seeding of endometrial tissue in ectopic sites. Endometrial and bone marrow-derived stem cells are progenitor cells which differentiate into endometrium and also contribute to ectopic endometrium.[3,4] These implants often persist for several years and result in consequent pelvic pain, infertility and inflammation.[5] Patients often present with other associated symptoms, including dysmenorrhea, dyspareunia, dyschezia and dysuria.[5,6] Endometriosis is a highly debilitating disease,[7] affecting 5-10% of all women of reproductive age[4-6,8] and 35-50% women with pelvic pain and infertility impacting quality of life.[7,9] The majority of women present symptoms in adolescence, but average delay to diagnosis is 7 years.[7,10,11] Clinical studies also report that endometriosis patients have increased risk for autoimmune diseases and ovarian cancer.[12]

Treatment options for endometriosis patients are limited to surgery, hormone therapy and analgesics.[6] No gene-targeted medical therapies exist to date, likely due to the fact that definitive pathogenesis-mechanisms of endometriosis are yet to be determined.

### Structure of the Human Endometrium

Endometrium is the inner mucosal lining of the uterus consisting primarily of two types of cells - the epithelial cells of the glands and lumen (the glandular and luminal epithelial cells) and the mesenchymal (stromal) cells. Other supporting mesenchymal cells are endothelial cells, fibroblasts and leukocytes. Endometrial glands are indistinctly separated from the underlying smooth muscle layer of the myometrium in the absence of submucosal tissue. Endometrium is functionally divided into two layers. The outer functionalis layer comprises the upper two-thirds and is composed of dense glandular tissue and loose connective stroma. The inner basalis layer rests on the subendometrial myometrium and contains the base of glands,

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dense stroma, large vessels, and germinal cells that help generate the new functionalis each month after menstrual shedding of the upper functionalis and partial basalis.[3]

### Theories of Endometriosis

Definitive etiopathogenetic mechanisms of endometriosis are yet to be discovered although exploration into genetic predisposition,[13,14] polymorphism in mitochondrial DNA, and altered immune response is ongoing.[6] Endometriosis can result from either primary or secondary retrograde menstruation,[2] the latter being a result of the congenital obstruction of the menstrual tract as seen in congenital Müllerian anomalies.

Retrograde menstruation theory is the most accepted theory of endometriosis.[2] Another theory proposed for the pathophysiology of endometriosis includes coelomic metaplasia, which explains that mesothelial cells in peritoneum differentiate into endometrial tissue.[15] Aberrant molecular and/or biochemical pathways in endometrium and overproduction of estrogens, cytokines, prostaglandins, and metalloproteinases due to abnormal biosynthetic pathways may also stimulate the migration of endometrial implants into ectopic sites. Immunological failure to get rid of these migrants sets up the establishment of implants.[5,6] Stem cells from endometrial tissues and bone marrow have been demonstrated to migrate the ectopic endometrial tissue implants.[3,4] Consequently endometriosis is multifactorial and polygenic in nature.

### Stem Cells in Endometriosis

Stem cells are highly self-renewable, primitive unspecialized cells which undergo differentiation to produce a vast array of specialized cells with minimal or no differentiation capacity. Therefore, stem cells are invaluable tools to develop disease models and to study the mechanism of pathogenesis of a disease as well as to test the drugs and therapy for a disease.[16] Genetic factors underlying a disease, detected in stem cell disease models, can thus be used as potential targets for drugs. Obtaining diseased cells, in many diseases, is a challenge, therefore, entails generation of an *in vitro* model to test novel therapeutic drugs and gene editing therapies in order to rectify the dysfunction of cells in a disease. Stem cells from diseased individual can be retrieved and differentiated in diseased cells with diseased phenotype. Alternatively, diseased cells can also be reprogrammed to generate Induced Pluripotent Stem Cells (IPSCs) to *in vitro* differentiate into large quantity of diseased cells. In both cases, characteristic phenotype of a disease can be investigated to study mechanism of pathogenesis of disease.

Endometrium is highly regenerative tissue. With each menstruation cycle, functionalis layer is shed and subsequently regenerated. The regenerative capacity of endometrium lies in the highly renewable and pluripotent adult stem or progenitor cells present in the basalis region.[17] Endometrial stem cells can differentiate into chondrocytes, adipocytes, smooth muscle cells and osteoblasts.[18] Partial shedding of the basalis region with each retrograde menstruation may lead to migration of endometrial stem cells and adult progenitor cells, which suggests that basalis layer and the inhabitant cells are potential contributors to endometriotic lesions. Studies have found an increased number of fragments of the shed basalis layer in the menstrual blood of women with endometriosis as compared to healthy controls. This suggests that basalis layer and its endometrial stem cells play an important role in endometriosis. Not only endometrial progenitor cells, but also hematopoietic stem cells has been purportedly involved in contribution of endometriosis.[19] These undifferentiated stem cells from endometrium and endometriosis can be useful tool to study the molecular pathogenetic mechanism of endometriosis and hence infertility.

### Need to Identify Biomarkers of Endometriosis

Endometriosis is the disease of menstruating species primarily humans and some non-human primates. At the time of clinical presentation, most women have endometriosis, therefore, possess no experimental evidence of physiological role in pathogenesis of endometriosis. Monitoring of progression requires repeated laparoscopies and thus controlled experiments in humans are limited due to ethical reasons and cost of handling. Definitive diagnosis of multifactorial endometriosis requires a surgical procedure. Therefore, patients suffer for several years until appropriate treatment is obtained. In order to facilitate an earlier stage diagnosis, identification of a specific biomarker which would indicate normal and pathogenic processes of disease progression is greatly needed. Studies have revealed the role of glycoproteins, inflammatory and non-inflammatory cytokines, adhesion molecules, and angiogenic and growth factors in pathogenesis and development of endometriotic lesions.[6] Other studies have isolated subpopulations of endometrial stromal and glandular cells which express characteristic genetic markers CD13 and CD9, respectively and regenerate into endometrium *in vitro*.[20] However, neither a single biomarker nor a panel of biomarkers has been proven to be a reliable non-invasive tool for endometriosis. A convenient experimental model is vital to study the pathophysiological mechanisms of development of endometriosis. In addition, an *in vitro* model of endometriosis would be instrumental to develop and test therapeutic strategies to prevent the onset and progression of endometriosis.

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