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Clinical Focus on

Fibroids

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CHAPTER 1

Understanding the Epidemiology and Risk Factors of Fibroids

Narendra Malhotra, Neharika Malhotra, Jaideep Malhotra, Manpreet Sharma, Shemi Bansal

INTRODUCTION

Fibroids, also known as uterine fibroids or leiomyomas, are noncancerous growths of the uterus that often appear during childbearing years. They can vary in size, ranging from as small as a seed to as large as a grapefruit.

These growths are composed of muscle and fibrous tissue and can develop either within the uterine wall, protrude into the uterine cavity, or extend outward from the uterus. While many women with fibroids experience no symptoms, others may have symptoms, such as heavy menstrual bleeding, prolonged menstrual periods, pelvic pressure or pain, frequent urination, difficulty emptying the bladder, or constipation.

The exact cause of fibroids is not well understood, but factors such as hormonal fluctuations, genetics, and ethnicity may play a role in their development.[1] Treatment options for fibroids depend on factors such as the size and location of the fibroids, the severity of symptoms, and whether the woman wishes to conceive in the future. Treatment options may include medication, minimally invasive procedures, or surgery such as a hysterectomy.

IMPORTANCE OF UNDERSTANDING EPIDEMIOLOGY AND RISK FACTORS

Understanding the epidemiology and risk factors associated with health conditions like fibroids is crucial for several reasons:[2]

- *Prevention and early detection:* Knowledge of risk factors allows healthcare providers to identify individuals who may be at a higher risk of developing fibroids. With this information, they can implement preventive measures or recommend screenings to detect fibroids at an early stage when treatment may be more effective.
- *Tailored interventions:* Understanding the epidemiology and risk factors helps in designing tailored interventions for different population groups. For example, if certain demographic groups or lifestyle factors are associated with a higher risk of fibroids, interventions can be targeted toward those groups to promote awareness, lifestyle modifications, or early screening.
- *Resource allocation:* By understanding the prevalence of fibroids and the

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populations most affected, healthcare resources can be allocated more efficiently. This includes directing funding toward research, prevention efforts, and healthcare services in areas with higher prevalence rates or among populations with increased risk factors.

- *Health equity:* Epidemiological studies can uncover disparities in the prevalence and management of fibroids among different demographic groups. This knowledge is essential for addressing health inequities and ensuring that all individuals have access to appropriate prevention, diagnosis, and treatment options.
- *Advancing research:* Epidemiological data provides a foundation for further research into the causes, mechanisms, and optimal management of fibroids. By identifying trends and associations, researchers can delve deeper into understanding the underlying biology of fibroids and develop new therapeutic approaches.
- *Patient education and empowerment:* Knowledge of risk factors empowers individuals to take proactive steps to reduce their risk of developing fibroids. Through education and awareness campaigns, individuals can learn about lifestyle modifications, reproductive health choices, and symptom recognition, enabling them to make informed decisions about their health.

Prevalence

Global Prevalence Rates

Estimating the global prevalence rates of uterine fibroids can be challenging due to variations in reporting methods, healthcare access, and population demographics across different regions. However, fibroids are a common gynecological condition, particularly among women of reproductive age. Prevalence rates may also vary based on factors such as ethnicity, genetic predisposition, and lifestyle factors. A general overview is as follows:

- *Overall prevalence:* Uterine fibroids are estimated to affect between 20% and 80% of women by the age of 50 years. However, the exact prevalence varies widely across populations and studies.
- *Ethnic and racial disparities:* There are significant ethnic and racial disparities in the prevalence of fibroids. For example, studies have shown that Black women tend to have a higher prevalence of fibroids and may experience more severe symptoms compared to women of other racial or ethnic groups.[1]
- *Geographic variations:* Prevalence rates may also differ based on geographic regions. While fibroids are common in developed countries, they may be less frequently reported in some developing regions due to differences in healthcare access, diagnostic methods, and reporting practices.
- *Age and reproductive status:* Fibroids are more common in women of reproductive age, particularly between the ages of 30 and 50 years. The prevalence tends to decrease after menopause when estrogen levels decline.
- *Impact of risk factors:* Certain risk factors, such as nulliparity (never having given birth), early onset of menstruation, obesity, and a family history of fibroids, may increase the likelihood of developing fibroids. Regions or populations with higher prevalence rates of these risk factors may also have higher overall prevalence rates of fibroids.
- *Economic and healthcare factors:* Access to healthcare services and diagnostic tools

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can influence the detection and reporting of fibroids. In regions with limited access to healthcare, under-reporting of fibroids may occur, leading to underestimated prevalence rates.

While precise global prevalence rates may be difficult to ascertain, it is clear that uterine fibroids represent a significant public health concern worldwide, impacting the quality of life and reproductive health of millions of women. Further research and efforts to improve awareness, access to healthcare, and treatment options are essential to address the burden of fibroids on a global scale.

Variation Among Different Populations

Variation in the prevalence of uterine fibroids among different populations can be influenced by a variety of factors, including genetics, ethnicity, lifestyle, reproductive history, and access to healthcare. How these factors contribute to variations is given in the following text:

- *Ethnicity and race:* There are notable differences in the prevalence of fibroids among ethnic and racial groups. Studies have consistently shown that Black women have a higher prevalence of fibroids compared to women of other racial or ethnic backgrounds. For example, in the United States, Black women are two to three times more likely to develop fibroids than White women. Hispanic and Asian women also have intermediate prevalence rates compared to Black and White women.[1]
- *Genetic predisposition:* Genetic factors play a significant role in the development of fibroids. Certain genetic variations and susceptibility genes have been identified that may increase the risk of fibroids. These genetic factors can vary among populations and contribute to differences in fibroid prevalence.
- *Reproductive factors:* Reproductive factors, such as parity (number of pregnancies), age at first childbirth, and use of hormonal contraceptives, can influence the risk of fibroids. Women who have never given birth (nulliparous) or had their first child at a later age may have a higher risk of fibroids. Differences in reproductive patterns among populations can contribute to variations in fibroid prevalence.[2]
- *Hormonal and lifestyle factors:* Hormonal factors, such as estrogen and progesterone levels, play a key role in the growth of fibroids. Lifestyle factors such as obesity, diet, and physical activity can also influence hormone levels and contribute to fibroid development. Variations in lifestyle behaviors among populations may impact fibroid prevalence.
- *Access to healthcare and diagnostic practices:* Disparities in access to healthcare, including preventive care and diagnostic imaging, can affect the detection and reporting of fibroids. In some populations or regions with limited healthcare resources, fibroids may be underdiagnosed or untreated, leading to lower reported prevalence rates.
- *Environmental factors:* Environmental exposures, such as endocrine-disrupting chemicals (EDCs) and pollutants, have been implicated in the development of fibroids. Variations in environmental exposures among populations may contribute to differences in fibroid prevalence.

Trends Over Time

Over time, several trends regarding uterine fibroids have been observed, influenced

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by changes in healthcare practices, demographics, lifestyle factors, and awareness. Some notable trends are as follows:

- *Increased awareness and diagnosis:* Awareness of uterine fibroids has grown over time, leading to increased diagnosis and reporting of the condition. Improved imaging techniques and greater awareness among healthcare providers and patients have contributed to earlier detection and diagnosis of fibroids.
- *Changing demographics:* Changes in demographics, including aging populations and shifts in racial and ethnic composition, can influence the prevalence of fibroids. For example, as populations age, the prevalence of fibroids among postmenopausal women may decline due to decreasing estrogen levels. However, the overall burden of fibroids may still increase due to population growth and changes in reproductive patterns.
- *Advancements in treatment options:* Over the years, there have been advancements in the treatment of fibroids, including minimally invasive procedures, such as laparoscopic or robotic surgery, uterine artery embolization, and MRI-guided focused ultrasound surgery. These advancements have provided more options for women seeking treatment, potentially impacting trends in fibroid management and outcomes.
- *Healthcare disparities:* Disparities in access to healthcare and treatment remain a concern, particularly among underserved populations and minority groups. Efforts to address healthcare disparities and improve access to care may impact trends in fibroid prevalence and outcomes over time.
- *Impact of lifestyle factors:* Changes in lifestyle factors, such as obesity rates, diet, and physical activity levels, can influence hormone levels and the development of fibroids. Increasing rates of obesity, for example, may contribute to a higher prevalence of fibroids in certain populations. Increased dairy intake and risk of fibroid have also been documented.[3]
- *Research and education initiatives:* Ongoing research efforts and educational campaigns aimed at increasing awareness of fibroids, promoting preventive measures, and advancing treatment options can influence trends over time. Increased knowledge and understanding of fibroids among both healthcare providers and the general population may lead to improvements in diagnosis, management, and outcomes.
- *Globalization and urbanization:* Globalization and urbanization have led to changes in lifestyle and environmental factors that may impact fibroid prevalence. Urban environments may be associated with higher stress levels, sedentary lifestyles, and exposure to environmental pollutants, which could potentially influence fibroid development.

Incidence

Incidence Patterns

The incidence patterns of uterine fibroids, or the rate at which new cases of fibroids occur within a population over time, can vary based on several factors. Some key patterns observed in the incidence of uterine fibroids are as follows:

- *Age-specific incidence:* The incidence of fibroids tends to increase with age, peaking during the reproductive years and declining after menopause. Fibroids are most commonly diagnosed in women

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aged 30–50 years, although they can occur at any age. The age-specific incidence reflects the hormonal influences on fibroid development, as estrogen and progesterone levels fluctuate throughout a woman's reproductive life.[4]

- *Racial and ethnic disparities:* Studies have consistently shown disparities in the incidence of fibroids among different racial and ethnic groups. For example, Black women have been found to have a higher incidence of fibroids compared to White women. Hispanic and Asian women also have intermediate incidence rates. These disparities may be influenced by genetic factors, hormonal differences, and socioeconomic factors.
- *Reproductive history:* A complete reproductive history should be taken and documented as stated above reproductive factors impact incidence and outcome of fibroids. Additionally, hormonal contraceptive use, particularly combined oral contraceptives (COCs), has been associated with a reduced risk of fibroids.[5]
- *Geographic and environmental factors:* Incidence patterns of fibroids may vary geographically and be influenced by environmental factors, such as diet, lifestyle, and exposure to EDCs. Urban environments, for example, may be associated with higher rates of fibroids due to factors such as stress, obesity, and pollution.
- *Advancements in diagnostic techniques:* The incidence of fibroids may be influenced by improvements in diagnostic techniques, leading to increased detection of asymptomatic cases. The widespread use of imaging modalities, such as ultrasound, magnetic resonance imaging (MRI), and hysteroscopy, has facilitated the detection of fibroids, potentially impacting incidence rates over time.
- *Changing healthcare practices:* Changes in healthcare practices, including increased access to healthcare, routine screenings, and preventive care, may also influence the incidence of fibroids. Greater awareness among healthcare providers and patients, as well as advancements in treatment options, may lead to earlier diagnosis and management of fibroids, affecting incidence patterns.

Factors Influencing Incidence Rates

Several factors influence the incidence rates of uterine fibroids, contributing to the development of this common gynecological condition. Some key factors are as follows:

- *Hormonal factors:* Hormones, particularly estrogen and progesterone, play a central role in the development and growth of fibroids. Fibroids often grow during the reproductive years when hormone levels are high and tend to shrink after menopause when hormone levels decline. Factors that affect hormone levels, such as hormonal contraceptives, hormone replacement therapy (HRT), and hormonal fluctuations during the menstrual cycle, can influence the incidence of fibroids.
- *Genetic predisposition:* Genetic factors contribute to an individual's susceptibility to fibroids. Family history studies have shown that women with a family history of fibroids are at an increased risk of developing them. Specific genetic variations and susceptibility genes associated with fibroids have been identified, although the exact genetic mechanisms underlying fibroid development are still being elucidated.

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- *Reproductive history:* Reproductive factors, such as nulliparity (never having given birth), late age at first childbirth, and infertility, are associated with an increased risk of fibroids. Conversely, factors that reduce lifetime estrogen exposure, such as early childbirth and prolonged breastfeeding, may decrease the risk of fibroids. The number of pregnancies and hormonal changes during pregnancy can also influence fibroid incidence.
- *Race and ethnicity:* There are significant racial and ethnic disparities in the incidence of fibroids, with Black women having the highest incidence rates compared to women of other racial and ethnic groups. Hispanic and Asian women also have intermediate incidence rates, while White women have the lowest rates. The reasons for these disparities are multifactorial and likely involve a combination of genetic, hormonal, and environmental factors.
- *Obesity:* This is associated with an increased risk of fibroids, possibly due to alterations in hormone metabolism and increased estrogen levels in obese individuals. A higher body mass index (BMI) is consistently associated with a greater risk of developing fibroids, and weight loss may reduce the risk or slow the growth of fibroids in some cases.
- *Lifestyle factors:* Certain lifestyle factors, such as diet, physical activity, and stress, may influence the incidence of fibroids. Diets high in red meat, processed foods, and sugar and low in fruits, vegetables, and fiber have been associated with a higher risk of fibroids. Regular physical activity and stress reduction techniques may help lower the risk of fibroids by modulating hormone levels and reducing inflammation.
- *Environmental exposures:* Exposure to environmental factors, such as EDCs [e.g., phthalates, bisphenol A (BPA)] and pollutants, may contribute to the development of fibroids. These chemicals can mimic or interfere with hormones in the body, potentially promoting the growth of fibroids.
- *Healthcare access and screening practices:* Disparities in healthcare access and screening practices can affect the detection and diagnosis of fibroids, potentially influencing reported incidence rates. Women with limited access to healthcare may have undiagnosed fibroids or delayed diagnosis, leading to underestimation of incidence rates in certain populations.

Demographic Patterns

Age Distribution

The incidence and prevalence of uterine fibroids vary across different age groups, reflecting the influence of hormonal changes, reproductive factors, and other demographic characteristics. How age distribution typically affects the occurrence of uterine fibroids is as follows:[6]

- *Reproductive age:* Uterine fibroids are most commonly diagnosed during the reproductive years, typically between the ages of 30 and 50 years. During this period, hormone levels, particularly estrogen and progesterone, are at their highest, which may contribute to the growth and development of fibroids. As a result, fibroids are more prevalent among women of reproductive age compared to other age groups.
- *Peak incidence:* The highest incidence of uterine fibroids is typically observed in women in their 40s, although fibroids can develop at any point during the

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reproductive years. Studies have shown that the incidence of fibroids increases with age until around the age of 45–50 years and then stabilizes or declines after menopause. This age-related pattern reflects the influence of hormonal changes and reproductive factors on fibroid development.

- *Perimenopausal transition:* The perimenopausal transition, which occurs in the years leading up to menopause, is a period of hormonal fluctuation and changes in menstrual patterns. During this time, fibroids may continue to grow or cause symptoms in some women, while in others, fibroids may stabilize or shrink due to declining estrogen levels. The incidence of fibroids may vary among women in the perimenopausal age-group, with some experiencing worsening symptoms while others may have symptom relief.
- *Postmenopausal period:* After menopause, when estrogen levels decline, the incidence of fibroids generally decreases. Fibroids may shrink or become less symptomatic in postmenopausal women, although they may still be present. The prevalence of fibroids among postmenopausal women is lower compared to women of reproductive age, reflecting the hormonal changes associated with menopause.
- *Age-related symptoms:* While fibroids may develop at any age during the reproductive years, they are more likely to cause symptoms such as heavy menstrual bleeding, pelvic pain, and pressure-related symptoms (e.g., urinary frequency, constipation) in older women. This is because fibroids tend to grow larger over time and may become symptomatic as women age.

Gender Distribution

Uterine fibroids primarily affect individuals assigned female at birth (AFAB) as they develop in the uterus. Therefore, the gender distribution of uterine fibroids is overwhelmingly skewed toward individuals who have a uterus, typically women. While fibroids can occur rarely in individuals with certain intersex variations or transgender men who have retained their uterus, the vast majority of cases occur in cisgender women.

As fibroids develop within the uterine tissue, their presence and potential impact on health are limited to individuals with a uterus. Therefore, the gender distribution of uterine fibroids is inherently tied to biological sex and the presence of female reproductive anatomy. However, it is important to recognize that gender identity and expression are distinct from biological sex, and individuals of diverse gender identities may be affected by fibroids if they have a uterus.

In summary, uterine fibroids predominantly affect individuals AFAB, reflecting their development within the uterus. While gender distribution aligns with biological sex in this context, it is crucial to acknowledge the diversity of gender identities and experiences among those affected by fibroids.

Ethnic and Racial Disparities

Ethnic and racial disparities in uterine fibroids' prevalence and outcomes are well documented, with significant differences observed among various racial and ethnic groups. An overview of these disparities is as follows:

- *Higher prevalence in Black women:* Black women have the highest reported prevalence of uterine fibroids compared to other racial and ethnic groups. Studies

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consistently show that Black women are two to three times more likely to develop fibroids than White women. Fibroids in Black women also tend to occur at younger ages, grow larger, and cause more severe symptoms.

- *Intermediate prevalence in Hispanic and Asian women:* Hispanic and Asian women have intermediate prevalence rates of uterine fibroids compared to Black and White women. While the prevalence of fibroids in these groups is lower than that of Black women, it is higher than that of White women. Studies have shown variations in fibroid prevalence among different Hispanic subgroups.
- *Lower prevalence in White women:* White women have the lowest reported prevalence of uterine fibroids compared to other racial and ethnic groups. However, fibroids still affect a significant proportion of White women, particularly as they age.
- *Impact on health disparities:* Fibroids contribute to health disparities, affecting various aspects of a woman's health and well-being. Black women with fibroids are more likely to experience symptoms, such as heavy menstrual bleeding, pelvic pain, and reproductive health issues compared to White women. Fibroids in Black women also tend to be diagnosed at more advanced stages and may require more invasive treatments.
- *Socioeconomic and healthcare access factors:* Socioeconomic factors, including income, education, and access to healthcare, contribute to racial and ethnic disparities in fibroid prevalence and outcomes. Black women are more likely to experience socioeconomic disadvantages and barriers to healthcare access, which can impact the timely diagnosis and management of fibroids.
- *Genetic and biological factors:* While genetic factors likely play a role in racial and ethnic disparities in fibroid prevalence, the exact mechanisms are not fully understood. Studies have identified genetic variations associated with fibroids that may contribute to differences in susceptibility among racial and ethnic groups. Additionally, biological differences in hormone metabolism and immune function may influence fibroid development and growth.

RISK FACTORS FOR FIBROIDS

Genetic Factors

Familial Predisposition

Familial predisposition to uterine fibroids suggests a genetic component in the development of this condition. How genetic factors contribute to familial predisposition is as follows:

- *Family history:* Women with a family history of uterine fibroids are at an increased risk of developing them themselves. Having a first-degree relative (such as a mother or sister) with fibroids significantly increases a woman's risk of also developing fibroids. This suggests that genetic factors passed down through families play a role in fibroid development.
- *Genetic studies:* Several genetic studies have identified variations in specific genes associated with an increased risk of uterine fibroids. While the exact genetic mechanisms underlying fibroid development are still being elucidated, researchers have identified candidate genes involved in processes such as cell proliferation, hormone receptor signaling, extracellular matrix regulation, and inflammation. Variations in these

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genes may contribute to an individual's susceptibility to fibroids.

- *Polygenic inheritance:* Uterine fibroids are considered a complex, polygenic disorder, meaning that multiple genetic variations across different genes likely contribute to an individual's risk of developing fibroids. These genetic variations may interact with environmental factors and hormonal influences to influence fibroid development.
- *Ethnic and racial differences*: Genetic studies have also revealed ethnic and racial differences in the genetic risk factors associated with fibroids. Certain genetic variations may be more prevalent or have stronger effects in certain racial or ethnic groups, contributing to the observed disparities in fibroid prevalence among different populations.
- *Gene–environment interactions:* While genetic factors play a significant role in fibroid development, they do not fully explain the variations in fibroid prevalence observed among different individuals and populations. Gene–environment interactions, such as exposure to EDCs, diet, lifestyle factors, and reproductive history, also influence fibroid risk. These environmental factors may interact with genetic predispositions to modulate an individual's susceptibility to fibroids.

Candidate Genes Associated with Fibroids

Several candidate genes have been identified as potentially associated with uterine fibroids through genetic studies. These genes are involved in various biological processes, including cell proliferation, hormone receptor signaling, extracellular matrix regulation, and inflammation. While the exact role of each gene in fibroid development is still being elucidated, some examples of candidate genes associated with fibroids are as follows:

- *COL4A5 (collagen type IV alpha 5): COL4A5* encodes a component of type IV collagen, a major structural protein in the extracellular matrix. Variations in *COL4A5* have been associated with an increased risk of fibroids, possibly due to alterations in extracellular matrix regulation and tissue remodeling processes.
- *MED12 (mediator complex subunit 12): MED12* is a component of the mediator complex, which regulates gene expression by facilitating interactions between transcription factors and RNA polymerase II. Mutations in *MED12* have been found in a subset of fibroids, particularly those with a specific histological subtype called "uterine leiomyoma with *MED12* mutation." *MED12* mutations may contribute to abnormal cell proliferation and growth in fibroids.
- *HMGA2 (high mobility group AT-Hook 2): HMGA2* is involved in chromatin remodeling and transcriptional regulation. Variations in *HMGA2* have been associated with an increased risk of fibroids, possibly through effects on cell proliferation and differentiation.
- *FSHR (follicle-stimulating hormone receptor): FSHR* encodes the follicle-stimulating hormone receptor, which is involved in ovarian function and hormone signaling. Variations in FSHR have been implicated in fibroid development, potentially through effects on hormone receptor signaling and ovarian function.
- *ESR1 (estrogen receptor 1)* and *ESR2 (estrogen receptor 2):* Estrogen receptors play a critical role in mediating the effects of estrogen on target tissues, including the uterus. Variations in *ESR1* and *ESR2* have been associated with an increased risk of fibroids, suggesting that dysregulation

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of estrogen signaling pathways may contribute to fibroid development.

- *CYP19A1 (cytochrome P450 family 19 subfamily A member 1): CYP19A1* encodes aromatase, an enzyme involved in estrogen biosynthesis. Variations in *CYP19A1* have been linked to fibroid risk, potentially through effects on estrogen production and metabolism.
- *COL1A1 (collagen type I alpha 1)* and *COL3A1 (collagen type III alpha 1):* Collagen genes, including *COL1A1* and *COL3A1*, are involved in extracellular matrix remodeling and tissue structure. Variations in these genes have been associated with fibroid risk, possibly through effects on tissue integrity and remodeling processes.

These are just a few examples of candidate genes associated with uterine fibroids. Research into the genetic basis of fibroids is ongoing, and additional genes and genetic pathways may be implicated in fibroid development as our understanding of the condition continues to evolve.

Genetic Susceptibility Studies

Genetic susceptibility studies aim to identify genetic variations or mutations associated with an increased risk of developing uterine fibroids. These studies typically involve analyzing the DNA of individuals with and without fibroids to identify genetic differences that may contribute to fibroid risk. An overview of genetic susceptibility studies conducted in the field of uterine fibroids is as follows:

- *Genome-wide association studies (GWAS):* GWAS are large-scale studies that analyze hundreds of thousands to millions of genetic variations across the entire genome to identify common genetic variants associated with fibroid risk. GWAS have identified several genetic loci associated with fibroids, including variations in genes involved in cell proliferation, hormone signaling, and extracellular matrix regulation.
- *Candidate gene studies:* Candidate gene studies focus on specific genes or genetic pathways implicated in fibroid development based on biological knowledge or previous research findings. These studies typically involve comparing the frequency of genetic variations in candidate genes between individuals with and without fibroids to identify potential associations with fibroid risk.
- *Exome sequencing and whole-genome sequencing:* Exome sequencing and whole-genome sequencing are comprehensive sequencing techniques that analyze the protein-coding regions of the genome (exome) or the entire genome (whole genome) to identify rare genetic variants or mutations associated with fibroid risk. These studies may uncover rare genetic mutations in genes involved in fibroid pathogenesis.
- *Family-based studies:* Family-based studies examine the inheritance patterns of fibroids within families to identify genetic factors contributing to familial predisposition. These studies may involve analyzing genetic data from multiple affected and unaffected family members to identify genetic variations segregating with fibroid risk within families.
- *Functional studies:* These aim to elucidate the biological mechanisms underlying genetic associations with fibroids. These studies may involve laboratory experiments to assess the functional effects of genetic variations on cellular processes relevant to fibroid development, such as cell proliferation, hormone signaling, and extracellular matrix remodeling.

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- *Meta-analysis and replication studies:* Meta-analysis and replication studies combine data from multiple genetic susceptibility studies to validate and replicate findings across different populations. These studies help confirm the association of specific genetic variants with fibroid risk and identify genetic loci with robust and consistent effects across diverse populations.

Hormonal Factors

Estrogen and progesterone play crucial roles in the development and growth of uterine fibroids. How these hormones influence fibroid growth as well as the relationship between hormonal therapies and fibroid risk is as follows:

- *Role of estrogen and progesterone:*
  - *Estrogen:* It stimulates the growth and proliferation of uterine cells, including those in fibroids. Estrogen receptors are present in fibroid cells, and estrogen binding to these receptors can promote cell division and fibroid growth.
  - *Progesterone:* Progesterone, another female sex hormone, also plays a role in fibroid growth. Progesterone receptors are expressed in fibroid tissues, and progesterone signaling can contribute to fibroid development by promoting cell proliferation and inhibiting cell death (apoptosis).
- *Hormonal fluctuations and fibroid growth:* Hormonal fluctuations during the menstrual cycle, pregnancy, and menopause can influence fibroid growth. Fibroids tend to grow in response to increased levels of estrogen and progesterone during the reproductive years.

  Fibroids may increase in size during pregnancy due to elevated hormone levels, but they may shrink after menopause when hormone levels decline. However, fibroids may continue to cause symptoms in some women even after menopause.
- *Hormonal therapies and fibroid risk:*
  - *Hormonal contraceptives:* COCs containing estrogen and progestin have been associated with a reduced risk of fibroids. These hormonal contraceptives suppress ovulation and reduce the production of endogenous estrogen and progesterone, which may help prevent fibroid growth.
  - Hormone replacement therapy (HRT) can have significant effects on uterine fibroids, which are non-cancerous growths in the uterus. Using a combination of estrogen and progestogen can sometimes help mitigate the growth-promoting effects of estrogen on fibroids.
  - *Selective estrogen receptor modulators (SERMs):* SERMs are a class of medications that modulate estrogen receptor activity. While some SERMs have been investigated for their potential use in treating fibroids, their efficacy and safety for this indication are still under evaluation.

In summary, estrogen and progesterone play pivotal roles in the development and growth of uterine fibroids. Hormonal fluctuations during the menstrual cycle, pregnancy, and menopause can influence fibroid growth. Hormonal therapies, such as hormonal contraceptives, HRT, and SERMs, may impact fibroid risk and growth by modulating hormone levels and receptor activity. However, the effects of these therapies on fibroids can vary among individuals, and careful consideration of the risks and benefits is essential when prescribing hormonal treatments for women with fibroids.

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Reproductive Factors

Reproductive factors such as parity (number of pregnancies), age at menarche (onset of menstruation), age at menopause, and fertility treatments can influence the risk of developing uterine fibroids and their clinical course. How these factors relate to fibroids is as follows:

- *Parity and pregnancy:*
  - *Parity:* Studies have shown that parity, or the number of pregnancies a woman has had, is inversely associated with the risk of developing fibroids. Women who have had more pregnancies, especially full-term pregnancies, tend to have a lower risk of fibroids compared to nulliparous women. The protective effect of parity may be attributed to hormonal changes and alterations in uterine structure that occur during pregnancy.
  - *Pregnancy:* This can have varying effects on fibroids. In some cases, fibroids may increase in size during pregnancy due to hormonal changes and increased blood flow to the uterus. Fibroids may also cause complications during pregnancy, such as miscarriage, preterm birth, or breech presentation. However, in other cases, fibroids may remain stable or even decrease in size after pregnancy, particularly following childbirth and breastfeeding.
- *Age at menarche and menopause:*
  - *Age at menarche:* Early age at menarche (onset of menstruation) has been associated with an increased risk of fibroids. Early menarche is thought to reflect longer exposure to estrogen over a woman's reproductive lifespan, which may contribute to the development of fibroids.
  - *Age at menopause:* The risk of fibroids tends to decrease after menopause when estrogen levels decline. Women who reach menopause at an older age may have a longer duration of estrogen exposure and may be at a slightly higher risk of developing fibroids compared to women who reach menopause at a younger age. However, fibroids can still cause symptoms in postmenopausal women and may require management.
- *Impact of fertility treatments:*
  - *Assisted reproductive technologies (ART):* Fertility treatments such as in vitro fertilization (IVF) and ovulation induction may influence the risk of fibroids or exacerbate existing fibroids. While the evidence is mixed, some studies suggest that fertility treatments, particularly gonadotropin stimulation used in IVF, may increase the risk of fibroids or lead to their growth. However, other factors, such as underlying infertility and hormonal factors associated with fertility treatments, may also contribute to fibroid risk.

Reproductive factors play a significant role in the development and clinical course of uterine fibroids. Understanding how parity, pregnancy, age at menarche and menopause, and fertility treatments influence fibroid risk and growth can help inform preventive strategies, management approaches, and counseling for women affected by fibroids.

Lifestyle and Environmental Factors

Lifestyle and environmental factors, including diet and nutrition, obesity and physical activity, and environmental exposures, such as endocrine disruptors, can influence the

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