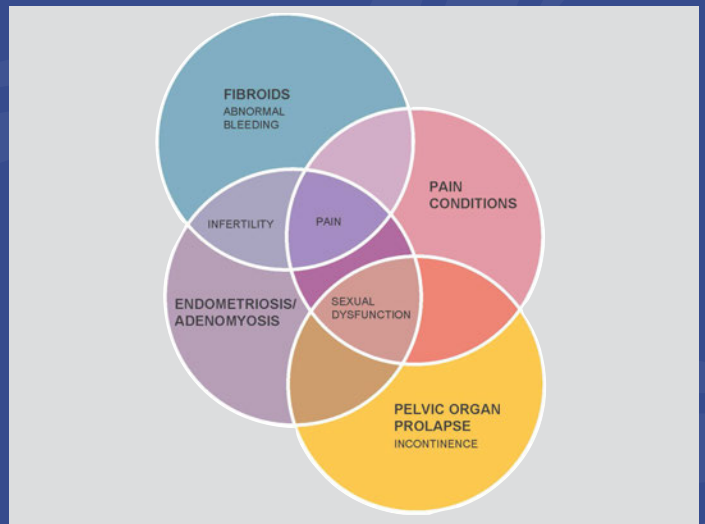
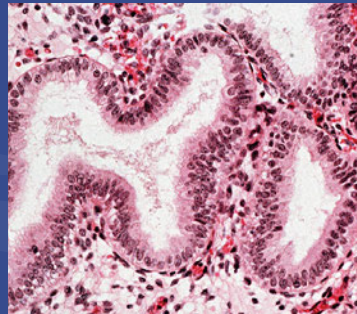
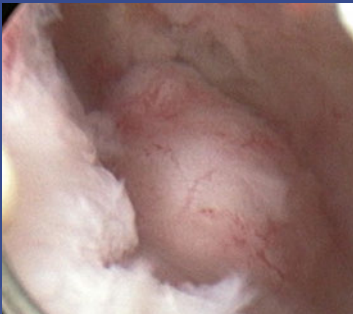




Eunice Kennedy Shriver National Institute  
of Child Health and Human Development

# Gynecologic Health and Disease Research at NICHD



## A Scientific Vision

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A Scientific Vision



*Eunice Kennedy Shriver* National Institute  
of Child Health and Human Development



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## Introduction

### ***Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD): Mission***

Since its inception in 1962, NICHD has dedicated its research to understanding the dynamic biological, behavioral, and social processes that dictate physical, emotional, and cognitive growth. The NICHD mission is to ensure that every person is born healthy and wanted, that women suffer no harmful effects from reproductive processes, and that all children have the chance to achieve their full potential for healthy and productive lives, free from disease or disability, and to ensure the health, productivity, independence, and well-being of all people through optimal rehabilitation.

### **Gynecologic Health and Disease Branch (GHDB)**

In 2011, coinciding with its 50th anniversary, NICHD underwent a year-long Scientific Vision process to identify the most promising scientific opportunities and public health needs of the next decade across the breadth of the institute's mission. NICHD stakeholders and participants in the Vision process saw the need for a reorganization of the extramural program and the opportunity to highlight gynecologic research; thus, the GHDB was created. As noted in the NICHD Scientific Vision, "Gynecologic disorders, including endometriosis, pelvic floor disorders, and fibroids, affect quality of life on multiple dimensions, especially when accompanied by comorbid conditions such as infertility, obesity, metabolic dysfunction, chronic pain, or mood disorders. Developing novel approaches to prevent, diagnose, and manage these often-interrelated conditions, premised on a detailed understanding of normative and pathologic mechanisms, could greatly improve quality of life for women across the lifespan."

---

***GHDB Mission:***

***To improve women's reproductive health by guiding and supporting research and career development programs in gynecologic health and disease***

***GHDB Vision:***

***A future in which women lead lives free of the effects of gynecologic disorders***

---

Established in late 2012, the GHDB supports basic, translational, and clinical research programs related to gynecologic health throughout the reproductive lifespan, beginning at puberty and extending into menopause. The branch portfolio includes studies on menstrual disorders, uterine fibroids, endometriosis, adenomyosis, ovarian cysts, polycystic ovary syndrome, and pelvic floor disorders, as well as

gynecologic pain syndromes, including chronic pelvic pain, vulvodynia, and

dysmenorrhea. These gynecologic conditions are associated with significant morbidity beyond their impact on fertility and contraception, areas supported by other branches within NICHD. Obstetric fistula and female genital cutting are also of interest as they apply to both international and immigrant communities. Efforts have focused on sponsoring research in selected gynecologic areas that have either been overlooked or underfunded, including socioeconomic, racial, and ethnic disparities in reproductive health outcomes. The branch also supports research training and career development programs for investigators interested in pursuing an academic career in women's reproductive health.

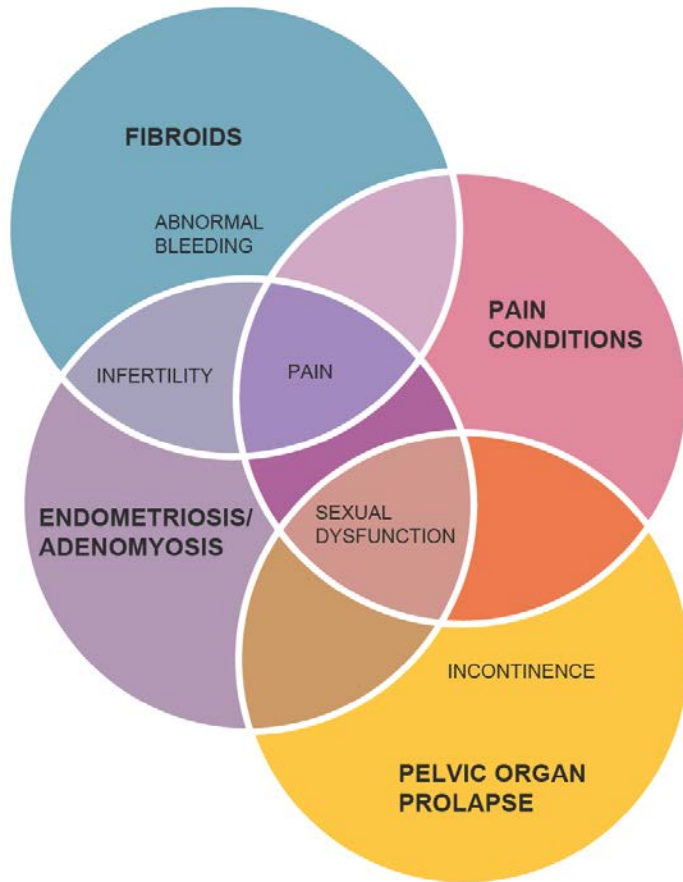
### **Request for Information (RFI)**

As an early step in establishing itself as a new branch at NICHD, GHDB set out to engage its stakeholders by publishing an RFI ([NOT-HD-15-030](#)) requesting "input from the public on the current state of the science, the highest priorities moving forward, and potential conceptual or technical barriers to overcome." We received responses from 9 individuals, 2 institutional departments, 2 professional societies, and 1 patient advocacy group. Feedback from the RFI helped frame the overall organization of the meeting, and guide the questions asked of participants.

### **GHDB Scientific Vision Meeting**

The goal of the GHDB Scientific Vision Meeting was to identify gaps that may provide future directions for gynecologic health and disease (GHD) research supported by NICHD. The meeting was also designed to help identify emerging priorities to advance the field of gynecologic research.

Meeting participants were selected to bring together diverse opinions that would generate new perspectives for existing research problems and assist in identifying new opportunities. Attendees included basic, translational, and clinical investigators from the extramural research community with broad expertise in relevant research areas including reproductive biology, gynecology, urology, and biomedical engineering. Representatives were also drawn from the Divisions of Extramural and Intramural Research within NICHD as well as the National Institute of Diabetes and Digestive and Kidney Diseases and the Office of Research on Women's Health (ORWH). A list of meeting participants can be found in [Appendix 1](#).



*Figure 1: Major topics of the GHDB portfolio: The four conditions comprise the majority of the branch research portfolio have many overlapping symptoms.*

Although branch interest and funding span an array of gynecologic disorders, the current portfolio of grants is focused on four primary gynecologic disorders: uterine fibroids, endometriosis, pelvic floor disorders, and gynecologic pain conditions. These four areas were chosen for emphasis at the meeting and in this document; however, participants were asked to consider other areas of potential importance throughout their discussions.

Groups were assigned to one research area, then asked to identify both: 1) scientific gaps and opportunities, and 2) potential solutions utilizing available tools, methodologies, and approaches. Questions asked of meeting participants are listed in [Appendix 2](#). During the second day, participants were assigned to a second

research area to address the same questions and issues to leverage the diverse interests and expertise of the attendees and maximize the perspectives applied to each disorder.

A set of seven cross-cutting themes emerged from each of these breakout groups. These themes represent both gaps in our current knowledge and opportunities for further research. Along with these themes, discussions in each of the breakout groups led to the identification of strategies that would be useful to implement or operationalize the themes' research opportunities. In the next section, background information is provided on the four selected gynecologic conditions to provide context for the themes and strategies that follow.



## Context and Scientific Landscape

### Uterine Fibroids (Leiomyoma)

Uterine fibroids, or leiomyoma, are the most common benign gynecologic tumors in women. They arise from smooth muscle cells in the wall of the uterus and are extremely heterogeneous in their number, size, location, and clinical symptomatology. Symptoms can include abnormal bleeding, pelvic pain, infertility, pressure symptoms, miscarriage, and preterm labor; however, some women remain asymptomatic, even with large fibroids. Fibroids occur in greater than 70 percent of women, with clinical symptoms in 25 percent to 50 percent of these women (Stewart et al., 2016). A clear racial disparity exists, with fibroids presenting earlier and with greater severity in African American women compared with white women. Data are limited for Hispanic and Asian women, but seem to be closer to rates among white women (Marshall et al., 1997). Despite this high prevalence, few studies have quantified the effects of fibroid symptoms on health-related quality of life in women. Most of the studies that do quantify these effects use a validated questionnaire specific to uterine fibroids, the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) assessment (Spies et al., 2002).

#### Racial Disparities of Uterine Fibroids

Among U.S. women of all races/ethnicities, ages 25 to 44, approximately 30% have symptoms of fibroids

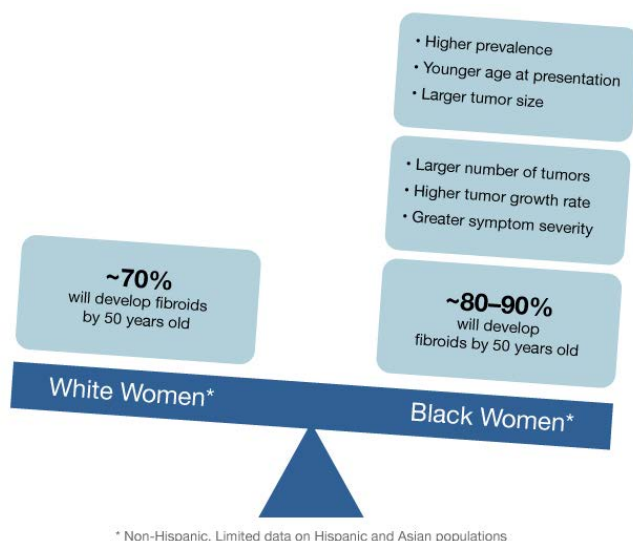


Figure 2: Differences exist in several characteristics of uterine fibroids (or leiomyomata) based on race. Sources: NICHD; Jacoby, Fujimoto, Giudice, Kuppermann, & Washington, 2010

#### Financial Cost of Disease

The health problems associated with fibroids consume a significant amount of healthcare resources in the United States, costing an estimated \$5.9 to \$34 billion annually (Cardozo et al., 2012).

#### Diagnosis

Fibroids can be diagnosed during clinical evaluation when the uterus is noted to be enlarged with irregular, firm masses. Ultrasound is frequently used to support the diagnosis and rule out other conditions such as benign ovarian cysts. Although expensive, magnetic resonance imaging (MRI) can also be used to further characterize fibroid location and number, as well as to distinguish from adenomyosis or even adenosarcoma. Serum-based biomarkers under development

currently lack adequate predictive value, but could be useful in distinguishing benign uterine fibroids from other conditions (Stewart et al., 2016). These distinctions are critical because adenomyosis is not amenable to local excision, and adenosarcoma requires assessment and treatment by a gynecologic oncologist. Unfortunately, these alternative diagnoses are often not made prior to surgery, highlighting an important goal for further research.

### Classification

The International Federation of Gynecology and Obstetrics has established a classification system for the causes of abnormal uterine bleeding in women of reproductive age that is based on imaging data and differentiates based on location of tumors. However, this classification system does not incorporate information on number or size of the tumors and underestimates the complexity of the clinical disease (Munro et al., 2011). A recent report has proposed two novel classification systems for fibroids and subsequent uterine reconstruction, but neither system has been widely evaluated or accepted (Juhasz-Boss et al., 2017).

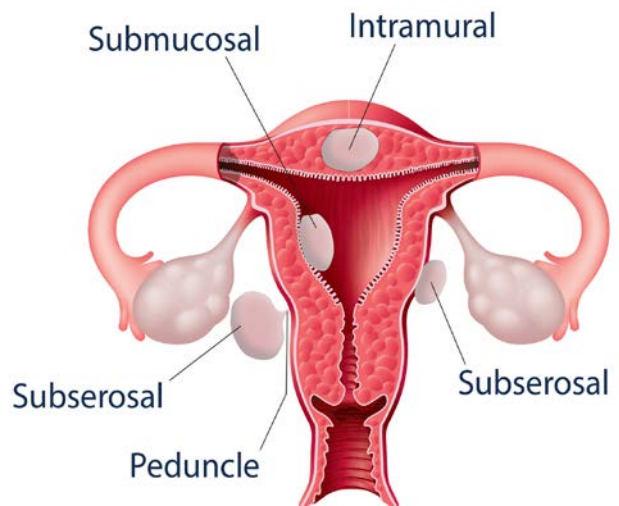


Figure 3: Possible anatomic locations of uterine fibroids

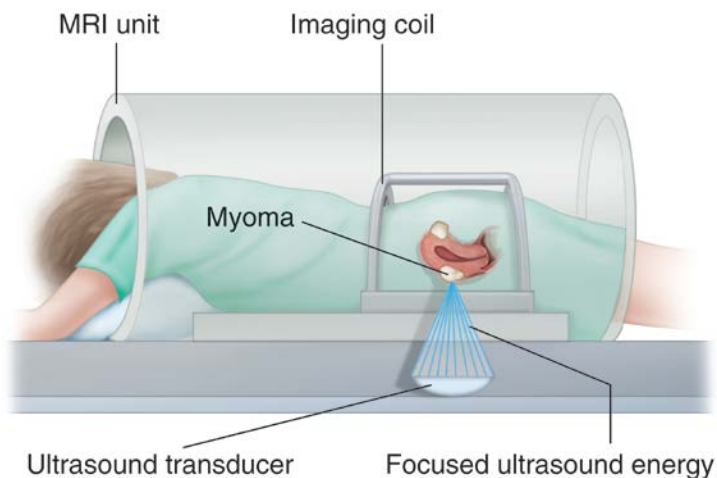


Figure 4: MRI-guided focused ultrasound for the treatment of fibroids (Figure courtesy of Williams Gynecology)

### Risk Factors

Factors that can increase the risk of fibroids include early age at menarche, prenatal exposure to diethylstilbestrol (DES), a diet heavy in red meat, alcohol consumption, and vitamin D deficiency. Factors that can decrease the risk of fibroids include exposure to long-acting progestins, green vegetable and fruit intake, and dairy consumption (Stewart et al., 2016). Some genetic mutations have been identified, including complex chromosomal rearrangements, mediator complex subunit 12 (*MED12*), fumarate hydratase

inactivation (Kampjarvi et al., 2016), high-mobility group AT-hook 2 (*HMG2*) overexpression, and collagen type IV  $\alpha 5$  (*COL4A6-COL4A5*) deletion (Mehine, Makinen, Heinonen, Aaltonen, & Vahteristo, 2014). Gene silencing can also play a role in the pathogenesis of uterine leiomyoma in African American women (Navarro et al., 2012). The roles of vitamin D and/or *MED12* mutations in the development of fibroids and as potential targets for future therapies have been particularly strong foci of research in recent years.

## Research Models

Uterine fibroid research continues to be hampered by the paucity of models that recapitulate the genetics and cellular behavior of human fibroids. The Eker rat strain, which carries a mutation in a tumor suppressor gene and develops fibroids at a high frequency, has been used in fibroid research for many years. However, a review (Stewart et al., 2016) revealed that this model is limited by high animal housing costs, the lack of a rat genome map, and the fact that some of the uterine lesions developed in the model can be malignant, rather than benign. Newer animal models being developed and utilized include murine models with xenografts of human tissue; other models using mice and the domestic hen are also being examined. Standard cell culture of dispersed leiomyoma cells and 3D culture of fibroid tissue have also been used (Malik & Catherino, 2012; Markowski et al., 2014).

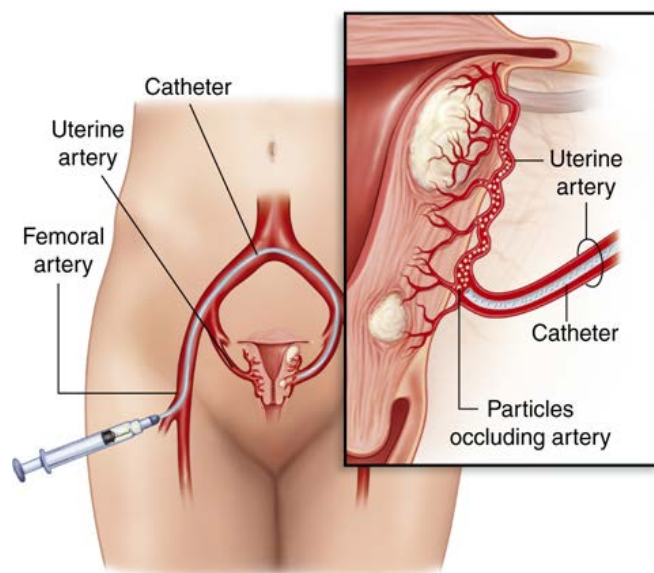


Figure 5: Uterine artery embolization is one treatment for fibroids (Figure courtesy of Williams Gynecology)

## Treatment

The most common treatment for fibroids is hysterectomy, although many women prefer uterine-sparing treatments. A major surgical procedure, hysterectomy precludes future childbearing and can be associated with significant morbidity and healthcare costs. According to the Centers for Disease Control and Prevention (CDC), approximately 1 of every 3 women have had a hysterectomy by the age of 60 (Prevention, 2017), and more than one-third of those are due to the presence of symptomatic leiomyoma. The currently available uterine-sparing approaches can be associated with obstetric complications, as well as the need for

future treatment following the growth of new fibroids. These include surgical excision of individual fibroids (myomectomy), embolization procedures (e.g., uterine artery

embolization), and thermoablative therapies (e.g., magnetic resonance-guided focused ultrasound [MRgFUS]).

Because fibroids are responsive to estrogen and progesterone, medical therapies used to treat fibroid-associated heavy menstrual bleeding include oral contraceptives, progesterone receptor modulators (e.g., ulipristal acetate), levonorgestrel intrauterine devices, and gonadotropin-releasing hormone (GnRH) agonists and antagonists. The antifibrinolytic (pro-clotting) medication, tranexamic acid, has also been used with success (Moravek & Bulun, 2015; Stewart et al., 2016). A wide array of potential therapeutic agents has been proposed and are undergoing investigation, such as aromatase inhibitors, cyclin-dependent kinase inhibitors, antiproliferative agents, antifibrotic medications, vitamin D, herbals, curcumin, nanocarrier technology, epigenetic targets, microRNAs, and histone modification enzymes (Segars et al., 2014). While medical management can be helpful in relieving symptoms such as heavy menstrual bleeding, a systematic review from the Agency for Healthcare Research and Quality reported the lack of high-quality evidence supporting the effectiveness of most medical therapies for symptomatic fibroids (Gliklich et al., 2011).

## Endometriosis

Endometriosis is defined as the presence of endometrium-like tissue (similar to the tissue that lines the uterus) outside of the uterine cavity, most commonly on the ovaries, fallopian tubes, or other tissues in the pelvis (American College of Obstetricians and Gynecologists, 2012).

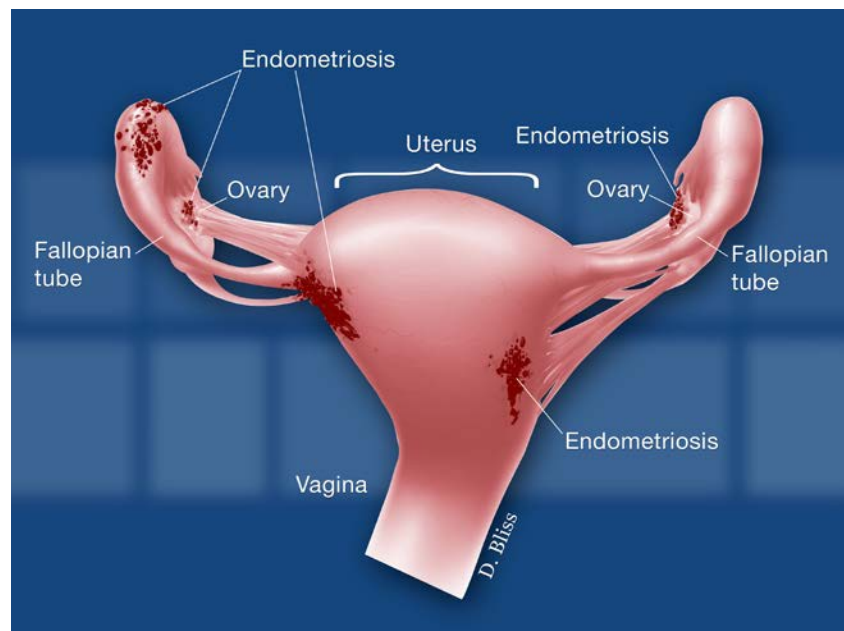


Figure 6: Locations along the female reproductive tract where endometriotic lesions can be found

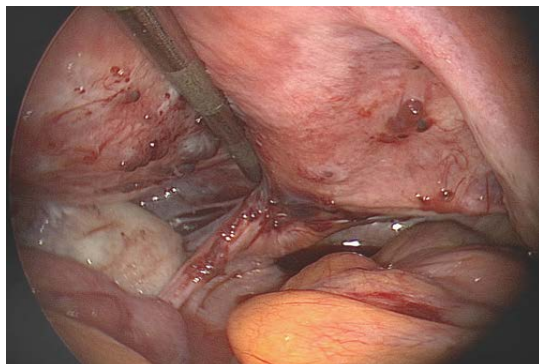
Multiple theories have been proposed for the etiology of endometriosis. Research suggests that retrograde menstruation, in which menstrual tissue expelled through the fallopian tubes attaches to pelvic tissues, may initiate the development of endometrial lesions, perhaps facilitated by local production of estrogen and prostaglandins in the endometriotic lesions or by failure of a dysfunctional immune system to remove this tissue. Alternative

theories, necessary to explain endometriosis outside the pelvis, include lymphatic or vascular spread as well as the conversion of undifferentiated stem cells into endometrial tissue.

An estrogen-dependent inflammatory disease, endometriosis can be associated with dysmenorrhea, dyspareunia, noncyclic pelvic pain, dysuria, defecatory pain, and/or infertility. Estimates suggest that 6 percent to 10 percent of women of reproductive age have endometriosis (Giudice, 2010; American College of Obstetricians and Gynecologists, 2010), or approximately 5 million women in the United States and up to 176 million women worldwide (Johnson, Hummelshoj, & World Endometriosis Society, 2013). Of interest, women can have extensive disease but limited symptomatology or, conversely, limited apparent disease despite substantial symptoms. Because the diagnosis can be missed in this former group, it is possible that prevalence estimates are low.

### Financial Cost of Disease

A 2016 review of the literature estimated the total direct costs (all healthcare service costs) of endometriosis to be about \$1,109 per patient per year in Canada, and up to \$12,118 in the United States. Indirect costs (related to lost productivity at work) ranged from \$3,314 per patient per year in Austria to \$15,737 in the United States (Soliman, Yang, Du, Kelley, & Winkel, 2016).



*Figure 7: Examples of endometriotic lesions in abdominal cavity (top) and on ovary (bottom) (Figure courtesy of Williams Gynecology)*

### Diagnosis

The diagnosis of endometriosis requires visualization of endometriotic lesions at the time of surgery (Hummelshoj, 2017). Although not required by current guidelines, diagnosis optimally includes histologic confirmation of endometrial glands and stroma in a biopsy specimen. Dysmenorrhea due to endometriosis can be misinterpreted as common menstrual cramps in adolescent girls and young women, delaying diagnosis by several years and allowing progressive pelvic organ damage and an increased risk for infertility (Greene, Stratton, Cleary, Ballweg, & Sinaii, 2009). Early diagnosis would be greatly aided by the identification of biomarkers, which would eliminate the need for surgical diagnosis. Proposed biomarkers include glycoproteins (e.g., cancer antigen 125 [CA125]), cytokines, immune cell populations, and noncoding RNAs, as well as broader

changes in the transcriptome, proteome, or metabolome (Ahn, Singh, & Tayade, 2017). Serum, peritoneal fluid, menstrual effluent, and endometrium obtained with biopsy are all under evaluation as potential sources for measurement.

### Classification

Endometriosis can range from mild endometriosis with small, isolated foci to severe endometriosis with large sheets of invasive endometriotic lesions affecting the function of pelvic organs, including the ovaries, fallopian tubes, intestines, and bladder. Although less common, endometriosis can also be found at sites distant to the pelvis. The most commonly utilized classification system was developed by the American Society for Reproductive Medicine and categorizes endometriosis into four stages based on lesion characteristics (size, anatomic location, and whether deep or superficial) and the extent of pelvic adhesions at the time of surgery (Borghese, Zondervan, Abrao, Chapron, & Vaiman, 2017). The Enzian classification system was developed to describe more severe disease, but it is rarely used. A third classification system, the Endometriosis Fertility Index, is the only validated classification system to predict pregnancy rates in infertility patients following surgical diagnosis and treatment of endometriosis (Adamson, 2011). In 2017, the World Endometriosis Society developed an international consensus that proposed use of all three of these staging systems, where appropriate. The Society also proposed wider use of the surgical and clinical data collection tools generated by the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project to improve classification of endometriosis in the future, ideally without the need for diagnostic surgery (Johnson et al., 2017).

### Risk Factors

The risk of developing endometriosis is believed to be greatly influenced by genetic and epigenetic factors, with the observed familial inheritance pattern supporting a genetic etiology. Genome-wide association studies (GWAS) have implicated genetic variants involved in steroid hormone metabolism, inflammation, angiogenesis, WNT/ $\beta$ -catenin signaling, and estrogen-induced cell growth, migration, adhesion, and invasion. Potentially detrimental alterations include single-nucleotide polymorphisms, copy number variation, loss of heterozygosity, and epigenetic abnormalities in DNA methylation (e.g., *TNFRSF1B*, *IGSF21*, and *TP73*) (Borghese et al., 2017).

Of note, endometriosis has a higher prevalence among women who underwent menarche at a younger age and, thus, experience prolonged estrogen exposure (Hummelshoj, 2017). Preliminary studies suggest a correlation between certain foods and the development of endometriosis, with a decreased risk in women with diets high in fruits and vegetables, fish oil, omega-3 fatty acids, and dairy products rich in calcium and vitamin D. Conversely, consumption of alcohol and foods rich in trans-unsaturated fatty acids, including red meat, can increase the risk for endometriosis (Jurkiewicz-Przondziona, Lemm, Kwiatkowska-Pamula, Ziolkko, & Wojtowicz, 2017). Exposure to

environmental toxins, particularly dioxin-like compounds, are also suspected to play a role in the development of endometriosis.

### Research Models

Experimental animal models have been developed in nonhuman primates and laboratory rodents by induction of endometriosis via autologous transplantation of endometrial tissue. Animals with induced endometriosis reveal impaired fecundity as observed in women and have been used to identify effects of ectopic endometrial tissue on adhesion formation, peritoneal fluid composition, ovarian function, endometrial gene expression, and embryo implantation (Grummer, 2013). *In vitro* models include culture of human endometrial tissue fragments and dispersed human endometrial cells.

### Treatment

Current treatments for patients with endometriosis can achieve temporary relief of symptoms during treatment, but they are not curative. Because endometriosis is an estrogen-dependent process, medical treatments aim to either remove estrogen stimulation or to inhibit growth through the suppressive effects of progestins. Therapeutic options include GnRH analogues, progestins, and oral contraceptive pills (Dunselman et al., 2014). Newer treatments under study include selective progesterone receptor modulators, aromatase inhibitors, immunomodulators, and antiangiogenic agents. Pain can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids. Fertility-sparing surgery can be performed to remove lesions and scar tissue; however, patients can ultimately require hysterectomy and removal of the ovaries. Most affected women experience significant less pain or even become symptom free after menopause (Hummelshoj, 2017).

### Pelvic Floor Disorders (PFDs)

GHDB supports research on PFDs, which encompass pelvic organ prolapse, urinary incontinence, fecal incontinence, and other disorders of the lower gynecologic, urinary, and gastrointestinal tracts. The prevalence of these disorders is difficult to ascertain because rates vary depending on whether data is collected via self-report or physical exam. Data from the National Health and Nutritional Examination Survey, which surveyed more than 7,900 women, demonstrated that nearly 1 in 4 women has at least one PFD (Wu et al., 2014). Specifically, 17.1 percent reported moderate to severe urinary incontinence, 9.4 percent had fecal incontinence, and 2.9 percent described prolapse symptoms. Other large survey reports have shown that the prevalence of urinary incontinence in women can be as high as 42 percent (Melville, Delaney, Newton, & Katon, 2005), and pelvic organ prolapse can occur in up to 50 percent when defined by vaginal examination (Barber & Maher, 2013).

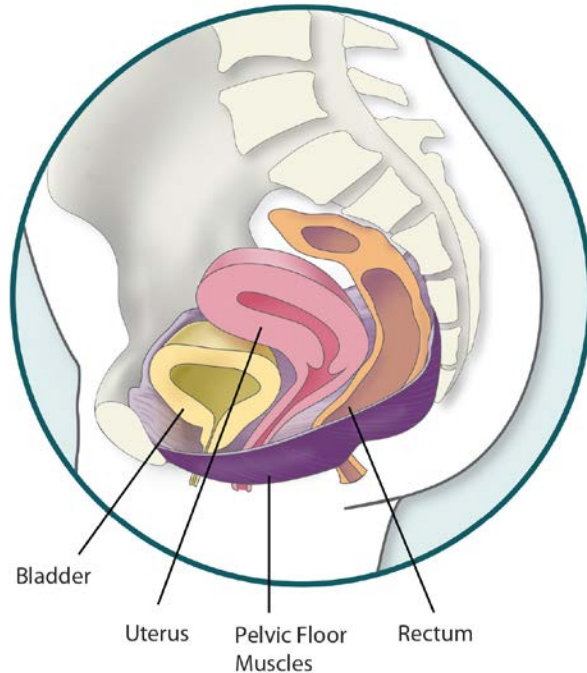


Figure 8: Pelvic floor anatomy

One in 5 women in the United States will require surgical intervention for a PFD, and the number of women impacted is estimated to rise in the coming decades (Dieter, Wilkins, & Wu, 2015). In addition, nearly one-third of women who undergo surgical repair for a PFD will ultimately require reoperation (Olsen, Smith, Bergstrom, Colling, & Clark, 1997). Importantly, these reports likely underestimate true prevalence because not all symptomatic women seek care. PFDs impact a patient's quality of life, sexual function, and overall morbidity and increase caregiver burden. Research efforts are actively examining these dimensions of PFD impact.

### Financial Cost of Disease

The cost of ambulatory care related to PFDs in the United States has been estimated at \$412 million for the years 2005 to 2006 (Sung, Washington, & Raker, 2010). The total economic burden (which includes direct costs, indirect costs, costs from lost productivity, and intangible costs) of urgency urinary incontinence in the United States was \$66 billion in 2007 (Milsom et al., 2014). According to the National Institutes of Health (NIH) compendium of disease-specific costs, pelvic organ prolapse surgery had a direct cost of \$1.01 billion in 1997, similar to the costs associated with treating breast cancer or managing infertility (reviewed by Hu et al., 2005). Costs are anticipated to continue to rise as the population ages. Effective preventative and curative regimens could significantly decrease the financial burden of these disorders.

### Diagnosis

#### Urinary symptoms

Most PFDs can be diagnosed by a woman's symptoms and physical examination. As part of her medical history, a voiding diary, which records urination and incontinence patterns during the day, can be useful. A physical exam is generally performed to evaluate for any neurologic components and assess general pelvic support. Typically, the healthcare provider also performs simple bladder evaluations, including assessment of urine retained after a voiding, bladder sensations, bladder capacity, and any urinary leakage. These evaluations can help distinguish the type of incontinence present.



Multichannel urodynamics is a minimally invasive tool that can sometimes be used to better categorize urinary symptoms, particularly in complicated cases.

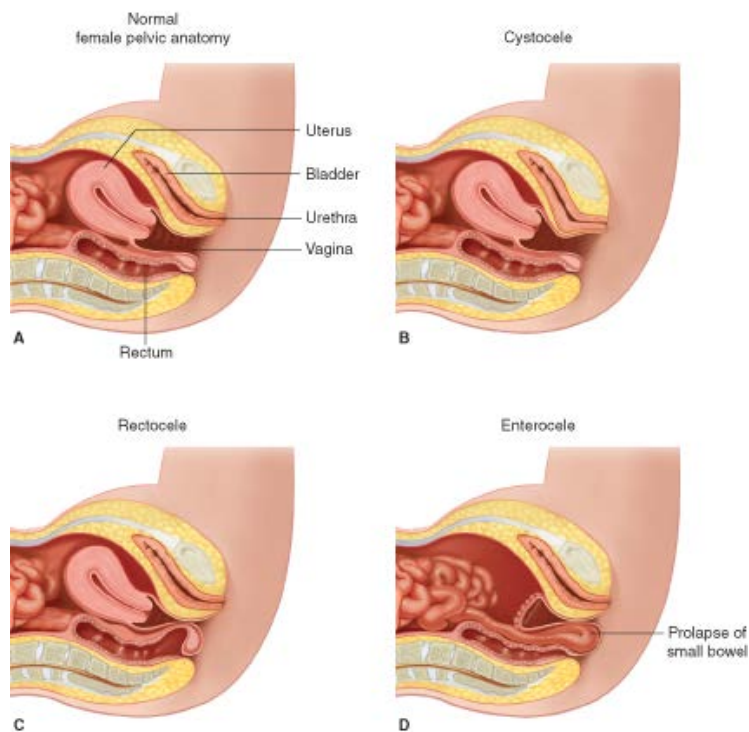


Figure 9: Different forms of vaginal wall prolapse and associated abnormalities (Figure courtesy of Williams Gynecology)

classified as stress urinary incontinence (SUI), urgency urinary incontinence (UUI), or mixed urinary incontinence (MUI). While other classifications, such as overflow incontinence and neurogenic bladder are also observed, most women are symptomatic from SUI, UUI, or MUI. SUI is urinary loss associated with increases in intra-abdominal pressure, such as coughing, laughing, sneezing, or exercise. UUI is leakage that is preceded by a strong urge to void, with an inability to make it to the restroom in a timely fashion. MUI is diagnosed when both symptoms of SUI and UUI are present. Another category of urinary symptoms that can be associated with incontinence is called overactive bladder syndrome (OAB), which includes frequent voiding or urgency symptoms that cause bother.

### *Pelvic Organ Prolapse*

Using the POPQ system, total vaginal length and eight additional measurements are obtained from the anterior vaginal wall, posterior vaginal wall, vaginal apex, and/or cervix. The measurements are reported as the distance in centimeters from the hymen. Based on the measurements, the prolapse is staged as stage 0, 1, 2, 3, or 4, which reflect increasing degree of severity.

### *Pelvic Organ Prolapse*

Pelvic organ prolapse is diagnosed via medical history and physical exam. The Pelvic Organ Prolapse Quantification (POPQ) system is the most commonly used method to quantify and stage the degree of prolapse (Persu, Chapple, Cauni, Gutue, & Geavlete, 2011). Diagnosis of this condition is via a vaginal examination, often using the single blade of a speculum to visualize the vaginal walls and cervix, while measuring the level to which the prolapse has occurred.

### **Classification**

#### *Urinary symptoms*

Urinary incontinence is often

## Risk Factors

PFDs share several putative risk factors. Factors associated with the development of SUI include obesity, parity (number of births), vaginal parity (number of vaginal births), family history, age, race/ethnicity, smoking, and possibly participation in high-impact activities (Stothers & Friedman, 2011). UUI symptoms are associated with a history of recurrent urinary tract infections or childhood bladder symptoms (Wood & Anger, 2014). Risk factors implicated in the development of prolapse include parity, vaginal parity, operative vaginal delivery (use of vacuum or forceps), large infant weight at birth, obesity, hysterectomy, race/ethnicity, chronic constipation, connective tissue disorders, congenital anomalies, and family history (Vergeldt, Weemhoff, IntHout, & Kluivers, 2015). Current studies are investigating nutritional variables such as saccharine, vitamin C, and vitamin D intake and their effects on the pelvic floor.

## Research Models

Animal models have helped reveal some of the underlying pathophysiology of urinary incontinence. Rat models have demonstrated that simulated birth injury appears to contribute to urethral, pelvic ganglia, and levator muscle changes, resulting in SUI (Lin, Carrier, Morgan, & Lue, 1998). Injection of stem cells into the muscles surrounding the urethra of rats leads to an increase in the bladder pressure at which the animals leak urine (Lee et al., 2003). Rat models have also provided insight into the role of noradrenergic pathways and angiotensin II in SUI (Kaiho et al., 2007; Phull, Salkini, Escobar, Purves, & Comiter, 2007).

Research to study pelvic organ prolapse has involved monkey and rodent models. A randomized controlled trial of vaginal versus cesarean deliveries in squirrel monkeys demonstrated that although cesarean delivery minimizes detrimental muscle changes associated with vaginal delivery, it does not fully protect pelvic support (Lindo et al., 2015). Studies in Rhesus macaques have helped to identify factors potentially involved in the successful or poor incorporation of mesh grafts in the treatment of prolapse (Liang et al., 2017).

Although useful, these animal models are significantly hampered by differences in pelvic architecture and musculature. In addition, because animals cannot express the urge to void, alternative outcomes must be studied.

## Treatment

Treatment options for PFDs can include expectant management, lifestyle modification, physical therapy, and medical or surgical approaches. In some cases, women are not significantly bothered by their condition and/or are simply seeking reassurance that their condition is not life-threatening. In such cases, expectant management is appropriate.

## Urinary symptoms

Noninvasive methods that can help treat urinary PFD symptoms include lifestyle modifications, such as weight loss, dietary changes that avoid irritating substances, such as caffeinated beverages, constipation management, smoking cessation, and timed voiding (also called bladder training).

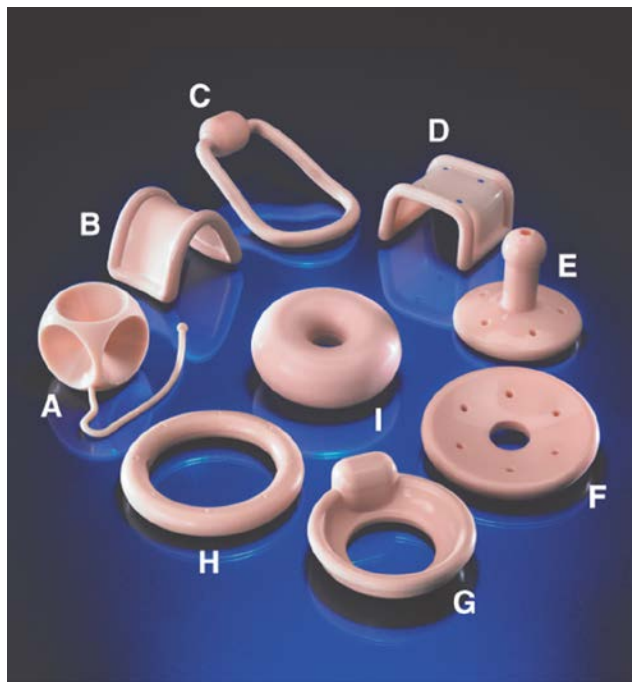


Figure 10: Different forms of pessaries used to treat uterine prolapse (Figure courtesy of Williams Gynecology)

Pelvic floor strengthening through pelvic floor muscle exercises has also been shown to be beneficial. Pessaries have been used with some success to treat SUI. Estrogen applied vaginally is used to treat atrophy that can contribute to SUI or UUI. Percutaneous tibial nerve stimulation, performed via an acupuncture needle placed behind the ankle that delivers electrical stimulation, has been shown to improve OAB symptoms. Data describing long-term benefits or need for maintenance of these therapies are lacking, and there is a paucity of general information regarding cure or recurrence with these modalities.

Medical treatments approved for the treatment of OAB or UUI include antimuscarinic agents or beta-3 agonists. Side effects associated with

antimuscarinics, such as dry mouth and constipation, can inhibit compliance with these medications or cause patients to cease taking them altogether. Furthermore, head-to-head comparative studies and research on long-term impacts of these medications are needed. Medication costs and lack of insurance coverage can often dictate which medication is selected for a patient, regardless of the appropriateness for that individual. Common surgical options for SUI include the midurethral sling, bladder neck slings, and injections of bulking agents into the urethra (American College of Obstetricians and Gynecologists, 2017). Though there is controversy surrounding the use of mesh in PFDs, its relatively safe and effective use in anti-incontinence surgery is supported by evidence (U. S. Food and Drug Administration, 2013). OAB/UUI can be treated with botulinum toxin injections into the muscle of the bladder or with sacral neuromodulation, an invasive implantation of a lead and battery to provide electrical stimulation (Amundsen et al., 2016). Research to evaluate the long-term efficacy, risks/benefits, and comparisons of these treatments are currently ongoing.

### *Pelvic Organ Prolapse*

Treatment for pelvic organ prolapse can include expectant management, pessary placement, physical therapy, and surgical management. Selection depends on the patient's medical status, desire for sexual function, and expectations. Repairs can be classified as reconstructive or obliterative. Both procedures can involve performing a concomitant hysterectomy. Reconstructive procedures attempt to restore the normal anatomy, can be approached vaginally or abdominally, and can incorporate the use of polypropylene mesh to affix the vaginal apex to the sacrum (i.e., sacrocolopexy). Obliterative procedures, such as colpocleisis or the LeForte procedure, remove or close off part or all of the vagina. These procedures are performed vaginally and confer the advantage of shorter operative times, lower risks of complications, and the potential to use only local anesthesia, making them desirable for women with comorbid conditions who no longer desire to maintain sexual activity.

There are no established recommendations regarding the optimal procedure for patients requiring prolapse correction as few comparative, randomized, or prospective studies are available. Data is also lacking regarding the risks associated with each procedure, the long-term outcomes, or the potential benefits of uterine-sparing procedures. The use of vaginally-placed mesh for the treatment of pelvic organ prolapse has received criticism, including a recent warning by the Food and Drug Administration (FDA) (U.S. Food and Drug Administration, 2011). Well-designed, adequately-powered research studying the long-term outcomes, utility, and safety of vaginally placed mesh by experienced surgeons is greatly needed.

## **Gynecologic Pain Syndromes**

Gynecologic pain conditions include chronic pelvic pain, painful menses (dysmenorrhea), painful sexual intercourse (dyspareunia) and vulvar pain syndromes. Chronic pelvic pain (CPP) is defined as non-cyclic, persistent pain in the pelvic area that is unrelated to pregnancy, and that lasts at least 3 to 6 months (Speer, Mushkbar, & Erbele, 2016). Alternatively, dysmenorrhea refers to recurrent, cramp-like, lower abdominal pain associated with menses. Dysmenorrhea can be primary or secondary. Localized vulvar pain syndromes (vulvodynia, vestibulodynia, vulvar vestibulitis, or focal vulvitis) are pain disorders located in the vulvar area and are typically categorized separately from CPP. Vulvodynia is a term used to describe chronic pain (lasting at least 3 months) of the vulva that does not have a clear cause, such as an infection or cancer.

## **Financial Cost of Disease**

The prevalence of pain syndromes is difficult to estimate, and financial burdens are similarly difficult to establish. In 1996, the direct outpatient costs for CPP visits for women age 18 to 50 years was estimated to be \$881.5 million per year in the United States alone (Mathias, Kuppermann, Liberman, Lipschutz, & Steege, 1996). While the

true prevalence of vulvodynia remains unknown, several million women in the United States are estimated to suffer from this syndrome. Researchers estimate that 9 percent to 18 percent of women between the ages of 18 and 64 could experience vulvar pain during their lifetimes (Arnold, Bachmann, Rosen, & Rhoads, 2007; Harlow & Stewart, 2003; Harlow, Wise, & Stewart, 2001). According to survey responses of members of the National Vulvodynia Association, total costs for vulvodynia diagnosis and treatment were approximately \$8,862 per patient over 6 months. Based on a prevalence of 3 percent to 7 percent in the United States, a second analysis estimated an annual national cost of \$31 to \$72 billion for vulvodynia alone (Xie et al., 2012).

## Diagnosis

The evaluation of CPP, dysmenorrhea, and vulvodynia are similar in that they involve a detailed history and physical examination. The history involves identifying precipitating and alleviating factors, associations with activities (such as sex, urination, defecation), and responses to prior treatments. A thorough review of systems is also performed to evaluate for urogynecologic, gastrointestinal, musculoskeletal, or psychoneurologic disorders. The symptoms associated with vulvodynia vary for each woman, making correct diagnosis difficult. Vulvodynia pain characteristics can vary for each woman, ranging from burning to aching to throbbing, and can be present at rest or only when precipitated by pressure on the vagina or vulva. The pain can be localized or more diffuse, and constant or intermittent. All of these factors make correct diagnosis of this disorder difficult (American College of Obstetricians and Gynecologists, 2014).

Physical examination focuses on identification of the involved dermatome, nerves, muscles, or tissues. Diagnostic testing is typically reserved for CPP or dysmenorrhea cases where concerning history or physical exam findings are identified, and can involve the use of ultrasound or other imaging modalities (Mathias et al., 1996).

## Risk Factors

As would be predicted, the risk factors for CPP are generally the same as those for the underlying etiology, if identified. Persistence of acute pain from any underlying etiology is a risk factor for developing a chronic pain syndrome (McGreevy, Bottros, & Raja, 2011).

Research has suggested that genetic, hormonal, immunologic, inflammatory, microbial, neurophysiologic, behavioral, environmental, and/or psychosocial factors can all contribute to the development of vulvodynia or other pain conditions. Individual sensory experience can influence an individual's pain perception, such that certain experiences can cause dramatic pain in one woman and no pain in another. Furthermore, pain in one organ can increase the risk of pain from another organ system. Thus, individuals predisposed to greater pain sensitivity are at more risk for developing CPP and other gynecologic pain disorders.



*Figure 11: Gynecologic pain conditions include chronic pelvic pain, painful menses (dysmenorrhea), painful sexual intercourse (dyspareunia) and vulvar pain syndromes.*

Particularly little is known about risk factors for vulvodynia. In addition to those noted above, postulated associations include changes in circulating estrogen levels, embryologic abnormalities, increased urinary oxalates, and immune factors (Haefner et al., 2005). Specifically, decreased estrogen can alter vulvar nerve density and sensory nociceptors, which may explain why vulvodynia often begins or worsens at the time of menopause.

Although additional study is warranted, in one systematic review, dysmenorrhea was associated with age younger than 30 years, body mass index less than 20 kg/m<sup>2</sup>, smoking, menarche before age 12, irregular or heavy menstrual bleeding, and history of sexual assault. Conversely, younger age at first

childbirth and higher parity were potentially protective against experiencing dysmenorrhea. A familial association has also been reported (Wyckoff, 2017).

## Research Models

Gynecologic pain research has primarily utilized human subjects and has focused on immunologic and microbiologic causes. Although techniques have advanced for studying pain in animal models, significant concerns remain about the degree to which these models recapitulate human pain disorders.

Additional concerns focus on the difficulty of accurately identifying and characterizing pain in these models. Behavioral responses were used as markers of visceral pain in one study evaluating effects of an irritant in the rat bladder (Abelli et al., 1989). While rodents have been used to study gynecologic pain syndromes, such as the role of estrogen receptors in endometriosis pain, the majority of pelvic pain research in rodent models has focused on the males and the prostate (Alvarez, Bogen, & Levine, 2014). Of interest, rodent studies have demonstrated that pain in one pelvic tissue can increase sensitivity to pain in other pelvic organs (Yoshikawa et al., 2015), which can help explain the presence of multiple chronic pain syndromes in the same individual.

## Classification

### *Chronic Pelvic Pain (CPP)*

CPP can stem from the following systems: gynecologic, mental health, urinary tract, gastrointestinal, musculoskeletal, or neurologic. Possible identified gynecologic disorders include: endometriosis, adenomyosis, leiomyoma, chronic pelvic inflammatory disease, interstitial cystitis/painful bladder syndrome, pelvic adhesions, pelvic congestion syndrome, ovarian remnant syndrome, and gynecologic neoplasia.

### *Vulvodynia*

According to the 2015 International Society for the Study of Vulvovaginal Disease, International Society for the Study of Women's Sexual Health, and International Pelvic Pain Society *Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia* (Bornstein et al., 2016), vulvar pain is divided into: A) pain caused by a specific disorder, and B) vulvodynia. Vulvodynia is defined as "vulvar pain of at least 3 months' duration, without clear identifiable cause, which can have potential associated factors." Descriptors include:

- Localized (e.g., vestibulodynia, clitorodynia), generalized, or mixed
- Provoked (e.g., insertional, contact), spontaneous, or mixed
- Onset (primary or secondary)
- Temporal pattern (intermittent, persistent, constant, immediate, delayed)

## Treatment

CPP and dysmenorrhea treatment can be empiric or targeted to a specific etiology. Treatment can include the use of NSAIDs, oral contraceptive pills, continuous progesterone therapy, GnRH agonists, or danazol. Treatment can also be geared toward generalized pain therapies such as tricyclic antidepressants, gabapentin, pregabalin, and serotonin-norepinephrine reuptake inhibitors (Speer et al., 2016). Alternative medical therapies such as acupuncture, transcutaneous electrical nerve stimulation, and surgical management have also been reported to be successful, but they have not been as well evaluated in the literature for CPP as they have for other pain syndromes (Paiva & Carneiro, 2013).

Because the etiology is often unknown, treatment for vulvar pain is frequently aimed at symptomatic relief. Treatment often begins with behavioral modification concentrating on the removal of potentially exacerbating factors. Vulvar hygiene approaches include wearing non-constrictive cotton underclothing and avoidance of products containing fragrance or other irritants. Epsom salt or oatmeal soaks can help, as well as application of ice packs to the vulva. Stress reduction via relaxation techniques is paramount.

Though exercise is encouraged, women are often cautioned against activities that cause direct contact to the vulva, such as bicycling. Physical therapy, psychological support, and medical management (e.g., topical lidocaine, topical estrogen, and antidepressants) are also often utilized.

## Training and Career Development

The GHDB Scientific Vision Meeting was not structured to provide a detailed analysis of training programs in the gynecologic field. Nevertheless, the importance of these programs was a topic of discussion throughout the meeting. Of note, the GHDB currently supports institutional and individual training and career development programs to help ensure that a diverse pool of highly trained investigators is available in appropriate scientific disciplines to pursue women's health research. These include two large institutional career development programs that support mentored development of junior faculty members. Initiated in 1998, the Women's Reproductive Health Research Program (WRHR) provides the opportunity for clinical faculty in obstetrics and gynecology (OB/GYN) departments to further their education and experience in basic, translational, or clinical research in OB/GYN subspecialty fields. More than 215 WRHR Scholars have been appointed to the Program, which currently consists of 15 sites throughout the nation. The branch also contributes to support of the Building Interdisciplinary Research Careers in Women's Health Program, an initiative of the NIH ORWH. These awards support junior physicians and scientists who will be engaged in interdisciplinary basic, translational, behavioral, clinical, and/or health services research relevant to women's health with an emphasis, where appropriate, on the influence of sex as a biological variable on health and disease.

## Themes

Over the course of the meeting, cross-cutting themes emerged for all four research topics in the areas of knowledge gaps and research challenges, as well as opportunities. These seven themes represent a continuum of gynecologic health research that can be reimaged and reassessed in light of new discoveries and emerging approaches (See Figure 8).

Importantly, this continuum emphasizes earlier windows of research opportunities. Through this shift, GHDB foresees, and intends to support, scientific breakthroughs leading to earlier diagnosis, interventions, and even prevention of debilitating gynecologic conditions, sometimes decades before they typically affect quality of life for women. In this framework for gynecologic research, each theme builds upon the others; the continuum of research themes will help to maximize resources and effectively capitalize on discoveries in any companion area.



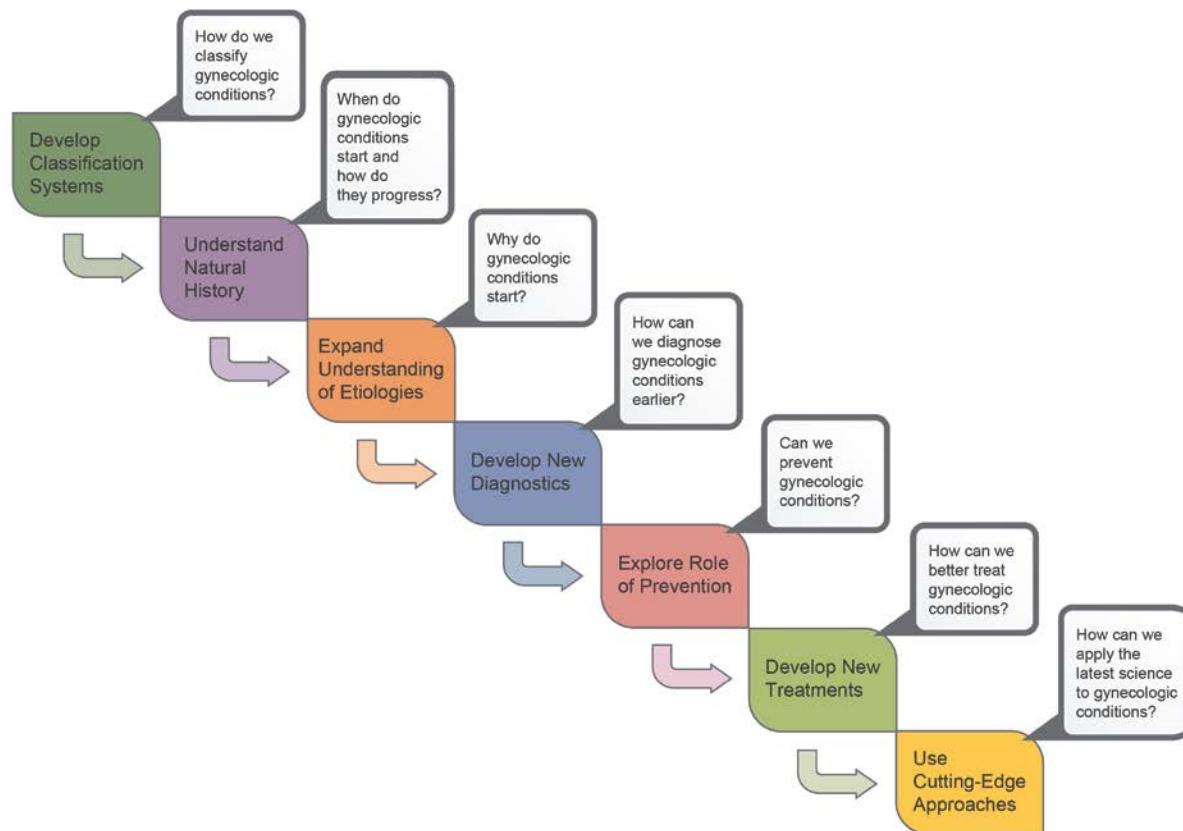


Figure 12: The cross-cutting themes that emerged from the breakout sessions represent a continuum of unanswered questions for gynecologic research.

## Theme 1: Classification Systems

The lack of standardized, broadly accepted consensus terminology and classification systems is an impediment to progress, particularly in the understanding of endometriosis, fibroids, and gynecologic pain syndromes. Ideal classification systems would help to define the disease and would be of use to investigators, clinicians, patients, and regulatory agencies such as the FDA. Well-defined, reproducible phenotyping based on accepted classification systems is critical for the design of robust clinical trials and genomic studies, as well as the development of personalized medical treatments for these disorders.

Common challenges to the development of classification systems exist across multiple gynecologic disorders. For example, while currently viewed by many as single disorders, fibroids and endometriosis could both be best considered syndromes with a variety of subtypes and phenotypes. The symptoms for both fibroids (pain, bleeding,

bulk symptoms, or a combination of these) and endometriosis (degrees of pain and potential fertility defects) can vary greatly between patients. Any classification system for these conditions would need to incorporate the heterogeneity in not only the existence/absence of these systems, but also the duration and severity. Accepted classification of these disorders could be further aided by the renaming of the conditions to terms that more clearly represent their syndromic nature and are better understood by patients. The World Endometriosis Society has published a consensus analysis of the available endometriosis classification systems that provides a valuable foundation (Johnson et al., 2017). There are no broadly accepted scoring systems for fibroids, although a recent report has proposed classification systems for the comprehensive localization of fibroids and for uterine reconstruction after myomectomy, which could justify further validation (Juhasz-Boss et al., 2017).

This challenge of how best to aggregate or disaggregate condition subtypes also exists for gynecologic pain. Grouping gynecologic pain conditions could be helpful in allowing scientists to answer epidemiological questions and ensuring that identified treatments are generalizable to more than one condition. However, splitting the conditions into subtypes could allow for a better understanding of the pathophysiology of a specific disorder. It could be most fruitful to group patients by etiology, such as inflammatory, infectious, or peripheral nerve sensitivity (i.e., a mechanistic versus anatomic approach), although this approach is complicated by the lack of clearly identified etiology in some patients.

### Opportunities

- Refine—on an ongoing basis—consensus terminology and classification systems for fibroids, endometriosis, and gynecologic pain syndromes.
- Ensure that classification systems account, as applicable to the disorder, for:
  - ▶ Number, size, and location of lesions
  - ▶ Range and severity of potential symptoms (i.e., bleeding, infertility, pressure, pain)
  - ▶ Location and characteristics of pain
  - ▶ Duration of disorder

## Theme 2: Natural History and Epidemiology

There is comparatively little known about the natural history or epidemiology of the discussed gynecologic conditions, including the role of *in utero* and early-life contributions to the development and severity of these disorders. Foundational studies are particularly lacking in the case of pain conditions and PFDs. There is also a need for

improved data surrounding the incidence, prevalence, presentation, and treatment responses of these gynecologic conditions across various socioeconomic, racial, and ethnic populations. There is the hope that improved epidemiologic data will provide insights into environmental and genetic risk factors and, conversely, a better understanding of why some women do not develop these disorders despite the presence of these risks.

Extended longitudinal studies are a critical step to understand the trajectory of these disorders and, ideally, identify opportunities for prevention. Perceived barriers to progress for these types of studies include the difficulty in obtaining funding for epidemiologic studies, in general, as well as extra costs and effort needed for retention and long-term follow-up. *De novo* studies can be difficult to fund, therefore strong consideration should be given to participation in ongoing studies, which could include the addition of relevant questions to studies as well as the analysis of data already collected in the original design. As an example, the NICHD-funded Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (NuMoM2b) study collected characteristics and biomarkers from 10,000 nulliparous women from diverse socioeconomic and racial backgrounds to investigate the mechanisms and prediction of adverse pregnancy outcomes. These data could also be utilized to better understand the development of PFDs in this population.

Future studies could start with young adolescents or perhaps even earlier, in the case of pain syndromes, and could extend at least to menopause for fibroids and endometriosis. PFDs and pain conditions require evaluation into later life. Natural history studies are needed that follow pregnant women after delivery to better understand the relationship of mode of delivery to subsequent pelvic organ prolapse, as well as epidemiologic studies tracking the link between surgery choice and long-term success. Recruiting children and adolescents can be challenging, especially for those who hesitate to involve their parents in the consent process. The increased use of central Institutional Review Boards could be helpful for the development of multisite studies in the future.

### Opportunities

- Pursue novel epidemiologic studies to better understand the natural history of gynecologic disorders.
- Identify opportunities to link to ongoing longitudinal studies.
- Emphasize inclusion of adolescents and the study of socioeconomically, racially, and ethnically diverse populations.

### Theme 3: Etiology

In the past decade, novel insights have been made in our understanding of the pathophysiology of several benign gynecologic disorders; however, essential gaps remain. In fact, recent advances have often suggested complexity within these disorders that was not previously appreciated. For example, current evidence suggests that endometriosis is not a single disease and that endometrial pathology, retrograde menstruation, immune dysfunction, and other poorly delineated factors all play key roles in its pathophysiology. There is also recognition of the need for marked improvement in understanding the alterations within central and peripheral nervous system pathways that contribute to chronic pain conditions due to endometriosis and other causes.

A need for additional basic science and mechanistic investigation is particularly strong within the pain and PFD fields. Computational, biomechanical, and virtual models of the pelvic floor, as well as improved tissue science, including the study of collagen and smooth muscle dysfunction in PFDs, are needed. The nature of the interaction between the extracellular matrix and myometrial or endometrial cells could provide critical insights into the development of fibroids or endometriosis.

Progress could also be achieved by studying women who are at high risk but do not develop a disorder or, conversely, who develop a disorder despite being at low risk. A classic example would be well-maintained pelvic support in a woman who has had multiple vaginal deliveries. It is also crucial to understand why a cell type undergoes transformation within one tissue but not another (e.g., the presence of fibroids in the uterus but not in other smooth muscle tissues).

The role of genetics and epigenetics in the etiology of gynecologic disorders remains in its relative infancy (discussed in more detail in Theme 7). Within the fibroid field, somatic mutations in the *MED12* gene has emerged as an important precursor. Research on familial incidence suggest a genetic component for endometriosis, but GWAS have not explained this apparent heritability. The importance of careful phenotyping for interpretation of genomic data has only recently been fully appreciated.

Environmental factors also likely contribute to the development of gynecologic disorders, both alone and through interaction with genetic factors. Potential implicated factors include diet, exercise, obesity, hormonal status, and environmental toxins. Endocrine disruptors including polychlorinated biphenyls, DES, and dioxin are also being investigated for a possible role in the development of endometriosis.

The importance of comorbid conditions is also an understudied area. For example, women with mood and anxiety disorders and early life stressors are more likely to experience chronic pain conditions. Diffuse pain conditions, such as fibromyalgia, can play a role in the development of gynecologic pain conditions. Evidence also suggests

an increased risk of pelvic floor prolapse in women with underlying connective tissue disorders.

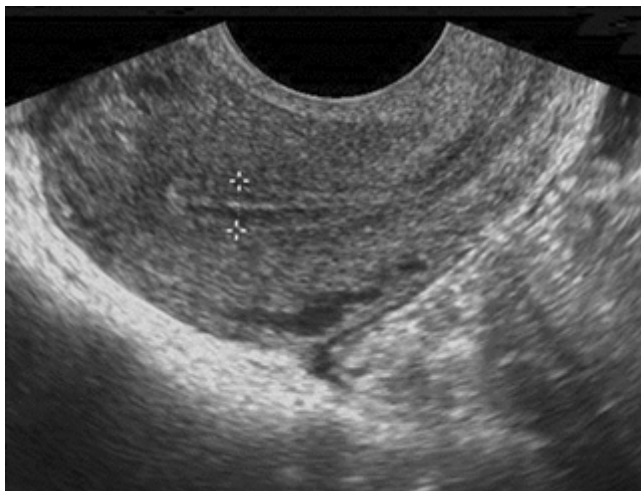
### Opportunities

- Pursue studies examining the independent and coordinated impact of genetics and environment as risk factors for the development of gynecologic disorders.
- Expand understanding of the critical windows of exposure to environmental factors which can impact the development of gynecologic disorders (i.e., whether exposure occurs during gestation, childhood, adolescence, or early adulthood).
- Examine the role of comorbid conditions in the etiology of these conditions.

### Theme 4: New Diagnostic Procedures

Emerging imaging techniques and insights into the biology of gynecologic tissues provide opportunities to develop innovative approaches for the early detection and clinical monitoring of gynecologic conditions. Despite the high prevalence of these conditions, considerable diagnostic challenges exist. Similar symptomatology can be present in an array of gynecologic and non-gynecologic conditions (e.g., pelvic pain can be caused by endometriosis, pelvic inflammatory disease, irritable bowel syndrome, or interstitial cystitis). Conversely, clinically significant gynecologic conditions can be present in the absence of symptoms. For these and other reasons, there can be a substantial delay from symptom onset to diagnosis, leading to unnecessarily prolonged patient suffering and greater socioeconomic cost.

Of interest are novel biomarkers from serum, saliva, or other samples that can be collected noninvasively; the use of menstrual effluent could be a potential source material poised for more research. The development of a noninvasive cell-free DNA



*Figure 13: Ultrasound of a healthy uterus with normal, proliferative endometrium (Figure courtesy of Williams Gynecology)*

diagnostic test from blood for gynecologic conditions could also positively affect diagnosis; this approach has changed the field of prenatal diagnosis and is under active investigation for the detection of occult malignancies. This technology could hold potential for endometriosis and fibroids, which have been associated with aneuploidies and gene mutations. The measurement of inflammatory cytokines in serum has shown limited success, and more recent studies focus on the measurement of microRNA

expression. Transcriptome data is already being investigated for the classification and staging of endometriosis (Tamaresis et al., 2014).

Advances in imaging technology have allowed better visualization of pelvic floor anatomy and provided insights about etiology and surgical outcomes at lower costs. Imaging techniques of note include ultrasound, computerized axial tomography (CAT scan), MRI, functional MRI (fMRI), and positron emission tomography (PET) scans with or without tags/tracer. It has been proposed that radiologic advances might be successfully applied to the localization of endometriotic lesions. Central analysis of pain pathways and treatment response could be aided by fMRI.

The utility of well-validated, standardized, broadly-utilized questionnaires should not be overlooked, particularly in the diagnosis of pain conditions or PFDs. The development of the Patient-Reported Outcomes Measurement Information System is a step forward but requires more rigorous validation. Computerized adaptive testing is a relatively new, sophisticated method of test delivery in which both the difficulty and quantity of items adapts to the examinee's ability level. Reviewers must be educated to be able to adequately review results obtained through these non-standard questionnaires.

The diagnosis of pain conditions is particularly difficult, as the underlying etiology can be poorly understood, and symptoms can reflect more than one condition. Expansion of the use of mobile health (mHealth) approaches could be beneficial for data collection with minimal burden, such as the collection of biometric measures in non-clinical settings using wearable technology such as a Fitbit®.

New diagnostic tests could also be useful in tracking disease progression in natural history studies, as well as in determining treatment responses. Adolescent populations could be included for proof of concept in the early detection of disease. Another aim is the development of improved methods to distinguish between benign and malignant conditions, such as uterine fibroids and leiomyosarcoma, and between benign uterine masses (e.g., fibroids versus adenomyosis). When possible, investigators could develop partnerships with small businesses and seek funding through the NIH Small Business Innovation Research Grant/Small Business Technology Transfer Grant programs.

New or improved diagnostic tests would need to meet a substantial number of characteristics: safe, noninvasive, rapid, inexpensive, highly sensitive and specific, reproducible, and widely accessible.

## Opportunities

- Develop and validate novel approaches, tools, or devices for the diagnosis of common gynecologic disorders.
- Identify novel diagnostic biomarkers, including the identification of factors at the gene, molecular, protein, and cellular levels.
- Apply existing advanced imaging techniques or generate new technologies to diagnose gynecologic conditions, including the development of targeted probes.
- Develop approaches to accurately distinguish between benign and between benign and malignant gynecologic disorders.

## Theme 5: Role of Prevention

Novel opportunities for prevention have arisen with improved understanding of risk factors for the development of gynecologic disorders. Preventive measures include primary prevention of the initiation of a disorder, as well as the prevention of progression. In addition, a distinction can be made between preventing symptoms versus blocking development of the underlying pathology (e.g., prevention of pain versus preventing the development of endometriotic lesions, which can still impact fertility). Effective prevention strategies require the ability to identify high-risk groups and to develop effective prevention messages for healthcare providers, educators, and patients. There is a strong need to target the adolescent period as a critical window for early prevention, including the need to better measure PFDs in children.

Much of the clinical research on fibroids, which is costly, has been supported by industry, but pharmaceutical companies focus primarily on treatment, rather than prevention. Similar biases likely apply to funding in other gynecologic fields.

Specific areas of investigation for fibroid prevention include studies into the role of ulipristal acetate as a combined contraceptive and fibroid preventative with the potential to maintain a woman's fertility. Vitamin D supplementation has also been proposed for fibroid prevention and treatment. The development of endometriosis has been linked to the presence of endocrine disruptors, such as bisphenol A, in the environment, leading some to propose avoiding microwaving food in plastic containers. Current clinical studies and patient cohorts could provide the ability to connect the 'O' to the 'G'—that is, to integrate obstetrical care to gynecologic outcome, specifically the development of PFDs, providing insights for preventative care. Additional areas of interest are the effectiveness of carefully-defined physical activity on the development of PFDs, the ability of pessaries to prevent progression, and the potential importance of treating women with asymptomatic prolapse to prevent development of discomfort or incontinence.

## Opportunities

- Improve understanding of the natural history and etiology of gynecologic disorders to provide opportunities for prevention in addition to treatment.
- Minimize the risk of gynecologic disorders starting in adolescence or even childhood.
- Ensure effective prevention measures, when identified, are broadly disseminated to healthcare providers and patients.

## Theme 6: New Treatments and Therapies

There are opportunities for new therapies that incorporate the concept of precision medicine, defined as an “emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person (U.S. National Library of Medicine, 2017).” The variability in the presentation of gynecologic disorders and the priorities of each patient can both influence treatment choice. For example, among patients with fibroids, one might be most concerned by heavy menstrual bleeding, while another is concerned about fertility preservation.

Several studies have indicated that patient priorities for treatment can differ from their physician’s. Providers can have a bias for certain types of treatments based on their experience with a specific technique or drug and might not convey the full range of options to the patient. Patients often have their own biases derived through conversations with friends, advertisements, online searches, or personal preferences. Patient acceptance of the chosen treatment can significantly impact adherence and, thereby, success.

Advances have been made in the development of treatment algorithms that could allow women and their providers to make more informed decisions. Validation of existing algorithms, perhaps through large healthcare systems, is still needed, as is provider education about the existence of these tools.

While symptom-specific treatments (e.g., pain control) can be appropriate in some cases, therapies that treat the underlying disorder are preferable. There is a need to better evaluate outcomes by including diverse populations (age, race, ethnicity, disability status, etc.), and by attempting to stratify results to these distinct groups.

Understanding the underlying pathophysiology of each gynecologic disorder is an important goal in directing preventative and therapeutic approaches. Therapies can be pursued with a limited evidence base in the hope of providing some relief. In some cases, treatment outcome rather than mechanistic studies could need to be a priority as mechanistic insight could be lacking. Nevertheless, care must be taken in this approach as the institution of new therapies before adequate trials have been completed can lead



to significant problems, exemplified most recently by FDA warnings on the use of transvaginal mesh for pelvic organ prolapse repair and power morcellation in the treatment of fibroids. To minimize this risk, new approaches must be found to accelerate drug and device trials. Although more expensive, investigators are starting to design long-term follow-up studies, which are critical to the field.

Specific treatment approaches of promise include the use of aromatase inhibitors, Selective Estrogen Receptor Modulators, Selective Progesterone Receptor Modulators, and oral GnRH antagonists in the treatment of endometriosis and fibroids. Non-hormonal medications targeting steroid and growth pathways can have different risk and tolerance profiles are also needed. Neuromodulators (e.g., gabapentin) and non-pharmacologic pain therapies are of high importance, particularly in the face of the current opioid addiction crisis. Complementary treatments and alternative medicines must be better understood. Well-designed clinical trials are needed to evaluate the effectiveness of low-risk therapies such as yoga, mindfulness, acupuncture, and dietary changes on gynecologic conditions.

Promising new surgical approaches and devices are under development. Pragmatic trials that gauge efficacy and effectiveness (e.g., between specialized and general surgeons) are taking place. Minimally invasive surgical techniques and radiologic approaches deserve rigorous study but require extensive expertise in some cases. New tools benefit from the ability to be deployed broadly and used without a high degree of expertise to maximize availability in low-resource settings. The use of mesh for the treatment of pelvic organ prolapse and urinary incontinence remains a viable option as the understanding of optimal mesh characteristics improves, including the potential use of absorbable mesh as a scaffold for tissue regeneration. Advances in our ability to modulate endogenous stem/progenitor cell behavior could also be transformative (discussed in greater detail in the next section).

### Opportunities

- Ensure that individual variability in genes, environment, and lifestyle are considered when developing and selecting benign gynecologic treatment options.
- Expand ongoing development of hormonal and non-hormonal approaches to treatment.
- Pursue pragmatic trials of devices and surgical approaches prior to wide dissemination, whenever possible.
- Rigorously evaluate complementary and alternative treatments as applied to gynecologic disorders.

- Validate new and existing decision-making tools to promote unbiased treatment offerings.

## Theme 7: Utilizing Cutting-Edge Approaches

Scientific research concepts, approaches, methodology, and technologies have undergone rapid advancement in the past decade. Many of these approaches have been significantly underutilized in the gynecologic field, despite their potential to provide substantial insights into the pathophysiology of specific disease states, as well as the ability to develop new, patient-specific treatments. Examples include progress in the areas of ‘-Omics’ (e.g., genomics, epigenomics, transcriptomics), gene therapy, (stem/progenitor) cell biology, and diagnostic and interventional radiology.

Global analysis of gene expression in an array of non-gynecologic disorders has demonstrated a complex interaction between genotype, epigenetics, the environment, and the presence or absence of disease. Increasing sophistication in the analysis of large amounts of data and decreasing costs are further accelerating advances in this area.

The concept is emerging that fibroids and endometriosis can exist as multiple phenotypes with different underlying etiology and biologic behavior. Phenome-wide association studies have proven effective for the identification of links between extensive sets of phenotypes and selected genetic variants and could be pursued further. GWAS are less likely to be of utility in the broad study of gynecologic pain fields without the ability to more precisely phenotype these complex disorders. Only recently have a limited number of genomic studies been performed to evaluate pelvic organ prolapse. Emphasis was placed on the critical need for centralized, broadly available, well-phenotyped, data and biospecimen resources for each gynecologic disorder.

Extensive support for stem/progenitor cell research throughout the NIH has led to significant advances in the understanding of the role of these cells in normal development, in the pathogenesis of multiple diseases, and as potential therapeutic targets. Within the gynecologic field, emerging data suggest a role for stem cells in normal and abnormal menstrual bleeding, in the pathophysiology of specific gynecologic disease states, and as targets for the treatment of gynecologic disorders, including regenerative therapy in PFDs. Mesenchymal stem cells, either locally-derived or bone marrow-derived, are critical to the cyclic regeneration of a healthy endometrium. Studies have begun to suggest that abnormalities in these cells are involved in the pathogenesis, persistence, and progression of endometriosis. Uterine fibroids are believed to be the result of clonal expansion of a single, mutated myometrial stem cell, likely due to somatic “driver” mutations; two such mutations (mut-*MED-12* and re-*HMGGA2*) have been identified thus far. Studies also suggest that activation of progenitor stem cells following vaginal delivery can be critical for the maintenance of pelvic

support, leading to proposals that alteration in endogenous stem cell activity or re-introduction of stem cells on degradable scaffolds could be developed as an effective treatment for pelvic organ prolapse. While intriguing as a group, these studies remain limited in scope and number.

There is a need to remain current on discoveries in a variety of cell biology fields with relevance to gynecologic disorders including vascular biology, smooth muscle biology, neuroscience, immunology, cell-cell interactions, and the deposition and remodeling of extracellular matrix. Advances in understanding the vaginal, bladder, and intestinal microbiome must also be incorporated into our understanding of gynecologic disorders. Similarly, the gynecologic research field must stay abreast of advances in radiologic diagnostics and therapeutic options (e.g., MRgFUS for the treatment of fibroids).

### Opportunities

- Encourage multidisciplinary investigation of the genome, epigenome, and/or transcriptome as they impact development, progression, and/or treatment response in gynecologic conditions.
- Investigate the role of endogenous stem cells in the etiology and pathophysiology of gynecologic disorders, including projects that utilize or develop stem-cell based therapeutics.
- Maintain working knowledge on advances in an array of pertinent basic science fields and specialties including cell biology, radiology, and biological/biomedical engineering.

### Strategies

The themes described in the previous section lay out a continuum of research opportunities that will strengthen the understanding of fibroids, endometriosis, PFDs, and gynecologic pain syndromes from prevention through new treatments and the utilization of cutting-edge technologies. Further discussion centers on ways in which the field could achieve this necessary progress. The strategies discussed in the following sections frame methods that could be used to fill identified research gaps and take advantage of research opportunities discussed in each theme, while considering constrained resources and other existing limitations.

#### Strategy 1: Utilize and Generate Research Resources

In an environment of fiscal constraint, studies that utilize existing resources, such as biorepositories, databases, animal models, and patient cohort resources, for research on gynecologic disorders could maximize funding support. Though versions of these

resources already exist, they could either be utilized more effectively or applied more comprehensively across a variety of research questions.

### **Databases/Datasets**

There is a need to create a master registry of data on gynecologic and pelvic disorders that is usable across conditions. Because of commonalities across disorders, an umbrella registry or portal that allows the probing of datasets from different sources could find correlations that are invisible in each separate dataset; new developments in natural language processing could also streamline linkage analysis between datasets.

Ideally, such a central dataset/portal would link to large genomic/transcriptomic and other “-omics” data, electronic medical records, and pharmacy and insurance records to allow the examination of incidence, etiology, disease course, development of opioid dependence, and other questions. A centralized database could also take advantage of large-scale longitudinal study data. As a long-term goal, it may be advantageous to create a large registry like those used in some European countries and Australia to track citizens from cradle to grave.

Any attempt to create a unified registry or to link individual databases will require careful standardization. Describing common data elements at the outset, or early in the process, will increase the usability of datasets across multiple endpoints. Common elements for gynecologic disorders are numerous and diverse but would likely include comprehensive metrics on characteristics of the menstrual cycle, abnormal bleeding, fecundity and fertility, and pelvic pain, as well as data on urinary incontinence, prolapse, fecal incontinence, sexual function, and surgical outcomes.

The [NICHD Data and Specimen Hub \(DASH\)](#) serves as a central repository for NICHD-funded datasets that can be further probed by interested investigators. The inclusion of biospecimens is an aim for this resource and is anticipated to begin in 2018. Through DASH, data-sharing policies, and funding opportunities to support secondary analysis of existing data, NICHD and NIH strive to facilitate utilization of extant datasets to help bypass the costs associated with collecting new data. Increased awareness of the existence of DASH and other datasets, appreciation for the benefits to be derived from their use, and development of the expertise required for effective performance of secondary analyses will decrease duplicative effort and accelerate scientific progress.

### **Tissue Banks/Biospecimen Repositories**

Ideally, tissue banks would have access to extensive information regarding the clinical phenotype of the patient from whom samples were obtained, and the ability to probe electronic medical records for comorbidity and demographic data of interest.

Additionally, these banks would have a multitude of different samples (such as endometrial biopsy and blood/saliva or pre- and post-operative samples that allow a

patient to serve as her own control) and be accessible to investigators outside the hosting institution. Although a few high-quality tissue banks exist, there is an overall lack of well-annotated specimens and too few tissue banks with high-quality samples.

Because few individual investigators or institutions possess the resources to host and curate large repositories, a centralized repository involving multiple institutions may be an objective for the field. Alternatively, existing tissue banks could be linked through a central portal that allows some degree of standardization to form a “virtual” National Tissue Bank. Each of these options are accompanied by the challenge of deciding the best way to collect, store, and distribute the specimens. Additional challenges include the need to recruit representative populations across the spectrum of disease classification, race/ethnicity, geographic location, socioeconomic status, and age. Capitalizing on ongoing clinical trials from academic and industry studies could be an effective way to obtain samples from large populations with minimal additional time and effort.

### **Animal Models**

Although animal models exist for studying some gynecologic processes, including the Eker rat model and *Med12* knockout models for uterine fibroids and the mouse model of vulvodynia, additional relevant animal models that better recapitulate human disease are greatly needed. For example, nonhuman primates develop endometriosis spontaneously, but it is an uncommon occurrence. Current animal models of endometriosis involve placing endometriosis in the animal’s abdominal cavity or using animals that are immunocompromised, but neither represents the heterogeneity and complexity of human endometriosis.

As is well-appreciated, animal models will never mimic all aspects of a disorder (infertility, pain, immune response, systemic effects, etc.) and characteristics of the model will invariably differ from the human condition (e.g., sutures used to implant tissue can affect results, four-legged models cannot recreate effects of gravity in pelvic floor disorders). Humanized models, which use human cells and/or tissue xenotransplants, are expected to better mimic human disease, but the enthusiasm for these models differs by condition and by aims of the specific trial. More specifically, clinical trials in women are still the gold standard of determining efficacy, but existing animal models are the safest way to test new drugs and technologies. For gynecologic health stakeholders, the prioritization of developing new animal models versus proceeding immediately to clinical work will depend on how well the animal models are expected to ever truly resemble the condition as it manifests in women.

### **Patient Cohorts/ Ongoing Studies**

For many large or longitudinal cohort studies, recruitment and maintenance of the study population is the portion of the study that requires the largest financial and time

commitment. Therefore, combining individual cohort studies would save significant financial resources. Adding questionnaires or sample collections that are relevant to gynecologic health to existing large cohort studies would capitalize on recruitment efforts already underway and provide huge rewards in data acquisition with minimal financial and time commitment. Several large cohort studies currently underway could serve as prime candidates for this type of research and recruitment symbiosis. Ideally, through new partnerships (discussed in Strategy 2), any new large cohort study that receives federal funding could include a steering committee with diverse expertise to ensure that multiple avenues of investigation, including gynecologic health, are explored through the chosen study population and generated protocol. Developing a patient registry for gynecologic research, perhaps through partnerships with professional societies, and/or expanding and utilizing current patient registries could be cost-effective ways of expediting clinical studies through more efficient recruiting.

## **Strategy 2: Develop and Strengthen Partnerships and Collaborations**

Although gynecologic conditions have traditionally been thought of as maladies that affect the uterus and other reproductive organs, each is multifactorial, and many involve systems that extend beyond the pelvic cavity. Therefore, expertise in addition to that of OB/GYNs or reproductive biologists is needed. For example, the way that endometriosis spreads, multiplies, and infiltrates resembles cancer metastasis, but endometriosis also has an immune component, so partnerships with oncologists and immunologists could yield important insights. Chronic gynecologic pain conditions likely share mechanisms with other chronic pain disorders and may be viewed in that light; gynecologic health investigators could partner with pain researchers to understand areas of overlap or divergence. Further possible partners include radiologists, pediatricians, neuroscientists, physical therapists, muscle biologists, and imaging physicists, among many others.

Reaching out to engineers could be an especially beneficial collaboration. For example, the loss of pelvic floor support can be viewed and studied as a biostructural engineering problem, so collaborations with engineers could change the entire perspective from which PFDs are investigated. Engineering partnerships are also needed to develop new surgical tools, and to test cost-effective or simpler technology before the devices are made available to the market.

Building and utilizing these new research partnerships could bring a new set of challenges, largely related to the new modes of communication that could be needed as each discipline speaks its own “language.” Ensuring that partners understand each other’s terminology and framework will likely take time and concerted efforts at cross-discipline training. Large meetings and symposia to bring together researchers from different disciplines could help align investigators in this aspect. Advances in low-cost,

easily accessible communication technology, such as webinar capabilities and social media, could foster the everyday communication necessary for successful cross-discipline partnerships.

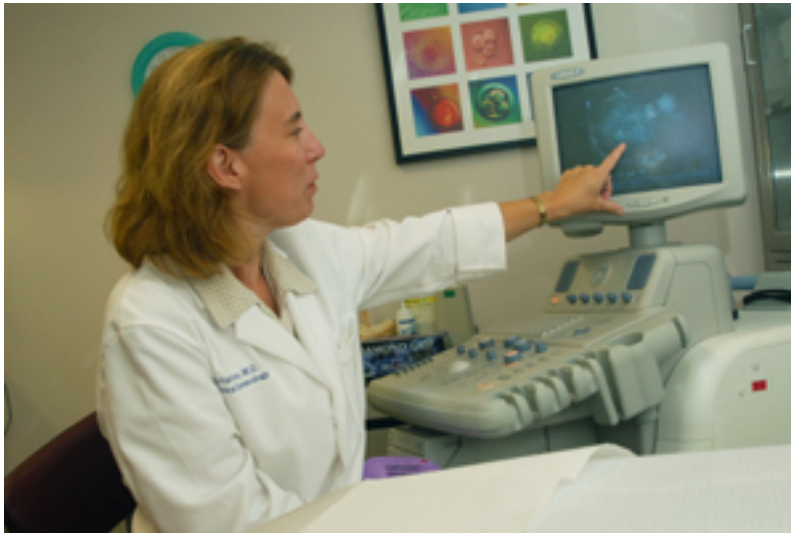
These research partnerships need not be limited to academia. Partnering with industry, pharmaceutical companies, and non-governmental organizations could combine the expertise of academic researchers with the resources and expanded capabilities of large companies. These public-private collaborations could be especially productive in the development or application of new technologies (such as mHealth intervention and assessment tools, wearable technology, noninvasive devices for diagnosis, new imaging modalities, etc.) to research questions in gynecologic health.

Furthermore, new partnerships could help tackle logistical challenges beyond the research questions themselves, including obstacles related to recruitment and information dissemination. Recruitment is difficult and costly; partnering with organizations, professional societies, and patient advocacy groups or utilizing patient registries could reduce costs and maximize efforts.

### **Strategy 3: Promote Patient and Provider Education**

Accurate and prompt diagnosis at the onset of a condition is critical for understanding etiology and natural history, as well as for providing opportunities for early intervention and, ultimately, prevention. Classification and natural history studies, as well as understanding of etiology and role of prevention, all benefit from an accurate and prompt diagnosis at the condition onset. Unfortunately, the diagnosis of gynecologic conditions is often incorrect or delayed. For example, the time between symptom onset and diagnosis can be between 5 and 10 years for endometriosis and can take even longer if the condition begins in adolescence. Improving awareness and knowledge of these conditions for both patients and providers is essential to reducing the diagnostic delay and the associated financial and quality-of-life burdens.

For patients, deficits can be due to lack of knowledge and/or the stigma attached to gynecologic conditions. Women commonly do not know how to assess their symptoms, such as whether their menstrual flow is unusually heavy, or how to describe the pain they experience. Rather than discuss their symptoms with their doctors, women can instead suffer in silence with the belief that their pain, heavy bleeding, or incontinence are the inevitable outcome of menstruation or childbearing. Additionally, discussion of gynecologic and reproductive topics can be considered taboo; some women are embarrassed or ashamed to bring up any problems with their physicians. This lack of awareness and/or sense of embarrassment can be especially true in adolescent populations, which is especially problematic given the adolescent onset for some gynecologic conditions.



*Figure 14: Physicians can help combat the stigma surrounding gynecologic conditions by directly discussing these concerns during routine visits.*

Combatting this lack of knowledge in patients through improved patient perception and patient education, as well as gaining an understanding of women's decision-making, are important measures to decrease diagnostic delay. Community outreach could help reach the populations of interest: describing abnormal menstruation patterns in sexual education and health classes could target adolescents, while birthing or breastfeeding meetings could help distribute information on

PFDs. Patient-centered research across diverse populations, including understanding patient behavior and decision making, the role of health literacy in seeking treatment, and the role of physician-patient relationships and treatment decisions could be useful in addressing these gaps.

Even among physicians and other healthcare providers, knowledge gaps and biases can prevent accurate, timely diagnosis and treatment. Women do not always see a gynecologist for their gynecological complaints and many primary care physicians, including pediatricians, are not well-trained in recognizing conditions like endometriosis and uterine fibroids. Physicians, like the patients themselves, can often misdiagnose the conditions as normal variants. Research has also shown that physicians can minimize reported pain from female patients; patient reports of gynecologic pain could therefore more often be overlooked or misattributed. Physicians could also help overcome the stigma patients feel in broaching gynecologic problems by directly asking about these problems during routine physicals or annual visits.

Further education of providers is not enough. To aid physicians, evidence-based guidelines and toolkits for decision making, such as models to predict risk and decision/diagnostic algorithms, are critical. Existing diagnostic and treatment algorithms must be tested, and providers educated about the existence of these algorithms.



## Conclusions and Steps Forward

The emergence of themes and opportunities that were strikingly similar across diverse conditions in gynecologic health demonstrated a convergence in the field that provided a platform for further work. GHDB has developed high priorities for the branch research portfolio that will drive decisions regarding the branch portfolio in coming years (these priorities are listed in [Appendix 3](#)). Additionally, in the time since the meeting was held, GHDB has issued three funding opportunity announcements designed to catalyze new research interests ([Appendix 4](#)).

Initiated by the meeting, conversations between stakeholders have spurred new partnerships and collaborations and challenged investigators to look towards gynecologic questions through a new lens. Together, GHDB and the members of the gynecologic health and disease research community are working together towards a shared vision of a future in which women lead lives free from the effects of gynecologic disorders.

## Appendix 1: Meeting Attendees (May 5-6, 2016)

\*Titles and affiliations are those at time of meeting

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## Appendix 2: Questions Asked at Scientific Vision Meeting

- What are the most significant advances over the past 5 years in the selected disorder? These could include insights into pathophysiology, risk factors, prevention, diagnosis, and/or treatment of the condition.
- What resources currently exist that could be used to glean more clinical or mechanistic insight into these disorders? Possible topics of discussion include: existing patient materials/specimen banks, current clinical studies or patient cohorts being followed prospectively, animal models, and big datasets.
- What are the most compelling opportunities/critical gaps to be addressed in order to further gynecologic research? Comments might include the opportunities which are most practical to pursue, and/or more high-risk approaches that could give the highest potential short-term and long-term payoffs.
- What are the most significant conceptual, practical, or technical challenges impeding progress in the field? What challenges are on the horizon for the next 3 to 5 years?
- What research tools, methods, or approaches should be developed to realize these scientific opportunities and further the advances already made? Discussion could include, but is not limited to:
  - ▶ What are research questions that can leverage existing resources (specimen banks, big datasets, clinical study cohorts etc.) to maximize scientific progress?
  - ▶ What new large datasets are needed to probe clinical outcomes?
  - ▶ What animal models are needed to expand our understanding of the mechanistic processes involved in the selected condition?
- What are the transformative fields of research and/or new technical capabilities that could have a significant impact on gynecological research and clinical practice in the next 10 years? What areas are well poised for translational or intervention research to move empirical evidence into practical/clinical application?
- What is the role for new partnerships and collaborative, interdisciplinary efforts in effectively addressing this disorder? How can these collaborations best be encouraged?
- What approaches could be utilized to overcome the conceptual, practical, or technical challenges identified?
- What are short- and long-term goals and how do we best achieve them? What are appropriate benchmarks for gauging progress in realizing these goals?

## Appendix 3: GHDB High Priority Research Areas

### Longitudinal Gynecologic Studies

- Gap: The natural history of fibroids, endometriosis, menstrual irregularities, dysmenorrhea, and other gynecologic disorders has been poorly studied, particularly in the early reproductive lifespan.
- Priority: Identify ways to participate in ongoing or soon-to-be initiated longitudinal studies to include relevant questions with an emphasis on inclusion of adolescents to better understand risk factors and pivot points for preventing these disorders.

### Mechanisms of Gynecologic Pain Syndromes

- Gap: Current understanding regarding the prevalence, biological mechanisms, psychological variables, and clinical risk factors responsible for the development of gynecologic pain syndromes is limited. New advances are needed in every area of chronic pain research, from molecular sciences to the behavioral and social sciences.
- Priority: Support multidisciplinary investigations to delineate the genetic, cellular, molecular, environmental, and psychosocial factors underlying the etiology of chronic gynecologic pain syndromes, including mechanisms both in common with and distinct from other chronic pain conditions.

### Non-Hormonal Treatments

- Gap: Current pharmacologic treatments for abnormal bleeding, fibroids, and endometriosis act primarily via modulation of the steroid hormonal milieu, thereby exerting broad effects across multiple steroid-responsive tissues. There is a need for medical therapies that specifically target abnormal gynecologic cell types.
- Priority: Encourage the development of novel, nonhormonal pharmacologic treatments for gynecologic disorders.

### Noninvasive Diagnostic and Assessment Tools

- Gap: Emerging imaging techniques and insights into the biology of gynecologic tissues provide opportunities to develop innovative approaches for the early detection and clinical monitoring of these diseases. These tests will ideally be noninvasive, rapid, inexpensive, and widely available as well as highly sensitive and specific.
- Priority: Promote the development and/or application of novel imaging methods and biomarkers to gynecologic disorders.

## “–Omics” in Gynecologic Disorders

- Gap: Development of powerful '-omics' approaches have been significantly undersupported in the gynecologic research field despite their potential to provide substantial insights into the pathophysiology of specific disease states, as well as the ability to develop new, patient-specific treatments.
- Priority: Encourage multidisciplinary investigation of the genome, epigenome, and/or transcriptome as they impact development, progression, and/or treatment response in gynecologic conditions. Examination of the interaction between environmental factors and genetic and/or epigenetic markers are of particular interest.

## Stem/Progenitor Cells in Gynecologic Health and Disease

- Gap: Emerging data suggest a role for stem cells in normal and abnormal menstrual bleeding, in the pathophysiology of specific gynecologic disease states, and as targets for the treatment of gynecologic disorders, including regenerative therapy in pelvic floor disorders.
- Priority: Support projects investigating the role of endogenous stem cells in the etiology and pathophysiology of gynecologic disorders, including those that utilize or develop stem-cell based therapeutics.

## Transdisciplinary Research

- Gap: To date, advances in relevant basic science fields have not been routinely incorporated into gynecologic research studies.
- Priority: Promote research based on findings from diverse fields to advance basic and mechanistic understanding of gynecologic health and disease. These fields include (but are not limited to) engineering, neurobiology, skeletal and smooth muscle biology, vascular biology, immunology, and relevant aspects of cell biology such as studies of extracellular matrix and cell-cell interactions. The development of new transdisciplinary collaborations is encouraged.

## **Appendix 4: GHDB Funding Opportunity Announcements (FOAs) in Response to Scientific Vision Meeting**

### **Integrative Research in Gynecologic Health (R01) (RFA-HD-18-017)**

The purpose of this FOA is to provide a platform to support novel, complex research with integrated studies that involve basic, translational and clinical science to focus on a single clinically-important, understudied gynecologic disorder, or a research question that cuts across disorders, while facilitating economy of effort, space, and equipment. Responsive topics: fibroids, endometriosis, adenomyosis, gynecologic pain syndromes (chronic pelvic pain, dysmenorrhea, vulvodynia).

### **Noninvasive Diagnostics to Improve Gynecologic Health (R43/R44 Clinical Trial Optional) (RFA-HD-19-006)**

The purpose of this FOA is to support projects using advanced technologies (e.g., bio-chips, microfluidics, and mobile technologies) to develop novel or improved diagnostic approaches, tools, or devices for endometriosis, adenomyosis, and uterine fibroids.

### **Stem/Progenitor Cells in the Pathogenesis and Treatment of Gynecologic Disorders (R01 Clinical trial Optional) (RFA-HD-19-013)**

Recent data suggest a role for abnormal stem/progenitor cell function in the pathogenesis of endometriosis, fibroids, and pelvic floor dysfunction. Applications are being sought to encourage investigation into the mechanisms behind this dysfunction as a key to identifying treatment options, for example through modulation of endogenous stem-cell activity.

## Appendix 5: Acronyms and Glossary

CA125	Cancer Antigen 125
CAT	Computerized Axial Tomography
CDC	Centers for Disease and Control Prevention
CPP	Chronic Pelvic Pain
DASH	Data and Specimen Hub
DES	Diethylstilbestrol
FDA	U.S. Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
FOA	Funding Opportunity Announcement
GHD	Gynecologic Health and Disease
GHDB	Gynecologic Health and Disease Branch
GnRH	Gonadotropin-Releasing Hormone
GWAS	Genome-Wide Association Studies
HMGA2	High-Mobility Group AT-hook 2
MED12	Mediator Complex Subunit 12
MRgFUS	Magnetic-Resonance-Guided Focused Ultrasound
MRI	Magnetic Resonance Imaging
MUI	Mixed Urinary Incontinence
NICHD	<i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development
NIH	National Institute of Health
NSAIDS	Nonsteroidal Anti-Inflammatory Drugs
OAB	Overactive Bladder (Syndrome)



OB/GYN	Obstetrics and Gynecology
ORWH	Office of Research on Women's Health
PET	Positron Emission Tomography
PFDs	Pelvic Floor Disorders
POPQ	Pelvic Organ Prolapse Quantification
RFI	Request for Information
SUI	Stress Urinary Incontinence
UFS-QOL	Uterine Fibroid Symptom and Quality of Life
UUI	Urgency Urinary Incontinence
WRHR	Women's Reproductive Health Research Program

<b>Term</b>	<b>Brief Definition</b>
3D Cell/Tissue Culture	An artificial culture environment in which cells/tissues are grown in three dimensions, as opposed to two-dimensional cultures in petri dishes
Adenomyosis	A condition in which tissue similar to the lining of the uterus (endometrium) grows into the muscular wall of the uterus
Agonist	A chemical that binds to a receptor and activates the receptor to produce a biological response
Ambulatory Care	Medical care performed on outpatient basis
Angiogenic	Relating to the formation of new blood vessels
Antagonist	A chemical that blocks the action of a receptor
Aromatase	An enzyme responsible for a key step in the production of estrogen
Autologous	Cells or tissues obtained from the same individual

<b>Term</b>	<b>Brief Definition</b>
Botulinum Toxin	Neurotoxic protein produced by the bacterium <i>Clostridium botulinum</i> that causes muscle paralysis
Chronic pelvic pain (CPP)	Non-cyclic, persistent pain in the pelvic area lasting at least 3 to 6 months and unrelated to pregnancy
Colpocleisis	A procedure involving closure of the vagina that is used to treat vaginal prolapse
Copy Number	The number of copies of a gene present in a cell
<i>De Novo</i>	Starting from the beginning; new
Defecatory	Related to voiding feces from the rectum
Diethylstilbestrol (DES)	A synthetic estrogen characterized as an endocrine disruptor
DNA Methylation	A process by which methyl groups are added to a DNA molecule in order to change activity of the DNA segment
Dysmenorrhea	Recurrent, cramp-like, lower abdominal pain associated with menstrual periods
Dyspareunia	Painful sexual intercourse
Dysuria	Painful urination
Ectopic	In an abnormal place or position
Embolization	A procedure to artificially block a blood vessel to cut off the blood supply it provides
Epigenome/epigenetic	All of the chemical compounds and proteins that can attach to DNA and turn the genes on or off in order to control the production of proteins by the cell
Etiology	Cause of a disease or abnormal condition
Extracellular Matrix	Collection of molecules that surround cells and provide structural and functional support

<b>Term</b>	<b>Brief Definition</b>
Fecundity	The actual reproductive rate of an organism or population
Gene Silencing	Prevention of a gene being expressed so that no protein is made from the gene's DNA sequence
Genome	The complete genetic material of an organism
Histologic	Relating to the structural study (especially microscopic study) of tissues
Hysterectomy	Surgical operation to remove all or part of the uterus
LeForte Procedure	Procedure involving partial surgical closure the vagina
Lesion	Abnormal damage or change in a tissue from injury or disease
Levator Ani Muscle	A broad, thin muscle situated on either side of the pelvis which is critical for maintaining support of the pelvic organs
Levonorgestrel	A progestin hormonal drug that is used as a contraceptive
Loss of Heterozygosity	An event when one copy of a gene is lost completely, so that part of the genome appears homozygous
Menarche	The onset of menstruation; the first menstrual cycle
Menstrual Effluent	The blood and tissue shed during menstruation
Mesenchymal Stem Cells	Cells that can differentiate into a variety of cell types including connective tissue, blood, fat, bone, and muscle
Metabolome	Total collection of metabolites (substances formed during metabolism when the body breaks down food, drugs, or its own tissue) that are present within an organism, tissue, or cell
mHealth	General term for the use of mobile phones and other wireless technology in medical care, most commonly to educate consumers about preventive health care services

<b>Term</b>	<b>Brief Definition</b>
Multichannel Urodynamics	Technique that uses two or more sampling locations or modalities to test the pressure-flow relationship between the bladder and urethra
Murine Model	Relating to mice or related rodents
Myomectomy	A surgical procedure in which fibroids are removed but the rest of the uterus is left in the patient
Myometrium	Smooth muscle tissue of the uterus
Neoplasm	A new and abnormal growth of tissue in some part of the body, especially as a characteristic of cancer
Nonadrenergic	Blocking or inhibiting the actions of nerve cells in which epinephrine (adrenaline), norepinephrine (noradrenaline), or a similar substance acts as a neurotransmitter.
Nulliparous	A female who has not delivered a live baby
Obstetric Fistula	Presence of a hole between the vagina and the rectum, ureter, or bladder that is caused by trauma during childbirth and can result in incontinence of urine or feces
Parity	The number of births a woman has had which reached viability
Pelvic Ganglia	Grouping of nerve cell bodies in the pelvic region
Percutaneous Tibial Nerve Stimulation	Electrical stimulation of the nerve responsible for bladder and pelvic floor function
Peritoneal Fluid	Fluid produced by the cells lining the abdomen (peritoneal cavity)
Pessaries	Elastic or rigid devices that are inserted into the vagina to support the uterus
Phenotype	The set of observable characteristics of an individual resulting from the interaction of its genotype with the environment

<b>Term</b>	<b>Brief Definition</b>
Polycystic Ovary Syndrome	A hormonal condition in women characterized by irregular menstrual cycles, small ovarian cysts, and excess body hair
Progestin	A type of hormone produced by the ovary and the placenta
Prostaglandins	A group of lipid compounds that exert a diverse set of effects in the body including inflammation
Proteome	The entire set of proteins that is or can be expressed by a cell, tissue, or organism
Single Nucleotide Polymorphisms	A variation in a single base pair in a DNA sequence that may or may not change gene function
Stroma	The supportive cells in a tissue which include connective tissues and blood vessels
Thermoablative/ Thermal Ablation	A procedure using heat to destroy tissue and its function
Transcriptome	The total of all the messenger RNA molecules (transcripts) expressed from the genes of an organism
Vulva	The external female genitalia, including the labia, the clitoris, and the vaginal opening
Vulvodynia	Chronic pain or discomfort around the opening of the vagina (vulva) for which there is no identifiable cause, and which lasts at least three months
Xenografts	A tissue graft or organ transplant in which the donor is a different species from the recipient

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