National Institute of Environmental Health Sciences

New Tools for Preventing and Treating Uterine Fibroids

NIEHS-funded scientists are uncovering risk factors for uterine fibroids and developing interventions to help the populations most affected.

Researchers supported by the National Institutes of Environmental Health Sciences (NIEHS) are examining the genetic and environmental causes of uterine fibroids. Fibroids are noncancerous, estrogen-fueled tumors that develop in the uterus during a woman's reproductive years and can cause severe menstrual bleeding, infertility, anemia, and preterm labor.

In the U.S., approximately 35 to 40 million women suffer from fibroids.[1] Clinical data shows that uterine fibroids are three times more common in Black women and twice as common in Hispanic women compared to White women.[2,3]

Historically, treatment has been limited to invasive surgery. But research funded by NIEHS over the past two decades has provided a better understanding of how and why fibroids develop and led to advancements in noninvasive treatment and prevention strategies. Funded by NIEHS, scientists across the U.S. are breaking new ground in uterine fibroid research, including: Ayman Al-Hendy, M.D., Ph.D., a professor at the University of Chicago and visiting professor at Khalifa University, Abu Dhabi, UAE; Sedar Bulun, M.D., of Northwestern University; Donna Baird, Ph.D., of the NIEHS Epidemiology Branch; and other at George Washington University and Columbia University.

A doctor points to uterine fibroids on a female reproductive anatomy model.

Impacts

Identifying Responsible Genes: Found that high expression of COMT, an estrogen-promoting gene, is more prevalent in Black women than White or Hispanic women, establishing a genetic link to increased fibroid development in this population.[4]

Understanding Environmental Factors: Determined that exposure to endocrine-disrupting chemicals (EDCs), such as diethylstilbestrol[5] and phthalates,[6] cause inflammation in the uterine wall that contributes to fibroid development,[7] as well as genetic mutations linked to fibroid growth.[30]

Investigating Lifestyle Factors: Found that vitamin D deficiency,[8] a lack of physical activity,[9] obesity,[10] and alcohol consumption[11] are linked to uterine fibroid development.

Pioneering Biomedical Approaches in Women's Health: For the first time ever, developed an approach for isolating stem cells from the uterus.[12] Stem cells are the original cells that a person harbors from birth, and studying them provides important clues about exposures and health changes over time.

Inspiring Effective Therapies: Found that increased estrogen effects in the uterus, coupled with inflammation, can spur fibroid development.[13] Pharmaceutical companies then developed two FDA-approved drugs[14,15] that shrink fibroids and reduce associated abnormal uterine bleeding by reducing estrogen production.

Developing Promising Interventions: Found that the use of certain supplements, including a green tea extract[16] and vitamin D supplements,[17] can shrink and prevent fibroids.

Focusing on Prevention Strategies: Found that biomarkers that indicate inflammation in the uterus significantly decreased in the urine samples of women who had undergone fibroid removal surgery,[18] suggesting a possible association between fibroids and inflammation.

Then and Now

- **Then:** Invasive surgery was the only option for removing large fibroids.
- **Now:** Al-Hendy's research was used to develop Elagolix[15] and Relugolix,[14] two FDA-approved drugs that effectively shrink fibroids and reduce bleeding by lowering estrogen production in the uterus.
- **Then:** It was unclear why Black and Hispanic women experience fibroids at higher rates than women across the general U.S. population.
- **Now:** Researchers identified a complex tangle of genetic and environmental factors that are linked to increased risk of fibroids.[19]
- **Then:** There were no approved methods for preventing fibroids.
- **Now:** Supplements, including a green tea extract[16] and vitamin D,[17] are recommended to women identified as at-risk for developing fibroids.

Timeline for Developing Approaches to Treat Uterine Fibroids

2002

Fundamental Questions

Determined that a particular estrogen-promoting gene, COMT, is more prevalent in Black women than White or Hispanic women and likely contributes to disparities in fibroid development.[4]

2006

Fundamental Questions

Determined that EGCG, a plant compound found in green tea, can inhibit the COMT gene in the uterus in cell studies.[21]

2009

Fundamental Questions

Observed that a diet infused with ECGC dramatically reduced the size of uterine fibroid tumors in mice.[20]

2012

Fundamental Questions

Linked vitamin D deficiency to uterine fibroid development.[23]

2012

Application and Synthesis

Developed an approach for isolating stem cells in the uterine wall so they can be more closely studied.[12]

2013

Application and Synthesis

Confirmed in a clinical trial pilot study that EGCG can shrink fibroids and decrease uterine bleeding in humans.[22]

2015

Fundamental Questions

Determined that early-life EDC exposure can lead to fibroid development using uterine stem cells and studies in rats.[24]

2021

Policy and Practice

Findings informed the development of two fibroid treatment drugs. The drugs work by reducing the production of a follicle-stimulating hormone, which stimulates the ovaries to produce estrogen. With less estrogen in the body, fibroids shrink and bleeding either stops or decreases.[14,15]

2023

Implementation and Adjustment

Identified uterine inflammation biomarkers that significantly decreased in urine samples after fibroid removal surgery, indicating a link.[18]

NIH National Institute of Environmental Health Sciences

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Pinpointing At-Risk Populations

While there is no clear cause for fibroids, NIEHS-funded studies have revealed that several factors drive the development or exacerbation of the disease. Increased uterine estrogen levels are one factor that increases the risk of fibroids. A gene called COMT, more prevalent in Black women, has been linked to increased estrogen production in the uterus, which promotes fibroid development.[4]

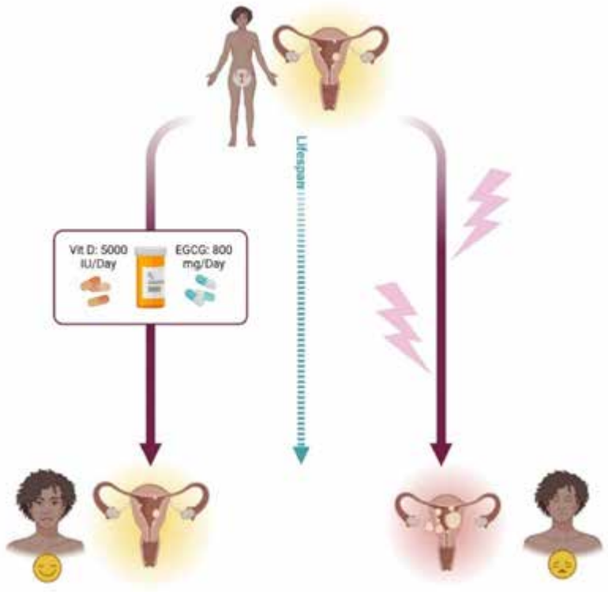
Researchers found that exposure to DES — a synthetic chemical formerly used in medicine — and phthalates, which can be found in cosmetics, plastics, cookware, and other household items, increases inflammation in the uterus, leading to fibroid development.[5,6,7]

"Environmental EDC exposure that causes chronic inflammation is one of the primary risk factors for fibroid development," said Al-Hendy. "The inflammation causes DNA damage and instability, which can eventually lead to the fibroid-causing mutation."

Vitamin D deficiency, which is more common in Black women, also contributes to inflammation in the uterus and fibroid development.[23] Other risk factors include limited physical activity,[9] obesity,[10] and alcohol consumption.[11]

Physicians can use these factors, along with age and family history, to pinpoint patients who would most benefit from early interventions. Vitamin D levels can be tested with a simple blood test, according to Al-Hendy, and testing should be conducted more often.

"We should be screening everyone for vitamin D deficiency, but especially high-risk individuals, such as Black women," said Al-Hendy.



The figure above shows Al-Hendy's vision for how interventions of 5,000 international units of Vitamin D and 800 milligrams of green tea extract per day over the course of a woman's lifetime can lessen her likelihood of developing fibroids. (Image courtesy of Ayman Al-Hendy)

Al-Hendy's team determined that a compound found in green tea can safely shrink fibroids.

Using Natural Products to Fight Fibroids

Fibroids can be a significant physical, financial, and health burden for women.[19] Women who do not receive regular health screenings may not realize they have fibroids until their symptoms become severe. By then, the only treatment option is surgery. NIEHS researchers have turned to abundant and cost-effective products that can be used to both prevent fibroids and reduce their symptoms.

They discovered that the green tea extract EGCG, which has been used to treat enlarged prostates in men, lowers the risk and severity of fibroids in rats by blocking the COMT gene.[16] In a follow-up clinical trial, Al-Hendy and colleagues confirmed that taking EGCG supplements safely shrinks fibroids and reduces uterine bleeding in women.[22]

Al-Hendy and colleagues also discovered that vitamin D supplementation in rats helps reduce inflammation in the uterus, preventing fibroid development.[17] A large randomized double-blind, placebo-controlled clinical trial in human populations is under development by Al-Hendy's team.

Promising Treatments on the Horizon

"Surgery is extremely expensive and invasive," said Al-Hendy. "The goal is to prevent fibroid development before it gets to that point."

Since 2020, NIEHS researchers have focused their efforts on several promising fibroid treatment strategies, including the development of a risk screening test and preventative vaccine.

The urinary biomarker screening test would allow physicians to screen patients who are most at risk for fibroids before they develop the disease and intervene earlier with supplements. NIEHS-funded researchers have found certain biomarkers in urine that decrease after fibroid surgery, but larger studies are needed to confirm the results.[18] Al-Hendy hopes the test could be used to screen patients as young as 14 years old.

Researchers are also developing a vaccine that would introduce fibroid-specific antigens to the immune system, training it to recognize and stop fibroids from forming in the uterus.

Al-Hendy, center, and his team at the University of Chicago, study the origins of gynecologic conditions, such as uterine fibroids, endometriosis, and infertility. (Photo courtesy of Ayman Al-Hendy)

Targeting Fibroids at the Molecular Level

Serdar Bulun, M.D., uncovered a mutation in the Med12 gene that leads to fibroid development when triggered by certain environmental exposures[25] and is developing an approach for counteracting the mutation.

He discovered that endocrine-disrupting compounds called phthalates increase the uptake of the amino acid tryptophan into cells.[30] Then, an enzyme metabolizes tryptophan into a compound that activates the aryl hydrocarbon receptor, which in turn stimulates fibroid growth.

"This molecular insight is critical," said Bulun. "If we can target this pathway, we may be able to stop fibroid growth.

Research Challenges and Solutions

Challenge:
Al-Hendy and colleagues were interested in studying whether prenatal exposures to EDCs is associated with developing uterine fibroids later in life. However, the only cells that can be traced back to a person's early development are stem cells, and uterine stem cells had never been isolated and studied before.

Solution:
Al-Hendy collaborated with stem cell biologists to develop a method for isolating uterine stem cells.[12] He then developed a 3D organoid model using patient cells, including stem cells, which allows researchers to test and explore questions about how uterine fibroids develop and how they can be treated.[20]

The SELF Study

To better understand why Black women face higher fibroid rates than the general U.S. population, Donna Baird, Ph.D., launched the Study of Environment, Lifestyle & Fibroids (SELF). From 2010-2012, the researchers enrolled nearly 1,700 Black women in Detroit, Michigan.[26]

At enrollment and then at approximately 20-month intervals, the team used standardized ultrasound examinations to screen for new fibroid cases and to measure fibroid growth. A fourth follow-up ended in 2023,[27] and a fifth has just begun. Extensive data on lifestyle and environmental exposures as well as other health outcomes is collected at time of each clinic visit.

SELF has been instrumental in identifying new information about factors influencing fibroid development. For example, they reported a link between more rapid fibroid growth and vitamin D deficiency,[28] and their data on early life exposures revealed higher fibroid incidence for those who had been fed soy-based infant formula.[29] SELF remains a valuable resource for advancing research on fibroids and other related health outcomes.