ICD-11

Leiomyomas

Clinical Guidelines

International Classification of Disease

endo ALLIANCE

endometriosisalliance.org

2E86.0 Leiomyoma of uterus

Parent

2E86 Benign smooth muscle or skeletal muscle tumour

Show all ancestors

Description

A well-circumscribed benign smooth muscle neoplasm characterised by the presence of spindle cells with cigar-shaped nuclei, interlacing fascicles, and a whorled pattern.

Inclusions

- Fibromyoma of uterus
- Leiomyoma of cervix uteri
- Parasitic leiomyoma
- Pedunculated leiomyoma

Exclusions

- Leiomyoma of ovary (2E86.1)
- Leiomyoma of fallopian tube (2E86.1)
- Leiomyoma of broad ligament (2E86.1)
- Leiomyoma of vagina (2E86.1)
- Leiomyoma of vulva (2E86.1)
- Benign non-mesenchymal neoplasms of uterus (2F31)

Postcoordination

Add detail to **Leiomyoma of uterus**

Specific anatomy *(use additional code, if desired .)*

Search

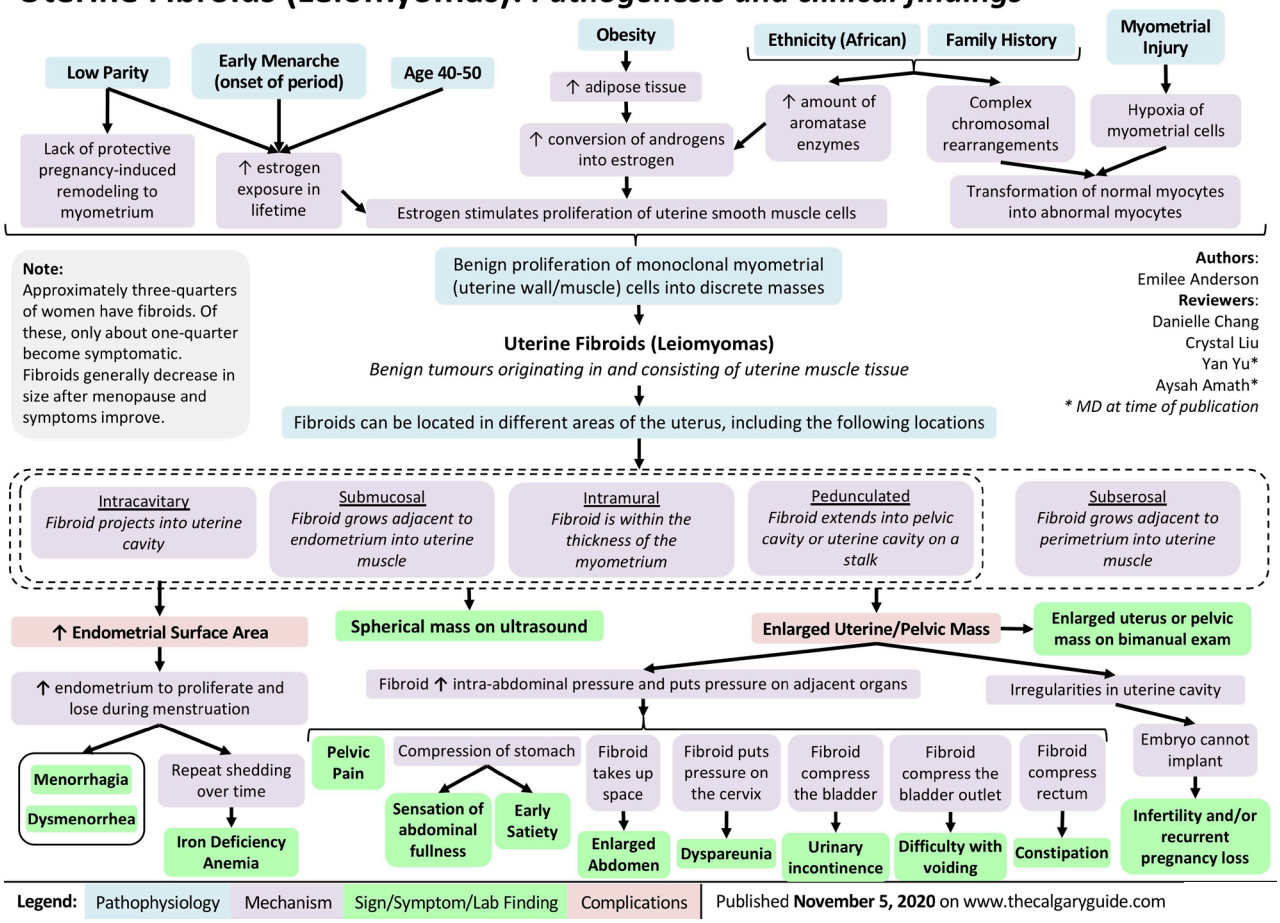
Histopathology *(use additional code, if desired .)*

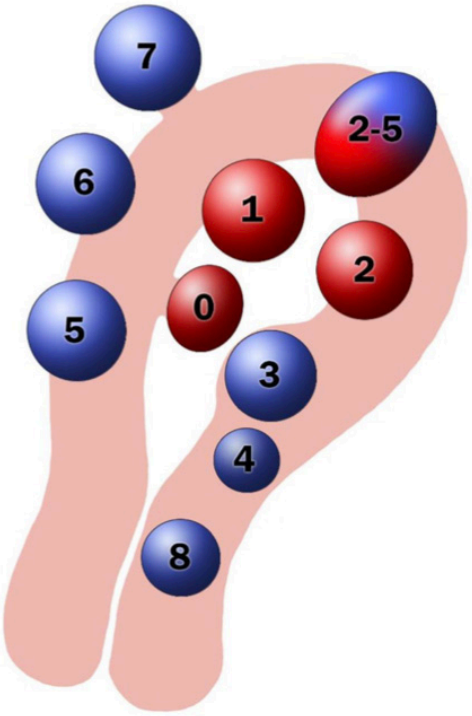
Search

Myomatous neoplasms, uncertain whether benign or malignant

XH60C2	Intravascular leiomyomatosis
XH2L80	Leiomyomatosis, NOS
XH1EX8	Metastasizing leiomyoma
XH1EN1	Smooth muscle tumour of uncertain malignant potential
XH00B4	Smooth muscle tumour, NOS
XH8MR2	Leiomyomatosis, peritonealis disseminata
XH22N2	Leiomyosarcoma, cutaneous

Uterine Fibroids (Leiomyomas): *Pathogenesis and clinical findings*





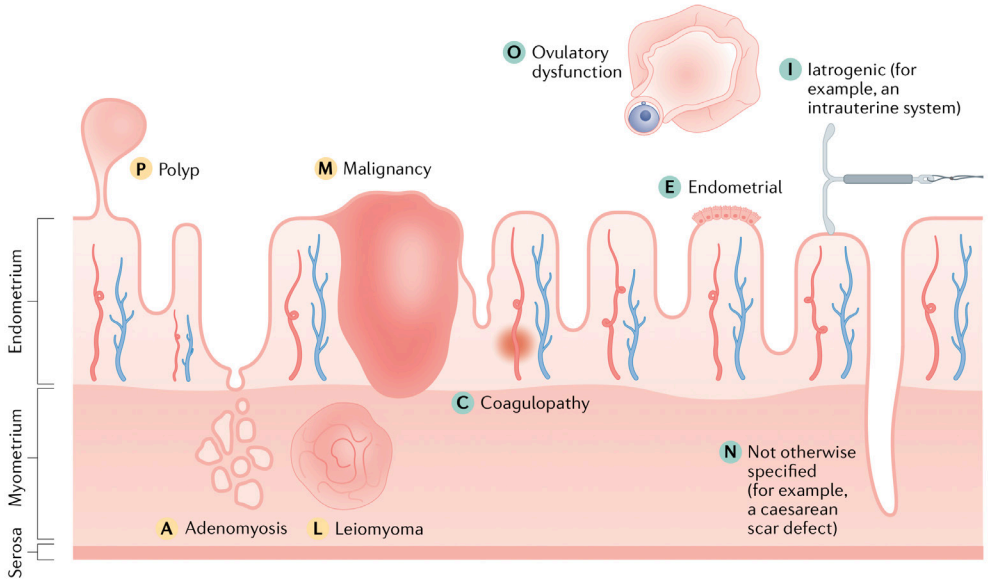
FIGO classification system for uterine fibroids

Group	Type	Description
Submucosal	0	Pedunculated intracavitary
	1	< 50% intramural (≥ 50% submucosal)
	2	≥ 50% intramural (< 50% submucosal)
Other	3	100% intramural, contacting endometrium
	4	100% intramural, no endometrial or subserosal contact
	5	Subserosal, ≥ 50% intramural
	6	Subserosal, < 50% intramural
	7	Pedunculated subserosal
	8	Non-myometrial location: e.g., cervical, broad ligament, parasitic
Hybrid	X–X	Both submucosal and subserosal components. First number designates the submucosal component and second number designates the subserosal component

Uterine bleeding: how understanding endometrial physiology underpins menstrual health.
One third of women globally will be affected by abnormal uterine bleeding (AUB)

FIGO Classification: abnormal uterine bleeding (AUB)

The causes of abnormal uterine bleeding are classified using the acronym PALM-COEIN, with each letter denoting a cause. The structural causes (denoted by yellow letters) are discrete entities and include polyp, adenomyosis, leiomyoma (uterine fibroids) and malignancy. The non-structural causes (denoted by green letters) are depicted for the illustration; however, they cannot be measured or imaged. They include coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not otherwise classified (for example, a caesarean scar defect).



Understanding the Impact of Uterine Fibroids on Human Endometrium Function
Uterine fibroids (leiomyomas) are the most common benign gynecological tumors in women of reproductive age worldwide. They cause heavy menstrual bleeding, usually leading to severe anemia, pelvic pain/pressure, infertility, and other debilitating morbidities.

One of the most common characteristics of fibroids is the excessive production of extracellular matrix (ECM) components, which contributes to the stiffness and expansion of fibroids. ECM may serve as a reservoir of profibrotic growth factors such as the transforming growth factor β (TGF-β) and a modulator of their availability and actions. Fibroids also elicit mechanotransduction changes that result in decreased uterine wall contractility and increased myometrium rigidity, which affect normal biological uterine functions such as menstrual bleeding, receptivity, and implantation. Changes in the microRNA (miRNA) expression in fibroids and myometrial cells appear to modulate the TGF-β pathways and the expression of regulators of ECM production. Taken together, these findings demonstrate an interaction among the ECM components, TGF-β family signaling, miRNAs, and the endometrial vascular system.

They cause irregular and heavy menstrual bleeding (HMB), leading to severe anemia, dysmenorrhea, pelvic pressure and pain, urinary incontinence, dyspareunia, infertility, preterm labor, and early and recurrent pregnancy loss

African American women are more likely to develop UFs at an early age and to present more severe clinical symptoms compared to Caucasian women (Kjerulff et al., 1996). Other risk factors for UFs include age, obesity, hypovitaminosis D, and endogenous and exogenous hormonal factors. UFs cause HMB and poor uterine receptivity and implantation leading to infertility, two major female reproductive disorders affecting millions of women in the United States and globally.

Several factors have been implicated in the development and growth of UFs, such as cytokines, chemokines, growth factors, extracellular matrix (ECM) components, factors involved in the DNA damage response and inflammation, vasoactive substances, and microRNAs.

One of the main characteristics of UFs is a remarkably excessive production of ECM components including collagens, fibronectin, proteoglycans, and laminins.

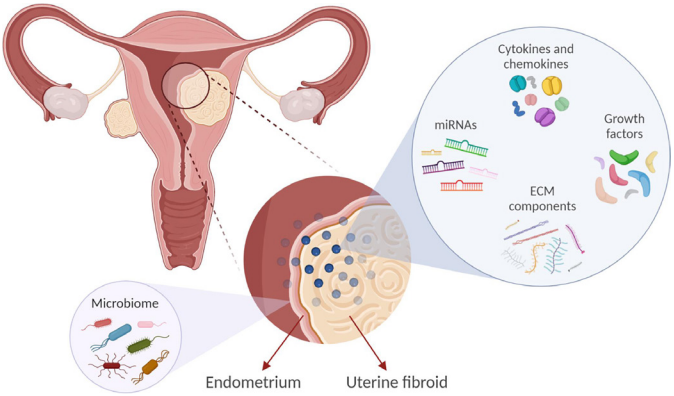
Front. Cell Dev. Biol., 25 May 2021 Sec. Molecular and Cellular Pathology https://doi.org/10.3389/fcell.2021.633180

Vascular biology of uterine fibroids: connecting fibroids and vascular disorder.

Fibroids are benign tumors caused by the proliferation of myometrial smooth muscle cells in the uterus that can lead to symptoms such as abdominal pain, constipation, urinary retention, and infertility. While traditionally thought of as a disease process intrinsic to the uterus, accumulating evidence suggests that fibroid growth may be linked with the systemic vasculature system, although cell-intrinsic factors are certainly of principal importance in their inception. Fibroids are associated with essential hypertension and preeclampsia, as well as atherosclerosis, for reasons that are becoming increasingly elucidated. Factors such as the renin–angiotensin–aldosterone system, estrogen, and endothelial dysfunction all likely play a role in fibroid pathogenesis. In this review, we lay out a framework for reconceptualizing fibroids as a systemic vascular disorder, and discuss how pharmaceutical agents and other interventions targeting the vasculature may aid in the novel treatment of fibroids.

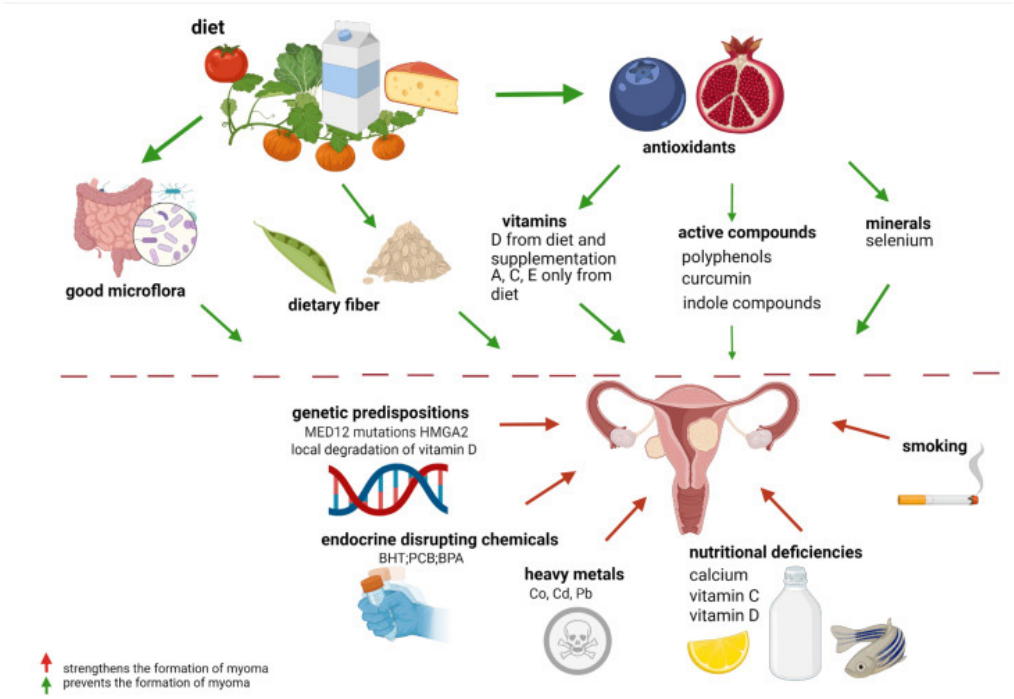
Kirschen, G. W., AlAshqar, A., Miyashita-Ishiwata, M., Reschke, L., El Sabeh, M., & Borahay, M. A. (2021). Vascular biology of uterine fibroids: connecting fibroids and vascular disorders, Reproduction, 162(2), R1-R18.

Understanding the Impact of Uterine Fibroids on Human Endometrium Function



Navarro A, Bariani MV, Yang Q and Al-Hendy A (2021) Understanding the Impact of Uterine Fibroids on Human Endometrium Function. Front. Cell Dev. Biol. 9:633180. doi: 10.3389/fcell.2021.633180

Uterine fibroids (leiomyomas) are the most common benign gynecological tumors in women of reproductive age worldwide. They cause heavy menstrual bleeding, usually leading to severe anemia, pelvic pain/pressure, infertility, and other debilitating morbidities. Fibroids are believed to be monoclonal tumors arising from the myometrium, and recent studies have demonstrated that fibroids actively influence the endometrium globally. Studies suggest a direct relationship between the number of fibroids removed and fertility problems. In this review, our objective was to provide a complete overview of the origin of uterine fibroids and the molecular pathways and processes implicated in their development and growth, which can directly affect the function of a healthy endometrium. One of the most common characteristics of fibroids is the excessive production of extracellular matrix (ECM) components, which contributes to the stiffness and expansion of fibroids. ECM may serve as a reservoir of profibrotic growth factors such as the transforming growth factor β (TGF-β) and a modulator of their availability and actions. Fibroids also elicit mechanotransduction changes that result in decreased uterine wall contractility and increased myometrium rigidity, which affect normal biological uterine functions such as menstrual bleeding, receptivity, and implantation. Changes in the microRNA (miRNA) expression in fibroids and myometrial cells appear to modulate the TGF-β pathways and the expression of regulators of ECM production. Taken together, these findings demonstrate an interaction among the ECM components, TGF-β family signaling, miRNAs, and the endometrial vascular system. Targeting these components will be fundamental to developing novel pharmacotherapies that not only treat uterine fibroids but also restore normal endometrial function.

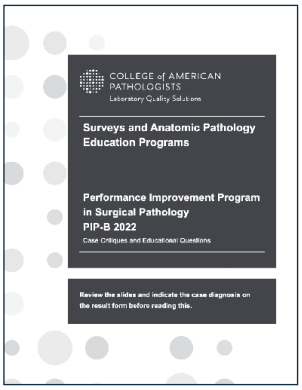


Dietary Natural Compounds and Vitamins as Potential Cofactors in Uterine Fibroids Growth and Development. Nutrients.
Dysbiosis may stimulate the pro-inflammatory cytokines or growth factors in Fibroids. Growth factors and cytokines interact through the estrogen and progesterone action, which plays an important role in uterine leiomyoma growth. A beneficial gut microbial environment can potentially affect the uterus environment and reduce the risk of uterine leiomyoma formation. Using natural compounds in the treatment of Uterine Fibroids appears to be a worthwhile endeavor. Natural compounds present as an alternative route in UF treatment, especially in patients with contraindications for hormonal therapy. In women treated conventionally, natural compounds can strengthen therapeutic effects. Some environmental contaminants can interfere with the beneficial effects of certain foods. These contaminants are known as endocrine-disrupting chemicals (EDC). By binding to hormone receptors, EDCs can stimulate these receptors and alter the function or production of natural hormones. Induction of both genomic and non-genomic signaling and pro-inflammatory effects of EDCs increase the risk of UFs.

Dietary Natural Compounds and Vitamins as Potential Cofactors in Uterine Fibroids Growth and Development. Nutrients. 2022 Feb 9;14(4):734. doi: 10.3390/nu14040734. PMID: 35215384; PMCID: PMC8880543.

Performance Improvement Program in Surgical Pathology

- Fumarate hydratase-deficient leiomyoma
- Leiomyoma
- Leiomyosarcoma
- Low-grade endometrial stromal sarcoma
- Smooth muscle tumor of uncertain malignant potential



Leiomyomas: Criteria for Diagnosis

Sections of the masses show cellular spindle-cell lesions arranged in fascicles that are well demarcated from the surrounding myometrium. No tumor necrosis, atypia, or increased mitotic activity is seen. This appearance, along with the gross presentation, is diagnostic of a uterine leiomyoma. Leiomyomas are benign mesenchymal tumors arising from smooth muscle and represent the most common tumor of the female reproductive organs. Up to 70% of hysterectomy specimens will have at least one leiomyoma, and these are typically considered an incidental finding. Leiomyomas can be intramural, submucosal, or subserosal; subserosal lesions may appear pedunculated. They are well-circumscribed and non-encapsulated. Leiomyomas can become hemorrhagic and necrotic or undergo degenerative changes, including calcification, cystic change, and hyaline degeneration. Leiomyomas are also variable in size and can become quite large. Patients are usually asymptomatic, though patients with bulky or numerous leiomyomas may experience feelings of fullness or infertility and pregnancy loss. A leiomyoma may also cause increased or abnormal uterine bleeding, especially when submucosal in location. Some patients may experience pain if lesions infarct or become hemorrhagic, or if there is torsion of a pedunculated leiomyoma. Rarely, benign leiomyomas may exhibit intravenous growth and cause thromboembolism or vascular insufficiency. Morcellation can cause tumor spill and peritoneal growth.

Histopathologic examination of a leiomyoma reveals intersecting fascicles of spindle cells with eosinophilic, fibrillary cytoplasm, elongated "cigar-shaped" nuclei, and indistinct cell borders. Nucleoli are often visible but small. Palisading of cells may be seen. Acellular areas due to hemorrhage, ischemia, hyaline change, or calcification are common. Some subtypes, listed below, may display larger atypical cells, increased mitotic activity, increased cellularity, or other changes that in most other lesions would denote aggressive or malignant activity. Some rare subtypes even metastasize and show vascular invasion; benign metastasizing leiomyomas and intravenous leiomyomatosis may present primarily or with recurrence in extrauterine sites such as lung, bone, or lymph nodes. Benign leiomyoma variants should only display one concerning feature, not several in concert, and remain rather well- circumscribed. Numerous subtypes of leiomyomas have been described, which together account for approximately 10% of cases. Among these are cellular leiomyoma, leiomyoma with bizarre nuclei, mitotically active leiomyoma, hydropic leiomyoma, apoplectic leiomyoma, lipoleiomyoma, epithelioid leiomyoma, myxoid leiomyoma, and dissecting leiomyoma. These subtypes are named descriptively for grossly or histologically apparent features that differentiate them from a typical leiomyoma.

All are still considered benign lesions but may exist as a component of a systemic process or as part of a syndromic constellation of findings. Immunohistochemical stains are not usually necessary for diagnosis, but conventional leiomyomas will display smooth muscle markers (desmin, caldesmon, SMA, MSA, calponin, SMMHC) as well as ER, PR, and nuclear WT1. Conventional leiomyomas rarely overexpress p16 or p53.

The most frequent molecular alterations in uterine leiomyomas are MED12 mutations (approximately 70%), followed by HMGA2 and HMGA1 rearrangements (25% to 29%). COL4A5 and COL4A6 deletions can be seen in about 4% of cases and are associated with Alport syndrome with diffuse leiomyomatosis. Fumarate hydratase-deficient leiomyoma is a type of leiomyoma seen often in younger patients (typically 20 to 30 years of age). These patients tend to present with multiple symptomatic leiomyomas. Genetic studies can show a range of somatic or germline fumarate hydratase (FH) mutations. Those with germline FH mutations are at a higher risk of renal cell carcinoma (hereditary leiomyomatosis and renal cell carcinoma syndrome). This type of leiomyoma represents approximately 1% of all leiomyoma cases. Histologic features suggestive of this type of leiomyoma include staghorn vasculature, eosinophilic nucleoli, perinuclear halos, and eosinophilic cytoplasmic inclusions. Diagnosis can be confirmed with immunohistochemistry showing loss of expression for fumarate hydratase and tumor testing for mutations in the FH gene.

Leiomyosarcoma typically presents as a single lesion with a soft, bulging, fleshy cut surface, often with areas of hemorrhage and necrosis. Many are quite large at diagnosis, but up to 25% may be less than 5 cm in diameter at diagnosis. The most common subtype is composed of spindle cells in long fascicles that appear disorganized in relation to each other. The cells can be relatively uniform, but pleomorphism is usually apparent and often includes multinucleated cells. Mitotic figures are frequently seen, with apparent atypical mitoses. Tumor cell necrosis, or single cell necrosis, is an important diagnostic feature and essentially rules out leiomyoma. Essential diagnostic criteria defined by the WHO are marked cytologic atypia, tumor cell necrosis, and 4 or more mitoses per square millimeter; a conventional uterine leiomyosarcoma meets at least 2 of these criteria. Epithelioid and myxoid subtypes are defined, with different diagnostic criteria.

A leiomyoma can rarely progress to a leiomyosarcoma (described in <3% of cases). Prognosis is poor, even when the mass is confined to the uterus and completely resected, perhaps due to poor response to chemotherapy.

Low-grade endometrial stromal sarcomas (LGESS) are typically symptomatic tumors of the uterine corpus, presenting with abnormal uterine bleeding or pelvic pain; some cases present with lymph node or lung metastasis. They appear yellow-tan and are ill-defined, with an infiltrative growth pattern. They show a predilection for vascular invasion, which may be grossly apparent. LGESS typically resemble proliferative-phase endometrial stroma, with a dense population of oval to fusiform nuclei and scant cytoplasm; however, variants can show smooth muscle differentiation. These tumors tend to be diffusely positive for CD10 and harbor gene fusions commonly involving JAZF1.

Familial hypercholesterolemia
Making sense of family heart disease

CardioSmart AMERICAN COLLEGE of CARDIOLOGY

Info sheet

Many people develop high cholesterol as they get older. But if you have familial hypercholesterolemia, or FH, your low-density lipoprotein (LDL) cholesterol is dangerously high early in life – often from birth. This happens because the body isn't able to get rid of the excess LDL cholesterol, also called the "bad" cholesterol.

Too much LDL cholesterol can clog arteries, which can lead to heart attacks and other heart issues.

Use this handout to learn more about FH, the two types, how they are treated, and questions to ask your health care team.

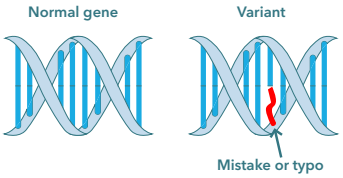
FH runs in families

FH is a genetic condition – that means it is passed down in families through the genes we inherit.

It happens when there is a change or typo (called a variant) in one of several genes that help instruct the body to recognize and clear cholesterol. You can get FH from one or both of your parents.

Without proper treatment, people with FH are much more likely to suffer a heart attack, cardiac arrest (when the heart stops suddenly) or stroke. Heart attacks and other heart issues happen at a much younger age for people with FH compared with others.

For some people, these events are the first clue that leads them to find out they have FH. For others, FH is suspected when LDL cholesterol levels aren't lowered as much as would be expected after starting treatment with lifestyle changes and medications.



Family screening

Finding out whether you or a family member has FH early on is important. Starting treatment as soon as possible can help prevent life-threatening events, such as heart attack or stroke.

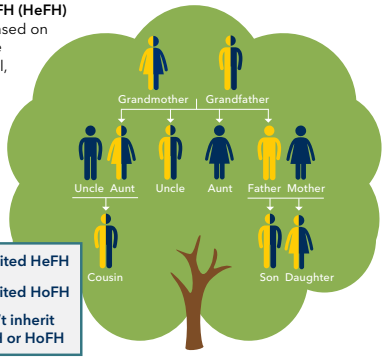
Ask about how to get family members tested for FH. Screening can save lives.

Two types of FH

There are two types of FH: **heterozygous FH (HeFH)** and **homozygous FH (HoFH)**, which are based on whether you inherited one or two FH gene variants from your birth parents. In general, if one of your parents has FH, you have a 50/50 chance of having it.

It's important to know which type of FH you have because treatments and the risk of heart problems can be different.

The type of FH you have also affects the likelihood of passing it on to a child.



How HeFH and HoFH differ

	Heterozygous FH	Homozygous FH
How common it is	• More common • Occurs in 1 in 250 adults	• Fairly rare • Occurs in 1 in 250,000 adults
What you inherit from your parents	• 1 healthy gene, 1 FH gene from a parent	• 2 FH genes – one from each parent
LDL cholesterol numbers Cholesterol levels are measured in milligrams (mg) of cholesterol per deciliter (dL) of blood.	• Higher than normal • Usually over 190 mg/dL	• Very high, often 4 times higher than normal levels • Usually over 400 mg/dL
How it affects heart health	• Heart attack, blocked arteries or stroke occur at a young age	• Heart issues and events early in life, sometimes in children

Uterine Malignant and Potentially Malignant Mesenchymal Tumours Histopathology Reporting Guide

Documentation of specimen integrity is crucial for reporting of malignant and potentially malignant uterine mesenchymal tumours as integrity affects evaluation of margins and can impact staging and prognosis of uterine sarcomas. It is important to document morcellation, a surgical technique performed in vivo after laparoscopic myomectomy or hysterectomy to reduce the size of the specimen into fragments small enough to be removed from the patient through the laparoscopic incision sites. Recurrence of uterine sarcoma has been reported when tumours are removed laparoscopically with morcellation. After this phenomenon was first documented in several series, certain protective measures were encouraged by the gynaecology community regarding use of this particular surgical technique.

Benign metastatic leiomyoma (BML) is a histologically benign disease with invasive biological behavior. Most patients are women of childbearing age with a history of uterine leiomyoma. The progress of the disease is relatively slow, the prognosis is good, and most patients can survive for a long time. The lung is the common metastatic site, and BML with metastatic lesions outside the lung is very rare. Benign metastatic leiomyoma (BML) is an extremely rare benign leiomyoma with invasive biological behavior. The disease was first proposed by Steiner, and most of the patients are women of childbearing age with a history of uterine leiomyoma surgery such as hysterectomy or myomectomy. The most common site of BML is the lung. It can also occur in the right atrium, pelvic and abdominal cavity, omentum, lymph nodes, muscle tissue, brain, bone, and in the abdominal wall skin and scars.

Up to now, the etiology and pathogenesis of BML are not clear. Among the proposed hypotheses, lymphovascular spread theory is most commonly accepted, which thinks the tumor cells can be spread along the blood or lymph vessels during the operation. Iatrogenic peritoneal seeding theory from ruptured leiomyoma in myomectomy or hysterectomy is more reasonable to explain the incidence of pelvic BML , just as the case reported by us here. It has been suggested that BML may evolve from multi-center proliferation of smooth muscle induced by hormonal stimulation, based on the positive immunohistochemical staining for ER and PR in the tumor cells. The antihormonal therapy can also favor this theory. There were some studies have presented cytogenetic mutations in BML, such as 19q, 22q, and 1p terminal deletion, 6p21 and 12q15 rearrangements, involving the HMGA2 and BMP8B. The mutation of MED12 gene on the long arm of X chromosome(Xq12.1), which is related to the regulation of RNA polymerase II transcription, may also be related to BML. Besides, coelomic metaplasia and metastasis of low-grade uterine leiomyosarcoma theories have also been suggested to explain the pathogenesis of BML.

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