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Review on Genetic Insights into Abnormal Uterine Bleeding and Leiomyoma Development

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Abstract

Background: Abnormal uterine bleeding is a prevalent issue among women of reproductive age, primarily stemming from hormonal imbalances. It is characterized by flow volume, duration, and frequency variations outside of pregnancy. Occurring frequently during perimenopause and menstruation, abnormal uterine bleeding is associated with several benign tumors within the female reproductive system, including leiomyomas and endometriomas. Leiomyomas, composed of smooth muscle cells originating from the uterine wall, are influenced by genetic and environmental factors.

Objective: This review explored the complications linked with abnormal uterine bleeding and identified crucial genes involved in developing leiomyomas.

Methods: The International Federation of Gynecology and Obstetrics (FIGO) has established a classification and terminology system for the causes of abnormal uterine bleeding (AUB). This standardization aims to enhance research efficiency, facilitate diagnosis, and improve the management of clinical cases. Articles in English were searched in the PubMed, Embase, Scopus, ScienceDirect, and MEDLINE databases using the terms abnormal uterine bleeding, leiomyomas, and genes. The selection included systematic reviews, meta-analyses, randomized controlled trials, and reviews. Data were searched from 2016 to May 2023.

Results: The research reveals that uterine leiomyomas affect a substantial percentage of females by age 50, underlining the need for a comprehensive understanding of their genetic underpinnings. The knowledge gained from this study contributes to the potential development of more targeted and efficient treatments for leiomyomas, offering hope for improved outcomes in managing these common gynecological disorders.

Conclusion

The findings underscore the complexity of abnormal uterine bleeding, emphasizing its connection with leiomyomas and the genetic factors influencing their development. By employing the FIGO classification system, researchers and clinicians can standardize their approach to diagnosis and management, paving the way for more efficient future research and diagnostics. Identifying critical genes associated with leiomyomas provides insights into the underlying mechanisms, particularly the involvement of hormones and genetic pathways.

Keywords: Uterine Bleeding, hormonal imbalance, menopause, estrogen, progesterone, non-malignant, leiomyoma

Introduction

Abnormal uterine bleeding is menometrorrhagia, bleeding between monthly cycles, persistent bleeding, or heavy menstruation. Fibroids, polyps, and hormonal shifts are all possible reasons. Women witness menstrual cycles from 11-12 to nearly 50 years; during these 40 years, a woman is likely to have a few episodes of bleeding that are not part of her normal cycle (Cheong et al.

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2017). An abnormal menstrual cycle is considered an AUB if it is characterized by irregularity, frequency, duration, and volume of flow that does not occur during pregnancy. An estimated one-third of women will experience abnormal uterine bleeding at some time; these abnormalities are most common during perimenopause and the menstrual cycle. Regular menstrual cycles last between 2 and 7 days, with a cycle period of 24 to 38 days and blood loss of 5 to 80 milliliters. An irregular uterine bleeding pattern occurs whenever there is a fluctuation in these four criteria, rather than using archaic terms such as oligomenorrhea, menorrhagia, or dysfunctional uterine bleeding to describe abnormal uterine bleeding.

A revised nomenclature was published in 2007, 2011, and 2018 by the International Federation of Obstetrics and Gynecology (FIGO). According to the FIGO systems, the most common aetiologies of abnormal uterine bleeding are alphabetized. These assertions can support chronic, nongestational AUB. The concept of irregular bleeding was added to intermenstrual bleeding in 2018, and hemorrhaging that falls outside the 75th percentile was defined as intermenstrual bleeding (Munro et al. 2018).

AUB is one of the most common conditions encountered in routine obstetrics and gynecology practice globally, affecting approximately 10%–30% of women of reproductive age over 35 years old (Sun et al., 2018). The percentage prevalence of AUB in females of various ages is classified as menarche (12.7%), reproductive age (82.9%), and postmenopausal (9.21%) in India (Faruqui et al. 2019). The prevalence of AUB in Brazil is 31.4% [4], India is 17.9% (Choudhury et al. 2020), and China is 57.7% (Sun et al. 2018).

Special attention must be given to abnormal uterine bleeding (AUB). The prevalence ranged from 5% to 65% among general population of Ethiopian women of reproductive age (Gerema et al. 2022), and AUB is most common between the ages of 20 and 34; however, the prevalence rate steadily dropped between the ages of 45 and 49, which may be connected to the fact that most women go through menopause around this time, along with a decline in ovarian function (sun et al. 2018) risk factors of abnormal uterine bleeding includes hemostatic disorders, genital tract pathology, infections, systemic diseases, endocrine disruption, obesity, and stress (Gerema et al. 2022). Among women of reproductive age, 14-25% suffer from AUB or heavy menstrual bleeding (HMB), which can impact their physical, social, emotional, and material well-being (Fraser et al., 2009; Shapley et al., 2004).

The number of women seeking treatment for AUB in the United Kingdom is approximately 800,000 annually. Significant economic and healthcare expenditures are associated with the incident and the immediate consequences for the woman and her family. The cost of lost work and home maintenance for every patient is more than $2,000 per year, according to a study conducted in the United States (Frick et al., 2009).

Identifying AUB requires a basic understanding of the normal menstrual cycle. Menstruation is controlled by the hypothalamic-pituitary-ovarian (HPO) axis, which secretes follicle-stimulating hormone (FSH) during the follicular phase of the menstrual cycle (Goldstein et al., 2017). Due to increased estrogen production, the granulosa cells produce more estrogen, and the endometrial lining thickens. Further, it increases LH levels and negatively influences FSH levels. It is expected that the surge in LH will result in ovulation. After ovulation, the corpus luteum secretes progesterone, which results in the secretory endometrium. During pregnancy, the corpus luteum and ovum degenerate if the ovum is not fertilized. This results in a decrease in estrogen and progesterone production. Women with anovulatory cycles are consequently subject to estrogenic endometrial stimulation, associated with irregular, excessively heavy bleeding that is longer than the required seven days (Jewson et al., 2020). During menstruation, the endometrium sheds due to the absence of progesterone. ESR1 has been identified as a tumour suppressor protein whose expression is adversely correlated with cancer development and stage.

An excess of estrogen or a deficiency of progesterone may cause heavy bleeding in many women. The presence of fibroids or polyps in the uterus may also result in bleeding.
There is a wide variety of monthly abnormalities (figure 1) among patients with polymenorrhagia (29%), menometrorrhagia (8%), menorrhagia (3%), oligomenorrhea (17%), hypomenorrhea (1%), and menorrhagia (3%) (Thakur et al., 2020). According to the FIGO classification, Leiomyomas are benign tumors forming in the uterus's smooth muscle and are common causes of irregular uterine bleeding. Leiomyomas of the uterus are the most prevalent benign tumors in women of reproductive age. Although they may appear asymptomatic, they can also create significant clinical symptoms (De La et al. 2017; Stewart et al., 2016). A fibroid is a lump of extracellular matrix containing collagen, fibronectin, and proteoglycan originating from the smooth muscle of the myometrium, which includes these components (Khan et al., 2014; Stewart et al. 2017). The frequency of fibroids varies according to study populations and diagnostic procedures. Approximately 25% of women of reproductive age develop clinically evident fibroids, which may result in unpleasant symptoms. A prevalence of 24% is reported in urban areas in India, whereas 37.65% is reported in rural areas (Munusamy et al., 2017).

Methods

In conducting our literature review, we comprehensively searched multiple electronic databases, namely PubMed, MEDLINE, Scopus, EMBASE, and ScienceDirect, spanning from January 2016 to May 2023. We employed the search terms "uterine leiomyomas," "abnormal uterine bleeding," "genes," and "pathophysiology." Papers were required to be in English without geographic restrictions. Additionally, we reviewed the reference lists of identified articles to identify relevant studies not captured in our initial searches. Three authors (KJG, IBK, and RV) independently assessed the search results and study eligibility. Inclusion criteria encompassed randomized clinical trials, retrospective studies, literature reviews, case reports, and series involving patients with uterine leiomyomas. Out of 219 studies reviewed, 104 met the inclusion criteria for our research. Any discrepancies were resolved through discussion to achieve consensus.

Major Complications associated with abnormal uterine bleeding

Various adverse effects may be related to AUB, and the treatment for these side effects will depend on the specific cause and intensity of the bleeding. AUB has severe impacts, including anaemia, endometrial cancer, and infertility.

Anemia

The World Health Organization (WHO) classifies anaemia as a public health issue in which the quantity of red blood cells or haemoglobin concentration is below the physiological range (Bursac et al., 2022). Gynecologic causes of Iron deficiency symptoms include menorrhagia and hypermenorrhea, iron deficiency anemia brought by irregular uterine bleeding can be dealt with ferric carboxymaltose (FCM) (Hagras et al. 2022). AUB patients develop iron deficiency anaemia (IDA) as a response to recent or ongoing blood loss; anaemia is one of the most typical diseases in India among every age group; women who lose more than 80ml per menstrual cycle are prone to iron deficiency anaemia which affects their regular activity. Prolonged bleeding can reduce iron stores, which results in anaemia and can cause chronic illness, fatigue, and depression. Menstrual disorders account for 5% - 10% of women with IDA (Mishra et al. 2018).

Iron deficiency (ID) is the most frequent micronutrient deficiency worldwide, affecting more than 20% of women during their reproductive years (Percy et al. 2017). The most common adverse effect of irregular uterine bleeding is anaemia, which can occur in women with abnormal uterine bleeding when it is severe or prolonged. Research indicates that anaemia may harm women's health, including fatigue, weakness, cognitive impairment, reduced productivity at

work, and a decreased quality of life. The authors also discuss how anaemia may exacerbate diabetes, chronic kidney disease, and cardiovascular disease. Anaemia should be screened in women with irregular uterine bleeding by their healthcare providers, and iron supplements, transfusions, or other necessary therapies should be administered as required. To minimize complications and improve women's overall health, the authors emphasize the importance of treating the underlying cause of bleeding (Agrawal et al. 2020).

Endometrial cancer

Endometrial cancer is a type of cancer in which tumor cells grow on the lining of the uterus (endometrium) and is also known as uterine cancer. Most women experience early symptoms of endometrial cancer; abnormal vaginal bleeding is the most prevalent sign of endometrial cancer. Around 90% of EC occurrences are preceded by premenopausal or perimenopausal uterine bleeding or postmenopausal bleeding (Clarke et al. 2020); the two most familiar causes of bleeding disturbance include primary endometrial abnormalities and cysts (Brennan et al. 2018); endometrial thickness of 8 mm or less is related to a lower risk of malignant diseases in premenopausal uterine hemorrhage (Getpook et al. 2006).

Cancer of the endometrium is a common adverse effect of AUB. Postmenopausal bleeding and heavy, prolonged, and irregular periods are all associated with endometrial cancer. Irregular uterine bleeding may be a sign of endometrial cancer, but not all cases are caused by it. Fibroids, uterine polyps, hormonal imbalances, and infections can cause irregular uterine bleeding. Detecting and treating endometrial cancer early can improve outcomes (Sung et al. 2022). According to a study published in 2018, irregular bleeding is one of the most common symptoms of endometrial cancer. The results of these studies suggest that detecting and treating AUB as soon as possible may result in a better outcome due to AUB's risk of recurrence and its poor prognosis due to early detection and treatment (Suh et al. 2018).

Infertility

Non-ovulating women may experience prolonged estrogen exposure without adequate progesterone levels to cause the endometrium to shred completely. Eventually, this could lead to irregular bleeding or significant bleeding. Infertility patients are more likely to develop uterine fibroids, the most common tumors in women. According to the study, fibroids may be responsible for 2-3% of infertility cases. Clinical manifestations include abnormal bleeding, pelvic pain, infertility, pelvic masses, and obstetric complications (Donnez et al. 2016 & Freytag et al. 2021).

Irregular uterine bleeding may be associated with infertility. In general, abnormal uterine bleeding is any bleeding that does not occur during a regular menstrual cycle. Various conditions, including polycystic ovarian syndrome, endometriosis, fibroids, adenomyosis, and thyroid disorders, can cause abnormal uterine bleeding. There may be a relationship between infertility and these concerns and other factors such as age, weight, and lifestyle. The same underlying condition can cause irregular uterine bleeding and infertility (Matthews et al. 2015)

AUB is not usually associated with fertility problems in women. Even though no study has specifically addressed AUB rates in the infertility population, to our knowledge, intracavitary abnormalities are present in approximately 16% of premenopausal women with infertility, and ovulatory dysfunction is present in approximately 20% to 40% of these women (Tur-Kaspa et al. 2006; Practice. 2015). A result of structural causes of AUB, such as polyps or submucosal fibroids, as well as possible systemic causes, such as anovulation and endometrial changes that affect gene expression, growth factors, and cellular immunity, may cause subfertility or infertility among women of reproductive age.

It remains unclear how endometrial disorders and structural abnormalities may affect fertility. This is despite widespread recognition of the impact of systemic causes of AUB, such as ovulatory dysfunction. AUB women's reproductive outcomes will need to be investigated in the

context of structural abnormalities and their treatment. By understanding how hormonal and structural abnormalities affect the uterine environment, we can better understand the relationship between abnormal uterine bleeding and infertility (Sacha et al. 2017).

FIGO Classification of abnormal uterine bleeding

AUB diagnostic and therapy keywords were integrated into the International Federation of Gynecology and Obstetrics' unique category system (FIGO) 2011 (Kahveci et al. 2021). The FIGO has developed a classification system based on the underlying causes of abnormal uterine bleeding. According to the FIGO classification system, AUB may be classified into three categories: structural, nonstructural, and ad hoc. An acronym PALM may be used to refer to a structural cause, while COEIN may be used to refer to a nonstructural cause.

Structural causes – PALM

Women with structural abnormalities may have several underlying causes and may, for various reasons, be asymptomatic. The PALM-COEIN classification system acknowledges that several causes can contribute to these structural abnormalities. These changes cause structural variations in the uterus. Endometrial polyps and abnormal uterine bleeding is known for the epithelial growth comprising various components like vascular, fibromuscular, glandular, and connective tissues, primarily asymptomatic in women (Munro et al. 2018) or the most common symptom is abnormal uterine bleeding (Tanos et al. 2017). These groupings correspond to possible underlying causes that may contribute to AUB. Patients may benefit from the PALM-COEIN classification to diagnose and treat their condition. Figure 3 illustrates the anatomical factors contributing to abnormal uterine bleeding.

Adenomyosis (AUB-A)

It is defined as an abnormal growth of endometrial tissue within the smooth muscles of the uterus (Diffuse or focal). The primary indications are dysmenorrhea, heavy menstrual bleeding, pelvic pain, and reduced fertility (Bourdon et al. 2021). They are associated with a 28% reduced clinical pregnancy rate and a double chance of miscarriage in women having IVF with autologous oocytes (Harmsen et al. 2019). Other gynecological conditions, including uterine fibroids and endometriosis, usually occur with adenomyosis (Vannuccini et al. 2019).

Magnetic resonance imaging (MRI) and transvaginal ultrasound (TVUS) are commonly used for diagnosis, and the presence of lesions is usually verified histologically when a surgical specimen is available (Chapron et al. 2020). There is no 'adenomyosis medicine,' but many off-label pharmaceuticals have been utilized over the years (Vannuccini et al. 2019). The prognosis for adenomyosis is usually favorable with the correct treatment, and in most cases, women can manage their symptoms and lead a normal, healthy lifestyle after being diagnosed. However, if you suffer from severe cramps, heavy or prolonged menstruation, or pain during sex, you should seek the advice of a physician.

Leiomyoma (AUB-L)

Uterine leiomyomas are benign uterine tumors that can be submucous, subserous, or intramural and induce abnormal uterine bleeding and (AUB-L) and bulk symptoms caused by fibroid size and the force they create on nearby organs (Wright et al. 2022). Leiomyoma is a benign soft tissue that develops from smooth muscle cells (Pulgar et al. 2021). Heavy menstrual flow and pain are the two most typical symptoms of uterine leiomyoma, leading to a hysterectomy or other medical or surgical intervention. Up to 80% of women by age 50 have been reported to have the most prevalent gynecological and pelvic tumor uterine leiomyomas (Bajaj et al. 2022).

A study published in 2020 examined the therapeutic benefits of different approaches to treating AUB-L. Patients with abnormal uterine bleeding typically undergo hysterectomy or

myomectomy to reduce bleeding and improve quality of life. The study indicated that hormone therapy and non-hormonal medical treatment may prove beneficial in certain situations, particularly for women who wish to preserve their fertility or not undergo surgery (Wu et al., 2020).

Malignancy and hyperplasia (AUB-M)

The abnormal growth of endometrial glands with an increase in the gland-to-stroma ratio compared to proliferative endometrium, along with the detection of atypical cells, is known as endometrial hyperplasia; this can cause endometrial malignancy if left untreated (Singh et al. 2022). Endometrial hyperplasia often presents as abnormal uterine bleeding, including intermenstrual bleeding, postmenopausal bleeding, and bleeding during hormone replacement therapy. The rate of endometrial hyperplasia is believed to be three times the number of instances of endometrial cancer. An early diagnosis of endometrial hyperplasia can prevent the progression of the disease to endometrial cancer (Siegal et al. 2018). The therapeutic efficacy of AUB-M depends on a variety of factors, and treatments range from conservative to aggressive. The use of progestin therapy may be a viable option for some women undergoing treatment for atypical hyperplasia and early-stage endometrial cancer. However, hysterectomy is often used to treat these conditions.

Non-structural classification-COEIN

Abnormal uterine bleeding (AUB) is classified based on its underlying causes according to the FIGO, also known as the COEIN classification. Figure 4 illustrates the possibility of abnormal uterine bleeding by non-structural causes (COEIN). It is an inconvenient procedure that causes bleeding, ovulatory dysfunction, endometritis, and iatrogenic disorders of the uterus, none of which affect the uterine structure.

Coagulopathy (AUB-C)

Systemic ataxias of hemostasis lead to heavy menstrual bleeding, for example, von Willebrand disease and hemophilia (Bacon et al. 2017). This condition affects the clotting factors, resulting in more or unstoppable bleeding during surgery, injury, and menstruation. Coagulation factor deficiencies can be caused rapidly if a considerable volume of blood is lost during serious surgery or trauma that would prompt fluid restoration treatment and an array of blood component treatments leading to haemodilution (Hofer et al. 2021). AUB-C's effectiveness as a treatment agent depends on the underlying cause of coagulopathy. The treatment of coagulopathy can include hormone therapy, tranexamic acid, desmopressin, or platelet transfusions, depending on the underlying cause. A study in 2018 assessed the effectiveness of various AUB-C therapeutic techniques. The study concluded that a personalized approach is essential for AUB-C to achieve maximum results, and the specific underlying cause of coagulopathy determines the appropriate treatment (James et al. 2011).

Ovulatory (AUB-O)

Ovulatory dysfunction is unusual, irregular (with 9 menstrual cycles per year), or absent ovulation or egg release (Jones et al. 2022). Abnormal uterine bleeding due to ovulatory dysfunction generates irregular or often heavy menstruation. The most prevalent cause of AUB throughout adolescence is anovulation. Growing menarche age is associated with prolonged ovulatory dysfunction Deligeoroglou et al. 2018). Obesity and polycystic ovarian syndrome (PCOS) are two conditions that might induce irregular ovulation (Anitha et al. 2020). Imaging and histological examinations can figure out structural reasons. AUB-O can be treated using various effective treatment options, such as hormone therapy, NSAIDs, tranexamic acid, and surgical

procedures, depending on the underlying cause of the bleeding, the patient's preferences, and the patient's treatment goals.

Endometrial (AUB-E)

The condition when the endometrium (womb lining) does not function well since it sheds and heals during menstruation is referred to as endometrial dysfunction, which further leads to symptoms like heavy and prolonged menstrual bleeding, which impacts almost one-third of women.

However, variations in cycle length and intermenstrual bleeding may also occur (Brennan et al. 2018). No particular medicines are currently available to address endometrial dysfunction (Whitaker et al. 2016). The treatment of AUB-E caused by endometrial causes depends on the underlying cause and the severity of the symptoms. Treatment goals include reducing bleeding, preventing complications, and improving patient quality of life. AUB-E is treated with hormonal therapy, including oral contraceptives, progestins, or gonadotropin-releasing hormone agonists, to regulate the menstrual cycle and reduce bleeding.

Iatrogenic (AUB-I)

Abnormal uterine bleeding brought on by treatments, devices, or medications that affect the endometrium, such as the Copper intrauterine device, which influences ovulation or interferes with clotting mechanisms, steroids, hypothalamic depressants, anticoagulants, digitalis, phenytoin, and intrauterine contraceptive devices is iatrogenic causes of AUB (Motta et al. 2017). Unscheduled endometrial bleeding associated with the use of hormonal contraceptives is one of the symptoms. To rule out different causes of bleeding, medical history and gynecological examination (including transvaginal ultrasound) should be performed (Maas et al. 2015). The effectiveness of AUB-I treatment depends on the cause of the disease, the extent of bleeding, and the response of each patient to the medicine. Therefore, it is imperative to consult with a healthcare professional to determine the best course of treatment for AUB-I.

Not otherwise classified (AUB-N)

This covers situations where pregnancy does not bring on abnormal uterine bleeding, structural pelvic changes, chronic illness, hormone imbalance, hormonal imbalance, or contraception (Grzechocinska et al. 2017). Myometrial hypertrophy, arteriovenous malformations, and uterine isthmocele caused by the uterine scar from a prior cesarean section are a few possible conditions; this category covers all other causes of problematic periods, including rare causes or conditions where bleeding may not be the main symptom**.** AUB-N may have a poor prognosis when caused by benign conditions, such as fibroids, polyps, or hormonal imbalances. It may typically be treated effectively with medication, hormone therapy, or minimally invasive procedures such as hysteroscopy or endometrial ablation (American College of Obstetricians and Gynecologists. 2018). In the case of endometrial or cervical cancer, the prognosis may depend on the cancer stage and the patient's response to treatment. Several types of cancer might have a better prognosis if detected early and treated.

An environmental factor can cause abnormal uterine bleeding.

AUB-N is associated with exposure to toxic chemicals, such as polychlorinated biphenyls (PCBs), dioxins, and phthalates, that cause the disease (Havelock et al. 2019). According to some reports, there is also evidence that exposure to air pollution increases the risk of AUB-N development. There has been evidence that chronic stress affects the menstrual cycle and increases the likelihood of developing AUB-N (Hu et al. 2020). People living sedentary lifestyles are likelier to develop AUB-N infections (Kaya et al. 2012) than those who lead active lifestyles. Research indicates that AUB-N risk may be related to the deficiency of certain nutrients,

including iron and vitamin D, that contribute to the development of the disease. Several environmental factors may influence the development of irregular uterine bleeding. It is essential to understand that several factors may cause irregular uterine bleeding and that each case is unique. Environmental factors like exposure to pollutants, toxins, or chemicals may also contribute to AUB (Wouk et al. 2019; Munro et al. 2011).

Abnormal uterine bleeding with leiomyoma

Fibroids in the uterus are sometimes known as leiomyomas or myomas, which develop in uterine myometrial cells and lead to proliferation and differentiation due to various genetic factors and conduct to myometrial hyperplasia by ECM deposition, addition, and angiogenesis through gonadal steroids, estrogen, and progesterone which finally results in the development of uterine leiomyoma (Noel et al.2019) (figure 5). Among these nine classifications, we are primarily concerned with leiomyoma development since it is believed that several factors may contribute to the association between leiomyoma and abnormal uterine bleeding, including changes in angiogenic, environmental, gene-associated, vasoactive substances, and mechanical changes to the uterus (Lasmar et al. 2017).

The role of fibroids (leiomyomas) in the development of AUB

Fibroids and AUB do not appear to interact in a well-understood manner. Fibroids are commonly found in women with perfectly normal bleeding patterns, which is strange. Furthermore, fibroids are more prevalent in female AUB patients. Previous hypotheses include an engorged vasculature associated with a perimyoma environment and an enhanced endometrial surface area (Munro et al. 2012). These enlarged arteries may result in increased circulation, counterbalancing the activity of platelets (Stewart et al. 1996).

Fibroids are associated with various cellular and molecular changes that influence angiogenesis, modulate vasoactive substrates and growth factors, and disrupt coagulation. Myomas affect the endometrium in a broad sense as opposed to being limited to the area containing the myoma. AUB may also be impacted by these changes and the endometrium's receptivity to implantation (Doherty et al. 2014; Sinclair et al. 2011). The matrix metalloproteinases (MMP) -2 and -11 levels are higher in fibroids (Palmer et al. 1998; Bogusiewicz et al. 2007), but it is unclear whether this increases endometrial bleeding. The effect of VEGF, bFGF, PDGF, and PTHrP on the endometrium in fibroids is still unknown, even though all these substances have the potential to be angiogenic. Women with fibroids have higher plasma interleukin (IL)-13, IL-17, and IL-10 in their blood (Wegienka et al. 2013).

Endometrial degeneration and repair have both been associated with immune systems and inflammation. There is no information regarding these polymorphisms. The prevalence of HMB was believed to be higher in women with SM fibroids, particularly those with distorting cavities. A significant degree of cavity distortion in women is widely debated as to whether it poses additional therapeutic challenges.

Genetics of leiomyoma

A uterine fibroid or leiomyoma is a benign tumor that grows in the smooth muscles of the uterus. Leiomyomas are inherently hereditary, although their exact cause is unknown. A variety of genetic factors, including estrogen and progesterone receptors, are capable of influencing leiomyoma development. We have reviewed several potential genes, among which are listed a few. The growth of leiomyomas can be attributed to mutations in genes such as ESR1, PRs, IGF1, TGF-β, FGF, IL-6, and FH, which are responsible for regulating the proliferation of smooth muscle cells.

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Role of estrogen and progesterone in leiomyoma and genes associated

Estrogen receptor 1

Numerous cellular functions, including growth, differentiation, and reproductive system operation, are regulated by estrogen. There is a transcription factor encoded by this gene that is activated by ligands and an estrogen receptor encoded by this gene. In many non-reproductive tissues, this gene encodes a protein that regulates the transcription of several estrogen-sensitive genes involved in growth, metabolism, sexual development, gestation, and other reproductive functions. This gene has been associated with breast cancer, endometrial cancer, and osteoporosis. ESR1 (estrogen receptor 1) gene is a protein-coding gene positioned on chromosome 6, the band - 6q25.1-q25.2. Estrogen receptor-alpha (ESR-α), which the estrogen receptor 1 encodes (ESR1), is mainly expressed in uterine tissues.

This receptor is vital in estrogen in premenopausal and menopausal women (tyan et al. 2023). Two significant forms of intracellular estrogen receptors designated ER-α and ER-β have been encoded by distinct genes (Bharathi et al. 2019). Accordingly, several genes have been linked to the development of leiomyomas, and both estrogen and progesterone play key roles in the development and progression of these cancers. The development of innovative treatment methods for leiomyomas may be made possible by understanding the molecular pathways that lead to the development of leiomyomas.

Progesterone receptor

Progesterone receptors (PRs) are nuclear hormone receptors of the NR3C family, containing mineralocorticoid, glucocorticoid, and androgen receptors. They exist as homodimers with Hsp90 or HMGB proteins that are removed upon activation. PR binds to thousands of DNA regions in uterine myomas' smooth muscles, regulating many genes and promoting survival, proliferation, and inappropriate ECM synthesis. Which occurs primarily during childbearing age, whereas insignificant hormone levels cause tumour degeneration due to menopause or GnRH analogue therapy (Maruo et al. 2004; Sabry et al. 2012). At the tissue level, a high standard of progesterone receptor expression in the smooth muscle is also linked to an expanding risk of developing uLM (Omar et al. 2019). However, progesterone is required for uLM development and perpetuation (Ishikawa et al., 2010).

Indeed, progesterone receptors are one of the most popular therapeutic targets in uterine leiomyoma therapy due to using particular progesterone receptor modulators such as ulipristal acetate (UPA) or mifepristone, which can promote apoptosis, suppress proliferation, and decrease tumor development and manifestation (Engman et al. 2009; Murji et al., 2017). The role of estrogen and progesterone in leiomyoma is shown in Figure 6. Proteins activated by progesterone receptors are known as "progesterone receptors." There is an increase in progesterone receptor expression in leiomyomas, suggesting that progesterone plays a critical role in their development. Developing customized treatments for leiomyomas may be possible by understanding the activity and relationship between these genes and progesterone signalling.

Other genes that are associated with leiomyoma development include

Even though mutations in these genes have been associated with developing leiomyomas, not all individuals with these mutations will develop leiomyomas. Leiomyomas are likely to grow depending on hereditary and environmental factors.

Insulin-like growth factor 1 (IGF1)

The IGF system is a combination of the biological system made up of peptide hormones such as insulin-like growth factor-1 and -2 (IGF-I and IGF-2) cell surface receptors and IGF binding proteins (IGFBPs) that synchronize a variety of critical biological processes such as cell migration, differentiation, proliferation, and smooth muscle cell survival. Insulin-like growth

factor-I (IGF-I) is probably one of the growth factors involved in the pathogenesis of fibroids (Swartz et al. 2005). Growth hormone can boost IGF-I synthesis, and its functions include cell proliferation and apoptosis inhibition (Jones et al. 1995). IGF-I promotes cell proliferation in uterine leiomyoma (fibroid) tissue (Jones et al. 1995).

Human myometrium and myoma tissues contain significant levels of extractable IGF-I, far more than other peptide growth factors (Eshet et al. 2004). When steroid hormones are absent, IGF-1 stimulates leiomyoma development, suggesting it is directly involved in leiomyoma pathogenesis. Steroid hormones have a crucial role in the molecular pathophysiology of tumor development as they interact with their receptors to enhance fibroid development (Andersen et al. 1996).

Furthermore, several leiomyoma-related genes regulate IGF1 expression and are believed to be involved in the onset and development of uterine leiomyomas. Additional research is necessary to understand these cancers' molecular mechanisms and identify potential therapeutic targets.

Transforming growth factor-beta

TGF-β signaling has a complicated function in the formation of UFs. TGF-β isoforms and their receptors are expressed in human myometrium and UF malignancies. TGF-β is a potent tumor suppressor in normal smooth muscle cells by inhibiting proliferation and stimulating apoptosis (Ciebiera et al. 2017). On the other hand, overexpression of TGF-β in uterine fibroids has been identified and appears to play a vital role in their growth and disease progression (Ciarmela et al. 2011; Bulun et al. 2013). TGF-β influences the formation of uterine leiomyoma directly or indirectly by modifying environmental estrogen interactions (Shen et al. 2018).

TGF signaling causes molecular alterations that aid in the genesis of leiomyomas. A variety of chemicals or medicines have been linked to the increased TGF signaling in the pathogenesis of leiomyomas, such as genistein (Di et al. 2012), halofuginone (Grudzein et al. 2008), asoprisnil (Ohara et al. 2007), relaxin (Roggero et al. 2009), gonadotropin-releasing hormone-analogs (GnRH-a), and tibolone (De et al. 2006). Although a relationship between TGFB overexpression and leiomyoma has been shown, the underlying mechanisms of TGF signalling in leiomyoma remain elusive (Li et al. 2014). There is strong evidence that TGF-signaling and its downstream targets are essential in developing and progressing leiomyomas. Novel therapeutic methods may be developed for these diseases if we can understand the molecular mechanisms underlying TGF-signaling.

Fibroblast growth factor

FGFs are a cytokine class that serves essential regulatory functions in development, tumourigenesis, hematopoiesis, and wound healing (Wolanska et al. 2006). It is well understood that neoplastic malignancies, including uterine leiomyomas, comprise neoplastic cells and stromal connective tissue. It is involved in tumor growth but also performs in typical cell growth, survival, differentiation, and angiogenesis (Korc et al. 2009). FGF stimulates cell division in endothelial cells expressing the FGFR, directly affecting tumor angiogenesis (Korc et al. 2009).

It has been shown that fibroblasts can interact with neoplastic cells, generates the extracellular matrix (ECM), and stimulate tumor cells to produce/secrete a range of soluble factors and proteins into the ECM, such as growth factors. Furthermore, fibroblasts and the ECM in tumours may benefit tumour progression (Moore et al. 2010). Numerous growth factors in the fibroblast growth factor family are essential to cellular migration, proliferation, differentiation, and growth. Liomyomas, a benign tumour from smooth muscle cells in the uterus, have been linked to FGF.

Interleukin-6

Interleukin-6 is a cytokine that performs a significant role in the communication of cells by the body's defence mechanism. The expression of this can activate the production of cellular components of blood and stimulate immune responses. Lately, it has been studied that cytokines such as IL-6 and tumor necrosis factor-α (TNF-α) contribute to the progression of uterine leiomyoma leading to anemia (Ohta et al. 2020). Along with IL-6, several other growth elements, including transforming growth factor-α, heparin-binding epidermal growth factor, and epidermal growth factor, induce leiomyoma by enhancing the growth of fibrous tissues. The proliferation of cells in the uterus is accelerated by reactive oxygen species and unbound ions (Amballi et al. 2017).

Lately, it has been observed that there is a link between IL-6 and adiponectin. Adiponectin is an inflammatory mediator secreted by adipocytes, whose levels get reduced significantly when there is an increase in the levels of IL-6. It has a higher accumulation of fat, which has a more significant effect on the myometrium and intensifies uterine leiomyomas' growth (Adediji et al. 2019). Figure 7 shows the mechanism of the IL-6 gene. While there is evidence that IL-6 may play a role in the etiology of leiomyomas, more research is required to understand its role in this condition. This gene family regulates various biological processes, including extracellular matrix remodelling, inflammation, and cell proliferation.

Fumarate hydratase gene

Fumarate hydratase (FH) gene mutations are commonly observed in hereditary leiomyomatosis and Reed syndrome. It is sometimes seen in uterine leiomyoma in younger people with a higher rate of incidence (Zhang et al. 2018). It is often associated with the pathogenesis of leiomyoma with bizarre nuclei (LBN), a rare variant of the endometrial neoplasm in the uterus (Gregova et al. 2020). Uterine leiomyomas that are FH-deficient are characterized by the stimulation of the NRF2 mechanism that includes upregulating the NRF2 target gene AKR1B10. The most common features typically observed are perivascular hypercellularity and cellular histopathology (Mehine et al. 2022).

In the case of hereditary leiomyomatosis and renal cell carcinoma, the FH gene is involved in tumor suppression. Biallelic inactivation of the gene causes higher levels of ATP, which is necessary for increased cell proliferation. Later revealed that women of African origin are highly susceptible to uterine leiomyoma (Mochado et al. 2021). The FH gene is responsible for the development of leiomyomas. Patients suffering from these tumors may experience severe clinical outcomes if this gene is changed. The molecular mechanisms underlying leiomyomas must be better understood to identify potentially effective therapeutic strategies for this often debilitating condition.

Conclusion

This review, focusing on leiomyomas, summarizes the prevalence, complications, genetic associations, and hormonal changes related to AUB and its various patterns. The FIGO PALM-COEIN categorization system is crucial for accurate diagnosis and treatment guidance.

Genetic insights into AUB are used to design personalized therapy techniques, identifying mutations affecting hormone control and coagulation pathways. Because genes such as FH, IL-6, FGF, TGF-β, IGF-1, PR, and ESR1 play a role in the pathogenesis of leiomyoma in various ways, such as cell proliferation and matrix remodelling, it may be possible to treat these tumours with targeted therapies. Future research should focus on identifying more complex genetic and environmental connections to improve diagnostic and treatment results. Explore biomarkers for early detection and diagnosis of leiomyomas, given their impact on women's health and quality of life. Collaboration among medical professionals is essential to develop effective treatments for uterine leiomyomas, considering their high prevalence and clinical impact.

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Abbreviations

AUB abnormal uterine bleeding; FIGO - The International Federation of Gynecology and Obstetrics; PALM polyps adenomyosis leiomyoma malignancy and hyperplasia; COEIN - coagulopathy, ovulatory dysfunction, endometrial, iatrogenic; HPO - hypothalamic pituitary ovarian; FSH - follicle-stimulating hormone; HMB - heavy menstrual bleeding; FCM - ferric carboxymaltose; ID - iron deficiency; IDA - iron deficiency anemia ; TVS - transvaginal ultrasonography; MRI - magnetic resonance imaging; TVUS - transvaginal ultrasound; PCOS - polycystic ovarian syndrome ; ECM - extracellular matrix; EDC - endocrine disrupting chemicals ; ESR - estrogen receptor 1; PR - progesterone receptor; IGF1- insulin-like growth factor 1; TGF-β - insulin-like growth factor beta; FGF - fibroblast growth factor; IL-6 - interleukin-6; TNF-α - tumor necrosis factor alpha; FH - fumaratee hydratase; GWAS - genome-wide association studies.

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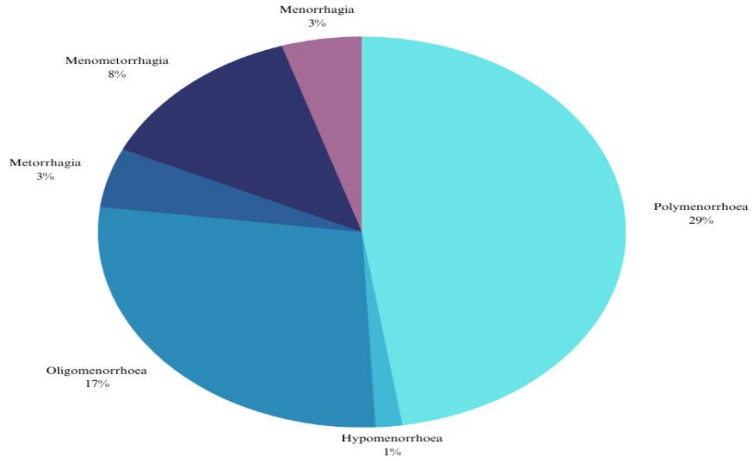

Figure 1. The prevalence of abnormal uterine bleeding

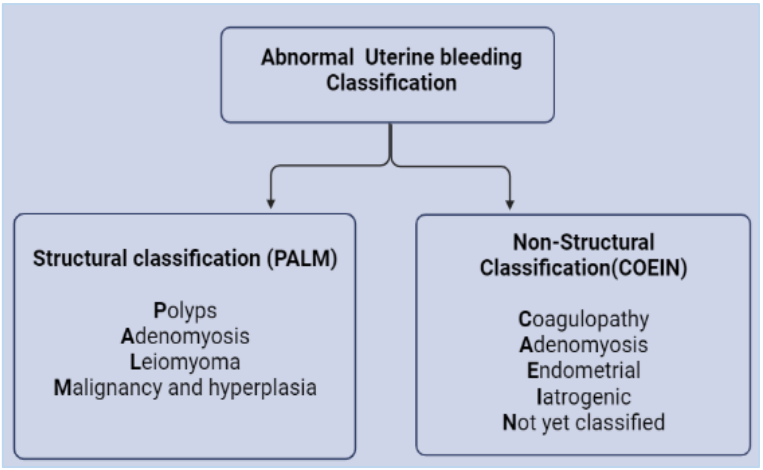

Figure 2. FIGO classification of abnormal uterine bleeding

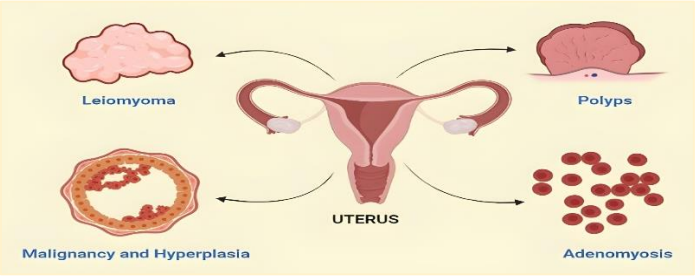

Figure 3. Structural causes of abnormal uterine bleeding PALM

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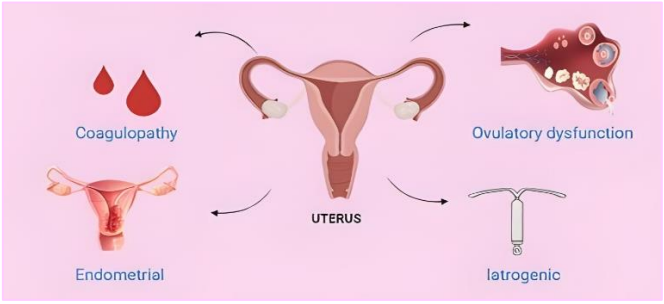

Figure 4. Non-structural causes of abnormal uterine bleeding COEIN

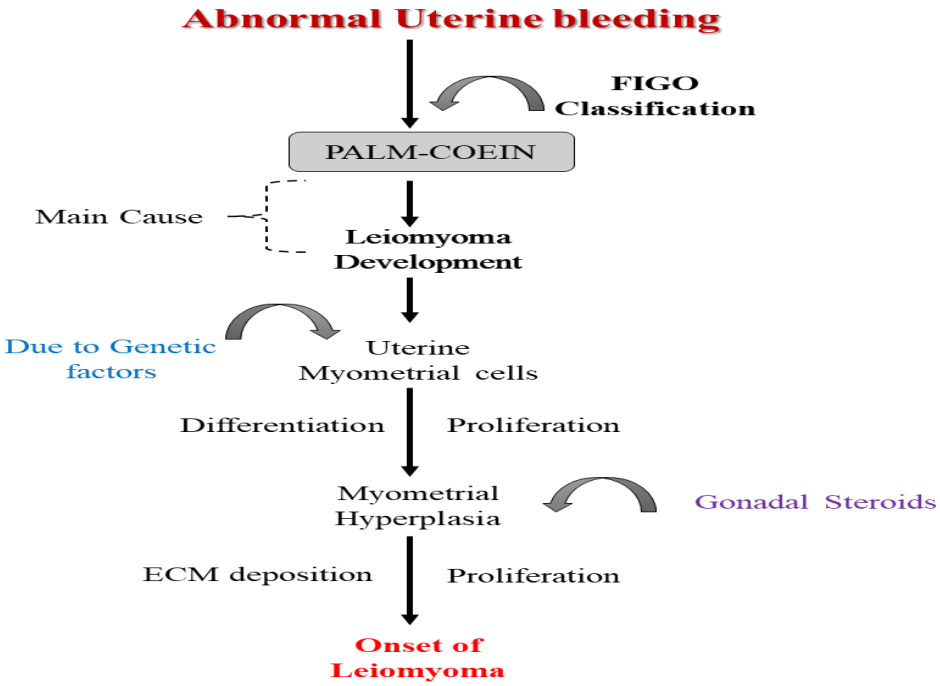

Figure 5. Overview of the association of AUB and the development of leiomyoma

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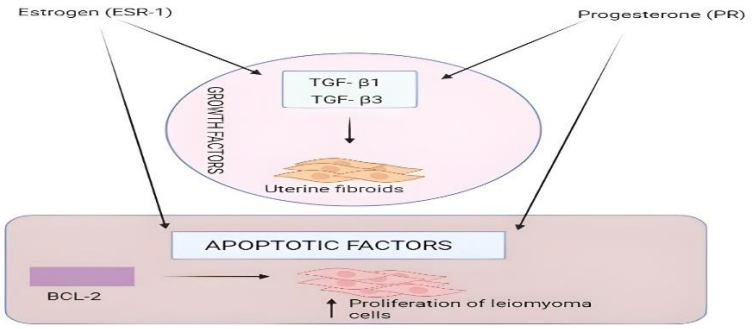

Figure 6. Mechanism of estrogen receptor gene and progesterone receptor gene

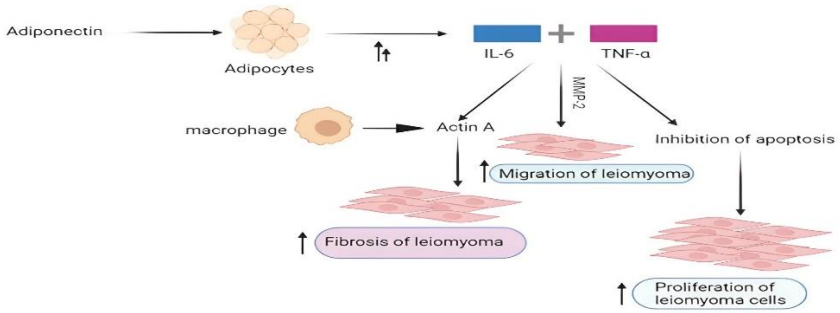

Figure 7. Mechanism of interleukin 6 gene in leiomyoma development

Table 1. An overview of the function, location, amino acids, and exons associated with leiomyoma development and hormones

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			Exon	Amino Acid	Function	References
Estrogen receptor-1	*ESR1*	6q25.1-q25.2	22	595	The ligand-activated transcription factor and the protein encoded by this gene control the transcription of numerous genes. In addition to growth, metabolism, pregnancy, sexual development, estrogen-inducible genes affect several reproductive processes.	[78]
Progesterone receptor	*PR*	11q22.1	10	933	As a member of the superfamily of steroid receptors, the encoded protein mediates progesterone's physiological effects. This hormone is predominant in reproductive events such as the onset and upkeep of pregnancy.	[80, 81]
Insulin-like growth factor-1	*IGF-1*	12q23.2	7	195	In terms of structure and function, this protein is similar to insulin. It belongs to a family of proteins that regulates growth and development. A precursor protein is processed, bound by a specific receptor, and secreted. Insulin-like growth factor I deficiency occurs due to mutations in this gene.	[87]
Transforming growth factor-beta	*TGF-β*	19q13.2	7	390	The TGF-beta superfamily of proteins' secreted ligand is encoded by this gene. These ligands bind to various TGF-beta receptors, causing the recruitment and activating of transcription factors as a result. from the SMAD family that control gene expression which regulates cell proliferation, differentiation, and growth factors such as tumour necrosis factor-alpha and interferon-gamma	[91]
Fibroblast growth factor	*FGF*	4q28.1	3	822	The protein encoded by this gene is a member of the immediate family of fibroblast growth factors (FGF). Several FGF family members have strong and broad mitogenic and angiogenic properties and can bind heparin. This protein modulates several biological processes, including the growth of the nervous system and limbs, the healing of wounds, and tumour growth.	[101]
Interleukin -6	*IL-6*	7p15.3	5	212	This gene produces a cytokine that activates the interleukin 6 receptor alpha to trigger transcriptional inflammation at acute and chronic inflammation sites. Additionally, it has been demonstrated that the encoded protein functions as an endogenous pyrogen that can cause fever in persons with autoimmune disorders or infections.	[105]
Fumarate hydratase	*FH*	1q43	10	510	A gene that produces an enzyme that assists cells in the body in using oxygen and producing energy. Cells with mutated (modified) fumarate hydratase genes may lose their capacity to utilize oxygen. As a result some cells particularly cancer cells and abnormal cells may develop more rapidly.	[108]