

# FIBROIDS

## COMPREHENSIVE GUIDE

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**Relieve Your Symptoms &  
Reclaim Your Life From Fibroids**



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As a healthcare provider, it is quite exciting and exhilarating to see the essence of what fibroids are — and how their complexity could have such a strong hold on women — captured in such a clear, inclusive, unbiased, and complete way. Fibroids are not just benign tumors. The impact they have on women and their lives even beyond the uterus is potentially as devastating as any malignant disease.

As a surgeon, passionate about educating, advocating, and obviously treating women with fibroids, I know my place but the connection between medicine, and the balanced approach to wellness and self-preservation, has been separated for far too long.

***FIBROIDS Comprehensive Guide*** is a comprehensive manual that provides an integrative understanding of the why behind fibroids and a vision for helping women gracefully reclaim their lives from fibroids.

**Soyini Hawkins, MD MPH FACOG Co-owner and Medical Director Fibroid and Pelvic Wellness Center of Georgia**

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# INTRO



Have you or your loved one been diagnosed with uterine fibroids by your gynecologist (GYN) and wondering, now what?

You've heard of fibroids before but don't know exactly what they are. How did you get them? How do you get rid of them? Are they cancerous and are there other options outside of surgery?

## **IN THIS BOOK, YOU WILL LEARN EVERYTHING YOU NEED TO KNOW ABOUT FIBROIDS:**

What are fibroids? The types and symptoms How and why Black women are disproportionately impacted by them Barriers to diagnosis and treatment The causes of fibroids Treatment options How TheDeToxNow.com can help

**Please note:** The information contained in this book is for educational purposes only. It is provided to support you in working with your physician to navigate your journey of healing. You should not use this information for diagnosing or treating a health problem or prescribing any medication.

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# WHAT ARE FIBROIDS?

Uterine fibroids, also referred to as fibroids or UFs, are the most common gynecologic non-cancerous tumors found in and around the uterus—the hollow, pear-shaped organ in a woman's pelvis where a fetus (unborn baby) develops and grows.

**There are many terms for fibroids. Here are a few:**

- Benign monoclonal neoplasms
- Tumors
- Uterine stone
- Uterine fibroid lesions
- Uterine fibroids
- Hormone-dependent benign tumors
- Leiomyomas
- Leiomyomata

Fibroids are made up of many disorganized extra cells, compounds, and collagens which contribute to the form, structure, and stiffness of the tumor. These cells are called extracellular matrix (ECM).

It is proposed that the structure of the fibroid composed of ECM, compounds and collagens is the reason for abnormal bleeding, and pelvic pain.

**ECM build-up is also affected by:**

- Growth factors (responsible for regulating the job of the cells)
- Cytokines (proteins in the body that sign cells)
- Steroid hormones
- MicroRNAs (responsible for regulating how genes work)

A better understanding of ECM composition needs to be explored to develop new treatments for fibroids.

Several genetic, hormonal, and biological factors contribute to the development and growth of fibroids.

But don't worry; we will cover this throughout the book.

Fibroids have significant medical and financial burdens on the patient and healthcare systems. A recent **study** reports that the surgical treatment of fibroids in the United States costs between **\$5.9 - \$34.4 BILLION a year!**

## FIBROIDS & MENOPAUSE

It's estimated that 80% of women under 50 have fibroids, and during perimenopause, the period before menopause, women are twice more likely to develop fibroids. This is due to the fact progesterone levels start to decline (lower), making estrogen the dominant (main) hormone due to lower progesterone levels.

During menopause, the risk of fibroids decreases.

Since estrogen is a growth hormone, when it is dominant, it significantly affects cells, putting women at risk for cysts and fibroid growth. Providers tell women during this stage they should wait it out if they have fibroids during perimenopause.

This is because, as these women go into menopause, their hormones will drop.

And, in many cases, the fibroids will resolve (get smaller or disappear).

However, this is not always the best idea because fibroids can cause a substantial amount of blood loss. This leads to iron deficiency and Anemia. Also, waiting to pursue treatment could also allow time for fibroid pain to get worse as the fibroid grows.

Furthermore, some women also use estrogen replacement therapy to control menopausal symptoms such as hot flashes. However, hormone replacement therapy has also been shown to stimulate fibroid growth.

## FIBROIDS & CANCER

"Black women are at a higher risk of developing uterine leiomyosarcoma (cancerous fibroids). It can also be misdiagnosed because providers may wait to treat fibroids. This increases the chances of cancer spreading and lowers survival rates."

Cancerous fibroids (uterine leiomyosarcoma) are very rare. But they are very aggressive malignant (cancer) tumors and have a poor outcome with low survival rates. Cancer comes from the smooth muscle layer in the uterus. It has many common characteristics of UFs. Signs and symptoms may include:

- Abnormal uterine bleeding
- Pelvic pain and pressure
- Pelvic mass (growth)

As previously mentioned, fibroids are largely benign tumors. They have not been shown to encourage the growth of uterine cancer or increase the risk of uterine cancer. Uterine cancer has not been documented or linked to fibroids.

However, certain surgeries to remove fibroids have been shown to increase cancer risk.

For example, the FDA warned in 2019 that a procedure called laparoscopic power morcellation was shown to increase the risk of cancer. The procedure uses a device to break uterine fibroids into small pieces. The small pieces are then resected (cut out) through a small incision in the abdomen.

The FDA looked at various studies for women undergoing this surgical treatment. They found that 1 in 225 women treated for fibroids with this surgery was found to develop uterine sarcomas (cancer) later in life. The FDA has since discouraged the use of this procedure to treat fibroids. Unfortunately, this surgery is still being used and consented to by patients.

Researchers have explored the risk of other cancers in correlation with fibroids.

For example, thyroid cancer is the 4th most common cancer in women. Since the uterus and thyroid are both hormone-

responsive organs, it is possible that the increased hormones from fibroids could influence the thyroid. Estrogen receptors have been found in neoplastic thyroid tissue (tissues with cancer cells) and normal thyroid tissue.

**Researchers have also found** that women with fibroids have significantly higher rates of thyroid nodules (growth of abnormal tissue). However, thyroid complications tend to show up before fibroids in women. This makes researchers believe that the thyroid plays a huge role in the pathological features of fibroids.

In **another study**, researchers found that women with a history of fibroids were at a higher risk of thyroid cancer. So, it is essential for women with fibroids to make sure that they are getting thyroid labs drawn to ensure they are tracking all their risk factors.



Breast cancer incidence is also significantly higher in women with fibroids than those without fibroids. The mortality rates from breast cancer are lower in women with fibroids.

You may ask yourself, “Are all fibroids the same?” Read on to find out.



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# FIBROID TYPES & SYMPTOMS

## Fibroids Are Classified By:

- Location Types
- Symptoms
- Diagnosis and Treatment

## Location:

- Anterior: forming in the front of the uterus
- Posterior: forming in the back of the uterus
- Fundal: forming in the upper part of the uterus

## Five Types of Uterine Fibroids:

- 1** Intramural
- 2** Submucosal
- 3** Subserosal
- 4** Pedunculated
- 5** Intracavitary





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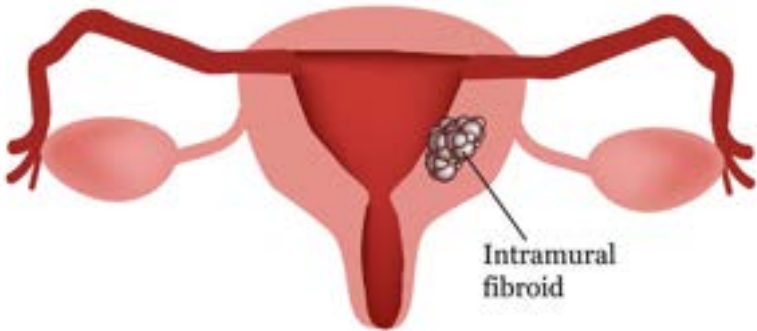
# INTRAMURAL FIBROIDS

The most common type of uterine fibroids. They grow and are contained within the muscular walls of the uterus.

This type of fibroid can make the weight of the uterus feel larger than normal and result in abdominal distention and weight gain.

## **Intramural Fibroids can cause:**

- Irregular and excessive menstrual bleeding—and/or bleeding in between periods
- Potential anemia caused by the heavy bleeding
- Frequent urination and/or constipation
- Lower back and pelvic pain
- Protruding abdomen Feeling heavy/full





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# SUBMUCOSAL FIBROIDS

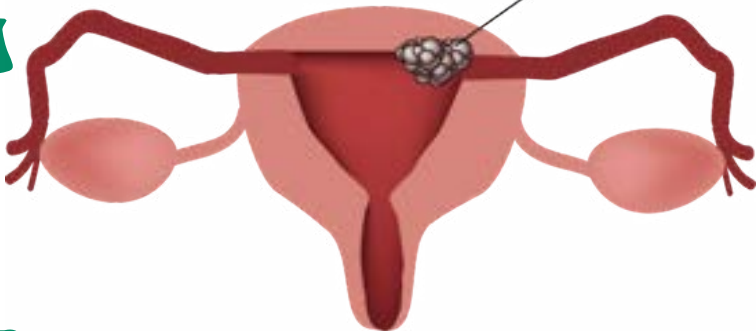
The rarest type of fibroid, they grow just below the thin layer of tissue found in the uterus called the submucosa.

These fibroids can protrude into the uterine cavity and block the fallopian tubes—tubes that connect the ovaries to the uterus. This can cause problems with fertility—blocking conception or carrying a baby to full term.

## These fibroids can cause:

- Infertility and miscarriage—blocking conception or carrying a baby to full term Irregular, prolonged and excessive bleeding / heavy flow—the heaviest caused by fibroids
- Frequent passage of blood clots while using the bathroom
- Severe anemia caused by the heavy bleeding
- Pelvic pain
- Fatigue and dizziness

Submucosal fibroid



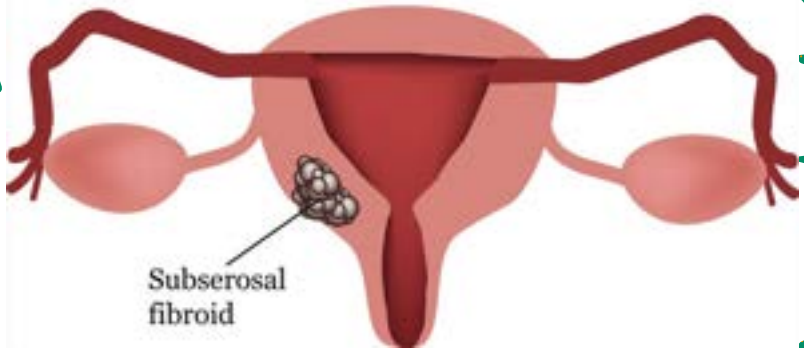
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# SUBSEROVAL FIBROIDS

One of the most common types of fibroids, these grow on the outer uterine wall, increase in size, and can eventually put pressure on the surrounding tissues. They can be attached directly to the uterine wall or via a narrow stalk called a peduncle.

## These fibroids can cause:

- Pelvic pain and pain during sex
- Pressure as they increase in size
- Abdominal pain or cramping
- Frequent urination, bloating and/or constipation
- Feeling of fullness or heaviness
- Lower back pain
- Protruding abdomen



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# PEDUNCULATED FIBROIDS

These fibroids grow on a stalk or stem attached to the uterine wall either outside the uterus or inside the uterine cavity.

## **This type of fibroids mainly causes:**

- More frequent painful episodes as the fibroid gets bigger and more prone to twisting
- Intense pain, similar to cramping, during your period
- Prolonged menstrual bleeding
- Abdominal and pelvic pain and pressure
- When attached to the outer uterine wall, they can cause a protruding abdomen
- When attached to the inner uterine wall, they can cause infertility and miscarriage—blocking conception or carrying a baby to full term



Redunculated  
subserosal fibroid  
(abdominal fibroid)

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# INTRACAVITARY FIBROIDS

Sometimes referred to as a type of submucosal fibroid, these rare tumors that occur inside the cavity of the uterus are called intracavitary myomas.

## **This type of fibroids mainly causes:**

- Infertility and miscarriage—blocking conception or carrying a baby to full term
- Excessive bleeding / heavy flow—the heaviest caused by fibroids
- Prolonged periods  
Severe anemia  
Frequently passage of clots
- Back and pelvic pain
- Leg pain
- Fatigue and dizziness
- Menopausal bleeding

## HOW ARE FIBROIDS DIAGNOSED?

To properly diagnose fibroids, a physical exam and diagnostic imaging are required to take pictures of inside the body. While your primary care provider performs your pelvic or gynecological (gyno) exam, fibroids are sometimes found unexpectedly.

Fibroids have historically gone misdiagnosed due to the normalization of premenstrual syndrome (PMS) symptoms. You may have gone to see your doctor complaining of heavy bleeding and painful periods. Instead of looking deeper into the issue, you may have been diagnosed as experiencing PMS and told it was “normal” or “you just bleed heavier.”

When a fibroid is suspected as the result of a pelvic exam, imaging such as ultrasound (an imaging device that will take pictures of your reproductive organs) is scheduled. These images or pictures will confirm the presence of fibroids.

A photograph of a female doctor with a stethoscope around her neck, smiling and talking to a patient whose back is to the camera. The image is overlaid with a green, dotted pattern.

# HOW FIBROIDS ARE TYPICALLY DIAGNOSED:

## **1** Ultrasound

One or both of the following ultrasounds to create a picture using sound waves.

## **2** MRI or Magnetic Resonance Imaging

This uses radio waves and magnets to create a picture of your uterus.

## **3** CT Scan or Computed Tomography Scan

This takes X-ray images to create a detailed look at the uterus.

## **4** HSG or Hysterosalpingogram

This uses an X-ray and contrast dye to take X-ray of the uterus.

Ultrasounds often do not provide enough information as to where fibroids are located. Other diagnostic imaging options become necessary, like MRIs.

MRIs can show the following:

- Size of the fibroid(s)
- Location of the fibroid(s)

Knowing the size and location of the fibroid(s) helps understand the possible treatment options. Other diagnostic tests include lab tests. If a woman has abnormal menstrual bleeding, anemia—low red blood cell count—must be ruled out.

If the lab test is positive, the root cause of the anemia will be investigated.

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# BARRIERS TO DIAGNOSIS & TESTING

You may be surprised when your provider informs you about finding a uterine fibroid. Fibroids often start small and have no symptoms, which causes many women to go undiagnosed until years after their fibroids first appear.

One of the biggest barriers to treatment is providers telling their patients not to worry about their fibroid(s). Their provider may say fibroids are both “common enough” and “small enough”; therefore, there is no present cause for concern. They may then recommend proceeding with what they call “watchful waiting”—keeping an eye on the fibroid with no recommended intervention.

This pause can provide the fibroid tumors the opportunity to grow quickly and become more symptomatic—diminishing the patient's health and quality of life.

Furthermore, when providers tell their patients to watch and wait, the options for noninvasive treatments—including lifestyle changes and

integrative approaches—significantly lessen, and invasive surgeries become the more attractive and sometimes most viable options.

Even in cases where women experience “PMS-like” symptoms like heavy periods, painful cramps, or bleeding between periods, these are too often dismissed. This further allows the condition to go undiagnosed and untreated.

One study that explored the barriers to testing and diagnosis for fibroids among Black women found that poor patient-provider interactions are one of the main barriers. Black women described how their provider dismissed their symptoms, especially their pain, or attributed the symptoms to other issues unrelated to fibroids.

If you feel like your provider isn't taking your concerns seriously, get a second opinion and notify your new provider of previous interactions. Your greatest weapon in the battle for your health is self-advocacy so never silence the inner voice that tells you something is wrong.

# ROOT CAUSES OF FIBROIDS



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Numerous factors contribute to the development of fibroids.

**In this chapter, we'll review some of the most common root causes, which include:**

- Stress
- Genetics/SNPs
- Uterine Fibroid Stem Cells
- Estrogen Dominance
- Endocrine Disruptors
- Vitamin D Deficiency
- Obesity and Inflammation

## **STRESS & TRAUMA OF RACISM**

The numbers don't lie.

Racial inequalities have been shown to affect health by:

- Limiting access to resources
- Delaying medical diagnosis and treatment
- Increasing stress

When the body is under stress it releases a hormone called cortisol.

Although not fully researched, studies show that cortisol can help trigger both the development and growth of fibroids by fueling estrogen dominance and stimulating progesterone levels. (Estrogen dominance is when the levels of estrogen in the body are higher than the levels of progesterone.)

The intensity of stress often coincides with how fast fibroids grow.



A pregnant woman is lying down, resting her head on a grey blanket. She is wearing a white shirt and dark shorts. A red heart is placed on her bare pregnant belly. The background is a soft, neutral color.

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# GENETICS (SNPS)

Genetic polymorphisms play a huge role in the formation of fibroids.

Genetic polymorphisms describe the many variations of a single gene in the body. Genes are what carry your DNA.

Specifically, Single-Nucleotide Polymorphisms (SNPs) are genetic polymorphisms that can up-regulate (increase the expression of a gene) or down-regulate (decrease the expression of a gene) physiological processes, especially the metabolism of estrogen.

A gene known as the Catechol-O-methyltransferase (COMT) is an essential enzyme that is responsible for breaking down two compounds catecholamines or catechol-estrogens, that are found in the cell. Particularly, the COMT gene plays a significant role in how catechol-estrogens are broken down and regulated in the body.

Women with high COMT activity tend to be more likely to develop fibroids. Fibroids generally have high COMT and aromatase (an enzyme) expression. Aromatase is involved in the breakdown of androgens into estrogens. So, when this happens, the estrogen levels in the body are even higher! We'll go more into Aromatase later.

Researchers have theorized that the reason why Black women are four times more likely than non-Black women to develop fibroids is because of the occurrence of SNPs in COMT and the role they play in estrogen dominance by either upregulating or downregulating estrogen. It's important to note that not all Black women have this gene variation. So, it can be helpful to get genetic testing to screen for SNPs in order to develop your best treatment plan.

When SNPs downregulate the metabolism of estrogen, they specifically slow down the COMT activity that converts hydroxy-estrogen into methylated estrogen. To unpack this further, the slowing down or decrease of COMT activity, in this case, is associated with decreased clearance of 2-hydroxy E2 (a form of estrogen).

This slowed-down clearing out of 2-hydroxy E2 can lead to a hypoestrogenic state.

A hypoestrogenic state simply means low levels of estrogen are found in the cells.

So, when this COMT activity is too low and reduces estrogen distribution into the cells, it can cause the estrogen levels to overflow and increase in the tissues. This can also lead to signs and symptoms of estrogen dominance.



## LET'S TAKE A MORE DETAILED LOOK.

When estrogen dominance occurs, inflammation occurs and, in turn, causes the overgrowth of tissue.

This can lead to the formation of fibroids.

This is why COMT gene activity needs to be BALANCED to metabolize estrogen properly.

Before we go further into the impact of COMT, let's look at Hydroxylation.

Hydroxylation is the beginning stage of estrogen metabolism. It is when estrogen is already absorbed and how the body deals with breaking it down.

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# WHAT IS HYDROXYLATION?

Hydroxylation is the process of adding an (-OH) hydroxyl group to an organic compound for the ultimate purpose of metabolism. This can happen in any part of the body.

Hydroxylation is one of the first steps when it comes to the decomposition, or the breaking down, of organic compounds. Organic compounds are chemical compounds joined together in the body.

Hydroxylation also plays an important role in detoxification. Detoxification is removing waste from the body.

Hydroxylation removes waste from the body by changing lipophilic compounds (lipids and fats) into water-soluble compounds. This process is carried out by hydroxylases, which is an enzyme. This is the beginning stage of estrogen metabolism.

Estradiol (E2), the primary form of estrogen during your reproductive years, goes through hydroxylation. It is one of the major routes of estrogen metabolism. Estrogen gets hydroxylated into catechol estrogens. A catechol estrogen is a steroidal estrogen that contains catechol (1,2-dihydroxybenzene) in its structure.

Estradiol and Estrone are key forms of estrogen synthesized from catechol estrogens via cytochrome P450 enzymes found mainly in the liver. This process involves hydroxylation, leading to the production of these essential steroid hormones, which can significantly influence various physiological processes in the body. Here's two examples.

## 2-Hydroxylated

This is the balanced form of estrogen:

- 2-Hydroxyestradiol
- 2-Hydroxyestrone
- 2-Hydroxyestriol

## 4-Hydroxylated

This is the excessive form of estrogen (high levels) that can cause estrogen dominance:

- 4-Hydroxyestradiol
- 4-Hydroxyestrone
- 4-Hydroxyestriol

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# WHAT IS METHYLATION?

## LET'S PAUSE TO LOOK AT METHYLATION — THE FINAL STAGE OF ESTROGEN METABOLISM

Methylation is a chemical reaction in the body in which a small molecule called a methyl group gets added to DNA, proteins, or other molecules. Adding methyl groups can affect how some molecules act in the body.

Methylation is the last process of metabolism. Its job is to stabilize everything.

The most abundant catechol estrogen serum (level) is 2-hydroxyestrone. Remember, COMT is the enzyme responsible for metabolizing hydroxy estrogens into methyl estrogens—estrogens that have been methylated.

COMT turns the hydroxy estrogens into the methoxylated estrogens methoxy estradiol and 4-methoxyestrone. One of the main reasons why the COMT enzyme needs to be efficient is because if the hydroxy estrogens are not metabolized properly, the catechol estrogen undergoes oxidation.

Oxidation contributes to estrogen-induced carcinogenesis. In other words, cancer.

While the 4-hydroxylated estrogens are more estrogenic than 2-hydroxylated estrogens, they are more neuroprotective. This means they protect the neurons in the body.

COMT enzymes are also responsible for the metabolism of other neurosteroids.

### **Examples of neurosteroids are:**

- Dopamine
- Norepinephrine
- Phytochemicals

The metabolites of estrogen are responsible for many of the positive and negative properties of estrogens.

Modulation of estrogen hydroxylation is important since some of the other metabolites increase the risk of:

- Breast and cervical dysplasia (abnormal cells)
- Cysts
- Benign tumors
- Other hormone-related cancers



## NUTRITION & METABOLISM

What you eat is one of the most effective tools you can use to lower your 4-hydroxy catechol estrogens.

Remember: 4-hydroxy is the form of estrogen that can cause estrogen dominance.

2-hydroxy catechol estrogens—the naturally balanced form of estrogen—are formed by the cytochrome enzyme CYP1A1. 2-hydroxy catechol estrogens are activated by nutritional phytochemicals found in cruciferous vegetables.

**Cruciferous vegetables include:**

- Cauliflower
- Broccoli
- Cabbage





Eating more of these foods and increasing Vitamin D helps to improve the ratio of 2 and 4 -hydroxy catechol estrogens. As a result, estrogen is properly regulated. As stated, nutritional phytochemicals can be very beneficial for COMT1 regulation. But some can be a double-edged sword. For instance, while Quercetin, an herbal supplement, is beneficial for women with fibroids, it has also been found to slightly decrease COMT1 activity. This results in the increased concentration of catechol estrogen in the kidneys (organs in your body that clear the blood of toxins.)

**4-hydroxy catechol estrogens are created from the cytochrome enzyme CYP1B1.**

It is mainly induced by petrochemical toxins.

**These toxins include:**

- Drugs
- Oils
- Phthalates
- BPA
- Pesticides
- Household chemicals

All of which contaminate our food, water, and air. It is important to minimize and, whenever possible, avoid exposure to these contaminants to lower our 4-hydroxy catechol estrogens.

There is a current lab test that checks the ratio of estrogens to assess health risks. One such test is the Estrogen Metabolism Assessment. You can ask your primary care physician, gynecologist or endocrinologist for this test.



# estrogen

NOW, LET'S RESUME THE CONVERSATION ON THE IMPACT OF

## COMT1

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While estrogen dominance does not play the primary role in fibroid growth, it does fuel the development of fibroids. And changes in the COMT1 gene can increase the risk of fibroids in women—more specifically, Black women.

**A study published in the Journal of the Society for Gynecologic Investigation included 328 women: 186 had fibroids, and 142 did not.**

The researchers examined genetic causes that might have played a role in the development of uterine fibroids. A common genetic frequency screened in these women was for SNPs the catechol-O-methyltransferase (COMT) gene. As stated before, not all Black women have this gene variation.

After discovering COMT1 SNPs increases the risk of fibroids, it was also clear that COMT1-inhibiting drugs (drugs that stop COMT) were shown to decrease certain genes that need estrogen. In these studies, fibroid cells then stopped growing and eventually died.

Fibroids are steroid hormone-dependent. Like most tumors found in the reproductive tract—the tissues and organs involved in sexual reproduction—they are hyperresponsive to estrogen. They also contain estrogen and progesterone receptors. Receptors are organs or cells that receive signals from the body.

But this does not make fibroids entirely dependent on estrogen. Fibroids do not seem to manifest in females before they have a menstrual cycle. This indicates that estrogen does play a role in development, but the role is very complex.

As previously mentioned, catechol estrogens are methylated by COMT.

The COMT enzyme uses magnesium (an important mineral in the body) and another molecule known as S-adenosylmethionine (SAMe) for methylation. SAMe is made in the body from methionine, an amino acid found in foods.

This means that a deficiency of magnesium and the amino acid methionine can cause COMT to behave differently.

There are also studies showing that childhood trauma can cause early COMT inhibition through activation of the Hippocampus—a complex brain structure embedded deep into the temporal lobe. The hippocampus has a major role in learning and memory. Childhood trauma can include stressful home environments caused by physical, emotional, and/or sexual abuse as well as neglect. COMT activity can also be inhibited through competition for the enzyme.

Additionally, research has found that certain endocrine disruptors such as Bisphenol A (BPAs) and Polychlorinated biphenyls (PCBs) have been shown to stop COMT activity.

## UTERINE FIBROID STEM CELLS

Stem cells are the beginning of all cells in the body. They are the raw materials the body is made out of and in the right environment, these stem cells divide and create more cells.

Although a hypothesis (educated guess), evidence is leaning towards UFs originating from stem cells in the myometrium (muscle wall of the uterus). The specific stem cell has yet to be discovered.

Why are stem cells and UFs important to mention? Evidence shows that these stem cells turn into tumor cells, or Uterine Fibroid Stems Cells, when there is instability in the body.



For example, when women are exposed to endocrine-disrupting chemicals (EDCs), chemicals that disrupt the endocrine system, these chemicals target the stem cells. As a result, increasing the risk of fibroids.

There is an entire section explaining EDCs a little later in the book.

DNA in the body repairs tissues, and other systems in the body. When the DNA damage response and repair gene isn't working, it can lead to the risk of UFs. Fibroid stem cells have been found to damage DNA and decrease the DNA repair gene.

Again, this may lead to the growth of uterine fibroids and the fibroids multiplying.

## **THE FOLLOWING STUDIES PROVIDE MORE EVIDENCE AND INSIGHT INTO THE CLAIM OF UTERINE FIBROIDS STEM CELLS:**

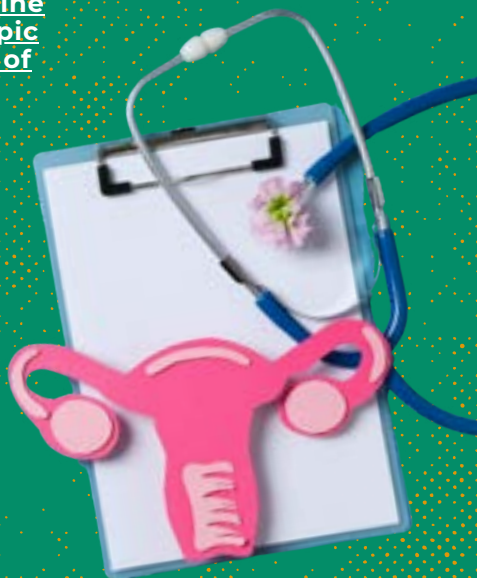
### **Uterine Fibroids**

**Side Population in Human Uterine Myometrium Displays Phenotypic and Functional Characteristics of Myometrial Stem Cells**

**Uterine Leiomyomas Exhibit Fewer Stem/Progenitor Cell Characteristics When Compared with Corresponding Normal Myometrium**

**Identification and Characterization of the Human Leiomyoma Side Population as Putative Tumor-initiating Cells**

**Putative Human Myometrial and Fibroid Stem Cell Markers**



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# ESTROGEN DOMINANCE

Estrogen dominance has long been considered one of the main causes of fibroid growth. However, further research now reveals that while estrogen does set the stage for the initial development of fibroids, it is the hormone progesterone that actually plays a more significant role in fibroid growth.

Because fibroids do have some estrogen dependency, estrogen must be present for fibroids to develop. There are four types of natural estrogen, but only three are relevant to non-pregnant individuals:

## ESTRONE (E1)

Estrone is the weakest type of estrogen; however, it does support sexual development and function.

## ESTRADIOL (E2)

Estradiol regulates tissue growth. Women suffering from fibroids, endometriosis, cysts, adenomyosis and more have high levels of estradiol that trigger inflammation (the overgrowth of tissue), which results in severe pain. This hormone is the strongest, as well as the most active and prominent, during a woman's reproductive years (from the time of her first period until she hits menopause).

## ESTRIOL (E3)

Estriol is the most plentiful of these estrogens, particularly in pregnant women who make high levels of this hormone because it helps their uterus grow and stay healthy.

## ESTETROL (E4)

Estetrol is produced by the human fetus and passed into the maternal blood.

In order to provide a framework for estrogen dominance, we need to first establish a baseline of what are considered normal estrogen levels. Below are the normal ranges of estrogen levels measured in picograms per millilitre (pg/mL):

- 10 to 200 pg/mL in women of reproductive ages, 12 to 45
- 30 to 400 pg/mL for premenopausal women
- 0 to 30 pg/mL for postmenopausal women
- 10 to 50 pg/mL for men

The role of estrogen and fibroid pathology is quite complex.

Let's be real; it's confusing! But we are going to break it down for you after we first discuss aromatase and aromatization.

## AROMATASE & AROMATIZATION

One of the key drivers of Estradiol (E2) levels is a naturally occurring physiological process called aromatization. To understand aromatization, we first must understand the enzyme aromatase and what it does.

Aromatase is the natural enzyme located in multiple tissues throughout the body and is most prevalent in women and men as follows:

- Women: the ovaries and the uterine lining.
- Men: the brain, muscles, and testicles.

Yes, biology class was a while ago, so here's a refresher! An enzyme is a substance that acts as a catalyst (or stimulant) in living organisms. It regulates the rate at which chemical reactions proceed without itself being altered in the process.

The biological processes that occur within all living organisms are chemical reactions, and most are regulated by enzymes. Still following?

This enzyme aromatase—also called estrogen synthetase or estrogen synthase—is responsible for a key step in the biosynthesis of estrogens compounding the production of this hormone.

The key function of aromatization is to convert androgens (like testosterone) into estrogen. When your testosterone production naturally increases, aromatization will occur at a rate that your body can handle. Natural testosterone production increase occurs by growing over time, not in an all-at-once spike. Because of this, aromatization due to natural testosterone optimization comes with some beneficial effects.

**For instance, when combined with testosterone, estrogen can:**

- Increase muscle mass
- Regulate libido

However, the synthetic estrogen-mimicking hormone called xenoestrogen will trigger a jarring increase in testosterone levels all at one time. We'll go more in-depth on xenoestrogens a little later.

The aromatization caused by these acute testosterone accelerations will sharply increase estrogen levels at a higher and less comfortable rate. This could result in some of the adverse effects of estrogen spikes.

Aromatization is triggered by the body's need to balance the testosterone (androgen) and estrogen ratio to maintain homeostasis. It works by converting (androgen) testosterone into estrogen to stabilize the growth and reproductive hormones.

Aromatase is involved in causing an inflammation feedback loop. This makes fibroids worse by causing excess tissue growth, heavy bleeding, and pain. But the loop starts with estrogen.



Estrogen has been shown to stimulate the expression of the enzymes that regulate inflammation thus causing an inflammatory response, which can then stimulate aromatase activity in uterine fibroids.

When this happens, it causes a constant production of an inflammatory response and the active form of estrogen E2 in fibroids tissue. Because of this feedback loop, estrogen promotes the development of uterine fibroids, consequently resulting in:

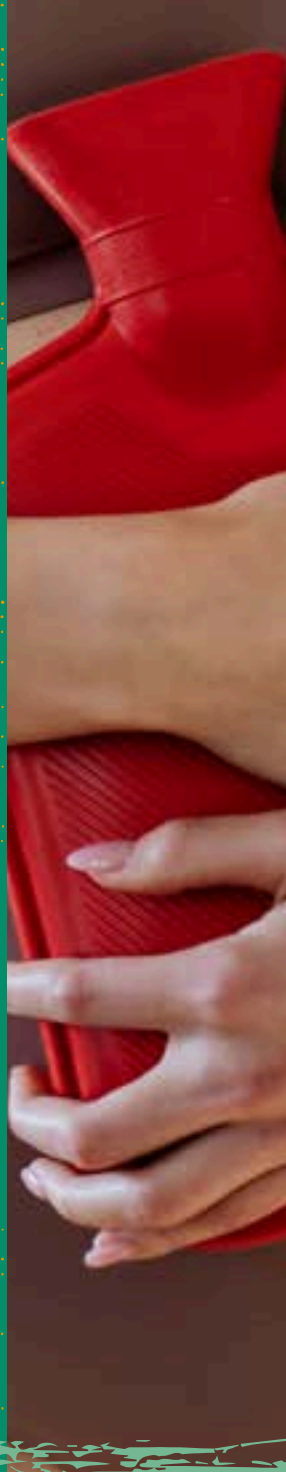
- Pain
- Heavy Bleeding
- Inflammation
- Infertility

You might be wondering why this is important. Well, this loop is the key to understanding the power of aromatase inhibitors and how they can help shrink, and eventually eliminate, fibroids.

The goal in this approach to treating fibroids is to reduce the effects of estrogen. The enzyme aromatase converts androgens into estrogens. When that enzyme is blocked, this decreases the amount of available estrogen that could potentially stimulate the development of this estrogen-dependent disease.

**In women with uterine fibroids, Estradiol arises from three major tissue sites that express aromatase.**

- The ovaries (which primarily convert cholesterol to Estradiol).
- Adipose tissue and skin (which convert androstenedione to large amounts of Estradiol and small amounts of Estrone).
- Fibroids tissue (which triggers the production of estrogen through the increase of aromatase).



Aromatase is responsible for catalyzing the conversion of androstenedione into Estradiol and Estrone. Estrogen is not just randomly produced by the uterine fibroids; Estradiol levels increase due to the upregulation of aromatase.

In summary, the higher the amount of aromatase circulating in the body, the more testosterone will be converted into estrogen during a testosterone spike.

This can be triggered by synthetic estrogen-mimicking hormones.



## ESTROGEN'S SPECIFIC ROLE IN UTERINE FIBROIDS

Estrogen is locally produced by fibroid cells through aromatase (enzyme) activity. It is reported that fibroid tissue contains high levels of aromatase. This results in higher levels of estrogen compared to the adjacent myometrium—or the muscle outside of the uterus.

Fibroid cells have intrinsic or natural aromatase enzyme activity independent of the ovaries. This means that the aromatase enzyme is targeted in the treatment of fibroids. Although plasma estrogen levels are similar in women with and without fibroids, tissue levels are higher in women with fibroids; this could be due to aromatase.

Fibroid tissue was extremely high in both aromatase and  $17\beta$ -hydroxysteroid dehydrogenase ( $17\beta$ -HSD), an enzyme that breaks down steroids in the body, compared to normal myometrium. This is primarily why aromatase inhibitors have been shown to stop the fibroid cells from multiplying and reduce tumor size in trials.



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# PROGESTERONE & FIBROID GROWTH

Progesterone is a hormone released by the ovaries that plays an important role in the menstrual cycle and in maintaining the early stages of pregnancy. Research shows that progesterone may play the most significant role in fibroid growth. It appears to be the main steroid hormone that starts to change the uterine muscle, therefore beginning the abnormal growth of the fibroid.

This happens in various ways.

## THERE ARE TWO THEORIES:

The theory of progesterone playing the biggest role in fibroid growth was investigated in the 1960s. In the study of 16 patients, 15 out of 16 patients with UFs were treated with synthetic progestin—a hormone that was created outside of the body. While on this synthetic hormone, the individuals' fibroids doubled in size, and when they were taken off of this synthetic hormone, the fibroids were returned to pretreatment size. (Sangkomkamhang U.S. et al, 2013).

Progesterone playing a major role in fibroid formation was also confirmed through research using progesterone antagonists. Progesterone antagonists were used for uterine fibroid treatment and resulted in stopping the growth of the fibroid.

Research has shown that estrogen does play a role in fibroid growth, but a very small role. It prepares the non-cancerous tumor, or fibroid, to continuously encourage progesterone levels to increase.

Correcting estrogen dominance is a pathway to help reduce the constant stimulation of progesterone and thereby shrink, eliminate and even prevent uterine fibroids.

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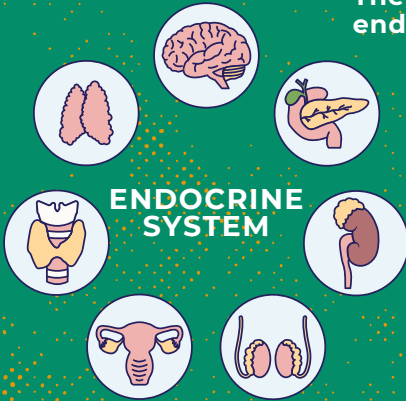
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# ENDOCRINE DISRUPTORS

Endocrine Disrupting Chemicals (EDCs) are chemical compounds that interact with the normal functioning of the endocrine system. The endocrine system manages the hormones in our bodies.

EDCs are often considered harmful when it comes to their role in causing uterine fibroids.

**There are many classes of endocrine disruptors, including:**



- Environmental phenols
- Phthalates
- Microplastics
- Parabens
- Organophosphate esters
- Benzene
- Polychlorinated biphenyls (PCBs)
- Pesticides
- Polyfluoroalkyls (PFOAs)

The exact harm of endocrine disruptors is hard to track over time, but research has found that a lot of endocrine disruptors:

- Become concentrated in the body
- Can mimic other hormones
- Can attack other receptors

Some endocrine disruptors can leach, migrate, or give off gas from products over time. They can enter the food chain and be transferred to humans from food and or water. They can enter the body through: inhalation or through the nose, the skin.

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When these endocrine disruptors are inhaled or absorbed through the skin, they can break down in the body. They then cause negative effects on the body. Some of them are excreted or removed from the body in urine and feces (poop). Although scientists know a lot about endocrine disruptors, they have not been fully studied.

Endocrine disruptors also combine to form nuclear receptors and change the function of hormones in the body. They are so clever that they will copy and pretend to function like certain hormones and block the important functions they do for the body!

Studies show that even small doses of endocrine disruptors can cause disease. For example, phthalates have been a cause for concern because at least one type, Di(2-ethylhexyl) phthalate (DEHP), has been found to influence biological processes in fibroids—causing them to grow.

Study found a significant positive link between DEHP found in urine and risk for fibroids.

Another recent study further explains the mechanisms behind that link.

The scientists discovered exposure to DEHP may activate a hormonal pathway that activates an environmentally responsive receptor (AHR) to bind to DNA and cause increased growth of fibroid tumors.

## MORE ABOUT PHTHALATES

Have you ever relaxed your hair?

Hair relaxers have been used by Black women for decades. There is a theory that the chemicals in hair relaxers are a possible reason Black women are burdened by fibroids more than women of any other ethnicity.

Most hair relaxers contain lye as the main ingredient and contain hormonally active compounds called phthalates, which are endocrine disruptors. Phthalates are often not required to be listed as ingredients because they are combined in the term fragrance or perfume.



As previously mentioned, phthalates can be absorbed or inhaled and have been shown to have estrogenic effects (effects on the hormone estrogen) in both cell models, which can affect the functionality of the cells, and human models, which can affect the functionality of human organisms. When hormones like estrogen are affected in the body, it may cause changes. One of the changes can be the growth of fibroids.

One 2012 study shows a direct correlation between women who frequently use chemical relaxers and fibroids. It showed a 5% increase. The percentage may have increased since then. So far, this has only been found to be an association—no direct cause and effect have been evaluated.

In this same white paper, called the Black Women's Health Study, the authors studied 23,580 premenopausal African American women who reported hair relaxer use from 1997 to 2009.

Through a series of self-reported questionnaires, the results showed that 7,146 women developed uterine fibroids confirmed via ultrasound or surgery. The study suggests that hair relaxer use increases the risk of developing fibroids.

There has even been a recent study connecting hair relaxers with uterine, breast, and ovarian cancers.

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# XENOESTROGENS

Xenoestrogens are a subcategory of endocrine disruptors that specifically have estrogen-like effects. "Xeno" means relating to a foreigner, so xenoestrogen means foreign estrogen.

Estrogen has some growth properties, especially during puberty. Since xenoestrogens are close enough in molecular structure to estrogen, they can stick to estrogen receptor sites with potentially hazardous outcomes.

## Sources of xenoestrogens include:

- Plastics
- Pesticides
- Chemicals
- Water systems
- Artificial colors, like FD&C Red No.3 used in food

Various synthetic xenoestrogens can be found in birth control pills (ethinylestradiol).



One of the most dangerous classes of xenoestrogens is represented by bisphenols—synthetic compounds. They are used in the production of certain plastics. Several bisphenols were found to be estrogenic by binding to both receptor subtypes.

One of the most widely diffused and dangerous synthetic xenoestrogens is bisphenol A (BPA).

**BPA can be found in things such as:**

- Plastic bottles
- Thermal paper-like receipts

A specific xenoestrogen compound known as diethylstilbestrol (DES)—a synthetic form of estrogen—was prescribed to women during the 1940s and 1970s to prevent miscarriage and premature labor.

It was later found to play a developmental role in uterine fibroids. It was also associated with a 100% risk of offspring breast cancer. Children of the women who used this type of birth control did end up getting diagnosed with breast cancer. Thankfully, this type of birth control is now banned.

At least one large study found a positive association between DES exposure and uterine fibroids risk. Researchers investigated the influence of prenatal DES exposure and uterine fibroids risk. 11,831 cases of uterine fibroids were diagnosed in a 1.3-million-person follow-up.

Prenatal exposure to DES increased the risk for uterine fibroids by 13% in women over age 35.



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# PHYTOESTROGENS

PHYTOESTROGENS ARE SUBSTANCES THAT OCCUR NATURALLY IN PLANTS. IT WAS THOUGHT THAT THEY PLAY A MAJOR ROLE IN FIBROID DEVELOPMENT.

But, it appears that only one type of phytoestrogen responds in the manner of fibroid growth. It is called genistein.

Genistein is a naturally occurring chemical found in soy.

**Here is a breakdown of one study:**

- One study found an increased risk of fibroid development linked to early life exposure to genistein.
- Another study found that infants fed soy-based formulas had an increased risk of dysmenorrhea—cramps and increased pain during their periods when they developed their menstrual cycles later in life.

## MORE ABOUT PHTHALATES

Since infants are still growing, soy-based formulas given in a critical development window, tend to alter female reproductive hormones. This is because genistein, unlike other phytoestrogens, has a strong bind, or likes to stick, to estrogen receptors.

This binding affinity has not been shown in the same manner for other phytoestrogens as with genistein.





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# VITAMIN D DEFICIENCY

Uterine fibroids are hormone-dependent benign tumors but are there other factors that can cause fibroids?

The short answer is YES! Hormones often indirectly impact other hormones, which is the case with Vitamin D. If you take a blood test and your primary care provider says you have low Vitamin D levels, you should take this seriously.

Vitamin D is a hormone that is synthesized (absorbed) through the skin when you're exposed to sunlight.

**Women with darker skin have a harder time absorbing ultraviolet (UV) rays from the sun and it gets even harder with:**

- Increasing age
- Your health
- The clothing you wear outside



Approximately 80% of African American Women have Vitamin D deficiency (low levels of Vitamin D in the body).

Conversely, only 20% of White Women are Vitamin D deficient.

Low levels of Vitamin D have been shown to drive several gynecological and obstetrical pathologies such as fibroids, infertility, and polycystic ovarian syndrome (PCOS), and some studies even show how vitamin D deficiency impacts the growth of Cysts.

Low levels of Vitamin D are believed to be a risk factor in the development of uterine fibroids.



## HERE ARE MORE FACTS ON LOW LEVELS OF VITAMIN D AND FIBROIDS:

One study showed women with fibroids had lower levels of Vitamin D than those without.

Black women, who are more likely to develop fibroids than white women, are also more likely to have a Vitamin D deficiency.

The same study found a significant inverse relationship between Vitamin D levels and the severity of fibroids in Black women. The lower the Vitamin D levels, the more severe the fibroid burden.

Two other studies found that only 10% of Black women and 50% of white women have sufficient Vitamin D levels.

In those studies, women with higher levels of vitamin D were less likely to have uterine fibroids.

Another study found that higher levels of Vitamin D block uterine fibroids growth.

**By recommendations from the Endocrine Society, Vitamin D status should always be evaluated in patients with fibroids.**

Taking a Vitamin D supplement (vitamin) may be necessary to increase your Vitamin-D levels.

**Here is the range for Vitamin D classified by the Endocrine Society if you were to take a blood test:**

- Sufficient  $\geq 30$  ng/mL
- Insufficiency 21 ng/mL - 29 ng/mL
- Deficiency  $<20$  ng/mL



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# TRANSFORMING GROWTH FACTOR- BETA

Vitamin D has also been found to play a significant role in shrinking fibroids by inhibiting the Transforming growth factor beta (TGF-B) molecule. TGF-B is the most relevant cytokine (a type of white blood cell) in increasing and changing uterine muscle tissue.

## **TGF-B is responsible for:**

- Wound healing
- Angiogenesis, or creating new blood vessels
- Cell growth and differentiation, or changing of the cell
- Immune regulation

In a healthy person, TGF-B plays a role in protecting the cell's development. It also plays an important role in the development and function of the reproductive system.

In fibroid tissue, the Transforming growth factor beta (TGF-B) molecule promotes its growth and fibrogenic process. Researchers have also identified the role of Vitamin D therapy as it interferes with the TGF-B pathway.

TGF-B is usually high in chronic inflammation. But targeting this molecule with Vitamin D therapy has shown positive shrinkage of uterine fibroids.

**The following studies provide more evidence and insight into the claim of the impact of Vitamin D on TGF-B and uterine fibroids:**

**Vitamin D and Uterine Fibroids—Review of the Literature and Novel Concepts**

**Role of Transforming Growth Factor  $\beta$  in Uterine Fibroid Biology**

**Influence of Vitamin D and Transforming Growth Factor  $\beta$ 3 Serum Concentrations, Obesity, and Family History on the Risk for Uterine Fibroids**

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# OBESITY & INFLAMMATION

Obesity, as it relates to the storage of fat tissue (adipose tissue), is directly linked to the key driver in the growth of fibroids. Fat tissue is metabolically active. This means that the more fat tissue someone has, the more hormones, cytokines, chemokines, and inflammatory markers are active in the body.

Research shows that the inflammatory molecules that come from fat tissue contribute to inflammation throughout the body. Therefore, it is the inflammation that creates the environment for fibroids to grow.

One study of 22,895 women who were perimenopausal, also called premenopausal, and had no prior diagnosis of uterine fibroids found that weight gain since the age of 18 is positively associated with an increased risk of self-reported fibroids.



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# ROOT CAUSE SUMMARY

**In summary, here is a recap of the root causes of uterine fibroids:**

**Stress:** Stress hormones can help trigger both the development and growth of fibroids by fueling estrogen dominance and stimulating progesterone levels.

**Genetics/SNPs:** It has been shown in women with an alteration in the catechol-O-methyltransferase (COMT) gene. The COMT Gene plays a role in how estrogen is metabolized, and women with high or low COMT Activity tend more likely to develop fibroids.

**Uterine Fibroid Stem Cells:** Evidence shows that stem cells turn into tumor cells, or Uterine Fibroid Stems Cells, when there is instability in the body. For instance, when women are exposed to endocrine-disrupting chemicals (EDCs), those chemicals target stem cells, increasing the risk of fibroids.

**Estrogen Dominance:** This has commonly been stated as one of the causes of fibroid growth, but as research has unfolded, it appears that progesterone has a bigger role in fibroid growth, but estrogen plays a key role in the development.

More specifically, fibroids development causes the increase of progesterone. This makes tissue that causes tumors more responsive to progesterone signals which in turn stimulates fibroid growth.

**Endocrine Disruptors:** Endocrine-disrupting chemicals (EDCs) are chemical compounds that interact with the normal functioning of the endocrine system. The endocrine system manages the hormones in our bodies. Studies show that even small doses can cause disease and recent studies show phthalates are a huge cause for concern with fibroids.

**Vitamin D Deficiency:** One study found a significant inverse relationship between Vitamin D serum levels and the severity of fibroids in African American women. This means that the lower the vitamin D levels were, the more severe the fibroid burden was. It was also found that Vitamin D3 can also inhibit and shrink fibroids.

**Obesity/Inflammation:** The research is clear that the inflammatory molecules that are secreted from adipose tissue contribute to body-wide systemic inflammation that sets the stage for fibroid growth.

## OTHER RISKS TO FIBROIDS

### UTERINE IRRITANTS

Uterine irritation may play a role in the many factors contributing to the cause of fibroids.

Researchers have theorized that these potential irritants mentioned below may contribute to fibroid growth in the uterus:

- The use of intrauterine devices (IUD)—both hormonal and non-hormonal
- Pelvic inflammatory disease (PID)
- Chlamydial infection
- Vaginal Steamers\*
- Yoni Pearls\*
- Talc usage, which is also an ingredient used in cosmetics



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# CONCLUSION



To effectively deal with uterine fibroids, you need a personalized approach. Everyone reacts to fibroids differently, so getting care that suits your needs is important. You can start by working closely with your healthcare provider. They will guide you through an evaluation process that includes tests to check the size, location, and symptoms of your fibroids. Knowing these details helps you understand your situation better. After this evaluation, consider booking a consultation with our Naturopathic Specialist and Master Herbalist to further assess your condition.

Adding holistic practices to conventional treatments can greatly support your health. Begin by making mindful dietary changes. Focus on whole, unprocessed foods to help reduce inflammation and balance hormones.

Regular exercise is just as important. Explore different forms of physical activity, such as strength training, yoga, or taking long, restorative walks in nature. Tailor your routine to what feels rewarding and energizing for you.



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# CONCLUSION

Don't overlook sleep; it's essential for healing. Try to keep a consistent sleep schedule and aim for 7 to 8 hours each night for your body to rest and recover. Spend time outdoors in the morning to get natural sunlight, which helps regulate your sleep cycle and supports hormone production necessary for managing fibroids.

Consider adding supplements to your health regimen as well. Products like the Herbal Healing Co. Fibroid Essentials Bundle contain specific nutrients that support hormonal balance and help your body resist fibroid growth.

As you look into treatment options, stay open-minded about what is available. This could include lifestyle changes or medical interventions like surgery, based on what works best for you.

By being proactive and informed about your health, you can make educated choices about your treatment. The aim is to create a plan that not only reduces fibroids but also improves your overall quality of life. Remember, managing this process is a team effort. With Herbal Healing Co. by your side, you can develop effective strategies for your unique path to wellness.



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